IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	C.A. No. 21-691 (GBW) **REDACTED - PUBLIC VERSION**
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	C.A. No. 21-1138 (GBW) **REDACTED - PUBLIC VERSION**
JAZZ PHARMACEUTICALS, INC. and JAZZ PHARMACEUTICALS IRELAND LIMITED, Plaintiffs, v. AVADEL CNS PHARMACEUTICALS LLC, Defendant.	C.A. No. 21-1594 (GBW) **REDACTED - PUBLIC VERSION**

JOINT SUPPLEMENTAL CLAIM CONSTRUCTION APPENDIX

VOLUME 1 OF 2: EXHIBITS 1-41

Original Filing Date: April 26, 2023
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Jazz's Exhibits

EXHIBIT	DESCRIPTION
Exhibit 1	Avadel's Amended Final Non-Infringement Contentions
Exhibit 2	Declaration of Steven R. Little, Ph.D. in support of Jazz's supplemental opening *Markman* brief
Exhibit 3	U.S. Patent No. 10,758,488
Exhibit 4	Excerpts of the supplemented opening expert report of William Charman
Exhibit 5	Prescribing Information for Avadel's New Drug Application product
Exhibit 6	Excerpts of the opening expert report of Alexander M. Klibanov, Ph.D.
Exhibit 7	Mamelak, et al., "The Effects of γ-Hydroxybutyrate on Sleep," Biol Psych (1977); 12 (2): 273-288.
Exhibit 8	Broughton, et al., "Gamma-Hydroxy-Butyrate in the Treatment of Narcolepsy: a Preliminary Report," (1976) Narcolepsy, Ny, N.Y., Spectrum Publications, Inc. 659-668.
Exhibit 9	Broughton et al., "The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate," Can J. Neural Sci (1979); 6(1): 1-6.
Exhibit 10	Broughton, et al., "Effects of Nocturnal Gamma-Hydroxybutyrate on Spell/Waking Patterns in Narcolepsy-Cataplexy," Can J. Neural Sci (1980); 7 (1): 23-31.
Exhibit 11	Published U.S. patent application US 2006/0210630 (Liang, et al.)
Exhibit 12	Ferrara, S. D., et al., "Pharmacokinetics of Y-Hydroxybutyric Acid in Alcohol Dependent Patients After Single and Repeated Oral Doses," Br. J. Clin. Pharmacol. (1992); 34: 231-235.
Exhibit 13	Gallimberti, L., "Gamma-hydroxybutyric Acid for Treatment of Alcohol Withdrawal Syndrome," Clinical Pharmacology, 2(8666), (1989), 787-789.
Exhibit 14	Gallimberti, L., "Gamma-Hydroxybutyric Acid in the Treatment of Alcohol Dependence: A Double-Blind Study," Alcohol Clin. Exp. Res. (1992), 16(4): 673-676.
Exhibit 15	Gessa, G. L., et al., "Gamma-hydroxybutyric acid (GHB) for treatment of ethanol dependence," European Neuropsychopharmacology, 3(3), (1993), 224-225.
Exhibit 16	Gessa, G. L., "Gamma-hydroxybutyric Acid in the Treatment of Alcohol Dependence," Clin. Neuropharm., 15 Suppl 1 Pt A, (1992), 303a-304a.
Exhibit 17	Palatini, P., "Dose Dependent Absorption and Elimination of Gamma-Hydroxybutyric Acid in Healthy Volunteers," Eur. J. Clin. Pharmacol. (1993); 45 (4): 353-356.
Exhibit 18	Roth, R. H., et al., "γ-Butyrolactone and γ-Hydroxybutyric acid-II. The Pharmacologically active form," J. Neuropharmacol. (1966); 5 (6): 421-428.
Exhibit 19	Roth, et al., "γ-Butyrolactone and γ-Hydroxybutyric Acid-I, Distribution and Metabolism," Biochemical Pharmacology (1966); 15 (9):1333-1348.
Exhibit 20	Snead, et al., "Ontogeny of γ-Hydroxybutyric Acid. I. Regional Concentration in Developing Rat, Monkey and Human Brain," Brain Res. (1981); 227 (4): 579-589.
Exhibit 21	Excerpts of the opening expert report of Robert S. Langer

Exhibit 22	May 2, 2019 Office Action in U.S. Patent Application No. 16/025,487
Exhibit 23	March 5, 2020 Declaration of Clark Allphin under 37 C.F.R. § 1.132 in U.S. Patent Application No. 16/025,487
Exhibit 24	U.S. Patent No. 11,077,079
Exhibit 25	Arena, et al., "Absorption of sodium γ-hydroxybutyrate and its Prodrug γ-butyrolactone: Relationship between in vitro transport and in Vivo absorption," Journal of Pharmaceutical Sciences (1980); 69 (3): 356-358.
Exhibit 26	Lettieri, et al., "Improved pharmacological activity via pro-drug modification: comparative pharmacokinetics of sodium gamma-hydroxybutyrate and gamma-butyrolactone," Research Communications in Chemical Pathology and Pharmacology (1978); 22 (1): 107-118.
Exhibit 27	U.S. Patent No. 11,147,782
Exhibit 28	February 24, 2021 Office Action in U.S. Patent Application No. 17/118,041
Exhibit 29	April 26, 2021 Interview Summary in U.S. Patent Application No. 17/118,041
Exhibit 30	May 20, 2021 Declaration of Clark Allphin under 37 C.F.R. § 1.132 in U.S. Patent Application No. 17/118,041
Exhibit 31	June 18, 2021 Office Action in U.S. Patent Application No. 17/210,064
Exhibit 32	August 2, 2021 Response to Office Action in U.S. Patent Application No. 17/210,064
Exhibit 33	*Curriculum vitae* of Steven R. Little, Ph.D.
Exhibit 34	Scientific Working Group for the Analysis of Seized Drugs Monograph for Gamma-Hydroxybutyrate (GHB) (2005)
Exhibit 35	McGraw-Hill Dictionary of Scientific and Technical Terms (5th Ed. 1994), definition of "acid"
Exhibit 36	Transcript of the April 6, 2023 Deposition of Alexander Klibanov, Ph.D.
Exhibit 37	Scharf, et al., "Pharmacokinetics of gammahydroxybutyrate (GHB) in narcoleptic patients." Sleep, (1998) Aug. 1;21(5):507-14. Scharf, "Sodium oxybate for narcolepsy," Expert Rev. Neurother., (2006) Aug;6(8):1139-46.
Exhibit 38	Excerpts of the supplemented opening expert report of William Charman
Exhibit 39	Opening expert report of Alexander M. Klibanov, Ph.D.
Exhibit 40	Supplemental expert report of Alexander M. Klibanov, Ph.D.
Exhibit 41	Transcript of the April 13, 2023 Deposition of Steven R. Little, Ph.D.

Avadel's Exhibits

EXHIBIT	DESCRIPTION
Exhibit A	3/17/2023 email
Exhibit B	3/22/2023 email
Exhibit C	Klibanov Declaration
Exhibit D	Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013
Exhibit E	US 2018/0021284 Patent Publication
Exhibit F	"And" Definition & Meaning (https://www.yourdictionary.com/and)
Exhibit G	US 2019/0274990 Patent Publication
Exhibit H	U.S. Patent No. 10,736,866
Exhibit I	Transcript of the April 13, 2023 Deposition of Steven R. Little, Ph.D.
Exhibit J	March 6, 2020 Request for Continued Examination
Exhibit K	4/19/2023 email
Exhibit L	U.S. Patent No. 10,758,488 Application canceling pending claims
Exhibit M	"Or" Definition & Meaning (https://www.merriam-webster.com/dictionary/or)
Exhibit N	Comparison between the claims of the Resinate patents and Avadel's claims
Exhibit O	Newman, et al., "Solid form changes during drug development: good, bad, and ugly case studies," AAPS Open (2016); 2 (2): 1-11.

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April 26, 2023

EXHIBIT 1

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JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW [redacted]

AVADEL'S AMENDED FINAL NON-INFRINGEMENT CONTENTIONS

Pursuant to the Scheduling Order entered in the above-captioned actions on December 21, 2021 (*see* D.I. 29),[1] Defendant Avadel CNS Pharmaceuticals, LLC ("Avadel"), hereby provides Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (collectively "Jazz" or "Plaintiffs") its final Non-Infringement Contentions regarding the asserted claims of U.S. Patent

[1] All matters listed in the caption above are proceeding on a coordinated schedule. All docket cites are to matter C.A. No. 21-cv-1138-MN unless otherwise noted.

Nos. 8,731,963 (the "'963 patent"); 10,758,488 (the "'488 patent"); 10,813,885 (the "'885 patent"); 10,959,956 (the "'956 patent"); 10,966,931 (the "'931 patent"); 11,077,079 (the "'079 patent"), and 11,147,782 (the "'782 patent") (collectively the "Asserted Patents").

I. INTRODUCTION

A. Asserted Claims

On September 7, 2021, Jazz provided Avadel with its Initial Infringement Contentions pursuant to Paragraph 4(c) of the Delaware Default Standard for the '963 patent, the '488 patent, the '885 patent, the '956 patent, and the '931 patent. In those Initial Infringement Contentions, Jazz asserted that FT218, as described in Avadel's New Drug Application ("NDA") No. 214755 ("Avadel's NDA"), will infringe [redacted] collectively the "Sustained Release Patents"). Jazz further asserted that "Avadel's activities in connection with the manufacture, use, sale, offer for sale and/or importation" of FT218 will infringe [redacted] (the "REMS Patent").[2]

On December 7, 2021, Jazz provided Avadel with its Initial Infringement Contentions for the '079 and '782 patents (collectively, the "Resinate Patents"). In those Initial Infringement Contentions, Jazz asserted that FT218 will infringe claims [redacted]

B. Avadel's FT218 Product

Avadel's FT218 product is a formulation of sodium oxybate designed to treat excessive daytime sleepiness (EDS) or cataplexy in adults with narcolepsy. Unlike Jazz's sodium oxybate products, which are twice-nightly formulations that require patients to wake up in the middle of

[2] As addressed below, it is unclear what Jazz actually accuses with respect to the REMS patent.

the night, FT218 is a revolutionary ***once-nightly*** formulation of sodium oxybate that avoids interrupting the patient's nighttime sleep. Because narcolepsy is a sleep disorder, waking up in the middle of the night for treatment is counterintuitive and presents a major problem for patients. FT218 therefore meets a significant need that is unmet by Jazz's twice-nightly sodium oxybate products.

FT218 is a composition of sodium oxybate [redacted]

[redacted]

FT218 will be dispensed through a Risk Evaluation and Mitigation Strategy ("REMS") to ensure that the product is distributed safely. The REMS for FT218 will be called the LUMRYZ REMS. [redacted]

C. Reservation of Rights

Avadel provides these Final Non-Infringement Contentions based on information that is currently available to it. Avadel reserves the right to supplement and/or amend these Final Non-Infringement Contentions under the Local Rules or any other applicable Rules or order of the Court based upon, among other things, Plaintiffs' Final Infringement Contentions, newly discovered or

newly understood grounds for non-infringement obtained through discovery, the Court's construction of the asserted claims, and/or as discovery proceeds in this case, including based on expert discovery disclosures and on any discovery materials that have not yet been produced or provided, upon fact and expert depositions, or upon further investigation. For example, no depositions have yet been conducted in this case, and Avadel reserves the right to rely on evidence developed during fact depositions as evidence of non-infringement.

Avadel's Final Non-Infringement Contentions are also limited by the information provided by Jazz in its Initial Infringement Contentions and Plaintiffs' responses to Avadel's discovery requests, many of which are deficient or incomplete. Indeed, Jazz's Initial Infringement Contentions and discovery responses are wholly inadequate, and although Avadel has pointed out to Plaintiffs a large number of deficiencies, Jazz has not remedied them. Avadel reserves the right to supplement these Final Non-Infringement Contentions after Jazz provides complete and proper contentions and discovery responses.

These Final Non-Infringement Contentions are also made pursuant to Rule 502 of the Federal Rules of Evidence. To the extent that these Final Non-Infringement Contentions contain any information protected from disclosure by the attorney-client privilege, the attorney work-product doctrine, the common-interest privilege, the joint-defense privilege, or any other applicable privilege, doctrine, or immunity, the disclosure of such in these Final Non-Infringement Contentions is inadvertent and does not constitute a waiver of any such privilege, doctrine, or immunity. The information set forth herein is provided without waiving: (1) the right to object to the use of any statement for any purpose at trial or a deposition in this or any other action on any appropriate grounds; (2) the right to object to any discovery or other request for information

involving or based upon any statements made herein; or (3) the right to revise, correct, supplement, or clarify any of the statements made herein at any time.

Additionally, the Final Non-Infringement Contentions set forth herein for the independent claims of the Asserted Patents are incorporated by reference into the Final Non-Infringement Contentions for any asserted claims that depend from such independent claims, as if such contentions were fully set forth therein. Further, the division of claim elements, and any parenthetical references, are not intended to be a modification of the claim language or an admission that the claims should be so construed, but rather is done for purposes of convenience of reference. These Final Non-Infringement Contentions respond to Jazz's Initial Infringement Contentions, and do not act to affirm or admit narratives provided by Jazz.

In providing these Final Non-Infringement Contentions, Avadel reserves and does not waive any and all claims, contentions, or arguments regarding the factual and/or legal details of these Contentions. These Final Non-Infringement Contentions are not designed to represent all evidence supporting non-infringement; rather, where specifics are provided, they provide examples of the manner in which the accused product does not infringe the asserted claims of the Asserted Patents. All citations to evidence are illustrative, and Avadel reserves the right to rely upon other portions of cited documents, or additional documents to support non-infringement, including all documents relied upon by Plaintiffs as purportedly showing infringement. Any omission of other specific citations or evidence does not constitute waiver of any right to rely upon such additional evidence at a later date, including for purpose of trial.

II. AVADEL'S FT218 PRODUCT DOES NOT INFRINGE THE SUSTAINED RELEASE PATENTS

A. Jazz's Contentions Do Not Establish That Avadel's FT218 Contains a "Sustained Release" Portion as Claimed

All the asserted claims of the Sustained Release Patents recite a "sustained release" limitation. As an initial matter, Jazz's Initial Infringement Contentions are vague, incomplete, and unintelligible as to this limitation, and do not satisfy the disclosure requirements under the Local Rules or establish that the subject limitation is satisfied. Jazz has also set forth no evidence for its conclusory assertion that this limitation is met under the doctrine of equivalents. As explained below, Jazz cannot meet its burden of establishing that Avadel infringes the asserted claims of the Sustained Release Patents either literally or under the doctrine of equivalents at least because FT218 does not contain a "sustained release" portion under either party's proposed construction of this term.[3]

Disputed Term; Patents and Claims	**Avadel's Proposed Construction**	**Jazz's Proposed Construction**
"sustained release" (Avadel) "sustained release portion" (Jazz) '488 Patent Claims 1-12, '866 Patent Claims 1-15; '956 Patent Claims 1-20, 23-25; '931 Patent Claims 1-15	a gradual, extended release, as opposed to releasing a majority of the drug within an hour upon exposure to intestinal pH	Plain and ordinary meaning, i.e., the portion of the formulation that is not immediate release and that releases over a period of time

1. Avadel Does Not Infringe The "Sustained Release" Portion Limitation Under Avadel's Proposed Construction

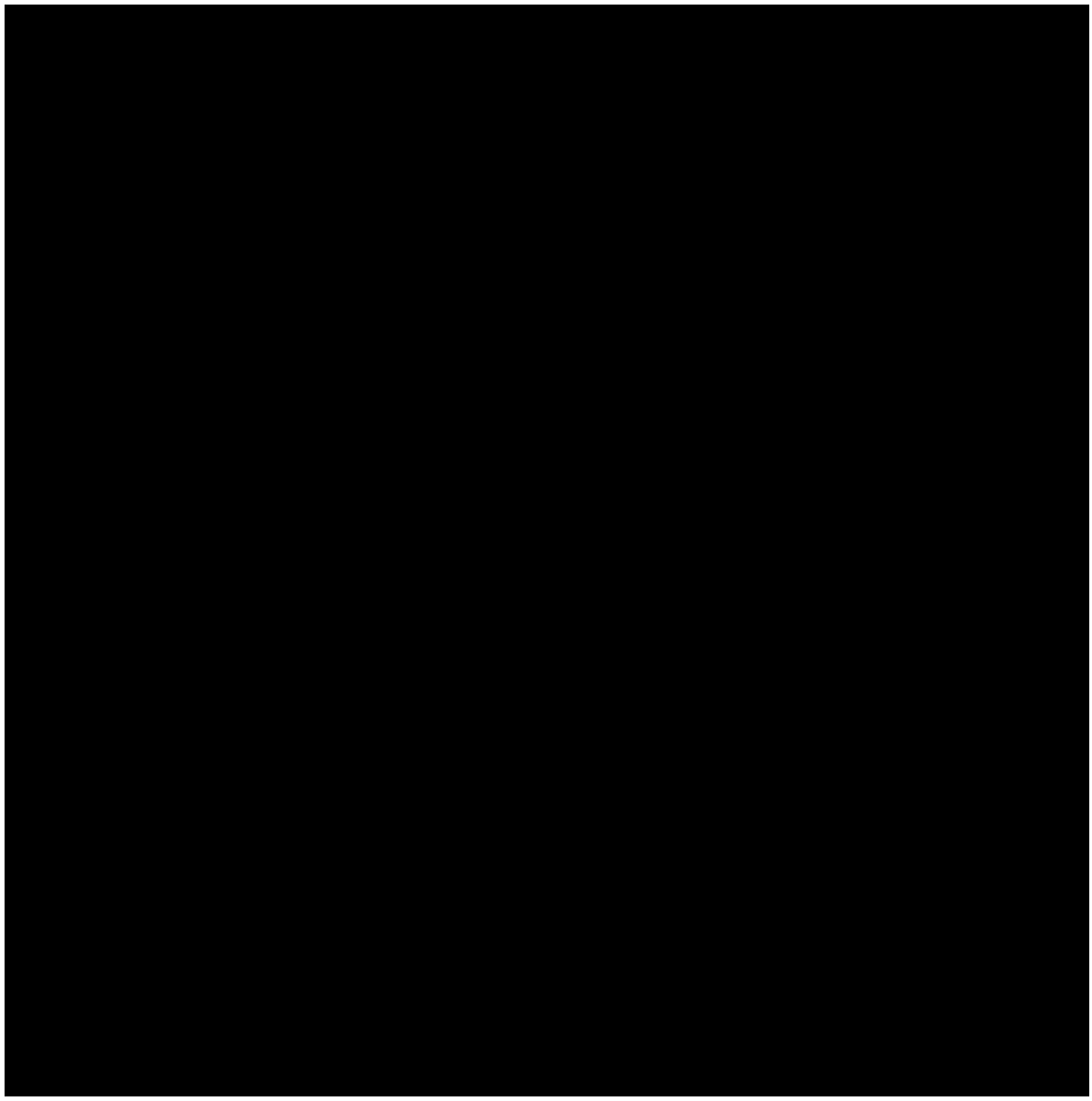
Jazz cannot meet its burden of establishing that FT218 has a "sustained release" portion under Avadel's proposed construction. As used in the asserted claims of the Sustained Release

[3] As set forth in Avadel's Invalidity Contentions dated October 13, 2021, the asserted claims of the Sustained Release Patents are invalid. Because invalid claims cannot be infringed, Avadel's FT218 does not infringe any of the asserted claims of the Sustained Release Patents for this separate reason.

Patents, "sustained release" describes "a gradual, extended release, as opposed to releasing a majority of the drug within an hour upon exposure to intestinal pH."

Avadel's FT218 product does not have a "sustained release" portion and cannot meet this limitation of the asserted claims of the Sustained Release Patents.

[redacted]



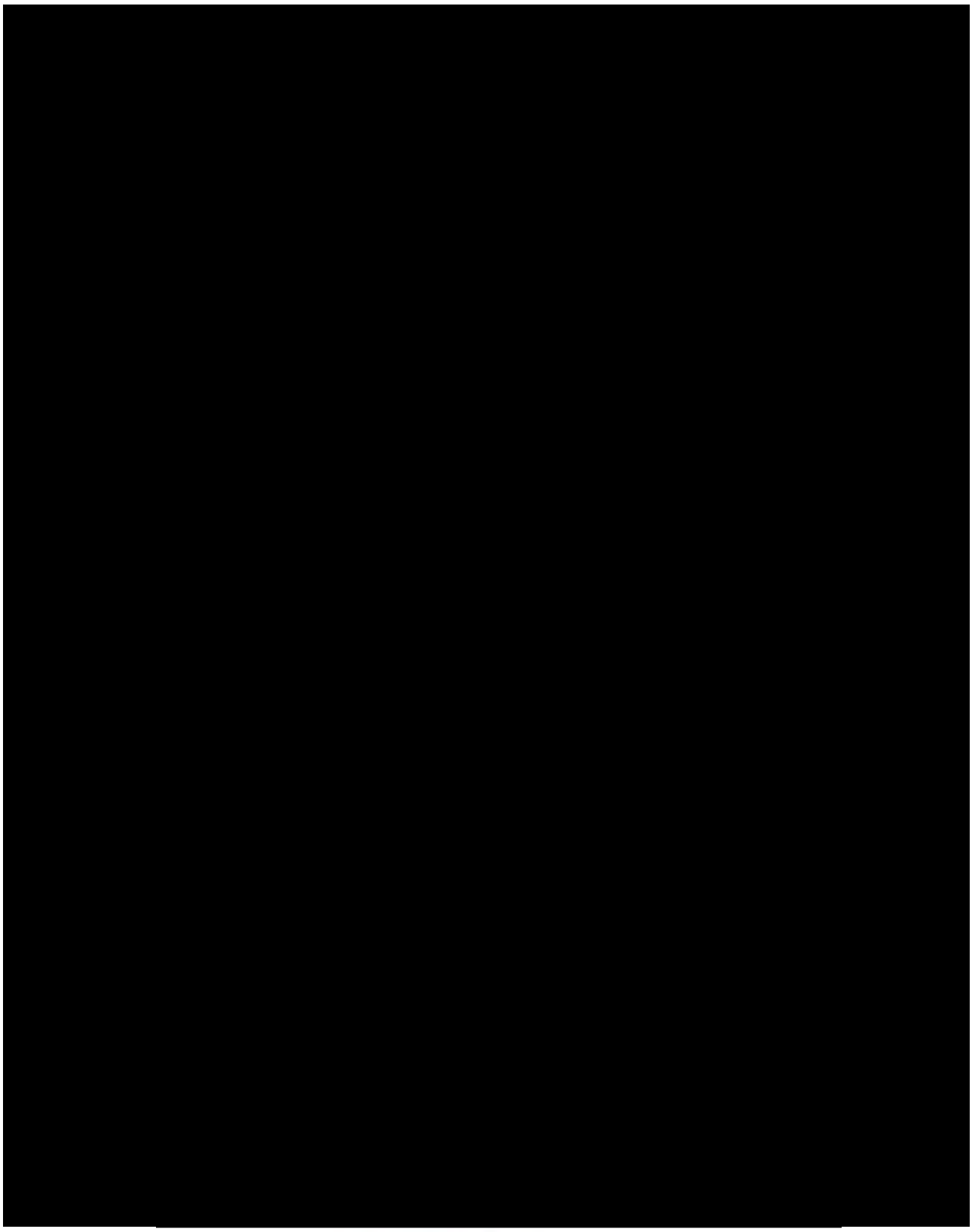
[redacted]

Jazz's contentions do not articulate any basis for infringement under Avadel's proposed construction (which reflects the meaning advanced by Jazz during prosecution to distinguish the prior art). *See, e.g.*, Jazz's Initial Infringement Contentions at 27. Instead, Jazz merely asserts, in conclusory fashion, that "Avadel's NDA uses the terms 'controlled release' and 'sustained release' interchangeably," and that "Avadel's proposed package insert states that Avadel's NDA Product 'contains a blend of immediate-release and controlled-release granules.'" *See, e.g.*, Jazz's Initial Infringement Contentions at 27. Jazz's conclusory citations to these documents—which do not refer or relate to how the term "sustained release" is used in the asserted claims of the Sustained Release Patents—does not show infringement under Avadel's proposed construction.

[redacted]

[redacted] As an initial matter, Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Local Rules or establish that the subject limitation is satisfied. Jazz has also set forth no evidence for its conclusory assertion that this limitation is met under the doctrine of equivalents.

[redacted]



[redacted]

C. Jazz's Contentions and Expert Reports Fail to Establish That Avadel's FT218 Product Contains And Releases Gamma-hydroxybutyrate As Claimed

The independent claims of the Sustained Release Patents recite a formulation (or method of using a formulation) comprising immediate release and sustained release portions, "each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate." *See, e.g.*, 488 patent, claim 1 preamble. The claims further recite that the sustained release portion of the formulation, and in some cases the formulation itself, release certain percentages of its gamma-hydroxybutyrate by specified time periods. *See, e.g.*, '488 patent claims 1-4, 12; '885 patent claims 1-3, 13-15; '956 patent, claims 1-4, 10, 11; '931 patent claims 1-3, 13-15. For example, the claims require that the "sustained release portion release greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm," that "the formulation releases at least about 30% of its gamma-hydroxybutyrate by 1 hour and a paddle speed of 50 rpm," and that "the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a

dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm." *See e.g.*, '488 Patent claim 1.

Jazz's infringement contentions and expert report of Dr. Little fail to identify *any* "gamma-hydroxybutyrate" present in or released from any portion of Avadel's FT218 product. "Gamma-hydroxybutyrate," according to its plain and ordinary meaning, is the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The specification of the Sustained Release Patents is fully consistent with this meaning, with both the specification and claims contrasting "gamma-hydroxybutyrate" with "pharmaceutically acceptable salts of gamma-hydroxybutyrate." *See e.g.*, '488 patent claim 1 ("A formulation comprising immediate release and sustained-release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate"); *id.* at 5:35-38. Indeed, the suffix "ate" is used to denote an anion. *See* Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013 at P-72.2.2.2.1.1, https://iupac.qmul.ac.uk/BlueBook/P7.html#7202020201 ("the endings 'ate' or 'ite' [are used] to name anions derived from acids."). Jazz never sought a construction of the term "gamma-hydroxybutyrate" that departs from its plain and ordinary meaning.

In its final infringement contentions concerning the sustained release patents, Jazz asserted that further testing would show that the alleged "sustained release portion" of Avadel's FT218 product releases "gamma-hydroxybutyrate," the anionic compound recited in various claim elements. Specifically, Jazz asserted:

> Further, testing of Avadel's NDA Product, as well as potential testimony from Avadel and potential third parties, will show that the sustained release portion of Avadel's NDA Product releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

Jazz Final Infringement Contentions, at 55.

However, Dr. Little's expert report contains no testing for gamma-hydroxybutyrate. Instead, Dr. Little's report relies solely on information about the presence of sodium oxybate in Avadel's FT218 product and the release of sodium oxybate from Avadel's FT218 product. *See, e.g.*, Little Rpt. at ¶¶ 28-31, 62-68. Thus, neither Jazz in its contentions, nor Dr. Little in his expert report, have pointed to any evidence of the presence or release of the claimed "gamma-hydroxybutyrate" from Avadel's FT218 product. [redacted] By failing (and being unable) to identify any of the claimed "gamma-hydroxybutyrate" present in or released from Avadel's FT218 product, Jazz has not demonstrated that Avadel's FT218 product meets each and every limitation of the Asserted Claims of the Sustained Release Patents. Nor has Jazz advanced any theory that Avadel's FT218 product infringes the Asserted Claims under the doctrine of equivalents.

III. THERE IS NO INFRINGEMENT OF THE ASSERTED CLAIMS OF THE REMS PATENT

As noted *supra*, Jazz asserts that Avadel will infringe claims 1-23, 25, and 28 of the REMS patent.[4] Jazz contends that "Avadel's activities in connection with the manufacture, use, sale, offer for sale and/or importation of the drug product that is the subject of Avadel's NDA will constitute direct infringement under 35 U.S.C. § 271(a) and indirect infringement under 35 U.S.C. §§ 271(b) and (c) of the asserted claims." Jazz's Initial Infringement Contentions at 2.

[4] As set forth in Avadel's invalidity contentions dated October 13, 2021, the asserted claims of the REMS Patent are invalid. Because invalid claims cannot be infringed, Avadel does not infringe any of the asserted claims of the REMS Patent for this separate reason.

Avadel disputes that Jazz's infringement contentions establish infringement of claims 1-23, 25, and 28 of the REMS patent. Avadel does not infringe the asserted claims of the REMS Patent under either party's claim construction for at least the reasons described below.

Disputed Term; Patent and Claims	**Avadel's Proposed Construction**	**Jazz's Proposed Construction**
"[single]/[central] computer database" '963 patent claims 1, 4, 5, 7-9, 14, 21-23, 25	One and only one computer database, having the recited functionality	No construction necessary
"reconcile inventory/reconciling inventory/cycle counted and reconciled" '963 patent claims 1, 20, 23, 28	Checking whether there is a mismatch between the aggregate amount of a drug reported in physical inventory and the aggregate amount in the database	No construction necessary
"database query that identifies that the narcoleptic patient is a cash payer/ database queries . . . for identifying: that the narcoleptic patient is a cash payer . . ." '963 patent claims 1, 23, 25	Plain and ordinary meaning, which is the query identifies that the form of payment used by the patient was physical currency	No construction necessary

A. Jazz's Contentions Do Not Establish Infringement Under § 271(e)(2)(A)

Jazz has not established an act of infringement under § 271(e)(2)(A).

1. Avadel Does Not Infringe the REMS Patent Under Avadel's Proposed Construction of the Asserted Claims

The asserted claims of the REMS Patent are properly construed as directed to systems and not to methods. As set forth in Avadel's motion for judgment on the pleadings,[5] because the REMS Patent is directed to a system and not a method, it was not properly Orange-Book listed. There is

[5] D.I. 21, C.A. No. 21-691-MN, and all other filings related to that motion, the full contents of which are incorporated herein as though fully set forth.

no infringement under 35 U.S.C. § 271(e)(2)(A) for a patent like the REMS Patent, which claims neither a drug nor its use. Jazz's infringement contentions thus cannot establish infringement under § 271(e)(2)(A).

2. Avadel Does Not Infringe the REMS Patent Under Jazz's Proposed Construction of the Asserted Claims

In its opposition to Avadel's motion for judgment on the pleadings (D.I. 43 C.A. No. 21-691-MN), Jazz identified purported method steps that it contended were required by the asserted claims of the REMS Patent. *See infra*. Performing those steps is not in fact claimed in the asserted claims of the REMS Patent, and for that reason, Avadel believes that Jazz will not obtain a construction that their performance is required to infringe. Additionally, during the parties' claim term exchange, Jazz did not propose ***any*** terms for construction, tacitly conceding that the asserted claims do not require re-writing to add the non-existent methods steps that Jazz included in its opposition brief. Avadel is thus aware of no explanation for Jazz's assertion of infringement under § 271(e)(2)(A).

B. Jazz's Contentions Do Not Establish Direct or Indirect Infringement of the Asserted Claims of the REMS Patent

Jazz has not established that there is direct or indirect infringement with respect to the asserted claims of the REMS Patent.

1. Avadel Does Not Infringe the REMS Patent Under Avadel's Proposed Construction of the Asserted Claims

The asserted claims of the REMS Patent are properly construed as directed to systems and not to methods. Jazz's infringement contentions cite the "use, distribution and/or administration of Avadel's NDA Product" as the purportedly infringing conduct, claiming that such use, distribution, and/or administration of the drug "(e.g., by Avadel, doctors, pharmacies, other healthcare professionals, and/or patients) pursuant to Avadel's REMS Program will meet, literally

or under the doctrine of equivalents, each limitation in claim 1 and will constitute direct infringement of claim 1." Jazz Initial Infringement Contentions at 3. Jazz has known that Avadel contends the REMS Patent covers systems and not methods since at least Avadel's July 23, 2021 motion for judgment on the pleadings (D.I. 21, C.A. No. 21-691-MN), and yet Jazz, in its September 7, 2021 infringement contentions, accused only actions—use, distribution, and/or administration. Jazz has identified no factual basis in its contentions that Avadel will use any system having the required elements of the asserted claims. Jazz has also not identified what action it contends constitutes infringement under 35 U.S.C. § 271(a) in the event that the claims of the REMS Patent are system claims, and has also failed to meet its burden in that regard.

Because indirect infringement requires an act of direct infringement, Jazz's failures to plausibly allege direct infringement under Avadel's proposed construction render Jazz's indirect infringement contentions likewise deficient. Jazz also has not identified facts constituting the additional elements of either induced infringement or contributory infringement.

2. Avadel Does Not Infringe the REMS Patent Under Jazz's Proposed Construction of the Asserted Claims

Even under Jazz's proposed construction, there is no direct or indirect infringement. If, as Jazz contends, the REMS Patent "claims methods of using a computer-implemented system . . . ," then Jazz has also failed to identify an act of direct infringement by or attributable to a single actor. Jazz vaguely alleges that the "use, distribution and/or administration of Avadel's NDA Product (e.g., by Avadel, doctors, pharmacies, other healthcare professionals, and/or patients) pursuant to Avadel's REMS Program will meet, literally or under the doctrine of equivalents, each limitation in claim 1 and will constitute direct infringement of claim 1." Jazz's Initial Infringement Contentions at 3. But even assuming *arguendo* that the individual steps of the method were carried out by actors on Jazz's non-exhaustive list of possible actors, that would not constitute direct

infringement unless all steps were performed by the same actor or the actions fit within some other accepted mode of proving direct infringement, neither of which Jazz alleges. Indeed, Jazz does not identify that any actor allegedly performs any particular step, let alone that any single actor allegedly performs all of the steps of any asserted claim under Jazz's proposed construction. For example, in its opposition to Avadel's motion for judgment on the pleadings, Jazz identified the following as method steps (all bullet points are quotes from Jazz's opposition, D.I. 43, C.A. No. 21-691-MN):

- Identifying "a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug"
- Reconciling "inventory of the prescription drug before the shipments for a day or other time period are sent."
- Identifying any "indicator of a potential misuse, abuse or diversion by the narcoleptic patient."
- Notifying "the physician that is interrelated with the narcoleptic patient" if any indicators of misuse are detected.
- "Selectively block[ing] shipment of the prescription drug to the patient" based upon identification of abuse potential.
- "Shipp[ing] to the narcoleptic patient if no potential misuse, abuse or diversion is found."
- Identifying "an insurer to be contacted for payment for prescription drugs of an associated patient."
- Identifying "a current pattern or an anticipated pattern of abuse of the prescription drug."

Performing these steps is not in fact claimed in the asserted claims of the REMS Patent, and for that reason, Avadel believes that Jazz will not obtain a construction that their performance is a requirement to infringe. But assuming *arguendo* that they were, Jazz's infringement contentions do not identify any individual who allegedly performs these steps, much less a single

actor that performs all of them. Nor has Jazz even attempted to articulate any basis for attributing the actions of various actors to Avadel. Given the circumstances, Avadel reserves the right to dispute any allegation that Jazz makes later in the case on this issue and preserves its ability to argue that Jazz has waived its ability to later advance such a contention. Jazz's infringement contentions thus do not establish an essential element of Jazz's burden to show infringement if these claims are method claims.

Because indirect infringement requires an act of direct infringement, Jazz's failures to plausibly describe a factual basis for direct infringement under Jazz's proposed construction render Jazz's indirect infringement contentions likewise deficient. Jazz also has not identified facts constituting the additional elements of either induced infringement or contributory infringement, including identification of an entity that direct or controls the performance of all the method steps or the existence of a joint enterprise.

C. Jazz's Contentions Do Not Establish That the LUMRYZ REMS Contains a [Single]/[Central] Computer Database

Avadel does not infringe the asserted claims of the REMS Patent at least because the LUMRYZ REMS does not contain a single/central computer database. As an initial matter, Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitation is satisfied. Jazz has also set forth no evidence for its conclusory assertion that all limitations are met under the doctrine of equivalents. In order to properly assert a doctrine of equivalents theory, Jazz needed to provide detail on an element-by-element basis, which it has not done.

1. The LUMRYZ REMS Does Not Contain a "[Single]/[Central] Computer Database" and Thus Does Not Infringe the REMS Patent

Under Avadel's Proposed Construction

Avadel proposes to construe this term to mean "one and only one computer database, having the recited functionality." [redacted]

Avadel's REMS system therefore does not meet this claim limitation, either literally or under the doctrine of equivalents.

That the LUMRYZ REMS does not have a single/central computer database also means that multiple other claim elements of the asserted claims of the REMS Patent are not satisfied, as those claim elements repeat the requirement for a single/central database and/or address

functionality of the claimed (but not present) single/central computer database. As an illustrative example, several dependent claims, including, *e.g.*, claims 4, 8, 14, and 22 impose further limitations on the single/central computer database. Because the LUMRYZ REMS lacks the recited single/central computer database, the additional elements likewise are necessarily not present. For that reason, too, there is no infringement of the REMS Patent.

2. The LUMRYZ REMS Does Not Infringe the REMS Patent Under Jazz's Proposed Construction of "[Single]/[Central] Computer Database"

Jazz states that no construction is necessary and therefore does not propose an alternative to Avadel's construction. But the plain language of the subject claim terms establishes the requirement for a single database and forecloses relying on multiple databases to establish the presence of this limitation in Avadel's REMS system. All of Avadel's non-infringement arguments set forth above apply equally even should the Court determine that it is not necessary to construe this claim.

[redacted] As an initial matter, Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitation is satisfied. Jazz has also set forth no evidence for its conclusory assertion that all limitations are met under the doctrine of equivalents.

In order to properly assert a doctrine of equivalents theory, Jazz needed to provide detail on an element-by-element basis, which it has not done.

[redacted]

E. Jazz's Contentions Do Not Establish That the LUMRYZ REMS Has the Recited "Reconcile Inventory/Reconciling Inventory/Cycle Counted and Reconciled" Functionality

Avadel does not infringe the asserted claims of the REMS Patent at least because the LUMRYZ REMS does not have the functionality to reconcile inventory in accordance with these claim terms. As an initial matter, Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitation is satisfied. Jazz has also set forth no evidence for its conclusory assertion that all limitations are met under the doctrine of equivalents. In order to

properly assert a doctrine of equivalents theory, Jazz needed to provide detail on an element-by-element basis, which it has not done.

1. The LUMRYZ REMS Does Not Have the Recited Inventory Reconciliation Functionality and Thus Does Not Infringe the REMS Patent Under Avadel's Proposed Construction

Avadel proposes to construe these terms to mean "[c]hecking whether there is a mismatch between the aggregate amount of a drug reported in physical inventory and the aggregate amount in the database." [redacted]

[redacted]

For the reasons set forth above, the LUMRYZ REMS does not literally meet this limitation. Jazz has also set forth no evidence for its conclusory assertion that this limitation is met under the doctrine of equivalents. Further, Jazz is precluded from asserting that this limitation is met under the doctrine of equivalents as a result of pharmacy audits or other steps to track the amount of drug in a pharmacy's possession. The "inventory reconciliation" limitation was amended in claim 1 to overcome a rejection over the prior art disclosing tracking the amount of drug in an order ('963 File History, 07/25/2013 Amendment, Applicant Remarks, at 11), and Jazz is thus estopped from asserting infringement over claim scope through the doctrine of equivalents. Furthermore, Jazz's

attempts to essentially eliminate this import of this claim term are belied by the PTAB's reliance on it during the IPR proceedings.

2. The LUMRYZ REMS Does Not Infringe the REMS Patent Under Jazz's Construction of the Inventory Reconciliation Limitations

Jazz states that no construction is necessary and therefore does not propose an alternative to Avadel's construction or explain what the term could mean other than Avadel's proposed definition. Furthermore, the plain language of this claim term requires that the REMS system perform a comparison between the physical inventory and the amount of product as reflected in the database. All of Avadel's non-infringement arguments set forth above apply equally even should the Court determine that it is not necessary to construe this claim.

F. Jazz's Contentions Do Not Establish That the LUMRYZ REMS Performs a "Database Query That Identifies That the Narcoleptic Patient Is a Cash Payer/Database Queries . . . for Identifying: That the Narcoleptic Patient Is a Cash Payer . . ."

Avadel does not infringe the asserted claims of the REMS Patent at least because the LUMRYZ REMS does not have the functionality to perform these steps. As an initial matter, Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitation is satisfied. Jazz has also set forth no evidence for its conclusory assertion that all limitations are met under the doctrine of equivalents. In order to properly assert a doctrine of equivalents theory, Jazz needed to provide detail on an element-by-element basis, which it has not done.

1. The LUMRYZ REMS Does Not Have the Recited Database Query Functionality and Thus Does Not Infringe the REMS Patent Under Avadel's Proposed Construction

Avadel proposes that these terms have their plain and ordinary meaning, which is the recited database query identifies that the form of payment used by the patient was physical currency. [redacted]

[redacted]

For the reasons set forth above, the LUMRYZ REMS does not literally meet this limitation. Jazz has also set forth no evidence for its conclusory assertion that this limitation is met under the doctrine of equivalents. Further, Jazz is precluded from asserting that this limitation is met under

the doctrine of equivalents by queries other than ones specifically identifying whether the narcoleptic patient is a cash payer. During prosecution, Jazz specifically amended the asserted claims to include this "cash payer" limitation in order to overcome an Examiner rejection over the prior art (*see* '963 patent File History, 12/31/13 Amendment), and Jazz is thus foreclosed from asserting infringement with regard to said limitation by way of the doctrine of equivalents. And once again, Jazz's attempt to effectively eliminate this claim term is belied by the PTAB's reliance on it during the IPR proceedings.

2. The LUMRYZ REMS Does Not Infringe the REMS Patent Under Jazz's Construction of the Database Query Limitations

Jazz states that no construction is necessary and therefore does not propose an alternative to Avadel's construction or explain what the term could mean other than Avadel's proposed definition. Furthermore, the plain language of this claim requires determining whether the narcoleptic patient is paying in cash. All of Avadel's non-infringement arguments set forth above apply equally even should the Court determine that it is not necessary to construe this claim.

G. Jazz's Contentions Do Not Establish That the LUMRYZ REMS Possesses an "Exclusive Database"

Avadel does not infringe Claims 4 and 21 of the '782 Patent at least because Jazz has failed to demonstrate that FT218 includes an "exclusive database." The '782 patent does not provide a meaning for the term "exclusive database," and Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitation is satisfied. In particular, Jazz's infringement contentions with respect to claim 4 assert that the LUMRYZ REMS will include a "single database"—which as set forth above, it will not—"that is an exclusive database" with no explanation to support its conclusory assertion. Nor has Jazz asserted that this claim limitation of claim 4 may be met under the doctrine of equivalents, much less provide a detailed explanation,

on an element-by-element basis, for how this limitation would allegedly be met under the doctrine of equivalents. With respect to claim 21, Jazz's infringement contentions once again assert, in conclusory fashion, that the limitations of the claim, including the "exclusive database limitation" are met by the LUMRYZ REMS. Nor has Jazz provided any explanation for its assertion that the limitations of claim 21, including the "exclusive database" limitation, are met under the doctrine of equivalents, much less provide a detailed explanation, on an element-by-element basis, for how this limitation would allegedly be met under the doctrine of equivalents.

IV. AVADEL'S FT218 PRODUCT DOES NOT INFRINGE THE RESINATE PATENTS

All of the asserted claims of the Resinate Patents recite either a "controlled release component" or "modified release particles" limitation. As an initial matter, Jazz's contentions as to these limitations are lacking, vague, and confusing, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitations are satisfied. Jazz has also set forth no evidence for its conclusory assertions that these limitations are met under the doctrine of equivalents. As explained below, Jazz cannot meet its burden of establishing that Avadel infringes the asserted claims of the Resinate Patents either literally or under the doctrine of equivalents at least because FT218 does not contain either a "controlled release component" or "modified release particles" under either party's proposed construction.[6]

Disputed Terms; Patents and Claims	**Avadel's Proposed Construction**	**Jazz's Proposed Construction**
"controlled release component" '079 Patent Claims 1-3, 5-12, and 14-18	Resinate compositions characterized by having at least one of the active components having a release	A formulation component with an active pharmaceutical ingredient having a release over a period of at least about 2 to about 8 hours

[6] As set forth in Avadel's Invalidity Contentions dated January 14, 2022, the asserted claims of the Resinate Patents are invalid. Because invalid claims cannot be infringed, Avadel's FT218 does not infringe any of the asserted claims of the Resinate Patents for this separate reason.

	over a period of at least about 2 to about 8 hours	
"modified release particles" '782 Patent Claims 1-24	Particles that are resinate compositions characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours	Plain and ordinary meaning, i.e., particles containing an active pharmaceutical ingredient with a release profile that is different from that of an immediate release particle

A. Jazz's Contentions Do Not Establish That FT218 Satisfies the "Controlled Release Component" Limitation of the '079 Patent

1. Avadel Does Not Infringe the '079 Patent Under Avadel's Proposed Construction of "Controlled Release Component"

Independent claims 1 and 10 of the '079 patent require the presence of a "controlled release component." Under Avadel's proposed construction, a "controlled release component" is construed as "resinate compositions characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours."

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[7] Jazz does not contend that FT218's IR meet the "controlled release component" limitation. *See e.g.*, December 7, 2021, Plaintiff's Initial Infringement Chart, at 5, 11-12 (citing the immediate release and controlled release components of FT218 as meeting the limitation "wherein the oxybate formulation comprises an immediate release component and a controlled release component").

[redacted]

B. Jazz's Contentions and Expert Reports Fail to Establish That Avadel's FT218 Product Will be Used in a Method of Treatment Comprising Administering A Single Daily Dose Comprising Sodium Oxybate, and Opening A Sachet Containing A Solid Oxybate Formulation

Avadel does not infringe the Asserted Claims of the '079 patent at least because Jazz has failed to demonstrate that Avadel's FT218 product will be used in a method of "administering a

single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate…wherein the administering comprises opening a sachet containing a solid oxybate formulation." '079 patent, claim 1. "Oxybate," according to its plain and ordinary meaning, is the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. This is consistent with the use of the term in the specification, *e.g.*, *id.* at 8:25-27 ("drugs including GHB as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof") and the express definition in the specification, *id.* at 3:59-61. Indeed, the suffix "ate" is used to denote an anion. *See* Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013 at P-72.2.2.2.1.1, https://iupac.qmul.ac.uk/BlueBook/P7.html#7202020201 ("the endings 'ate' or 'ite' [are used] to name anions derived from acids."). Jazz never sought a construction of the term "gamma-hydroxybutyrate" that would depart from its plain and ordinary meaning. What's more, the '079 patent specification defines "gamma-hydroxybutyrate" and "oxybate" as the "negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid." *Id.* at 3:59-61. Thus, even if the plain meaning were something other than the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid, the patentee's lexicography controls. At the very least, [redacted] *Id.* at 8:25-27.

Jazz has only pointed to evidence that Avadel's FT218 product includes "sodium oxybate" contained within unit dose stick packs. *See* Jazz 5/6/2021 Final Infringement Contentions at 215-216; Little Expert Rpt. at ¶¶ 348-49, 28-31. Again, in its final infringement contentions, Jazz suggested that it would perform testing to establish the presence of oxybate (i.e., "gamma-hydroxybutyrate") in Avadel's FT218 product:

> Further, testing of Avadel's NDA Product, as well as potential testimony from Avadel and potential third parties, will show that the sustained release portion of Avadel's NDA Product releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

Jazz Final Infringement Contentions, at 55.

However, Dr. Little's report contains no testing for oxybate pursuant to the plain and ordinary meaning of that term in the '079 Patent. In relying only on evidence that Avadel's FT218 product includes "sodium oxybate," rather than "oxybate," Jazz has failed to prove that Avadel's FT218 product will be (or can be) administered as a single daily dose, wherein "administering comprises opening a sachet containing a solid oxybate formulation," as the Asserted Claims require. Jazz has also failed to demonstrate that Avadel's FT218 Product will or can be administered in "a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate," and has not pointed to any evidence or testing showing presence of 4.0 g to 12 g of gamma-hydroxybutyrate in a single dose of Avadel's NDA product. Nor has Jazz advanced any theory that Avadel's FT218 Product will be used in a manner that infringes the Asserted Claims under the doctrine of equivalents.

C. Jazz's Contentions Do Not Establish That Avadel's FT218 Satisfies the "Modified Release Particles" Limitation of the '782 patent

1. Avadel Does Not Infringe the '782 Patent Under Avadel's Proposed Construction

Independent claims 1 and 14 of the '782 Patent require the presence of "modified release particles." Under Avadel's proposed construction, the term "modified release particles" is properly construed as "particles that are resinate compositions characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours."

[redacted]

[redacted] FT218 therefore does not infringe independent claims 1 and 14 of the '782 patent. Because the remaining asserted claims of the '782 patent depend from claims 1 and 14 and incorporate this limitation, FT218 does not infringe those claims for the same reasons.

[redacted]

[redacted]

D. Jazz's Contentions and Expert Reports Fail to Establish That Avadel's FT218 Product Is a "Formulation of Gamma-hydroxybutyrate" Comprising "Immediate Release" and "Modified Release" Particles "Comprising Gamma-hydroxybutyrate."

Avadel does not infringe the Asserted Claims of the '782 patent at least because Jazz has failed to demonstrate that Avadel's FT218 product is a formulation of gamma-hydroxybutyrate comprising "a plurality of immediate release particles comprising gamma-hydroxybutyrate" and "a plurality of modified release particles comprising gamma-hydroxybutyrate." '782 patent, claim 1. "Gamma-hydroxybutyrate," according to its plain and ordinary meaning, is the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. This is consistent with the use of the term in the specification, *e.g., id.* at 8:26-28 ("drugs including GHB as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof") and the express definition in the specification, *id.* at 3:60-62. Indeed, the suffix "ate" is used to denote an anion. *See* Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013 at P-72.2.2.2.1.1, https://iupac.qmul.ac.uk/BlueBook/P7.html#7202020201 ("the endings 'ate' or 'ite' [are used] to name anions derived from acids."). Jazz never sought a construction of the term "gamma-hydroxybutyrate" that would depart from its plain and ordinary meaning. What's more, the '782 patent specification defines "gamma-hydroxybutyrate" and "oxybate" as the "negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid." *Id.* at 3:60-62. Thus, even if the plain meaning were something other than the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid, the patentee's lexicography controls. At the very

least, the term excludes sodium oxybate because the specification distinguishes between gamma-hydroxybutyrate and its salts. *Id.* at 8:26-28.

Jazz has only pointed to evidence that Avadel's FT218 product is a formulation that contains granules comprising sodium oxybate. *See* Jazz 5/6/2021 Final Infringement Contentions at 225-26; Little Expert Rpt. at ¶¶ 394-96, 28-31. Again, in its final infringement contentions, Jazz suggested that it would perform testing to establish the presence of gamma-hydroxybutyrate in Avadel's Product:

> Further, testing of Avadel's NDA Product, as well as potential testimony from Avadel and potential third parties, will show that the sustained release portion of Avadel's NDA Product releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

Jazz Final Infringement Contentions, at 55.

But Dr. Little's Expert Report contains no such testing data. In relying only on evidence that Avadel's FT218 Product contains sodium oxybate, rather than gamma-hydroxybutyrate, Jazz has failed to (and cannot) prove that Avadel's FT218 product is a formulation of gamma-hydroxybutyrate comprising a plurality of immediate release particles comprising gamma-hydroxybutyrate and a plurality of modified release particles comprising gamma-hydroxybutyrate, as the Asserted Claims require. Nor has Jazz advanced any theory that Avadel's FT218 product infringes the Asserted Claims under the doctrine of equivalents.

E. Jazz's Contentions Do Not Establish That Avadel's FT218 Satisfies the "Unit Dose" Limitation of Claims 14-24 of the '782 patent

Avadel does not infringe Claims 14-24 of the '782 Patent at least because Jazz has failed to demonstrate that FT218 includes a "unit dose" of a formulation of gamma-hydroxybutyrate. The '782 patent does not provide a meaning for the term "unit dose," and Jazz's contentions as to this limitation are vague, incomplete, and unintelligible, and do not satisfy the disclosure

requirements under the Court's practices or establish that the subject limitation is satisfied. In particular, Jazz's infringement contentions only assert that FT218 is "a formulation of gamma-hydroxybutyrate" without providing any explanation for how FT218 allegedly meets the "unit dose" requirement. Nor has Jazz asserted that this claim limitation may be met under the doctrine of equivalents, much less provide a detailed explanation, on an element-by-element basis, for how this limitation would allegedly be met under the doctrine of equivalents.

F. Jazz's Contentions Do Not Establish That Avadel's FT218 Satisfies the "Blood Concentration" Limitations of Claims 11, 12, and 19 the '782 patent

Avadel does not infringe Claims 11, 12, and 19 of the '782 patent at least because Jazz has failed to demonstrate that FT218 meets the requirement of providing the recited blood concentrations of gamma-hydroxybutyrate. Claim 11 requires providing gamma-hydroxybutyrate "blood concentration ranging from 10 mg/mL to about 40 mg/mL" while claims 12 and 19 require providing gamma-hydroxybutyrate "blood concentration ranging from 15 mg/mL to about 30 mg/mL." Jazz's contentions as to these limitations are vague, incomplete, and unintelligible, and do not satisfy the disclosure requirements under the Court's practices or establish that the subject limitation is satisfied, at least because the limitations recite a range of gamma-hydroxybutyrate blood concentrations that are likely fatal in humans.

Dated: February 16, 2023

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EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

DECLARATION OF STEVEN R. LITTLE, Ph.D.
IN SUPPORT OF JAZZ'S SUPPLEMENTAL OPENING *MARKMAN* BRIEF

TABLE OF CONTENTS

Page

I, Steven R. Little, Ph.D., submit this declaration in support of Plaintiffs Jazz Pharmaceuticals, Inc.'s and Jazz Pharmaceuticals Ireland Limited's (together, "Jazz") Supplemental Opening *Markman* Brief to offer my opinion on the meanings of "gamma-hydroxybutyrate" and "oxybate," as used in the claims of the patents-in-suit, to one of ordinary skill in the art at the time of invention.

I. EXPERT QUALIFICATIONS

A. Educational and Professional Background

1. My curriculum vitae includes my degrees, positions, honors, awards, publications, invited talks at universities as well as national and international conferences, presentations, and service through active membership in a wide variety of scientific societies and as a peer reviewer for a wide variety of scientific journals. *See* Ex. 33.[1]

2. I received my Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology (MIT) as a National Science Foundation Graduate Research Fellow. I received the American Association for Advancement of Science's (AAAS) Excellence in Research Award for my thesis research. I received my Bachelor of Engineering in Chemical Engineering at Youngstown State University where I graduated Summa Cum Laude with minors in both Chemistry and Mathematics.

3. I am currently the Chair of the Department of Chemical Engineering as well as the William Kepler Whiteford Endowed Professor of Chemical Engineering, Bioengineering, Pharmaceutical Sciences, Immunology, Ophthalmology and the McGowan Institute for Regenerative Medicine at the University of Pittsburgh. I am also the Director of the Controlled

[1] "Ex. __," cited herein refers to exhibits attached to Jazz's Supplemental Opening *Markman* Brief.

Release and Biomimetic Research Laboratories at the University of Pittsburgh. In September 2021, I was appointed to the special rank of "Distinguished Professor" by the Chancellor of the University of Pittsburgh, which is the University's highest honor for faculty and recognizes extraordinary, internationally recognized scholarly attainment in the field.

4. As Chair of the Department of Chemical Engineering, my responsibilities include serving as the Executive Director of all major functions of the Department, such as the Chemical Engineering research enterprise of the faculty as well as oversight of the instruction of all chemical engineering graduate and undergraduate courses and other educational activities.

5. As a member of the faculty of the Department of Chemical Engineering, Bioengineering, Pharmaceutical Sciences, Immunology, Ophthalmology and the McGowan Institute for Regenerative Medicine at the University of Pittsburgh, my responsibilities include instruction of courses including Biomaterials, Introduction to Controlled Release Systems, and Fundamentals of Transport Processes (aka Transport Phenomena) including mass transport issues such as diffusive and convective mass transport processes.

6. As Director of the Controlled Release and Biomimetic Research Laboratories at the University of Pittsburgh, my responsibilities include serving as the principal investigator on over $25M of research activities over the past fifteen years in the area of controlled release systems and sustained release systems. The laboratories consist of approximately 10-15 full- and part-time researchers, including research assistant professors, post-doctoral associates, Ph.D. students, master's students, and undergraduate researchers. My work is funded by the National Institutes for Health, the National Science Foundation, the US Food and Drug Administration, the U.S. Army, the U.S. Department of Defense, the Defense Advanced Research Projects Agency (DARPA), the American Heart Association, the Commonwealth of Pennsylvania, the

Arnold and Mabel Beckman Foundation, the Wallace H. Coulter Foundation, the Camille and Henry Dreyfus Foundation, Research to Prevent Blindness, several industrial sources, and several internal Centers and Institutes.

7. I was previously elected and served in the position of Representative of Special Interest Groups on the Board of Directors of the Society for Biomaterials (an international organization) by the Society's membership. In this capacity, I was responsible for overseeing the direction of the Divisions of the society (called "Special Interest Groups"), their educational programs, the annual program for its national and international conferences in the area of controlled release and drug delivery, and the promotion of controlled release and drug delivery research, amongst other things. I have also been previously appointed as the Representative of the Board of Directors for Focus Groups in the Controlled Release Society, which established Focus Groups in the areas of Oral Drug Delivery, Ocular Drug Delivery, Nanomedicine and Nano-Scale Drug Delivery, Gene Delivery and Gene Editing, Biomimetic Drug Delivery, Immuno Drug Delivery, and Transdermal and Mucosal Drug Delivery.

8. Since 2004, I have published over 100 peer-reviewed publications and peer reviewed book chapters in the areas of controlled release, sustained release, and immediate release in well-known journals such as Journal of Controlled Release, Proceedings of the National Academy of Sciences, Advanced Materials, Pharmaceutical Research, Molecular Pharmaceutics, Angewandte Chemie, Journal of Materials Chemistry, Journal of the American Chemical Society, Biomaterials, Journal of Biomedical Materials Research Part A, Journal of Molecular Medicine, and Science, Advances. I have been invited to speak over 80 times about my research at national and international venues.

9. Since 2004, I have been the primary inventor on over 30 issued and pending patents (with 3 of these being licensed for use by industry to date).

10. I am also a co-founder of Qrono Inc. Controlled Release Solutions, a specialty pharmaceutical company focused upon treatments for head and neck cancer. I am also a co-founder of Oraxis Inc., a startup focused upon treatments for inflammatory diseases and disease of destructive inflammation.

B. Honors and Awards

11. I have received a number of national and international awards, including the 2021 Distinguished Service Award from the Controlled Release Society, the 2015 Curtis McGraw Research award by American Society Engineering Education ("ASEE"; the only winner in the US in all engineering disciplines), Research to Prevent Blindness' Innovative Ophthalmology Research Award Winner in 2014, one of only two Chemical Engineering "Camille Dreyfus Teacher-Scholars" in 2012, both a Phase I and Phase II Wallace H. Coulter Translational Research Award Winner (2010 and 2013), the only recipient (worldwide) of the Society for Biomaterials Young Investigator Award in 2012, the only recipient (worldwide) of the Controlled Release Society's Young Investigator Award in 2019, one of only 16 "Beckman Young Investigators" by the Arnold and Mabel Beckman Foundation in 2008, the American Heart Association Career Development Award, and the recipient of a K-Award from the United States National Institutes for Health.

12. I currently stand as the only individual in University history to receive all three "Chancellor's Distinguished Awards" (Distinguished Research in 2012, Distinguished Teaching in 2013, and Distinguished Service in 2019). I also have been elected as a Fellow of the Biomedical Engineering Society (BMES), a Fellow of the American Institute for Medical and Biological Engineering (AIMBE), a Fellow of the Controlled Release Society (CRS), and a

Fellow of the American Institute for the Advancement of Science (AAAS). In June of 2022, I was elected to the status of Fellow to the National Academy of Inventors (one of the four U.S. National Academies).

II. MATERIALS CONSIDERED

13. I submit this declaration in support of Jazz's Supplemental Opening *Markman* Brief. The materials that I have reviewed in support of my opinions include: the patents-in-suit[2]; the prosecution histories for the '488, '079, and '782 patents; Jazz's and Avadel's proposed claim constructions; Avadel's Amended Final Noninfringement Contentions; and any other documents cited herein.

14. The opinions below are based on the education, knowledge, and experience that I have acquired during my time practicing, teaching, and consulting in the field of pharmaceutical sciences, as well as the information available to me as of the date of this declaration.

15. I reserve the right to rebut any expert opinion, argument, or additional documents offered by Avadel in support of its proposed claim constructions. I further reserve the right to modify or expand my opinions to the extent that I may learn of information not currently available to me, including, but not limited to, information provided in Avadel's Responsive *Markman* Brief and any evidence and/or declarations submitted therewith. I further reserve the right to modify or expand my opinion to the extent that the Court adopts any construction that differs from those proposed by Jazz.

[2] The "patents-in-suit" refers to U.S. Patent Nos. 10,758,488 ("the '488 patent," Ex. 3), 10,813,885 ("the '885 patent"), 10,959,956 ("the '956 patent"), 10,966,931 ("the '931 patent"), 11,077,079 ("the '079 patent," Ex. 24), and 11,147,782 ("the '782 patent," Ex. 27). I sometimes refer to the '488, '885, '956, and '931 patents, collectively, as the "Sustained Release Patents."

16. Compensation for my time on this case is my standard rate of $1200 per hour. Payment is in no way contingent upon the substance of my testimony or the outcome of this case.

III. PERSON OF ORDINARY SKILL IN THE ART

17. I use the following definition of a POSA in my opinions: someone who has at least a Ph.D. in Pharmaceutical Sciences, Chemistry, or Chemical Engineering (or related field) and 2 to 4 years of experience in the field of drug delivery technology or a similar technical field. Alternatively, such a person may have had a lower educational level (such as a M.S. or even a B.S. academic degree) in one of those fields with commensurately more experience in formulating pharmaceuticals and drug delivery. It is further my opinion that a POSA may rely on individuals with knowledge and experience in the treatment of narcolepsy.

IV. THE PARTIES' PROPOSED CONSTRUCTIONS

18. I understand from counsel that the parties have proposed the following constructions for the disputed term "gamma-hydroxybutyrate"/"oxybate":

Claim Term	Jazz's Proposal	Avadel's Proposal
"gamma-hydroxybutyrate" (Sustained Release Patent Family)	Plain and ordinary meaning: i.e., (1) gamma-hydroxybutyric acid or (2) the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid	the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid
"gamma-hydroxybutyrate" / "oxybate" ('079/'782 Patent Family)	the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid	the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid

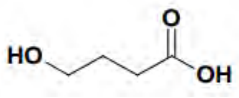
19. Further, based on my review of Avadel's Amended Final Non-Infringement Contentions and discussions with counsel, I understand that Avadel contends that its construction of "gamma-hydroxybutyrate" and "oxybate" is distinct from, or excludes, salts of gamma-hydroxybutyrate such as sodium gamma-hydroxybutyrate, which is also referred to as sodium

oxybate. Ex. 1, Avadel's Final Non-Infringement Contentions at 18, 37. As explained further below, I disagree that the negatively charged anionic form excludes salts of gamma-hydroxybutyrate.

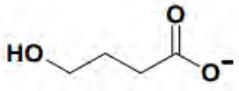
V. BACKGROUND

20. As used in the art, the term "gamma-hydroxybutyrate" would be understood to encompass the gamma-hydroxybutyrate negative anion, gamma-hydroxybutyric acid, and other forms of gamma-hydroxybutyrate such as salts. *See* Ex. 34, Gamma-Hydroxybutyrate Monograph, Scientific Working Group for the Analysis of Seized Drugs (2005).

21. An acid is a molecule that is capable of donating a hydrogen ion (H^+) in a reaction. Ex. 35, McGraw-Hill Dictionary of Scientific and Technical Terms. Gamma-hydroxybutyric acid has the following structure:



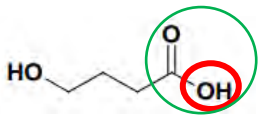
22. The negatively charged gamma-hydroxybutyrate anion (the conjugate base of gamma-hydroxybutyric acid)[3] has the following structure:



Ex. 34, Gamma-Hydroxybutyrate Monograph.

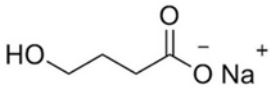
23. The hydrogen atom of gamma-hydroxybutyric acid that is capable of being donated in a reaction is covalently bonded to an oxygen atom in the carboxylic acid. This covalent bond (O-H) is circled in red below:

[3] A conjugate base is a reaction product that results when a hydrogen is donated from an acid (here, gamma-hydroxybutyric acid).



A covalent bond is one where two atoms share a pair of electrons. Here the sharing of electrons is between an oxygen within the carboxylic acid (the -COOH functional group, circled in green above) and hydrogen.

24. When gamma-hydroxybutyrate is in the salt form, the negatively charged gamma-hydroxybutyrate anion is ionically bonded to a positively charged cation, such as sodium. The structure of sodium gamma-hydroxybutyrate, or sodium oxybate, is shown below:



The bond between the positive and negative ion is known as an ionic bond, or electrostatic bond. An ionic bond is one where one atom transfers one or more electrons to another atom. Here, the sodium atom donates an electron to become a positively charged cation and gamma-hydroxybutyrate accepts an electron to become a negatively charged anion. The gamma-hydroxybutyrate anion can be combined with different cations such as calcium, potassium, or magnesium to form different gamma-hydroxybutyrate salts. Regardless of what is used as the cation, however, the salt form of gamma-hydroxybutyrate always contains the negatively charged gamma-hydroxybutyrate anion, which is ionically bound to the positively charged cation (e.g., sodium).

25. In solid form, the negatively charged gamma-hydroxybutyrate anion and positively charged sodium cation that make up sodium oxybate are held together by electrostatic forces. Notably, the negatively charged gamma-hydroxybutyrate anion (on its own without any other bonded counter-ion) cannot exist in solid form on its own because it cannot satisfy electroneutrality (meaning that a negatively charged ion must be neutralized to form a stable

solid). In order to satisfy electroneutrality, there must be either a covalent bond with a hydrogen atom in the form of gamma-hydroxybutyric acid or an ionic bond, for example, with a sodium cation in the form of sodium oxybate. Consequently, in my opinion, it would be understood by a POSA that a reference to a solid dosage form containing gamma-hydroxybutyrate would necessarily either mean gamma-hydroxybutyric acid or the gamma-hydroxybutyrate anion with something ionically bound to it such as a cation.

26. Prior art references discussing the use of gamma-hydroxybutyrate also confirm that the term was understood to refer to both gamma-hydroxybutyric acid and salts containing the gamma-hydroxybutyrate anion. For example, a 1977 article by Mamelak refers to "sodium γ-hydroxybutyrate" as "GHB." Ex. 7 at 273.[4] Similarly, an article by Broughton from 1979 refers to the "sodium salt of gamma-hydroxybutyrate" and "GHB" interchangeably. Ex. 9 at 2. Further, a published patent application by Liang refers to "Sodium gamma-hydroxybutyrate (GHB or sodium oxybate)." Ex. 11 at [0002]. In addition, other references refer to "gamma-hydroxybutyric acid" or "γ-hydroxybutyric acid" as "GHB." *See* Ex. 12, Ferrara (1992) at 231; Ex. 13, Gallimberti (1989) at 787; Ex. 15, Gessa (1993) at 224; Ex. 17, Palatini (1993) at 353; Ex. 18, Roth (1966) at 421; Ex. 20, Snead (1981) at 579 (referring to both "γ-hydroxybutyrate" and "gamma-hydroxybutyric acid" as "GHB"). Accordingly, in my opinion, a POSA would have understood gamma-hydroxybutyrate to refer to both gamma-hydroxybutyric acid and the gamma-hydroxybutyrate anion (e.g., in salt form).

[4] "γ" is the Greek letter for "gamma."

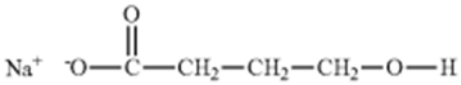
VI. THE PATENTS-IN-SUIT

A. The Sustained Release Patents

27. There is not any definition of "gamma-hydroxybutyrate" provided in the Sustained Release Patents. Instead, in my opinion, the patents use the term "gamma-hydroxybutyrate" consistent with how a POSA would have understood as described above, namely in the form of gamma-hydroxybutyric acid (with a covalent O-H bond) or in the form of the gamma-hydroxybutyrate anion, including a form that is ionically bound to something such as a cation in the salt form.

28. For example, the Sustained Release Patents refer to controlled release drug formulations produced as unit dosage forms for oral administration. Ex. 3, '488 patent at 1:26-28. Those patents go on to describe "[a]n example of a drug that is administered at a high dose, has a low molecular weight, and high water solubility, is gamma-hydroxybutyrate (GHB), particularly the sodium salt of GHB." *Id.* at 1:38-41. In my opinion, this portion of the specification is describing sodium gamma-hydroxybutyrate as a specific form of the drug gamma-hydroxybutyrate that may be used in the inventions. This identification of the sodium salt as a specific form is in agreement with my opinion expressed above that a POSA would understand the term "gamma-hydroxybutyrate" to be inclusive of gamma-hydroxybutyric acid or forms where something is ionically bound to the negatively charged gamma-hydroxybutyrate anion such as a cation (which would be a salt). *See supra* at ¶¶ 24-25.

29. The patents further describe making products with "forms of GHB, such as the sodium salt of GHB." Ex. 3, '488 patent at 5:18-19. The specification provides the structure of the sodium salt form of gamma-hydroxybutyrate, including the positively charged sodium cation and the negatively charged gamma-hydroxybutyrate anion:



Id. at 4:55-60. In addition, all of the examples of the Sustained Release Patents refer to using either sodium oxybate or calcium oxybate. *Id.* at 19:21, 21:29, 24:28, 24:60-61, 25:23. As a POSA would expect, there are no examples or discussion in the Sustained Release Patents of the negatively charged gamma-hydroxybutyrate anion alone (excluding neutral, bound forms) being used to make a dosage form. Accordingly, in my opinion, a POSA would understand that the use of term "gamma-hydroxybutyrate" in the Sustained Release Patents would include various forms of gamma-hydroxybutyrate such as salt forms that would be stable as a solid, rather than excluding such forms.

30. My opinion is also supported by the claims of the Sustained Release Patents. The claims of the Sustained Release Patents require "[a] formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein . . ." the formulation or sustained release portion "releases [a certain percentage] of its gamma-hydroxybutyrate [within a certain period of time]." *See, e.g.*, Ex. 3 at 27:24-44. In my opinion, a POSA would understand that the language "its gamma-hydroxybutyrate" is referring to the gamma-hydroxybutyrate initially contained in the sustained release portion or formulation, which the claims say can be "selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate." *Id.* My opinion is supported by the specification which explains release profiles in terms of release of "the drug initially contained" within the dosage form. *Id.* at 5:63-6:8. As such, it is my opinion that a POSA would understand that the "gamma-hydroxybutyrate" that is being released can be

in the form of gamma-hydroxybutyric acid or salts of gamma-hydroxybutyric acid (e.g., the sodium salt form of gamma-hydroxybutyrate). It is also my opinion that a POSA would further recognize the sodium salt of gamma-hydroxybutyrate to be within the scope of the claims based on dependent claims of the Sustained Release Patents, such as claims 6 and 7 of the '488 patent, which require a salt form (including the sodium salt form) of gamma-hydroxybutyrate. *Id.* at 28:17-21.

31. My opinion is further supported by the prosecution history of the Sustained Release Patents. In particular, Jazz's application for the '488 patent was rejected by the Patent Office based on a disclosure in the prior art reference Liang 2006 of "a controlled release oral dosage form . . . comprising gamma-hydroxybutyric acid ('gamma-hydroxybutyrate') that may be in the form of its potassium or sodium salt." Ex. 22 at 10-11. One of the inventors for the Sustained Release Patents, Clark Allphin, submitted a declaration in response to the rejection of the claims. The declaration referred to formulations of the invention "wherein the sustained release portion releases less than 10% of its GHB within the first hour and at least about 40% of its GHB by 4 to 6 hours when it is tested at a neutral pH (i.e., in DI water)." Ex. 23 at ¶ 10. Mr. Allphin described "the dissolution profile of a sustained release portion of a GHB formulation meeting the limitations of the claims," and stated that "[t]he sustained release portion contains GHB (as sodium oxybate)." *Id.* at ¶ 13. In my opinion, this shows that both the Patent Office and Mr. Allphin viewed the term "gamma-hydroxybutyrate" as including sodium oxybate, rather than excluding it. This use of "gamma-hydroxybutyrate" by the Patent Office and Mr. Allphin to include a salt such as sodium oxybate is in agreement with how a POSA would understand that term.

B. The ’079/’782 Patents

32. In the ’079 and ’782 patents, the inventors provide a more specific definition of “gamma-hydroxybutyrate” than how that term is used in the art in general, and in the context of the Sustained Release Patents. Specifically, the ’079 and ’782 patent explicitly state that: “[a]s used herein, the term gamma-hydroxybutyrate (GHB) or ‘oxybate’ refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid.” Ex. 24, ’079 patent at 3:59-61.

33. As discussed above, the term “gamma-hydroxybutyrate” was used in the art to refer inclusively to gamma-hydroxybutyric acid and the negatively charged gamma-hydroxybutyrate anion. *See supra* at ¶¶ 24-26. The more specific definition provided for “gamma-hydroxybutyrate” in the specification of the ’079 and ’782 patents, however, would make it clear to a POSA that the inventors were referring specifically to the anion rather than gamma-hydroxybutyric acid.

34. The claims of the ’079 and ’782 patents refer to solid dosage forms of gamma-hydroxybutyrate. Specifically, the claims of the ’079 patent refer to “a sachet containing a solid oxybate formulation.” Ex. 24, ’079 patent at 24:57-63. The claims of the ’782 patent refer to “particles comprising gamma-hydroxybutyrate.” Ex. 27, ’782 patent at 25:14-18. Given that the negatively charged gamma-hydroxybutyrate anion cannot exist as a solid by itself, a POSA would understand that the gamma-hydroxybutyrate anion must be ionically bound to something.

35. My opinion in this regard is supported by the specification of the ’079 and ’782 patents which refer to gamma-hydroxybutyrate being bound in either the salt form, or in an ion exchange resin. For example, the specification refers to gamma-hydroxybutyrate being administered as Xyrem, which is the sodium salt of gamma-hydroxybutyrate. Ex. 24, ’079

patent at 3:59-4:3. The specification also describes a method of making "GHB" that cites an article discussing the production of "Sodium γ-Hydroxybutyrate." *Id.* at 5:14-21.

36. An ion exchange resin is a compound that attracts negatively or positively charged ions. In the case of gamma-hydroxybutyrate, the negatively charged anion is bound to the ion exchange resin. The specification of the '079 and '782 patents describes gamma-hydroxybutyrate being "bound" to the resin. *Id.* at 15:33, 16:4, 16:27. In addition, all of the examples of the '079 and '782 patents refer to gamma-hydroxybutyrate or oxybate being bound to a resin. *Id.* at 22:24-24:55. These disclosures support my opinion that the gamma-hydroxybutyrate or oxybate claimed in the '079 and '782 patents represents that negatively charged gamma-hydroxybutyrate anion bound to either a cation in salt form or an ion exchange resin.

37. Further, claims of the '079 and '782 patent refer to a "single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate" (e.g., '079 patent at 25:24-26) and a "formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate" (e.g., '782 patent at 25:42-44). In my opinion, this shows that the oxybate or gamma-hydroxybutyrate claimed is contemplated to be bound to something such as a cation or a resin. Specifically, the molecular weight of sodium oxybate is 126.0 g/mol. Ex. 34, Gamma-hydroxybutyrate Monograph. The molecular weight of the negatively charged gamma-hydroxybutyrate anion is 103.1. *Id.* So, 4 g of sodium oxybate would be equivalent to 3.27 g of the negatively charged gamma-hydroxybutyrate anion and 12 g of sodium oxybate would be equivalent to 9.82 g of the negatively charged gamma-hydroxybutyrate anion. The inventors could have just claimed these dosage amounts for the negatively charged gamma-

hydroxybutyrate anion. Given, however, that the inventors claimed the dosage amount in terms of "equivalent" to sodium oxybate shows, in my opinion, that a POSA would understand that the gamma-hydroxybutyrate could be bound to different cations or resins having different molecular weights such as, for example, calcium oxybate (246.27 g/mol), potassium oxybate (142.2 g/mol), or sodium oxybate (126.0 g/mol).

38. In addition, the file histories of the '079 and '782 patents do not indicate an intent on the inventors' behalf to define "gamma-hydroxybutyrate" or "oxybate" in a way that would exclude salts of gamma-hydroxybutyrate. Instead, the Patent Office examiner and the inventors both referred to forms that included salts. *See, e.g.*, Ex. 28 at 5 (examiner rejecting '079 patent based on reference "directed to sodium oxybate"); Ex. 30 at ¶ 4 (inventor declaration responding to rejection and stating "oxybate salts are known to be hygroscopic"); Ex. 31 at 6 (Patent Office rejection citing reference to salts of GHB); Ex. 32 at 7-8 (Jazz responding to rejection by stating that a reference teaches a "GHB-containing formulation"). Accordingly, in my opinion, a POSA would understand that the Patent Office and the inventors did not interpret "gamma-hydroxybutyrate" to exclude salts of GHB.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: March 24, 2023

Steven R. Little, Ph.D.

EXHIBIT 3

US010758488B2

(12) **United States Patent**
Allphin et al.

(10) **Patent No.: US 10,758,488 B2**
(45) **Date of Patent: Sep. 1, 2020**

(54) **CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES**

(71) Applicant: **JAZZ PHARMACEUTICALS, INC.**, Palo Alto, CA (US)

(72) Inventors: **Clark Allphin**, Seattle, WA (US); **James Pfeiffer**, Palo Alto, CA (US)

(73) Assignee: **JAZZ PHARMACEUTICALS, INC.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/025,487**

(22) Filed: **Jul. 2, 2018**

(65) **Prior Publication Data**

US 2018/0318222 A1 Nov. 8, 2018

Related U.S. Application Data

(63) Continuation of application No. 13/071,369, filed on Mar. 24, 2011, now abandoned.

(60) Provisional application No. 61/317,212, filed on Mar. 24, 2010.

(51) **Int. Cl.**

A61K 9/20	(2006.01)
A61K 9/28	(2006.01)
A61K 31/19	(2006.01)
A61K 9/24	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/2054*** (2013.01); ***A61K 9/209*** (2013.01); ***A61K 9/284*** (2013.01); ***A61K 9/286*** (2013.01); ***A61K 9/2833*** (2013.01); ***A61K 9/2846*** (2013.01); ***A61K 9/2853*** (2013.01); ***A61K 9/2866*** (2013.01); ***A61K 9/2893*** (2013.01); ***A61K 31/19*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

Controlled release dosage forms are described herein. The controlled release formulations described herein provide prolonged delivery of high dose drugs that are highly water soluble and highly hygroscopic. In specific embodiments, controlled release dosage forms for delivery of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. The controlled release dosage forms described herein may incorporate both controlled release and immediate release formulations in a single unit dosage form.

12 Claims, 9 Drawing Sheets

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Office Action dated Nov. 21, 2001 in European Application No. 99964320.8.
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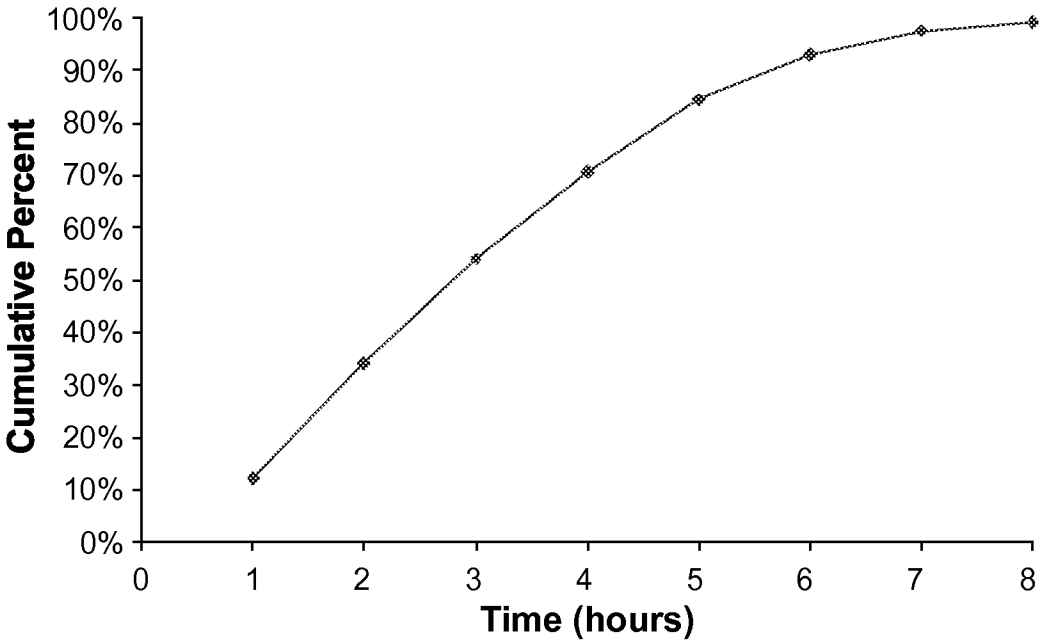
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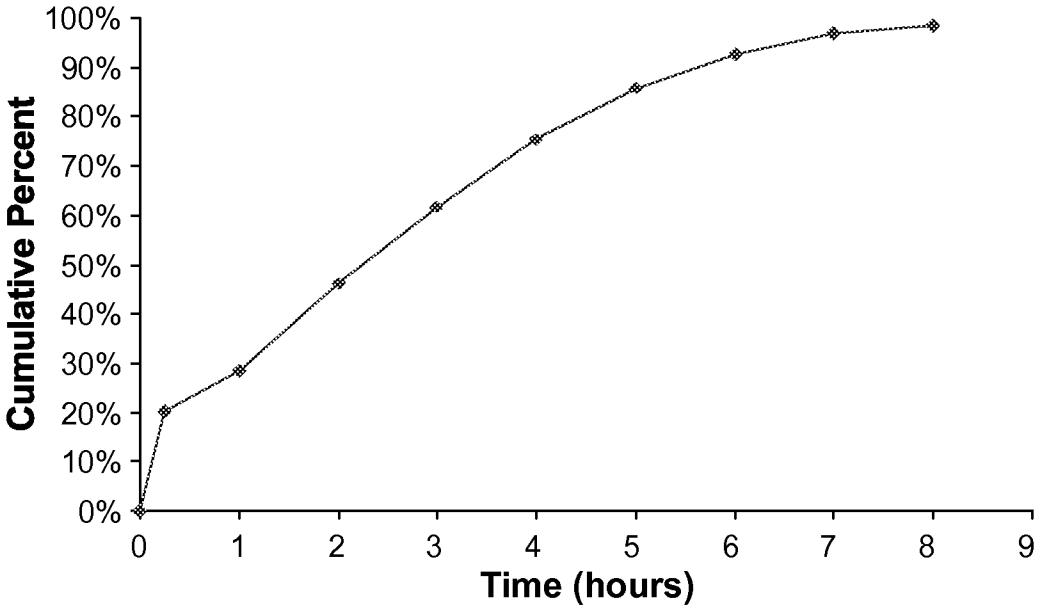
Time (hours)

FIG. 1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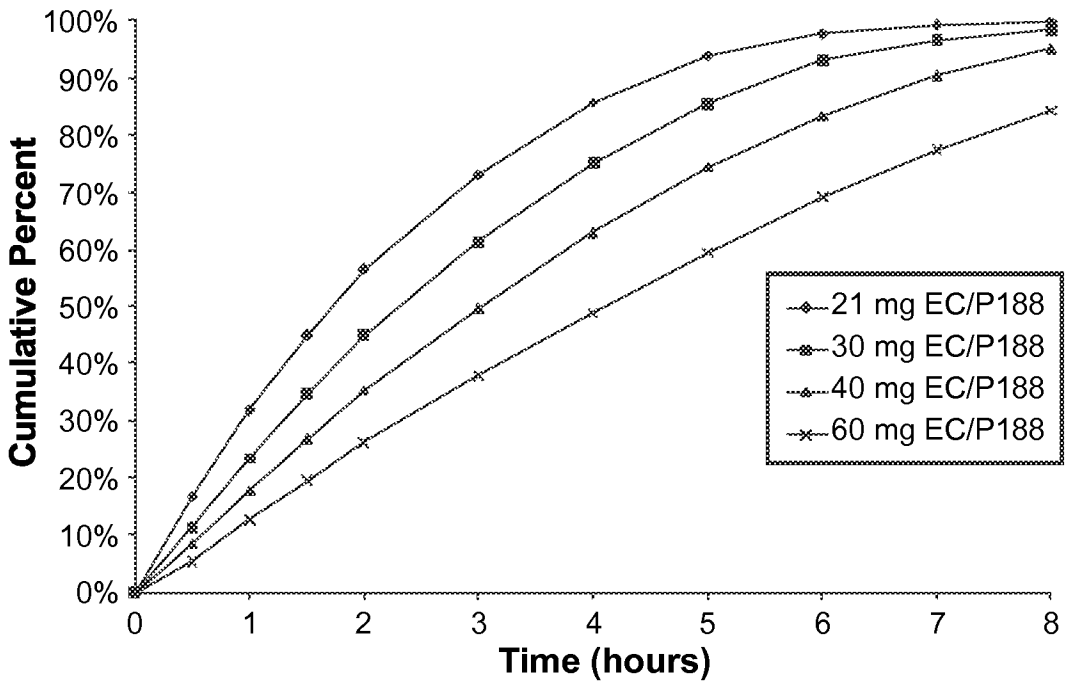
Time (hours)

FIG. 2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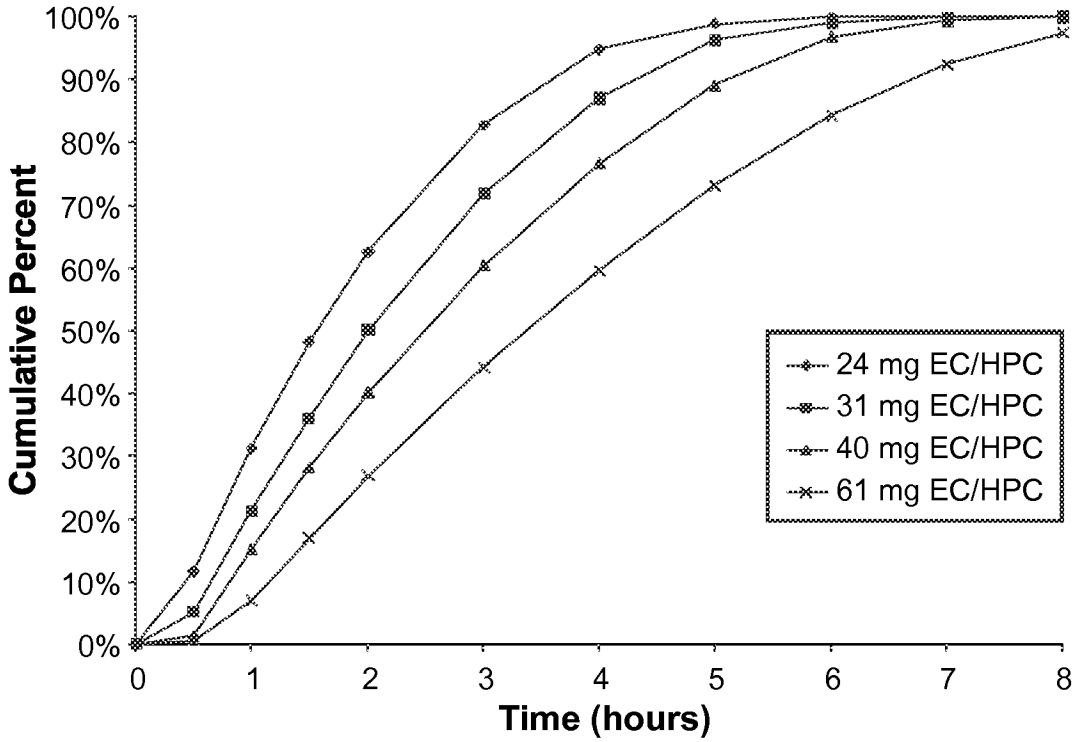
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3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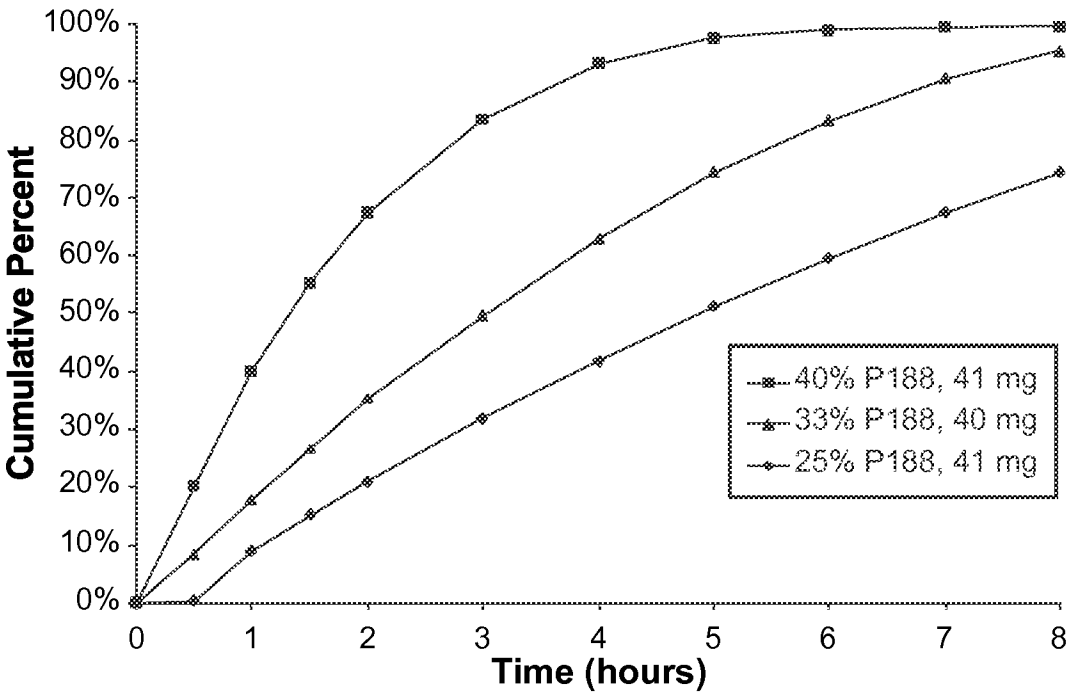
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4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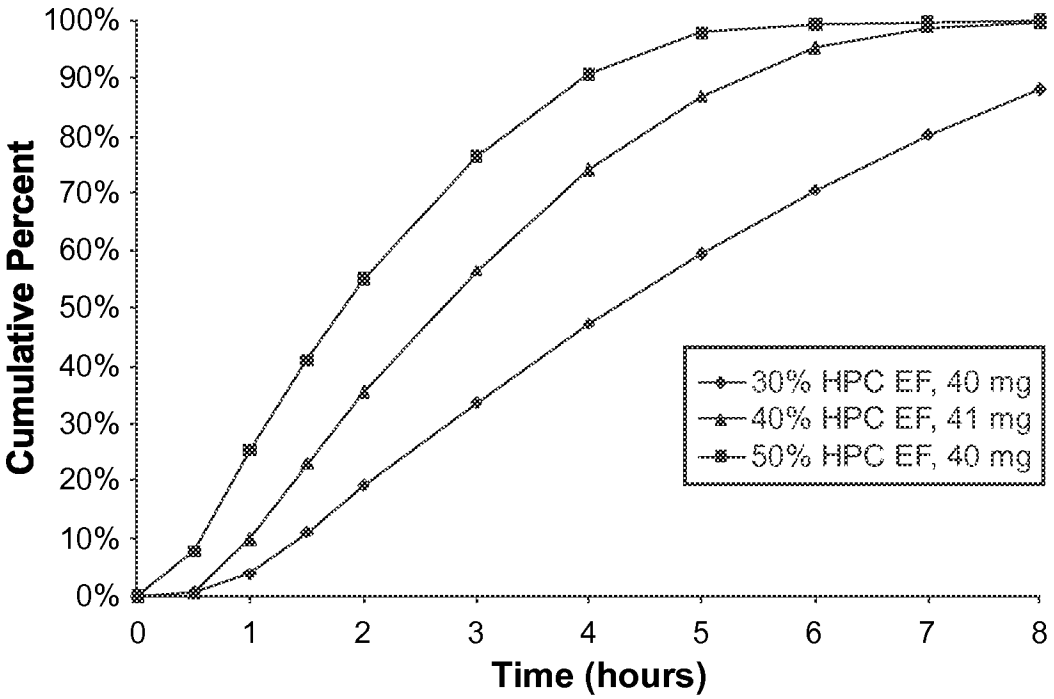
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5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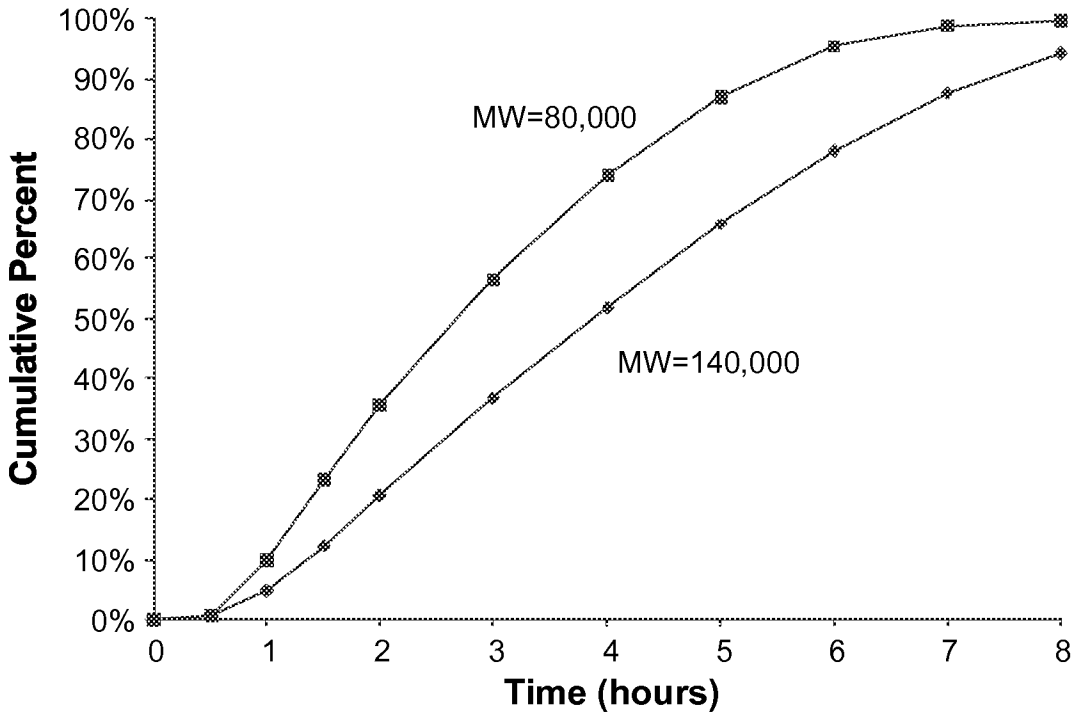
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6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10%
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Cumulative Percent
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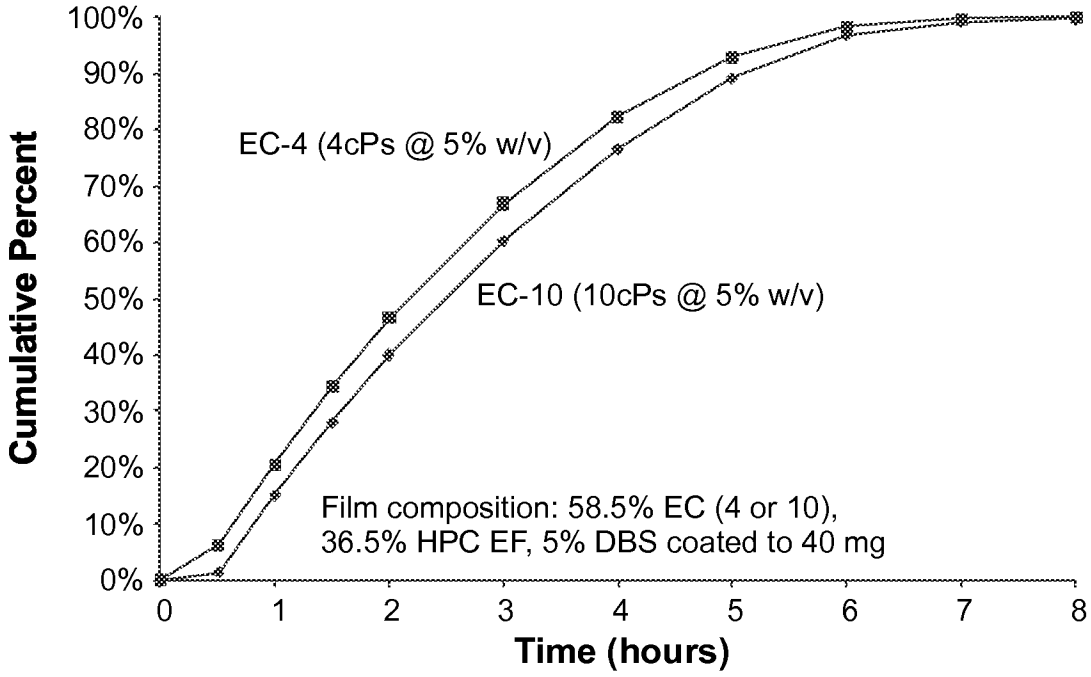
8
Time (hours)

FIG. 7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10%
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Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
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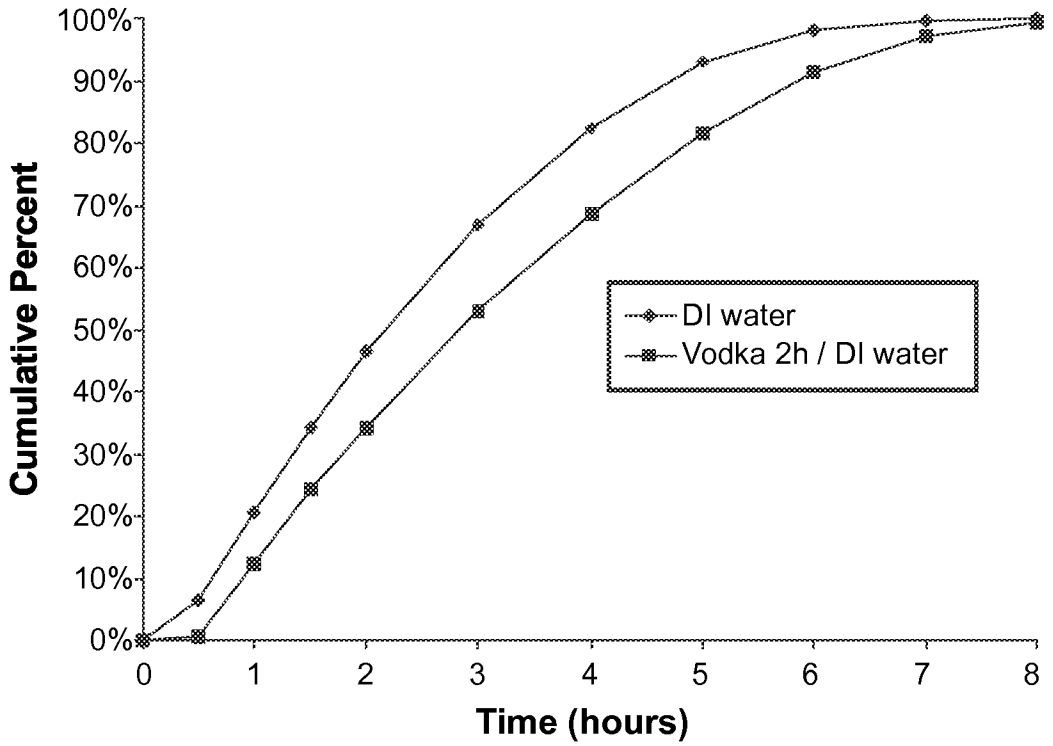
7
8
Time (hours)

FIG. 8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Cumulative Percent
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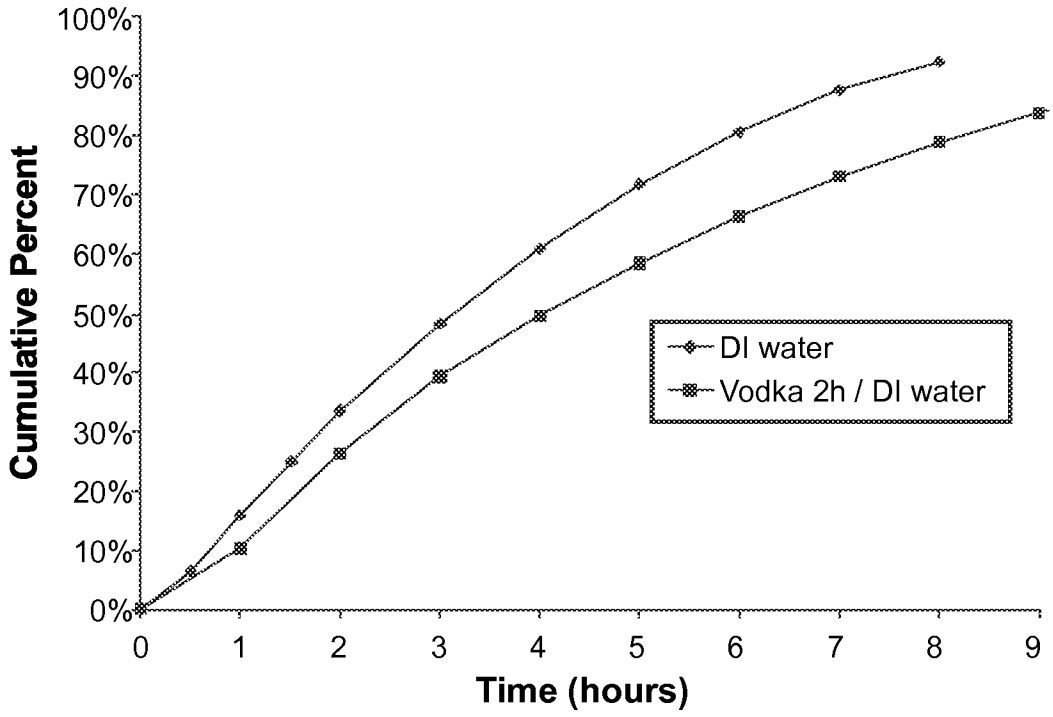
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A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Cumulative Percent
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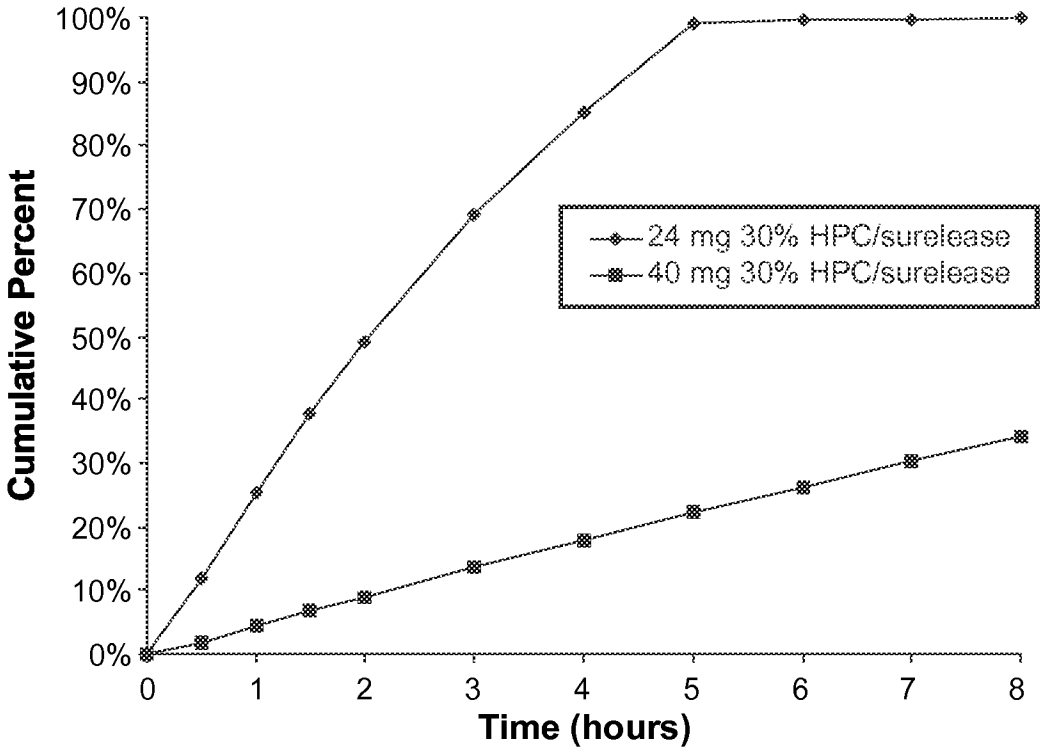
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B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Cumulative Percent
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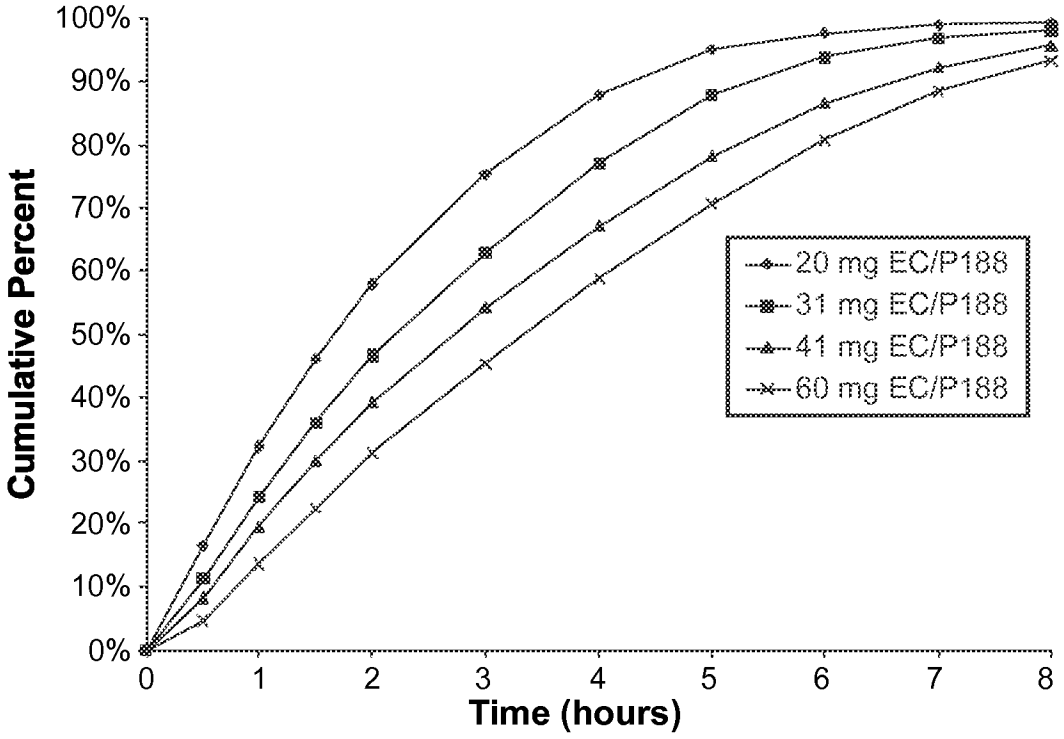
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10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Cumulative Percent
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Time (hours)
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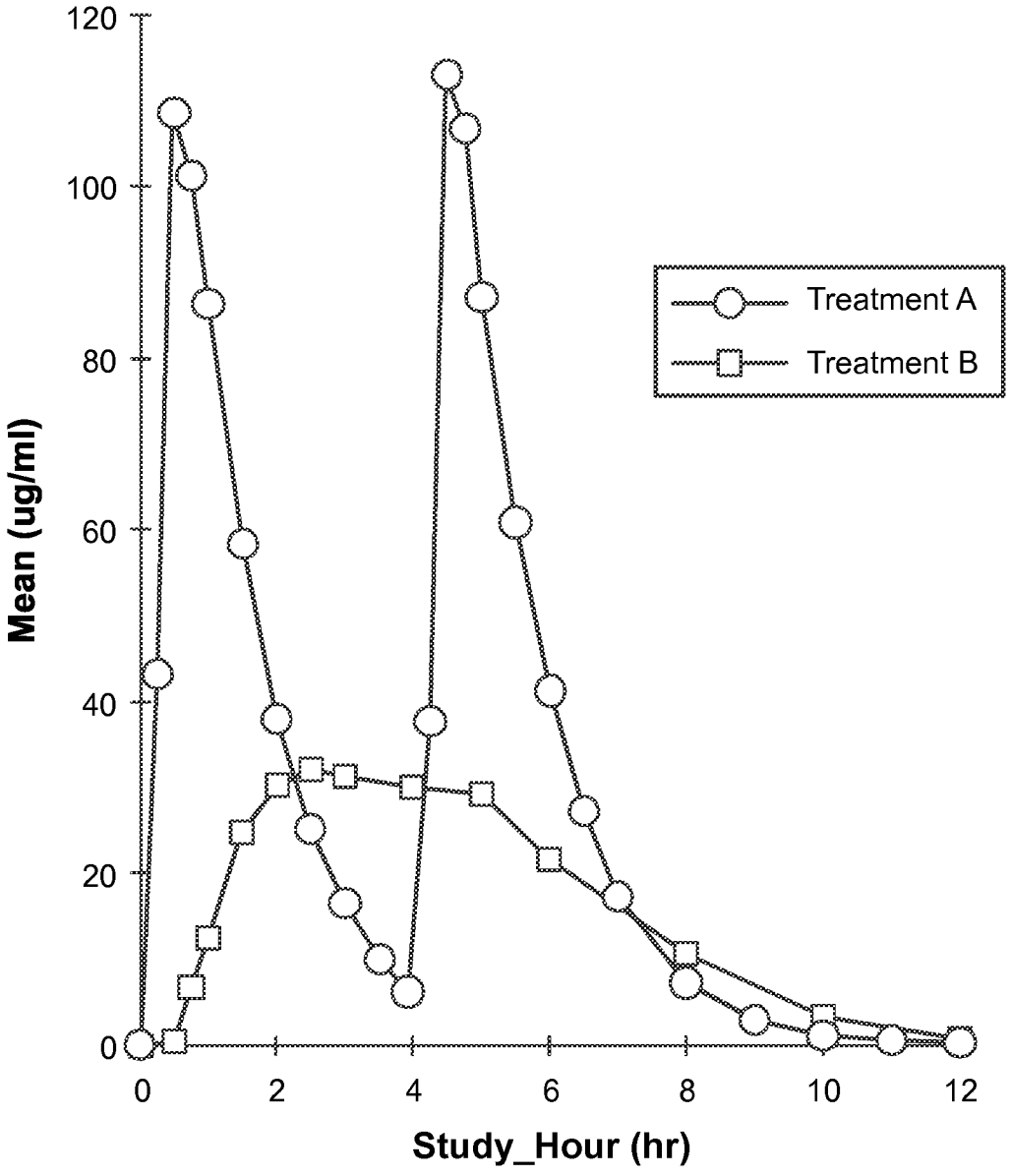
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11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Mean (ug/ml)
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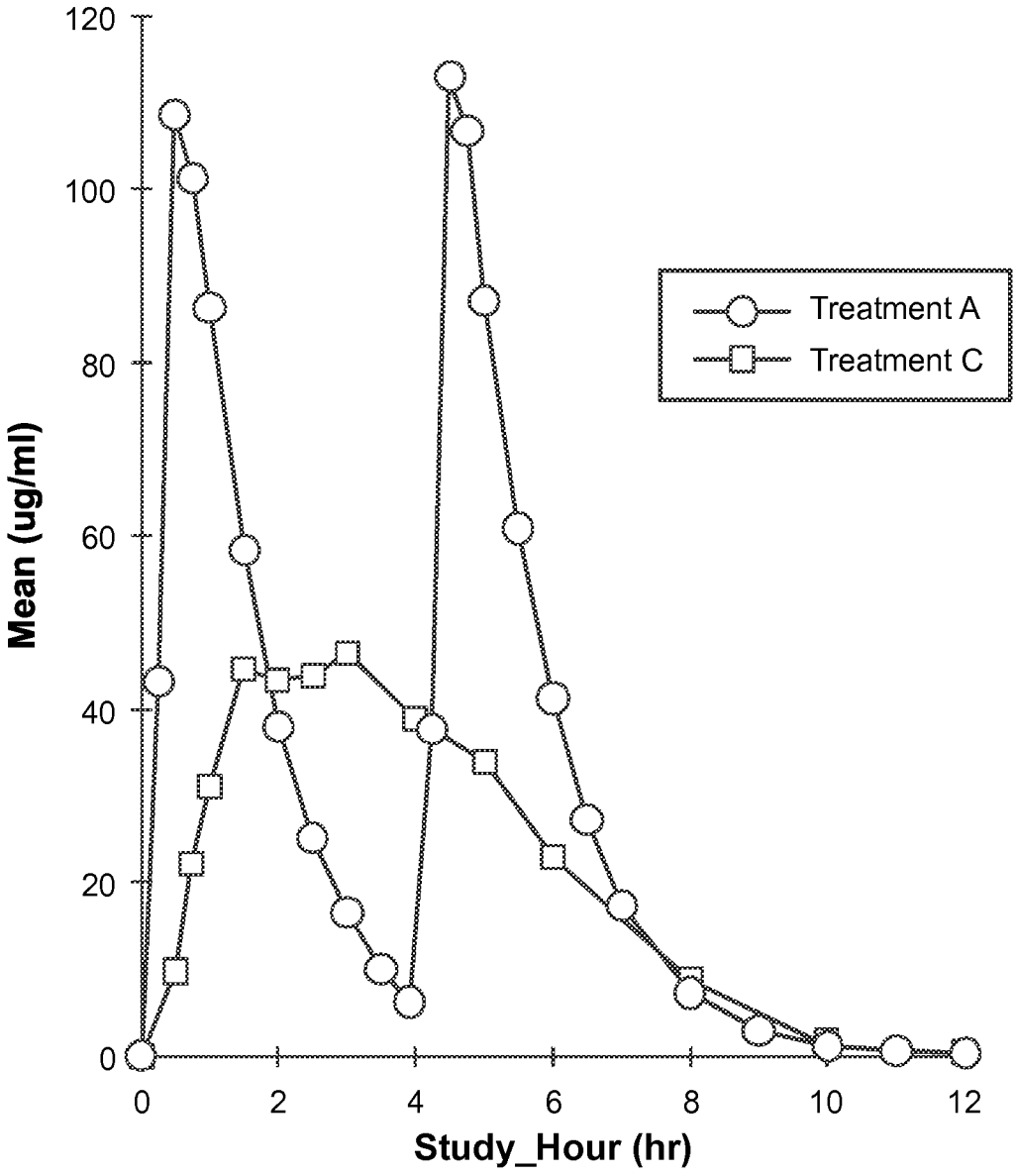
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12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6
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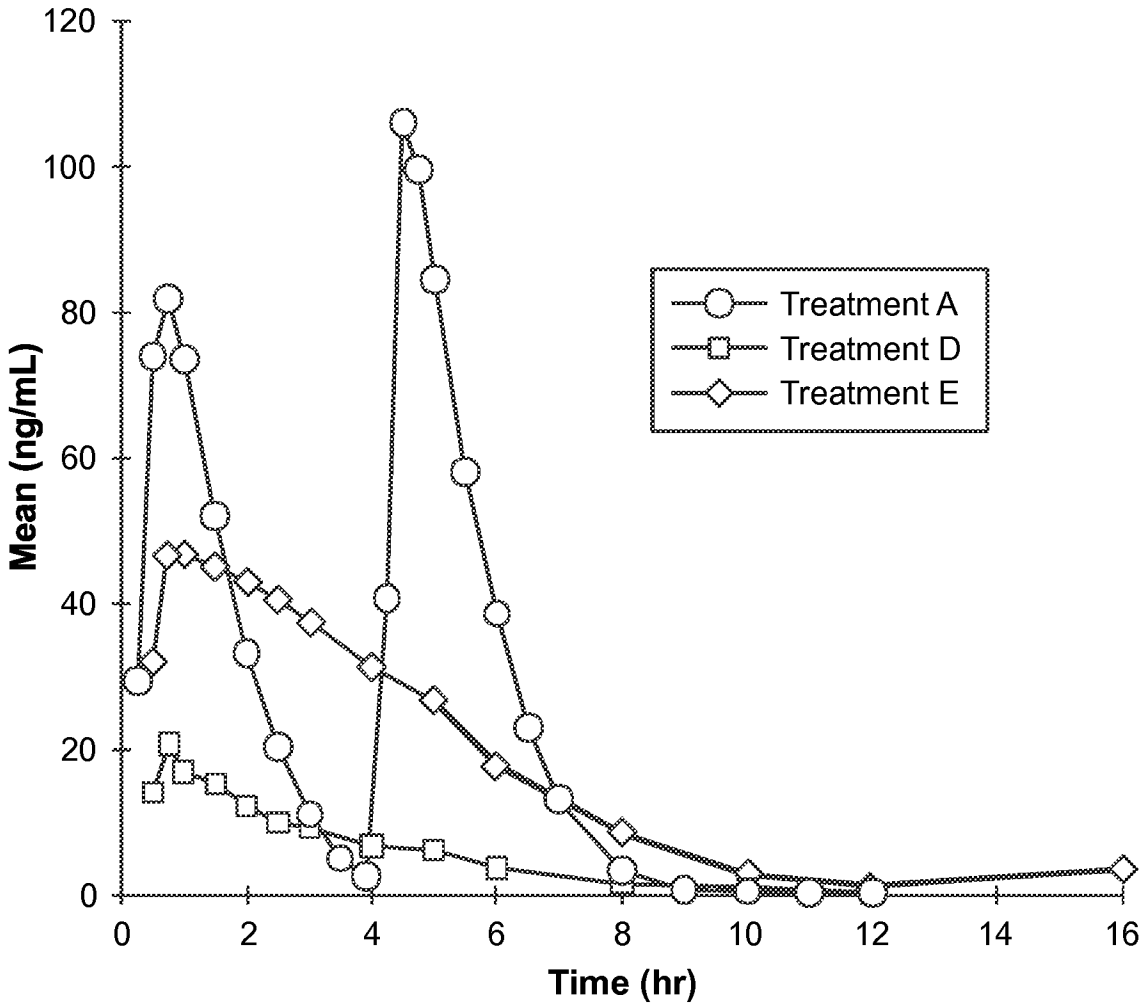
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13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Mean (ng/mL)
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6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

CONTROLLED RELEASE DOSAGE FORMS FOR HIGH DOSE, WATER SOLUBLE AND HYGROSCOPIC DRUG SUBSTANCES

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

For some drugs, it is difficult to formulate a controlled release dosage form that maintains an effective concentration of the drug over a sustained period of time. In particular, drugs that are administered at a high dose, drugs having a low molecular weight, and drugs with high water solubility make formulation of a controlled release dosage form challenging. For example, in the context of a controlled release drug formulation produced as a unit dosage form for oral administration, drugs that must be administered at a high dose constrain the amount of rate controlling excipients that can be used in formulating a drug composition that is both capable of sustained delivery of therapeutic doses of the drug and exhibits a size and shape suited to oral administration. Low molecular weight and high-solubility drugs may also readily permeate films and matrices that might otherwise be used to control release, and high solubility drugs are not suited to some drug delivery approaches, particularly where zero-order release kinetics are desired. An example of a drug that is administered at a high dose, has a low molecular weight, and high water solubility, is gamma-hydroxy butyrate (GHB), particularly the sodium salt of GHB.

Initial interest in the use of GHB as a potential treatment for narcolepsy arose from observations made during the use of GHB for anesthesia. Unlike traditional hypnotics, GHB induces sleep that closely resembles normal, physiologic sleep (Mamelak et al., Biol Psych 1977:12:273-288). Therefore, early investigators administered GHB to patients suffering from disorders of disturbed sleep, including narcolepsy (Broughton et al. in Narcolepsy, NY, N.Y.: Spectrum Publications, Inc. 1976:659-668), where it was found to increase total nocturnal sleep time, decrease nocturnal awakenings and increase Stage 3-4 (slow wave) sleep. Three open-label and two placebo-controlled studies provided a body of evidence demonstrating that improvements in nocturnal sleep were associated with a reduction in cataplexy and improvements in excessive daytime sleepiness (Broughton et al., Can J. Neurol Sci 1979; 6:1-6, and Broughton et al., Can J. Neurol Sci 1980; 7:23-30).

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often

reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., J. Muscoloskel. Pain, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., Psychosom. Med., 37, 341 (1975).

Fibromyalgia patients frequently report symptoms similar to those of patients with post-infectious neuromyasthenia, also referred to as chronic fatigue syndrome (CFS). CFS is a debilitating disorder characterized by profound tiredness or fatigue. Patients with CFS may become exhausted with only light physical exertion. They often must function at a level of activity substantially lower than their capacity before the onset of illness. In addition to these key defining characteristics, patients generally report various nonspecific symptoms, including weakness, muscle aches and pains, excessive sleep, malaise, fever, sore throat, tender lymph nodes, impaired memory and/or mental concentration, insomnia, and depression. CFS can persist for years. Compared with fibromyalgia patients, chronic fatigue patients have similarly disordered sleep, localized tenderness, and complaints of diffuse pain and fatigue.

Scharf et al. conducted an open-label study to evaluate the effects of GHB on the sleep patterns and symptoms of non-narcoleptic patients with fibromyalgia (Scharf et al., J Rheumatol 1998; 25: 1986-1990). Eleven patients with previously confirmed diagnosis of fibromyalgia who reported at least a 3-month history of widespread musculoskeletal pain in all body quadrants and tenderness in a least 5 specific trigger point sites participated in the study. Results showed that patients reported significant improvements in the subjective assessments of their levels of pain and fatigue over all 4 weeks of GHB treatment as compared to baseline, as well as a significant improvement in their estimates of overall wellness before and after GHB treatment.

WO 2006/053186 to Frucht describes an open label study of 5 patients with hyperkinetic movement disorders including ethanol responsive myoclonus and essential tremor. Sodium oxybate, a sodium salt of GHB, was reported to produce dose-dependent improvements in blinded ratings of ethanol responsive myoclonus and tremor and was said to be tolerated at doses that provided clinical benefit.

XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration during the night.

Liang et al. (published U.S. patent application US 2006/0210630 A1) disclose administration of GHB using an immediate release component and a delayed release component. The delayed release component of the formulations taught in Liang et al., however, function in a pH dependent manner.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the delivery profile of sodium oxybate controlled release formulations as described herein.

FIG. **2** shows the delivery profile of integrated dosage forms as described herein having an immediate release component and a controlled release component.

FIG. **3** provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. **4** provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the coating weight of a functional coating.

FIG. **5** provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. **6** provides a graph further illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by altering the amount of pore former included within a functional coating.

FIG. **7** provides a graph illustrating that the controlled release profile of dosage forms prepared according to the present description can be altered by varying the molecular weight of a pore former included within a functional coating.

FIG. **8** provides a graph illustrating that suitable controlled release profiles from dosage forms prepared according to the present description can be achieved even with functional coatings formed using different grades of the same base polymer material.

FIG. **9**A and FIG. **9**B provide graphs illustrating the effects of alcohol on the delivery profile of sustained-release formulations prepared as described herein.

FIG. **10** provides a graph illustrating the controlled release performance achieved by dosage forms as described herein having functional coatings prepared from aqueous dispersions of ethylcellulose as the base polymer.

FIG. **11** provides a graph illustrating the controlled release performance achieved by dosage forms as described herein incorporating calcium oxybate as the drug.

FIG. **12** provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment B).

FIG. **13** provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein (Treatment C).

FIG. **14**. provides a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E).

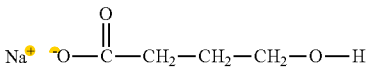
DETAILED DESCRIPTION

Formulations and dosage forms for the controlled release of a drug are described herein. Formulations described herein are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dosage form, and in one such embodiment, the controlled release formulation is provided as a coated tablet.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a controlled release (CR) unit dosage form or may be a separate immediate release composition. Therefore, an immediate release (IR) component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the IR component may also be formulated as part of a single dosage form that integrates both the IR and CR components. In such an embodiment, the pharmaceutical formulation may be provided in the form of the coated tablet or capsule.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

An example of a drug that may be used with the controlled release dosage forms described herein is GHB. It should be noted that embodiments of controlled release dosage forms comprising GHB, and other drugs, are presented herein for purposes of example only and not for purposes of limitation. The formulations and unit dosage forms provided herein can be utilized to achieve controlled release of GHB, as well as pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The structure of the sodium salt of GHB, sodium oxybate, is given as formula (I):



Methods of making GHB salts are described, for example, in U.S. Pat. No. 4,393,236, which is incorporated herein by reference.

Formulating GHB into a unit dosage form presents various challenges, and such challenges are magnified in the context of formulating a unit dosage form providing controlled release of GHB. For instance, GHB is very soluble, generally requires a relatively high dose, has a low molecu-

lar weight, and exhibits a short circulating half-life once administered. Therefore, a controlled release unit dosage form of GHB should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration. However, controlled release formulations typically require the addition of significant amounts of excipients or rate controlling materials to control the delivery of drug, and the presence and need for such materials often limits the drug loading available for a given controlled release technology. Additionally, low molecular weight drugs, such as GHB, typically exhibit high permeability through films and matrices. Even further, high water solubility increases drug mobility and may preclude the use of some approaches utilized to achieved a controlled release dosage form.

Another challenge to achieving a formulation capable of delivering GHB over a sustained period of time is the fact that some forms of GHB, such as the sodium salt of GHB, sodium oxybate, are extremely hygroscopic. As used herein, the term "hygroscopic" is used to describe a substance that readily absorbs and attracts water from the surrounding environment. The hygroscopic nature of sodium oxybate presents significant challenges to the formulation, production, and storage of dosage forms capable of delivering sodium oxybate over a sustained period of time. Despite the challenges noted, formulations and unit dosage forms providing controlled release of GHB are described herein.

A. Controlled Release Formulations

As used herein, the term "controlled release" describes a formulation, such as, for example, a unit dosage form, that releases drug over a prolonged period of time. The controlled release compositions described herein may be provided as a unit dosage form suitable for oral administration. In each embodiment of the controlled release compositions described herein, the drug incorporated in such compositions may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB.

In certain embodiments, the controlled release compositions described herein are formulated as unit dosage forms that deliver therapeutically effective amounts of drug over a period of at least 4 hours. For example, controlled release unit dosage forms as described herein may be formulated to deliver therapeutically effective amounts of drug over a period selected from about 4 to about 12 hours. In specific embodiments, the controlled release dosage forms described herein deliver therapeutically effective amounts of drug over a period selected from about 4, about 5, about 6, about 7, about 8, about 9, about 10 hours, and about 12 hours. In other such embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours, about 6 to about 10 hours, about 6 to about 12 hours, about 7 to about 10 hours, about 7 to about 12 hours, about 8 to about 10 hours, and from about 8 to about 12 hours. In yet other embodiments, the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 5 to about 9 hours, about 5 to about 8 hours, about 5 to about 7 hours, and about 6 to about 10 hours, about 6 to about 9 hours, and about 6 to about 8 hours.

The compositions described herein facilitate production of controlled release dosage forms that provide a substantially constant drug release rate. In one embodiment, the controlled release dosage forms may be formulated to deliver not more than approximately 30% of the drug initially contained within the controlled release dosage form in the first hour post-administration. When referencing the amount of drug initially contained in the controlled release dosage form or "initial drug content" of the controlled release dosage form, for purposes of the present description, such amount refers to the total amount of drug included in the controlled release composition prior to administration to a patient.

As is detailed herein, the controlled release dosage forms according to the present description include a controlled release component (also referred to as a controlled release "formulation") and, optionally, an immediate release component (also referred to as an immediate release "formulation" or an immediate release "coating"). In specific embodiments, the controlled release dosage forms described herein may be formulated to deliver drug to the gastro-intestinal tract at desired rates of release or release profiles. For example, in some embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more than about 10% to about 60% of the drug initially contained within the controlled release component of the controlled release dosage form during the first two hours post-administration, and not more than about 40% to about 90% of the drug initially contained within the controlled release component of the controlled release dosage form during the first four hours post-administration. In other embodiments, controlled release dosage forms as described herein are formulated to release to the gastro-intestinal tract not more not more than about 40% of the drug initially contained within the controlled release component in the first hour post-administration, not more than about 60% of the drug initially contained within the controlled release component during the first two hours post-administration, and not more than about 90% of the drug initially contained within the controlled release component during the first four hours post-administration. In still other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 30% of the initial drug content in the controlled release component in the first hour post-administration, not more than about 60% of the initial drug content in the controlled release component during the first two hours post-administration, and not more than about 90% of the initial drug content of the controlled release component during the first four hours post-administration. In other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 50% of the initial drug content of the controlled release component during the first hour post-administration, between about 50 and about 75% of the initial drug content of the controlled release component after two hours, and not less than 80% of the initial drug content of the controlled release component after four hours post administration. In still other embodiments, a controlled release dosage form as described herein may be formulated release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component during the first hour post-administration, between about 5 and about 30% of the initial drug content of the controlled release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described

herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

Due to the rapid clearance of GHB from the plasma, when GHB is administered in an immediate release formulation, even large doses of the drug (e.g., a dose of between about 2.25 g and 4.5 g) generally result in plasma levels below 10 ug/mL within 4 hours of ingestion. In order to achieve therapeutic efficacy, therefore, a second, equal, dose is often required within 4 hours after administration of the first dose, and some patients may require administration of a second as soon as 2.5 hours after administration of the first dose. In such an instance, in order to maintain therapeutic efficacy, 4.5 g to 9 g of drug must be administered to the patient in two separate doses within 2 to 5 hours. This also requires that the second dose be administered during the night, which requires that the patient be awakened to take the second dose. The result is that the Cmax/Cmin ratio of GHB over an six hour period can be greater than 4 and is often greater than 8. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 μg/mL. In certain such embodiments, a GHB controlled release dosage form as described herein provides a Cmax to Cmin ratio of GHB over a prolonged period of time after administration selected from less than 3 and less than 2. Therefore, in specific embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 3 and less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. For example, in particular embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 3 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 μg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours. In still other embodiments, the controlled release dosage forms described herein provided controlled delivery of GHB that results in a Cmax to Cmin ratio of GHB selected from less than 2 over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours, while also providing GHB plasma concentrations of at least 10 μg/mL over a period of time selected from up to about 5 hours, up to about 6 hours, up to about 7 hours, up to about 8 hours, up to about 9 hours, and up to about 10 hours.

Drug delivery performance provided by the dosage forms described herein can be evaluated using a standard USP type 2 or USP type 7 dissolution apparatus set to 37° C.±2° C. under the conditions described, for example, in the experimental examples provided herein. The dissolution media may be selected from dissolution media known by those of skill in the art such as at least one of purified water, 0.1N HCl, simulated intestinal fluid, and others.

In particular embodiments, the controlled release formulations described herein work to reduce inter patient variability in delivery of GHB. In particular, controlled release formulations described herein provide time dependent release of GHB over a sustained period of time. Previous references have described targeted release dosage forms of GHB that function in a pH dependent manner. However, due to inter-subject variability in gastrointestinal pH conditions, delivery of GHB from such dosage forms can be inconsistent. Moreover, because relatively high doses of GHB are typically required for therapeutic effect, unit dosage forms of GHB are also relatively large and may be retained for a period of time in the stomach, which can lead to intra- and inter-patient variability in dose delivery of GHB from pH dependent delivery systems due to variability in gastric retention time. Further, patients with fibromyalgia have an increased chance of also suffering from irritable bowel syndrome (see, e.g., Fibromyalgia in patients with irritable bowel syndrome. An association with the severity of the intestinal disorder, Int J Colorectal Dis. 2001 August; 16(4): 211-5.) Irritable bowel syndrome is also associated with delayed gastric emptying and variable gastric emptying (see, e.g., Dyspepsia and its overlap with irritable bowel syndrome, Curr Gastroenterol Rep. 2006 August; 8(4):266-72.) Therefore many patients with fibromyalgia and suffering from irritable bowel syndrome may experience more variability in gastric transit or prolonged gastric transit. By operating in a time dependent manner once placed in an aqueous environment, controlled release formulations described herein offer consistent GHB delivery characteristics and reduce the likelihood of undesirable intra- and inter-patient inconsistencies in dose delivery that may result from variances in gastric retention time that can occur between different patients and different patient populations.

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present description is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

The controlled release dosage forms described herein may comprise a relatively high concentration of drug that can, in

some instances, harm a patient if the formulation releases the drug at a rate that is faster than the intended sustained rate. This rapid release of the drug is sometimes referred to as "dose dumping." To avoid this potential danger, certain embodiments of the controlled release dosage forms described herein may comprise formulations that are resistant to dose dumping. Some users may intentionally attempt to increase the drug release rate of the controlled release dosage form using alcohol (e.g., potential abusers may take the controlled release dosage form prior to, simultaneously with, or after consuming an alcoholic beverage or, alternatively, may seek to extract the drug from the controlled release dosage form by placing the dosage form in solution containing alcohol). Other users may take the dosage form with alcohol, not necessarily in a manner considered abuse of the drug or alcohol, but without regard for the potential risks of dose dumping or contraindication of the two substances. In one embodiment, a controlled release dosage form as disclosed herein may include a coating composition that is resistant to alcohol or that does not dissolve substantially faster in alcohol. In one such embodiment, the controlled release dosage form may comprise the drug sodium oxybate and include a coating composition including ethylcellulose that is resistant to dose dumping in alcohol. In another embodiment, the controlled release dosage form may include a coating composition that is resistant to dose dumping after administration. For example, the controlled release dosage form may include a coating composition that is resistant to dose dumping in the GI tract after being exposed to gastric fluid and intestinal fluid.

In certain embodiments, the controlled release formulations described herein are provided as a coated tablet composition having a controlled release core coated by a functional overcoat. The composition of the controlled release core provided in such embodiments facilitates high drug loading, thereby, rendering the coated tablet suitable for formulation and sustained delivery of drugs administered at high doses. The functional overcoat works to control delivery of drug from the controlled release core and maintain the structural integrity of the dosage form over time. In addition to the controlled release core and functional overcoat, the coated tablet composition as described herein may further include a moisture barrier or cosmetic coating disposed over the functional overcoat.

I. Controlled Release Component

Where the controlled release formulations described herein are formulated as a coated tablet having a controlled release core (CR core), the CR core includes at least one drug substance to be delivered from the controlled release dosage form. The drug included in the CR core may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. Examples of suitable salts of GHB include the calcium, lithium, potassium, sodium and magnesium salts. The CR core is formulated and configured to be suitable for oral administration. In one embodiment, coated tablets as described herein may be administered to provide a dose of GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvate or complex of GHB in a range of about 500 mg to about 12 g of drug in one or more tablets. In particular embodiments, a CR core included in a controlled release dosage form according to the present description may include an amount of drug selected from about 100 mg to about 2,000 mg. In some such embodiments, the amount of drug included in the CR core may be selected from up to about 250 mg, 400 mg, 500 mg, 600 mg, 700 mg, 750 mg, 800 mg, 900 mg, 1,000 mg, 1,100 mg, 1,200 mg, 1,400 mg, 1,500 mg, 1,600 mg, 1,700 mg, 1,800 mg, 1,900 mg, and 2,000 mg. In certain such embodiments, the amount of drug included in a CR core as described herein may range from about 500 mg to about 2,000 mg, such as, for example, about 500 mg to 1,000 mg, about 600 mg to 1,000 mg, about 600 mg to 900 mg, about 600 mg to 800 mg, about 700 mg to 1,000 mg, about 700 mg to 900 mg and about 700 mg to 850 mg. In other such embodiments, the amount of drug included in a CR core as described herein may range from about 700 mg to about 2,000 mg, such as, for example, about 700 mg to 1,500 mg, about 700 mg to 1,400 mg, about 700 mg to 1,300 mg, about 700 mg to 1,200 mg, about 700 mg to 1,100 mg, about 700 ring to 1,000 mg, about 700 mg to 900 mg, and about 700 mg to 850 mg.

In one embodiment, the controlled release dosage form comprises a CR core wherein the relative amount drug in the CR core is at least 90% or greater by weight. In another embodiment, the relative amount of drug in the CR core ranges from between about 90% and 98%, about 91% and 98%, about 92% and 98%, about 93% and 98%, about 94% and 98%, about 95% and 98%, about 96% and 98%, and between about 97% and 98% by weight of the CR core. In yet another embodiment, the relative amount of drug in a CR core may be present at an amount selected from about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, and 98% by weight of the CR core. In certain such embodiments, the amount of drug in the CR core may range from about 94 to 98%, 94 to 97%, 94 to 96%, 95 to 98%, 95 to 97%, and 95 to 96.5 by weight of the CR core.

In one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with one or more excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment, a CR core as disclosed herein can include one or more binders that are known for use in tablet formulations. In one such embodiment, a CR core may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the CR core included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about

1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

The CR core may also include one or more surfactants. In certain embodiments, the CR core may include a tableted composition that may comprise one or more surfactants selected from, for example, ionic and non-ionic surfactants. In one such embodiment, CR core may include at least one anionic surfactant, including docusate sodium (dioctyl sulfosuccinate sodium salt) and sodium lauryl sulfate. In yet another embodiment, the CR core may include at least one non-ionic surfactant selected from including polyoxyethyelene alkyl ethers, polyoxyethylene stearates, poloxamers, polysorbate, sorbitan esters, and glyceryl monooleate. In specific embodiments, one or more surfactants included in a CR core as disclosed herein may be present, for example, in an amount of up to about 3.0% by weight of the CR core. For example, in certain embodiments, the CR core may include one or more surfactants present in a range selected from about 0.01% to 3%, about 0.01% to 2%, about 0.01% to 1%, about 0.5% to 3%, about 0.5% to 2%, and about 0.5% to 1% by weight of the CR core.

The CR core included in controlled release dosage form as disclosed herein may also include fillers or compression aids selected from at least one of lactose, calcium carbonate, calcium sulfate, compressible sugars, dextrates, dextrin, dextrose, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, powdered cellulose, and sucrose. In another embodiment, a CR core may be prepared by blending a drug and other excipients together, and the forming the blend into a tablet, caplet, pill, or other dosage form according to methods known by those of skill in the art. In certain embodiments, a controlled release formulation as described herein may comprise a solid oral dosage form of any desired shape and size including round, oval, oblong cylindrical, or triangular. In one such embodiment, the surfaces of the CR core may be flat, round, concave, or convex.

The CR core composition included in a controlled release formulation provided as a coated tablet dosage form as described herein may be manufactured using standard techniques, such as wet granulation, roller compaction, fluid bed granulation, and direct compression followed by compression on a conventional rotary tablet press as described in Remington, 20th edition, Chapter 45 (Oral Solid Dosage Forms).

II. Functional Coating Composition

Where the controlled release formulations as described herein are provided as a coated tablet composition, the CR core is coated with a functional coating. The coating composition works to preserve the integrity of the unit dosage form post administration and serves to facilitate controlled release of drug from the CR core. In certain embodiments, the coating composition is formulated to facilitate controlled release of a drug selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In one such embodiment, the coating composition is sufficiently robust to preserve the integrity of the coated tablet pre- and post-administration, yet is subject to disintegration or crushing as it passes through a patient's gastrointestinal tract and after all or substantially all the drug substance contained within the controlled release formulation has been delivered. Such a feature reduces the risk that bezoars formed from intact dosage form shells will form or be maintained within the GI tract of a patient, which may be of particular concern where the drug to be delivered must be administered at high doses using multiple unit dosage forms.

In one embodiment, a functional coating composition as disclosed herein may control, at least in part, the rate of release of the drug to be delivered from the CR core into the gastrointestinal tract. In one embodiment, the functional coating composition provides a functional coat that partly or fully covers the CR core included in the controlled release dosage form. In one embodiment, the functional coating composition as disclosed herein may include a polymer or blends of compatible polymers that are water soluble or that are water insoluble and selected to exhibit desired permeability characteristics. In one embodiment, the functional coating composition has a permeability that may be adjusted according the solubility of the drug used in the CR core. In one such embodiment, the functional coating composition may comprise one or more water insoluble polymers that may swell but do not substantially dissolve in the GI tract. For example, in particular embodiments, a functional coating composition as disclosed herein may comprise a rate-limiting film that includes at least one of ethylcellulose, cellulose acetate, such as CA-398. In other embodiments, the functional coating may include combinations of ethylcellulose with ammonio methacrylate copolymers, such as EUDRAGIT RS, EUDRAGIT RL, and combinations thereof. Suitable ethylcellulose materials are readily commercially available, and include, for example, ETHOCEL ethylcellulose polymers. Where ethylcellulose is used to form the functional coating, the physical characteristics of the coating composition and residual shell may be modified by adjusting the molecular weight of the ethylcellulose. For example, different grades of ethylcellulose, including, but not limited to, 4 cP, 7 cP, 10 cP, and 20 cP grades, may be used to achieve a coating composition having desired physical characteristics.

A functional coating composition as disclosed herein may include one or more base polymer and at least one pore-former. In one embodiment, the base polymer content may range from about 50% to about 80% by weight of the coating composition. In certain embodiments, the base polymer may be present in an amount ranging from about 50% to 75%, about 55% to 75%, about 60% to 75%, and about 65% to 75% by weight of the coating composition. In one such embodiment, the base polymer may be present in an amount selected from about 50%, 55%, 60%, 65%, 70%, 75%, and 80% by weight of the coating composition. In cases where a filler material is used (e.g., insoluble, non film-forming material such as magnesium stearate, talc, or fumed silica), these limits apply to the composition of the remaining non-filler components in the film.

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former,

such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

Where used in the functional coating composition, a pore former or a pore-forming agent can be selected to modify the permeability of the coating composition provided over the CR core. For example, the permeability of the functional coating composition may be increased by including one or more pore formers or pore-forming agents in the coating composition. In one embodiment, the pore formers disclosed herein may be soluble in water. In one such embodiment, when a CR dosage form comprising a functional coating composition with at least one pore former is swallowed by a patient and contacted with gastric fluid, the water-soluble pore formers may dissolve and form pores or channels in the coating through which the drug is released. It is possible to use an enteric component as part or all of the pore former in the coating composition. Examples of such materials that may be used as a pore former in the context of the present description include cellulose acetate phthalate, methacrylic acid-methyl methacrylate copolymers, and polyvinyl acetate phthalate. However, incorporating enteric components in the film may result in delivery characteristics that exhibit some level of sensitivity to gastric and intestinal transit times.

Where included, the amount and nature of the pore former included in the functional coating composition can be adjusted to obtain desired release rate characteristics for a given drug substance. In one embodiment, the functional coating composition may include an amount of pore former that ranges from about 20% to about 50% by weight of the coating composition. For example, the pore former may be present in an amount ranging from about 20% to 45%, about 25% to 45%, about 30% to 45%, and about 35% to 45% by weight of the functional coating composition. In one such embodiment, the pore former may be present in an amount selected from about 20%, 25%, 30%, 35%, 40%, 45%, and 50% by weight of the functional coating composition.

The functional coating composition as disclosed herein may also comprise one or more plasticizers. In certain embodiments, the functional coating composition may include a plasticizer such as triethyl citrate or dibutyl sebacate. In one such embodiment, a plasticizer may be present in the functional coating composition in an amount ranging from about 5% to 15% by weight relative to the base polymer. In certain embodiments, the functional coating composition may include a plasticizer in an amount selected from about 5%, 8%, 10%, 12%, and 15% by weight relative to the base polymer.

The functional coating composition as disclosed herein may also include an anti-tack agent. For example, certain embodiments of the functional coating composition may include an anti-tack agent selected from one or more of talc, glyceryl monostearate, and magnesium stearate. Many of the anti-tack agents are also suitable fillers. Addition of fillers, especially magnesium stearate, is one way to make the film more brittle and the dosage form more prone to crushing as it transits through the GI. Depending on forces encountered in the GI, varying the filler level in the film may allow one to adjust the duration, or extent of drug delivered, at which breach of the film and abrupt release of remaining contents occurs.

The functional coating composition as disclosed herein may be applied to a CR core at a weight that facilitates a suitable combination of sustained drug release and dosage form structural integrity. In certain embodiments, the functional coating composition may be applied at a weight of about 10 to about 100 mg. In particular embodiments, for example, the functional coating may be applied at a weight selected from about 20 to 60 mg, about 20 to 50 mg, about 20 to 40 mg, about 20 to 30 mg, about 30 to 60 mg, about 30 to 50 mg, about 30 to 40 mg, about 40 to 60 mg, about 40 to 50 mg, and about 50 to 60 mg. These ranges are useful for oval tablets of about 500 mg to about 1000 mg in weight. Alternatively, for a given tablet size or weights, the functional coating composition as disclosed herein may be applied at between about 2.5% and 7.5% of the tablet weight. For example, in one such embodiment, where the tablet is a 2,000 mg oval tablet, a functional coating composition may be applied at a weight ranging from about 50 mg to about 150 mg.

In addition to adjusting the amount or nature of the pore former included in the functional coating composition, the release rate of drug provided by the controlled release dosage form disclosed herein may be adjusted by modifying the thickness or weight of the functional coating composition. For example, a more rapid release rate will generally be achieved as the amount of a given pore former included in the functional coating composition is increased or the thickness or weight of the coating composition applied over the CR core is decreased. Conversely, a slower or more controlled release may be achieved, generally, as relatively less of a given pore former is included in the functional coating composition or the thickness or weight of the coating composition applied to the CR core is increased. Additionally, in certain embodiments, the release rate of drug from the CR core may be adjusted by modifying the water content of the functional coating composition. For example, increasing the water content of the functional coating composition may increase the release rate of drug the CR core.

The functional coating compositions as disclosed herein may be applied to a CR core according to conventional coating methods and techniques. In one embodiment, the functional coating composition as disclosed herein may be applied using a conventional perforated pan coater. In another embodiment, the functional coating composition may be applied using an aqueous pan-coating process. In one such embodiment, the use of an aqueous pan-coating process may include the use of a latex dispersion. For example, a latex dispersion such as SURELEASE may be used for an ethylcellulose pan-coating process. In another example, a latex dispersion such as EUDRAGIT RS 30 D may be used in a pan-coating process for ammonio-methacrylates. In yet another embodiment, the functional coating composition may be applied using a solvent-based pan-coating process. In one such embodiment, a solvent-based pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet

another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

When a controlled release formulation or dosage form is provided as a coated tablet, in some embodiments, it may be coated with a moisture barrier or a moisture-resistant coating composition. For example, a controlled release dosage form as disclosed herein comprising GHB as the drug substance may include a moisture barrier. In another example, a moisture barrier may be particularly useful where sodium oxybate is used as the drug substance. In one embodiment, the moisture barrier may be a polyvinyl alcohol-based coating, such as OPADRY AMB (Colorcon Inc., Harleysville, Pa.). In another embodiment, the moisture barrier may be a hydroxypropyl methylcellulose (HPMC)/wax-based coating, such as AQUARIUS MG (Ashland Aqualon, Wilmington, Del.). In yet another embodiment, the moisture barrier may be a HPMC/stearic acid-based coating. The moisture barrier as disclosed herein, in some embodiments, may be formed using a reverse enteric material, such as EUDRAGIT E, and may be coated from alcohol or alcohol/water solutions or from an aqueous latex dispersion. In embodiments where the controlled release dosage form is provided as a tablet of about 500 mg-1000 mg in weight, for example, the moisture barrier coating may be applied at a weight selected from about 10 mg to about 60 mg/tablet and about 25 mg to about 50 mg/tablet. In general, a minimum weight is needed to ensure complete coverage of the tablet in light of imperfections in the tablet surface, and a maximum weight is determined by practical considerations, such as coating time, or by the need for better moisture protection.

As will be readily appreciated, the controlled release dosage form can be further provided with a cosmetic top coat. In one embodiment, a top-coat may be applied to an existing coating composition such as a moisture barrier. In certain embodiments, a cosmetic top-coat may include at least one of HPMC and copovidone. For example, when the controlled release dosage form includes a coated tablet comprising sodium oxybate as the drug, a top-coat including HPMC, such as for example an HPMC material selected from one or more of HPMC E3, E5, or E15, may be applied over a moisture barrier to improve the effectiveness of the moisture barrier by reducing any seepage of sodium oxybate and water from the surface of the coated tablet.

B. Immediate Release Formulations

The controlled release formulations described herein can be dosed together with an immediate release (IR) formulation. In one embodiment, the IR formulation may be provided as a separate formulation or dosage form that may be dosed together with a dosage form provided by a controlled release dosage form as described herein. The IR formulation may be provided in any suitable form, such as a dry powder formulation, a tablet or capsule unit dosage form, or a liquid formulation such as a solution or suspension formulation. As used herein, "immediate release" refers to a drug formulation that releases more than about 95% of the drug contained therein within a period of less than one hour after administration. In particular embodiments, the IR component of the compositions described herein release more than about 95% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration. In other embodiments, the IR component of the compositions described herein release more than about 80% of the drug contained therein within a period selected from less than 45 minutes, less than 30 minutes, and less than 15 minutes post-administration.

In certain embodiments, the IR formulation is provided as an immediate release component of a controlled release dosage form as described herein. In one such embodiment, the IR component is provided as a coating over a controlled release component or formulation as described herein. A unit dosage form that integrates both controlled release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time. Furthermore, where the drug to be delivered is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, dosing controlled release and immediate release formulations together may avoid the disadvantages of the current GHB dosing regimens, which can result in highly pulsatile plasma concentrations.

I. Immediate Release Component

When the immediate release formulation is provided as an integrated IR component of a controlled release dosage form, the amount of drug included in the IR component may range from about 10% to 50% by weight of the total drug included in the integrated dosage form. As used herein, "integrated dosage form" refers to a single unit dosage form that includes both immediate release and controlled release components as described herein. For example, where the drug to be delivered from the immediate release and controlled release formulations incorporated into an integrated dosage form is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB in some embodiments, the drug included in the IR component may comprise about 10% to about 50% by weight of the total drug included in the unit dosage form. In one such embodiment, the drug included in the IR component of an integrated dosage form may comprise about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50% by weight of the total drug included in the unit dosage form. For example, an integrated dosage form as described herein may contain 1000 mg sodium oxybate, wherein 100 mg to 500 mg sodium oxybate (10% to 50% by weight) is contained within and delivered from the IR component and 500 mg to 900 mg sodium oxybate (50% to 90% by weight) is contained within and delivered from the CR component.

Where the IR component is provided as a coating over a controlled release dosage form, in certain embodiments, the drug included in the IR component may account for between about 75% and 98% by weight of the IR formulation. In the context of describing an IR component provided over a controlled release dosage form as described or disclosed herein, the controlled release dosage forms referred to include the controlled release formulations described herein, including, in specific embodiments, CR cores coated with a functional coating as described herein. Again, the drug included in such an embodiment may be selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB. In certain embodiments, the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

An IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a tableted overcoat according to conventional tablet coating

and binding methods. Alternatively, an IR component formed as a coating over a controlled release dosage form as disclosed herein may be applied as a film coating, such as, for example, from a solution containing a suitable amount of drug and film former. In one such embodiment, wherein sodium oxybate is the drug included in the IR component, the coating forming the IR component may be coated over a controlled release dosage form from a coating solution that utilizes an alcohol and water solvent. For example, a suitable immediate release coating may be formed using a 20% solution of sodium oxybate in a 60%/40% (w/w) alcohol/water solution that contains a suitable film-former.

Where the IR component is provided as a film coat and includes one or more film-formers, suitable film formers may be selected from, for example, copovidone, hydroxypropyl cellulose, HPMC, and hydroxymethyl cellulose materials. An IR component containing sodium oxybate as the drug can be applied as a suspension or as a solution by adjusting the water content of the coating mixture. For a suspension, little or no water is added to the alcohol, and the example film formers should be suitable. To prepare a solution, however, the water content of the solvent is increased, for example to 40%, and a smaller set of film formers would be suitable due to the precipitation of most common film formers in the presence of sodium oxybate solution. Hypromellose is one of several potential film formers that is suitable. It is further possible, with more difficulty, to apply the sodium oxybate from an aqueous solution; however, the same limitations on film former applies, and processing is complicated by the hygroscopic nature of the drug. In one embodiment, the IR component useful for use in a controlled release dosage form as described herein includes 91% sodium oxybate and 9% hypromellose (HPMC E-15) that is applied from a solution containing 20% sodium oxybate and 2% HPMC E-15 in a 60/40 w/w ethanol/water solvent.

Where the IR component of an integrated dosage form is provided as a coating over the controlled release dosage form, the coating forming the IR component may further include one or more of an anti-tack agent and a plasticizer to facilitate processing and to improve film properties. Furthermore, addition of one or more surfactants, such as sodium lauryl sulfate, may improve the dissolution of IR coatings that contain hydrophobic components (such as anti-tack agents or water-insoluble film formers).

In embodiments where the IR component is provided as a coating over a controlled release formulation as described herein, the IR component may be positioned directly over the functional coating of the controlled release formulation. Where desired or necessary based on the drug to be delivered from the IR component and controlled release formulation included in such an integrated dosage form, the outer surface of the IR component may then be coated with a moisture barrier layer. For example, where the drug delivered by the integrated dosage form is highly hygroscopic, such as, for example, sodium oxybate, a moisture barrier layer over the immediate release coating forming the IR component may be provided.

The formulation and structure of integrated dosage forms as described herein can be adjusted to provide a combination of immediate release and controlled release performance that suits a particular dosing need. In particular, the formulation and structure of integrated dosage forms as described herein can be adjusted to provide any combination of the immediate release and controlled release performance characteristics described herein. In particular embodiments, for example, the drug delivered from an integrated dosage form as described herein is selected from GHB and pharmaceutically acceptable salts, hydrates, tautomers, solvates and complexes of GHB, and the integrated dosage form sustains delivery of GHB over a period of from about 4 to about 10 hours. In one such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug as the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours. In another such embodiment, the IR component of the integrated dosage form provides rapid onset of action, releasing more than about 90% of the drug contained therein within a period of time selected from less than one hour, less than 45 minutes, less than 30 minutes and less than 15 minutes after administration, while the controlled release composition included in the integrated dosage begins to deliver drug after the IR component is released and continues to deliver drug for a sustained period of between about 4 and about 10 hours.

Moreover, the ratio of drug release from the IR component and CR component can be adjusted as needed to facilitate a desired dosing regimen or achieve targeted dosing. A dosage form as described herein that integrates both IR and CR components may be formulated to deliver as much as 2,000 mg of a desired drug, such as GHB or a pharmaceutically acceptable salt, hydrate, tautomer, solvates or complex of GHB. In particular embodiments, the total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg. For example, in certain such embodiments, the total amount of drug may be selected from between about 500 mg and 1,400 mg, about 500 mg and 1,200 mg, about 500 mg and 1,100 mg, about 600 mg and 1,200 mg, about 600 mg and 1,100 mg, about 600 mg and 1,000 mg, about 600 mg and 950 mg, about 600 mg and 850 mg, about 600 mg and 750 mg, about 750 mg and 1,200 mg, about 750 mg and 1,100 mg, about 750 mg and 1,000 mg, about 750 mg and 950 mg, and about 750 mg and 850 mg. In an integrated IR/CR dosage form, the relative amounts of drug delivered from the IR component and CR components may be adjusted as desired as well. In particular embodiments, the ratio of drug released from the IR component to drug released from the CR component is from about 1:2 to about 1:4. In certain embodiments, such ratio is selected from about 1:2, 1:2.5, 1:3, 1:3.5 and 1:4.

In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form maybe formulated and configured such that start-up of delivery of drug from the controlled release composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag

time is desired, the delay may be accomplished or adjusted by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

EXAMPLES

Example 1

Controlled Release Core

A granulation used to form CR cores as described herein was manufactured in a 25 L high shear granulator according to the formula in Table 1A. Klucel EXF was divided into two equal portions; half of the Klucel EXF was dissolved in the ethanol, and half was dry blended with sodium oxybate. The material was initially granulated with 10% w/w ethanol and then titrated with another 3.5% w/w ethanol solution to achieve desired granule growth. A suitable wet mass was obtained at a total ethanol concentration of 13.5% w/w. The wet granules were divided into two sub lots and then each sub lot was dried in a 5-liter Niro fluid bed dryer. The dried granules were combined and milled through a COMIL equipped with a 14 mesh screen. Granulation parameters and particle size distribution are shown in Tables 1B and 1C, respectively.

The granulation was then combined with 2% magnesium stearate lubricant, and tablets were compressed on a 16-station press fitted with chrome-plated 0.325"×0.705" modified oval tooling. The average tablet hardness was 10.7 kilo-ponds.

TABLE 1A

Controlled Release Core Tablet Formulation

	Ingredient(s)	% w/w	mg/tablet
1	Sodium Oxybate	96.0	750.0
2	Hydroxypropyl cellulose, NF (Klucel EXF)	2.0	15.6
3	Ethanol, USP (200 proof)*	13.5	
4	Magnesium Stearate, NF	2.0	15.6
	TOTAL	100.0	781.2

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters
WET GRANULATION

GRANULATION SOLUTION ADDITION RATE (G/MIN)	250	
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES	
IMPELLER SPEED (RPM)	300	
CHOPPER SPEED (RPM)	1800	
DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET TEMPERATURE (° C.)	70	70
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE AT END OF DRYING (° C.)	47	48
LOD (% WT LOSS)	0.84	0.92

TABLE 1C

Screen Analysis of Milled Granulation

Screen size US Std mesh	Opening size microns	Wt Retained (%)
20	850	2.1
40	420	10.4
60	250	19.8
80	180	25.0
120	125	22.9
200	75	12.5
Pan	<45	7.3

Example 2

Functional Coating

Tablets from Example 1 were coated with a solution prepared according to the formulation in Table 2A. The ethylcellulose was first added to a 95/5 w/w mixture of ethanol and water and stirred until dissolved. Next, the hydroxypropyl cellulose and dibutyl sebacate were added and stirred until completely dissolved. 4.7 kg of tablets from Example 1 were then charged to an 8" pan Driam tablet coater and coated with the solution to 5.1 wt % gain (40 mg/tablet). The tablets were then dried for 5 minutes in the coater, and then finally cooled in the pan to an exhaust temperature below 30° C.

The dissolution profile was measured in de-ionized water using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm. Samples were analyzed by HPLC. As shown in FIG. **1**, the coated tablets exhibited controlled release with duration of approximately 6 hours. The dosage form released 12% of its contents after 1 hour, 34% after 2 hours, 71% after 4 hours, 93% after 6 hours, and 99% after 8 hours.

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
5	Sodium Oxybate tablet core		95.13	781.25
6	Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80	14.80
7	Dibutyl sebacate	5.0	0.24	2.00
8	Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82	23.20

TABLE 2A-continued

Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
9	Ethanol, USP (200 proof)*			
10	Purified water*			
	TOTAL	100.0	100.00	821.25

*Coating solvent, removed during processing

TABLE 2A

Coating Parameters for Driam 8" Pan Coater

CR COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	46	42-55
EXHAUST TEMPERATURE (° C.)	43	41-46
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2.0
SPRAY RATE (G/MIN)	35	32-37
PAN SPEED (RPM)	6	5-7

Example 3

Immediate-Release Overcoat

A solution of 20% sodium oxybate as active and 2.0% hypromellose E-15 (HPMC E-15) as film-former was prepared in 60/40 (w/w) ethanol/water. The coating solution was manufactured by first dissolving the HPMC E15 in water, then adding the ethanol and sodium oxybate. 3 kg of 750-mg strength sustained-release tablets from Example 2 were charged to a Driam tablet coater equipped with an 8" pan and preheated to 40° C. The entire coating solution was applied according to the parameters listed in Table 3A. The tablet weight gain was monitored every 5 minutes, and the coating was stopped when the entire solution was sprayed (the theoretical weight gain is 33.5%). The tablets were dried for 15 minutes; the tablets did not lose any weight during the 15 minute drying time, and so it was assumed that the drying was complete. The tablets were then cooled in the pan to an exhaust temperature of <30° C.

Analysis by HPLC revealed an overall potency of 961 mg, and thus a drug overcoat potency of 211 mg. Dissolution testing using USP Apparatus 2 set to 37° C.±2° C. with paddles at 50 rpm, shown in FIG. **2**, demonstrates substantially the entire immediate-release overcoat is dissolved in 15 minutes and that controlled release is maintained for approximately 6 hours thereafter. Higher amounts of drug can be applied to the immediate release overcoat by using higher amounts of coating solution and extending the coating time accordingly.

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	59	55-63
EXHAUST TEMPERATURE (° C.)	51	50-53
PRODUCT TEMPERATURE (° C.)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8

TABLE 3A-continued

Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

The following examples illustrate aspects of the sustained-release coating formulation with several evaluations using tablets from Example 1.

Example 4

Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

One means of controlling dissolution is by adjustment of the coating thickness, or amount of film applied to each tablet. This was illustrated with a film consisting of 33% poloxamer 188 (P188) and 67% ethylcellulose 10 cPs (EC-10). The coating solution was prepared by dissolving 3.59 grams of EC-10 and 1.77 grams of P188 in a mixture of 80 grams denatured alcohol ("alcohol") and 4 grams de-ionized water. (Denatured alcohol, S-L-X manufactured by W. M. Barr, is approximately a 50/50 w/w blend of methanol and ethanol.)

Twelve tablets from Example 1 were coated in a Caleva Mini-coater/Drier 2 under parameters listed in Table 4A. Periodically, the tablets were removed and weighed to determine film weight. Three tablets were removed at times corresponding to 21 mg, 30 mg, 40 mg, and finally 60 mg weight gain.

The dissolution profiles were measured with USP Apparatus 7 (Vankel Bio-dis) set to 37° C.±2° C. and using a dipping rate of 30/minute, tablets fixed in plastic holders and intervals corresponding to 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h, 8 h, and 14 h (each interval is 50 ml volume). The tubes were analyzed by conductivity, and results are calculated as percent of total amount. The results demonstrate that controlled release is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

TABLE 4A

Standard Parameters for Sustained-Release Coating in Caleva Mini-Coater/Drier 2

Parameter	Setting
Batch size	3-12 Tablets
Inlet temperature	40° C.
Air flow setting	70-85%
Solution flow rate	18 ml/hr
Agitator setting	32
Atomization pressure	0.5 bar
Gun position	Adjusted to achieve desired deposition

Example 5

Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting

of 7% solids in 95/5 alcohol/water. The results shown in FIG. **4** demonstrate that controlled release over a relevant time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6

Effect of Poloxamer Level in Functional Coating

In addition to adjustment of membrane weight, another useful means of controlling release rate or duration is by adjustment of the pore-former content of the formulation. Following procedures of Example 4, two additional solutions consisting of (a) 25% P188 by weight/75% EC-10 by weight and (b) 40% P188 by weight/60% EC-10 by weight were prepared as 7% (w/w) solutions in 95/5 alcohol/water. In each of the two separate coatings, four tablets from Example 1 were coated to 41 mg. The dissolution profiles are shown in FIG. **5**, along with that of the 40 mg set of Example 4 for comparison. The results demonstrate that poloxamer level can be adjusted at least over the range of 25%-40% by weight, while still providing controlled release of the drug.

Example 7

Effect of Hydroxypropyl Cellulose Level in Functional Coating

In a fashion similar to Example 6, the effect of HPC level in the functional coating was evaluated over the range of 30%-50% by weight. Three separate coating solutions were prepared with 30%, 40%, and 50% HPC-EF; 5% DBS; and the balance EC-10. All solutions were prepared with 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The dissolution profiles shown in FIG. **6** demonstrate controlled release of the drug was achieved with HPC levels of at least 30-50% by weight.

Example 8

Effect of Hydroxypropyl Cellulose Molecular Weight when used in Functional Coating

Hydroxypropyl cellulose is supplied in several molecular weight grades, many of which may be suitable for use as pore-formers in ethylcellulose films. Two such grades (Klucel "EF" and "JF", supplied by Ashland) corresponding to 80,000 daltons and 140,000 daltons were evaluated with other components fixed. Following procedures of Example 4, solutions were prepared with 40% HPC, 5% DBS, and 55% EC-10 (all percentages by weight) using 7% total components in 95/5 alcohol/water. In each coating, 4 tablets from Example 1 were coated to 40-41 mg/tablet weight gain. The results shown in FIG. **7** demonstrate a modest effect of molecular weight and that the two grades tested provide for acceptable release profiles.

Example 9

Effect of Ethylcellulose Molecular Weight or Viscosity

Another consideration is the molecular weight, or viscosity, of ethylcellulose. Two grades were evaluated, corresponding to 4 cPs and 10 cPs viscosity for a 5% solution. Following procedures of Example 4, two solutions were prepared corresponding to 58.5 wt % ethylcellulose (EC-4 or EC-10), 36.5 wt % HPC-EF, and 5.0 wt % DBS having 7% w/w total components in 95/5 alcohol/water. Tablets from Example 1 were coated to 40 mg/tablet weight gain, and dissolution profiles are shown as FIG. **8**. The results indicate both grades of ethylcellulose provide for acceptable profiles, and suggest that other ethylcellulose grades (such as 20 cPs) may also be acceptable.

Example 10

Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

Co-administration of sustained-release dosage forms with alcoholic beverages is a relevant concern, as ethanol is known to dissolve certain rate-controlling components that would not otherwise be dissolved. In some dosage forms, this may lead to dose-dumping. As ethanol is rapidly absorbed in the stomach, a relevant test involves dissolution of the dosage form in vodka (40% ethanol nominal) for 2 hours (representing gastric retention time), followed by normal dissolution in de-ionized water.

This test was performed on sustained-release tablets from Example 9 (36.5 wt % HPC EF, 5 wt % DBS, 58.5 wt % EC-4). The analysis of sodium oxybate by conductivity was corrected for the different response in vodka vs. de-ionized water. The results shown in FIG. **9**A indicate that dissolution is slower in Vodka, and that no dose-dumping occurred.

Likewise, a similar test was performed on sustained-release tablets with a film comprised of 33 wt % P188 and 67 wt % EC-10. Those results, shown in FIG. **9**B, also indicate slower release in vodka and no dose-dumping.

Example 11

Aqueous Coating of Controlled Release Film

Due to the hygroscopic nature of sodium oxybate, coating the rate-controlling film from an alcoholic solution is desirable. However, use of ethylcellulose aqueous dispersions is attractive for environmental and cost considerations. A film consisting of 30 wt % HPC EF and 70 wt % Surelease (aqueous ethylcellulose dispersion) was deposited on tablets from Example 1 as follows. First, 1.37 grams of HPC EF was dissolved in 22.6 grams de-ionized water. This was then poured into 32.5 grams of Surelease E-7-19040-clear while stirring. Eight tablets were coated in the Caleva Mini-coater/Drier 2 with flow rate of 15 ml/hr and 58° C. inlet temperature. Samples removed at 24 mg and 40 mg were then tested for dissolution, with no post-coating heat treatment. The results are shown in FIG. **10**.

Example 12

Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma,

Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"×0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. **11**. These results using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13

Clinical Evaluation of Controlled Release Dosage Forms

An open-ended, randomized, crossover study was conducted to evaluate controlled release dosage forms as described herein. The controlled release dosage forms were formulated to deliver sodium oxybate and were compared to a sodium oxybate oral solution (commercially available as Xyrem® (sodium oxybate) oral solution). The study was conducted in healthy male and female volunteers.

Four different sodium oxybate formulations were administered to patients. The first, designated herein as Treatment A, was the sodium oxybate oral solution containing 375 mg/ml sodium oxybate. Treatments B through E, as designated herein, involved administration of three controlled release dosage forms (Treatments B through D), with one of the controlled release dosage forms being used to administer two different doses of sodium oxybate (Treatments D and E). The controlled release dosage forms administered as Treatment B included 750 mg sodium oxybate per dosage form and were produced with a CR core and functional overcoat as described in Example 1 and Example 2, the controlled release dosage forms administered as Treatment C included 750 mg sodium oxybate per dosage form and were produced as described in Example 1 and Example 4, and the controlled release dosage forms administered as Treatments D and E included 1,000 mg sodium oxybate per dosage form and were produced with a CR core (750 mg sodium oxybate), functional overcoat, and IR overcoat (250 mg sodium oxybate) as described in Examples 1 through 3.

Patients were divided into two groups. The first group received Treatment A, Treatment B, and Treatment C over the course of the clinical study, with a washout period between each treatment. Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments B and C were administered to each patient only at time zero, with each treatment being administered as 8 tablets, providing a total dose of 6 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 29 patients received Treatment A, a total of 19 patients received Treatment B, and a total of 19 patients received Treatment C. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. **12** (Treatment A and Treatment B) and FIG. **13** (Treatment A and Treatment C), and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 5.

TABLE 5

Summary of PK Parameters for Treatments A, B, C

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
			Treatment A			
N	29	29	29	29	29	29
Mean	1.22	0.60	4.50 (0.5, 4.75)	130.79	350.84	351.20
SD	0.27	0.13		31.52	116.74	116.74
CV %	21.93	22.61		24.10	33.27	33.24
Mean	1.19	0.58		127.37	333.33	333.72
			Treatment B			
N	18	18	19	19	19	18
Mean	0.62	1.22	2.00 (1.50, 5.00)	41.78	188.23	196.25
SD	0.16	0.40		18.40	103.60	102.50
CV %	26.44	32.58		44.03	55.04	52.23
Mean	0.59	1.17		38.46	163.80	173.33
			Treatment C			
N	19	19	19	19	19	19
Mean	0.74	0.99	2.50 (1.00, 5.00)	50.49	221.64	222.60
SD	0.16	0.23		15.83	106.85	106.80
CV %	22.25	22.93		31.35	48.21	47.98
Mean	0.72	0.96		48.10	200.08	201.12

The second group was administered Treatment A, Treatment D, and Treatment E during over the course of the clinical study, with a washout period between each treatment. Again, Treatment A was administered to each patient as two 3 g doses given four hours apart (one dose at time zero and the second dose four hours later), for a total dose of 6 g sodium oxybate. Treatments D and E were administered to each patient only at time zero. Patients receiving Treatment D were administered 4 tablets at time zero, providing a total dose of 4 g sodium oxybate, and patients receiving Treatment E were administered 8 tablets at time zero, providing a total dose of 8 g sodium oxybate. Blood samples from each patient were taken at various intervals and analyzed by LC/MS for total sodium oxybate content in the plasma. A total of 30 patients received Treatment A, and a total of 30 patients received Treatments D and E. The mean plasma concentration of sodium oxybate over time achieved by each of the treatments is shown in FIG. **14**, and a summary of pharmacokinetic parameters provided by Treatments A through C are provided in Table 6.

TABLE 6

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
			Treatment A			
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
			Treatment D			
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55

TABLE 6-continued

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr*ug/ml)	AUCinf (hr*ug/ml)
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

[a] Tmax is summarized as median (min, max).

It will be obvious to those having skill in the art that many changes may be made to the details of the above-described embodiments without departing from the underlying principles of the invention. The scope of the present invention should, therefore, be determined only by the following claims.

The invention claimed is:

1. A formulation comprising immediate release and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, wherein:

a. the sustained release portion comprises a functional coating and a core, wherein the functional coating is deposited over the core, wherein the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; the sustained release portion comprises about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;

b. the immediate release portion comprises about 75% and about 98% by weight of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, and the amount of gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the immediate release portion is about 10% to 50% by weight of the gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

c. the formulation releases at least about 30% of its gamma-hydroxybutyrate by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and

d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

2. The formulation of claim **1** wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

3. The formulation of claim **1** wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 6 hours when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

4. The formulation of claim **1** wherein the sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

5. The formulation of claim **1** wherein the sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

6. The formulation of claim **1** comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

7. The formulation of claim **6** comprising a sodium salt of gamma-hydroxybutyrate.

8. The formulation of claim **1** wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

9. The formulation of claim **1**, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

10. An oral dosage form comprising the formulation of claim **1**.

11. The formulation of claim **1** wherein the sustained release portion releases about 10% or less of its gamma-hydroxybutyrate by about 1 hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

12. A formulation of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate, comprising immediate release and a solid sustained release portions:

a. wherein the immediate release portion comprises about 55 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

b. wherein the sustained release portion comprises from about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate and a functional coating deposited over a core comprising the at least one pharmaceutically active ingredient, wherein the functional coating comprises one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating; and the sustained release portion releases greater than about 40% of its gamma-hydroxybutyrate by about 4 to 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm;

c. the formulation releases at least about 30% of its gamma-hydroxybutyrate or salt thereof by one hour when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm; and

d. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 hours when tested in a

dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

* * * * *

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

SUPPLEMENTED OPENING EXPERT REPORT OF WILLIAM CHARMAN

HIGHLY CONFIDENTIAL

CHARMAN OPENING REPORT

I. INTRODUCTION

1. I have been retained by counsel for Defendant Avadel CNS Pharmaceuticals, LLC ("Avadel") as an expert witness in the above captioned action.

2. I understand that Plaintiff Jazz Pharmaceuticals ("Jazz") has filed a lawsuit against Avadel alleging infringement of U.S. Patent Nos. 10,758,488 ("'488 patent"), 10,813,885 ("'885 patent"), 10,959,956 ("'956 patent"), and 10,966,931 ("'931 patent") (together, the "Sustained Release patents"), as well as U.S. Patent Nos. 11,077,079 ("'079 Patent") and 11,147,782 ("'782 patent") (together, the "Resinate patents") (collectively, the "Patents-in-Suit").

3. I understand the following claims of the Patents-in-Suit are being asserted by Jazz: claims 1-12 of the '488 patent; claims 1-15 of the '885 patent; claims 1-20, 23-25 of the '956 patent; claims 1-15 of the '931 patent; claims 1-3, 5-12, 14-18 of the '079 patent; and claims 1-24 of the '782 patent (collectively, the "Asserted Claims").

4. I have been asked by counsel for Avadel to consider the validity of the Asserted Claims. In particular, I have been asked to consider whether the Asserted Claims meet the written description and enablement requirements of 35 U.S.C. § 112, whether the Asserted Claims are anticipated under 35 U.S.C. § 102, and who is properly considered to have invented and publicly disclosed the subject matter of the Asserted Claims.

5. My opinions are set forth in this report based on the materials I have reviewed (listed in Exhibit A), my experience and training in the relevant field, including my experience with drug formulation and testing, and the applicable legal principles provided by Avadel's counsel.

II. BACKGROUND AND QUALIFICATIONS

6. I am currently a Sir John Monash Distinguished Professor in the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University in Melbourne, Australia.

7. I have over 35 years of experience in the field of pharmaceutical sciences, pharmacology, and drug delivery, and I have been recognized as an expert in these fields.

8. Prior to my current position, I served as the Dean, Faculty of Pharmacy and Pharmaceutical Sciences from 2007 to 2019 at Monash University. While I was Dean, I was also the Founding Director of the Monash Institute of Pharmaceutical Sciences from 2007-2017. The Faculty and Institute is currently ranked first in the world in Pharmacy and Pharmacology.

9. In 2011, I was appointed as the eighth Sir John Monash Distinguished Professor, the University's most prestigious title conferred to Professors. Prior to serving as Dean, I held academic appointments as Professor of Pharmaceutics from 1995 to 2006, and Associate Dean (Research) from 1999 to 2002, both at Monash University.

10. I co-founded and was a Non-executive director of Acrux Ltd., a specialty pharmaceutical company that commercialized a drug delivery technology, from which two FDA-approved formulations were commercialized.

11. I received my Bachelor of Pharmacy degree in 1981 from the Victorian College of Pharmacy (now the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University). In 1985, I completed my Ph.D. in Pharmaceutical Chemistry (awarded with honors) from the University of Kansas.

12. In 2021, I was appointed as an Officer of the Order of Australia, one of Australia's highest civilian honors, for my achievements and meritorious service to tertiary education, particularly the pharmaceutical sciences. I also was the Chair of the International Pharmaceutical

Federation ("FIP") Education Program, and a member of the FIP Board of Directors in The Hague, The Netherlands.

13. I am an author on over 380 publications and communications, including various U.S. patents and patent applications. I have given over 200 invited national and international presentations and lectures. Many of these publications and presentations relate to my research interests and expertise in pharmaceutical sciences, formulation sciences, drug delivery, and pharmacology.

14. I have been a member of the editorial advisory boards for five peer-reviewed research journals: the Journal of Pharmaceutical Sciences, the International Journal of Pharmaceutics, the Journal of Pharmacy and Pharmacology, Die Pharmazie, and Experimental Parasitology.

15. I have received numerous honors and awards in the pharmaceutical sciences such as the GlaxoWellcome International Achievement Award in Pharmaceutical Sciences awarded by the Pharmaceutical Society of Great Britain, the Career Achievement Award in Oral Drug Delivery from the Controlled Release Society, a Fellowship of the American Association of Pharmaceutical Scientists, an Honorary Fellowship of the Royal Pharmaceutical Society of Great Britain, and am a medalist of the Australasian Pharmaceutical Sciences Association. I have been awarded both a Pharmaceutical Sciences World Congress Achievement Award and a Lifetime Achievement Award in Pharmaceutical Sciences from the International Pharmaceutical Federation. I have also received a Doctor of Science (honoris causa) degree from the University of London.

16. I am or have been a member of various professional societies, including the American Association of Pharmaceutical Scientists, the International Pharmaceutical Federation, the Australian Pharmaceutical Sciences Association, and the Pharmaceutical Society of Australia.

17. Accordingly, I consider myself to be an expert in the pharmaceutical sciences, pharmacology, and drug delivery, and I believe I am qualified to provide opinions as to what the person of ordinary skill in the art ("POSA") would have understood, known, or concluded regarding the subject matter of the Sustained Release patents and Resinate patents as of the relevant priority dates of the Patents-in-Suit.

18. A copy of my curriculum vitae, including references to the publications I authored, is attached to this report as Exhibit B.

19. I have served as an expert witness before. Specifically, in the last five years I have served as an expert for (i) Merck Sharp and Dohme B.V. and Merck Sharp and Dohme Corp in Civil Action No. 20-2576 (CCC) (LDW) (CONSOLIDATED) United States District Court, District of New Jersey, and (ii) I have provided Affidavits to the Federal Court of Australia as an independent expert witness, having been retained by the Solicitors acting for Biogen International GmBH.

III. COMPENSATION

20. I am being compensated at my ordinary and customary consulting rate of $900 per hour, plus reimbursement for expenses, for time spent working on this matter. My compensation in no way depends on the opinion or testimony I provide or the outcome of this action.

IV. SUMMARY OF OPINIONS

A. Sustained Release Patents

- In my opinion, the Sustained Release patents are invalid for lack of written description, lack of enablement, and anticipation. I have also provided opinions regarding the factual support for Avadel's contention that the Sustained Release patents are invalid based on derivation and improper inventorship. I summarize my opinions at a high level below:

  The Sustained Release patents are invalid for lack of written description because the

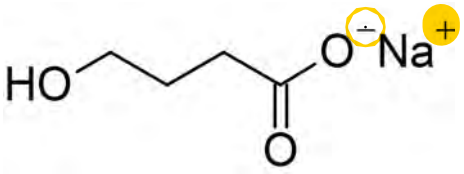
F. Gamma-hydroxybutyrate

1. Background

77. Gamma-hydroxybutyrate ("GHB"), or oxybate,[2] is a neuroactive compound with a variety of central nervous system pharmacological properties.

78. GHB is used for the treatment of narcolepsy and cataplexy, among other things.

79. The most common form of oxybate is the sodium salt form, known as sodium oxybate:



80. Oxybate, however, can also exist in other salt forms, including calcium, potassium, lithium, sodium and magnesium salts.

81. Sodium oxybate is currently marketed commercially for the treatment of narcolepsy and cataplexy by Jazz Pharmaceuticals as Xyrem®.

82. Xyrem is a liquid formulation of sodium oxybate, and patients who are prescribed sodium oxybate for their narcolepsy typically take two doses of Xyrem: once at bedtime and a second dose in the middle of the night.

83. Jazz also markets an oxybate formulation known as Xywav® that contains a mixture of different oxybate salts for the treatment of narcolepsy and cataplexy. Like Xyrem, Xywav is a twice-nightly liquid formulation.[3]

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[2] For the purposes of this report, unless specifically indicated, I use the terms GHB and oxybate interchangeably.

[3] Xywav is approved for once nightly administration for Idiopathic Hypersomnia (IH) but not narcolepsy.

2. Formulation and Dosing Challenges

84. As the Patents-in-Suit acknowledge, the properties of GHB present numerous formulation challenges, particularly with respect to sustained or delayed release formulations.

85. First, GHB is highly hygroscopic. Indeed, GHB is sufficiently hygroscopic as to undergo deliquescence. *See, e.g.*, '488 patent at 5:16-19. This means GHB turns into a liquid when moisture is pulled in from the surrounding environment, which "complicates the mechanics [and] logistics of performing process development because of the need for humidity controls." *See* Ex. C, C. Allphin Tr. at 29:15-20.

86. Second, GHB is highly soluble and has a low molecular weight. The combination of these properties makes it difficult to control the release of GHB. *See*, *e.g.*, '079 patent at 5:49-60.

87. Third, GHB requires a high dose to achieve a therapeutic effect. *See* '079 patent at 5:27-47. This creates challenges when attempting to formulate a controlled release dosage form. *See, e.g.*, Ex. C, C. Allphin Tr. at 31:9-11 ("The high dose and low molecular weight created some challenges, the high dose being the larger challenge."), 61:1-12 (GHB doses are already "substantial" and "higher than desired" for delayed-release formulations containing GHB).

88. Further, GHB has a short half-life when administered. Because of this, currently existing oxybate products require twice-nightly dosing. *See, e.g.*, '079 patent at 3:63-66.

a. <u>Sustained Release Formulations of GHB</u>

89. The various challenges in developing a sustained release formulation containing GHB, which I described above, as well as others, are reflected in the specification of the Sustained Release patents.

90. The Sustained Release patents describe one "challenge to achieve a formulation capable of delivering GHB over a sustained period of time is the fact that some forms of GHB,

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Jan 26, 2023
Date

William N. Charman
William N. Charman

EXHIBIT 5

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUMRYZ™ safely and effectively. See full prescribing information for LUMRYZ.

LUMRYZ (sodium oxybate) for extended-release oral suspension, CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and ABUSE AND MISUSE
See full prescribing information for complete boxed warning.
Central Nervous System Depression
• LUMRYZ is a CNS depressant, and respiratory depression can occur with LUMRYZ use (5.1, 5.4)
Abuse and Misuse
• LUMRYZ is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death (5.2, 9.2)
LUMRYZ is available only through a restricted program called the LUMRYZ REMS (5.3)

INDICATIONS AND USAGE

LUMRYZ is a central nervous system depressant indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy (1).

DOSAGE AND ADMINISTRATION

Dosing Information
- Initiate dosage at 4.5 g once per night orally (2.1).
- Titrate to effect in increments of 1.5 g per night at weekly intervals (2.1).
- Recommended dosage range: 6 g to 9 g once per night orally (2.1).

Important Administration Information
- Prepare the dose of LUMRYZ prior to bedtime; suspend dose in approximately ⅓ cup of water in the mixing cup provided (2.2).
- Allow 2 hours after eating before dosing (2.2).
- Take LUMRYZ while in bed and lie down after dosing (2.2).

DOSAGE FORMS AND STRENGTHS

For extended-release oral suspension: Packets of 4.5 g, 6 g, 7.5 g, or 9 g (3)

CONTRAINDICATIONS

- In combination with sedative hypnotics or alcohol (4)
- Succinic semialdehyde dehydrogenase deficiency (4)

WARNINGS AND PRECAUTIONS

- CNS depression: Use caution when considering the concurrent use of LUMRYZ with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that LUMRYZ does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
- Confusion/Anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).
- High sodium content in LUMRYZ: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥ 5% and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Avadel CNS Pharmaceuticals, LLC at 1-888-828-2335 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking LUMRYZ (8.5).
- Hepatic Impairment: Because of an increase in exposure, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made (8.6).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: month/year

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION AND ABUSE AND MISUSE

Central Nervous System Depression

LUMRYZ (sodium oxybate) is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with LUMRYZ at recommended doses *[see Warnings and Precautions (5.1)]*. Many patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants *[see Clinical Trials (14)]*.

Abuse and Misuse

LUMRYZ (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death *[see Warnings and Precautions (5.2)]*.

Because of the risks of CNS depression and abuse and misuse, LUMRYZ is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the LUMRYZ REMS *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

LUMRYZ is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dosage is 4.5 grams (g) once per night administered orally. Increase the dosage by 1.5 g per night at weekly intervals to the recommended dosage range of 6 g to 9 g once per night orally. The dosage may be gradually titrated based on efficacy and tolerability. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

2.2 Important Administration Instructions

LUMRYZ is taken orally as a single dose at bedtime. Prepare the dose of LUMRYZ prior to bedtime. Prior to ingestion, the dose of LUMRYZ should be suspended in approximately 1/3 cup (approximately 80 mL) of water in the mixing cup provided *[see Instructions for Use]*. Do not use hot water *[see Clinical Pharmacology (12.3)]*. After mixing, consume LUMRYZ within 30 minutes.

Take LUMRYZ at least 2 hours after eating *[see Clinical Pharmacology (12.3)]*.

Patients should take LUMRYZ while in bed and lie down immediately after dosing as LUMRYZ may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking LUMRYZ, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of LUMRYZ.

2.3 Switching Patients from Immediate-Release Sodium Oxybate

Patients who are currently being treated with immediate-release sodium oxybate may be switched to LUMRYZ at the nearest equivalent dosage in grams per night (e.g., 7.5 g sodium oxybate divided into two 3.75 g doses per night to 7.5 g LUMRYZ once per night).

3 DOSAGE FORMS AND STRENGTHS

For extended-release oral suspension: LUMRYZ is a white to off-white powder provided in packets of 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate.

4 CONTRAINDICATIONS

LUMRYZ is contraindicated for use in:

- combination with sedative hypnotics *[see Warnings and Precautions (5.1)]*
- combination with alcohol *[see Warnings and Precautions (5.1)]*
- patients with succinic semialdehyde dehydrogenase deficiency *[see Clinical Pharmacology (12.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

LUMRYZ is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in patients treated with immediate-release sodium oxybate at recommended doses in clinical trials and may occur in patients treated with LUMRYZ at recommended doses. LUMRYZ is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of LUMRYZ with other CNS depressants, including but not

limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating antiepileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with LUMRYZ is required, dose reduction or discontinuation of one or more CNS depressants (including LUMRYZ) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with LUMRYZ should be considered. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate *[see Clinical Pharmacology (12.3)]*.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that LUMRYZ does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking LUMRYZ. Patients should be queried about CNS depression-related events upon initiation of LUMRYZ therapy and periodically thereafter.

LUMRYZ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.2 Abuse and Misuse

LUMRYZ is a Schedule III controlled substance. The active ingredient of LUMRYZ, sodium oxybate, is the sodium salt of gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) *[see Warnings and Precautions (5.3) and Drug Abuse and Dependence (9.2)]*.

LUMRYZ is available only through a restricted program under a REMS *[see Warnings and Precautions (5.3)]*.

5.3 LUMRYZ REMS

LUMRYZ is available only through a restricted distribution program called the LUMRYZ REMS because of the risks of central nervous system depression and abuse and misuse *[see Warnings and Precautions (5.1, 5.2)]*.

Notable requirements of the LUMRYZ REMS include the following:

- Healthcare providers who prescribe LUMRYZ are specially certified.

- LUMRYZ will be dispensed only by pharmacies that are specially certified.
- LUMRYZ will be dispensed and shipped only to patients who are enrolled in the LUMRYZ REMS with documentation of safe use conditions.

Further information is available at www.LUMRYZREMS.com or by calling 1-877-453-1029.

5.4 Respiratory Depression and Sleep-Disordered Breathing

LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported *[see Overdosage (10)]*.

Increased apnea and reduced oxygenation may occur with LUMRYZ administration. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with LUMRYZ.

In adult clinical trials of LUMRYZ in patients with narcolepsy, no subjects with apnea/hypopnea indexes greater than 15 were allowed to enroll.

In an adult study assessing the respiratory-depressant effects of immediate-release sodium oxybate at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of four patients with preexisting moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In an adult study assessing the effects of immediate-release sodium oxybate 9 g per night in 50 patients with obstructive sleep apnea, immediate-release sodium oxybate did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking immediate-release sodium oxybate, and clinically significant oxygen desaturation (≤55%) was measured in three patients (6%) after administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

In adult clinical trials in 128 patients with narcolepsy administered immediate-release sodium oxybate, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued immediate-release sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in adult patients with narcolepsy administered immediate-release sodium oxybate, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

5.5 Depression and Suicidality

Depression, and suicidal ideation and behavior, can occur in patients treated with LUMRYZ.

In an adult clinical trial in patients with narcolepsy administered LUMRYZ *[see Adverse Reactions (6.1)]*, there were no suicide attempts, but one patient developed suicidal ideation at the 9 g dose. In adult clinical trials in patients with narcolepsy (n=781) administered immediate-release sodium oxybate, there were two suicides and two attempted suicides in patients treated with immediate-release sodium oxybate, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used immediate-release sodium oxybate in conjunction with other drugs. Immediate-release sodium oxybate was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with immediate-release sodium oxybate, with four patients (<1%) discontinuing because of depression. In most cases, no change in immediate-release sodium oxybate treatment was required.

In a controlled trial in adults with narcolepsy administered LUMRYZ where patients were titrated from 4.5 g to 9 g per night, the incidences of depression were 0% at 4.5 g, 1% at 6 g, 1.1% at 7.5 g, and 1.3% at 9 g. In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night immediate-release sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose of immediate-release sodium oxybate, the incidences of depression were 1.7%, 1.5%, 3.2%, and 3.6% for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

The emergence of depression in patients treated with LUMRYZ requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking LUMRYZ.

5.6 Other Behavioral or Psychiatric Adverse Reactions

Other behavioral and psychiatric adverse reactions can occur in patients taking LUMRYZ.

During adult clinical trials in patients with narcolepsy administered LUMRYZ, 2% of 107 patients treated with LUMRYZ experienced a confusional state. During adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate, 3% of 781 patients treated with immediate-release sodium oxybate experienced confusion, with incidence generally increasing with dose.

No patients treated with LUMRYZ discontinued treatment because of confusion. Less than 1% of patients discontinued the immediate-release sodium oxybate because of confusion. Confusion was reported at all recommended doses of immediate-release sodium oxybate from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to immediate-release sodium

oxybate in fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In that controlled trial, the confusion resolved in all cases soon after termination of treatment. In one trial where immediate-release sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate, confusion resolved either soon after termination of dosing or with continued treatment.

Anxiety occurred in 7.5% of 107 patients treated with LUMRYZ in the adult trial in patients with narcolepsy. Anxiety occurred in 5.8% of the 874 patients receiving immediate-release sodium oxybate in adult clinical trials in another population.

Other psychiatric reactions reported in adult clinical trials in patients with narcolepsy administered LUMRYZ included irritability, emotional disorder, panic attack, agitation, delirium, and obsessive thoughts. Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy administered immediate-release sodium oxybate and in the postmarketing setting for immediate-release sodium oxybate include hallucinations, paranoia, psychosis, aggression, and agitation.

The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking LUMRYZ should be carefully monitored.

5.7 Parasomnias

Parasomnias can occur in patients taking LUMRYZ.

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 3% of 107 patients with narcolepsy treated with LUMRYZ. No patients treated with LUMRYZ discontinued due to sleepwalking. Sleepwalking was reported in 6% of 781 patients with narcolepsy treated with immediate-release sodium oxybate in adult controlled and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. In controlled trials, rates of sleepwalking were similar for patients taking placebo and patients taking immediate-release sodium oxybate. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of sleepwalking with potential injury or significant injury were reported during a clinical trial of immediate-release sodium oxybate in patients with narcolepsy.

Parasomnias, including sleepwalking, have been reported in the postmarketing experience with immediate-release sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated, and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

LUMRYZ has a high sodium content. In patients sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment), consider the amount of daily sodium intake in each dose of LUMRYZ. Table 1 provides the approximate sodium content per LUMRYZ dose.

Table 1: Approximate Sodium Content per Total Nightly Dose of LUMRYZ (g = grams)

LUMRYZ Dose	Sodium Content/Total Nightly Exposure
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

6 ADVERSE REACTIONS

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS Depression *[see Warnings and Precautions (5.1)]*
- Abuse and Misuse *[see Warnings and Precautions (5.2)]*
- Respiratory Depression and Sleep-Disordered Breathing *[see Warnings and Precautions (5.4)]*
- Depression and Suicidality *[see Warnings and Precautions (5.5)]*
- Other Behavioral or Psychiatric Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Parasomnias *[see Warnings and Precautions (5.7)]*
- Use in Patients Sensitive to High Sodium Intake *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

LUMRYZ was studied in one placebo-controlled trial (Study 1) *[see Clinical Studies (14)]* in 212 patients with narcolepsy (107 patients treated with LUMRYZ and 105 with placebo).

Adverse Reactions Leading to Treatment Discontinuation

In Study 1, 21.5% of patients treated with LUMRYZ discontinued because of adverse reactions, compared to 2.9% of patients receiving placebo. The most common adverse reaction leading to discontinuation was dizziness (4.7%). For LUMRYZ, 6.5% of patients discontinued due to adverse reactions on 4.5 g, 6.2% on 6 g, 5.7% on 7.5 g, and 6.5% on 9 g dose.

Most Common Adverse Reactions

The most common adverse reactions (incidence ≥ 5% and greater than placebo) reported for any dose of LUMRYZ were nausea, dizziness, enuresis, headache, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or Greater

Table 2 lists adverse reactions occurring in 2% or more of LUMRYZ-treated patients on any individual dose and at a rate greater than placebo-treated patients in Study 1.

Table 2: Adverse Reactions Occurring in 2% or More of LUMRYZ-Treated Patients and Greater than for Placebo-Treated Patients in Study 1

Adverse Reaction	Placebo (N=105) %	LUMRYZ 4.5 g (N=107) %	LUMRYZ 6 g (N=97) %	LUMRYZ 7.5 g (N=88) %	LUMRYZ 9 g (N=77) %
Gastrointestinal Disorders					
Vomiting	2	3	3	6	5
Nausea	3	6	8	7	1
Investigations					
Weight Decreased	0	1	0	0	4
Metabolism and Nutritional Disorders					
Decreased Appetite	0	4	4	3	3
Nervous System Disorders					
Dizziness	0	6	4	6	5
Somnolence	1	0	1	2	4
Headache	6	7	5	6	0
Psychiatric Disorders					
Enuresis	0	2	4	9	9
Anxiety	1	3	1	3	1
Somnambulism	0	1	2	0	0

Dose-Response Information

In the clinical trial in adult patients with narcolepsy, a dose-response relationship was observed for enuresis and somnolence.

Additional Adverse Reactions

Adverse reactions observed in clinical studies with immediate-release sodium oxybate (≥2%), but not observed in Study 1 at a frequency of higher than 2%, and which may be relevant for LUMRYZ: diarrhea, abdominal pain upper, dry mouth, pain, feeling drunk, peripheral edema, cataplexy, muscle spasms, pain in extremity, tremor, disturbance in attention, paresthesia, sleep paralysis, disorientation, irritability, and hyperhidrosis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sodium oxybate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Arthralgia, decreased appetite, fall*, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, nocturia, panic attack, vision blurred, and weight decreased.

*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

LUMRYZ is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of LUMRYZ *[see Warnings and Precautions (5.1)]*. In addition to coadministration of LUMRYZ and alcohol being contraindicated because of respiratory depression, consumption of alcohol while taking LUMRYZ may also result in a more rapid release of the dose of sodium oxybate *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no

clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Labor or Delivery

LUMRYZ has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m^2) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and postnatal developmental toxicity in rats is less than the MRHD on a mg/m^2 basis.

8.2 Lactation

Risk Summary

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMRYZ and any potential adverse effects on the breastfed infant from LUMRYZ or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of LUMRYZ in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was

observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested.

8.5 Geriatric Use

Clinical studies of LUMRYZ or immediate-release sodium oxybate in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials of immediate-release sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Because of an increase in exposure to LUMRYZ, LUMRYZ should not be initiated in patients with hepatic impairment because appropriate dosage adjustments for initiation of LUMRYZ cannot be made with the available dosage strengths *[see Clinical Pharmacology (12.3)]*. Patients with hepatic impairment who have been titrated to a maintenance dosage of another oxybate product can be switched to LUMRYZ if the appropriate dosage strength is available.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

LUMRYZ is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of LUMRYZ could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

LUMRYZ (sodium oxybate), the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing

drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of LUMRYZ according to state and federal regulations. It is safe to dispose of LUMRYZ down the sanitary sewer.

9.3 Dependence

Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of LUMRYZ have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with immediate-release sodium oxybate in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to LUMRYZ has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended LUMRYZ dosage regimen. Clinical studies of immediate-release sodium oxybate in the treatment of alcohol

withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of LUMRYZ in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with LUMRYZ is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances, the co-ingestion of other drugs and alcohol was common and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials of immediate-release sodium oxybate, two cases of overdose with sodium oxybate were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of sodium oxybate and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with LUMRYZ derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported.

Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of LUMRYZ can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB

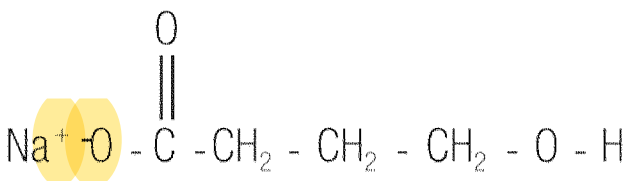
overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in LUMRYZ for extended-release oral suspension. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white solid powder.

Each packet of LUMRYZ contains 4.5 g, 6 g, 7.5 g, or 9 g of sodium oxybate, equivalent to 3.7 g, 5.0 g, 6.2 g, or 7.4 g of oxybate, respectively. The inactive ingredients are carrageenan, hydrogenated vegetable oil, hydroxyethyl cellulose, magnesium stearate, malic acid, methacrylic acid copolymer, microcrystalline cellulose, povidone, and xanthan gum.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LUMRYZ is a CNS depressant. The mechanism of action of LUMRYZ in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound and metabolite of the neurotransmitter GABA. It is hypothesized that the therapeutic effects of LUMRYZ on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

12.3 Pharmacokinetics

Absorption

Following oral administration of LUMRYZ, the peak plasma concentrations (C_{max}) following administration of one 6 g dose was 66 mcg/mL, and the time to peak plasma concentration (T_{max})

was 1.5 hours. Following oral administration of LUMRYZ, the plasma levels of GHB increased dose-proportionally for C_{max} and more than dose-proportionally for AUC (respectively 2.0-fold and 2.3-fold increases as total daily dose is doubled from 4.5 g to 9 g).

Effect of Food

Administration of LUMRYZ immediately after a high-fat meal resulted in a mean reduction in C_{max} and AUC of GHB by 33% and 14%, respectively; average T_{max} increased from 0.5 hours to 1.5 hours *[see Dosage and Administration (2.2)]*.

Effect of Ethanol

An in vitro study showed alcohol-induced dose-dumping of sodium oxybate from extended-release oral suspension at 1 hour in the presence of 40% alcohol, and approximately 60% increase of drug release at 2 hours in the presence of 20% alcohol *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Effect of Water Temperature

An in vitro dissolution study showed that LUMRYZ mixed with hot water (90°C) resulted in a dose-dumping phenomenon for the release of sodium oxybate, whereas warm water (50°C) did not significantly affect the drug release from the extended-release suspension *[see Dosage and Administration (2.2)]*.

Distribution

GHB is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At GHB concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Elimination

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for GHB, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle, and secondarily by β-oxidation. The primary pathway involves a cytosolic $NADP^+$-linked enzyme, GHB dehydrogenase, which catalyzes the conversion of GHB to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α-ketoglutarate. An alternate pathway of biotransformation involves β-oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Excretion

The clearance of GHB is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. GHB has an elimination half-life of 0.5 to 1 hour.

Specific Population

Geriatric Patients

There is limited experience with LUMRYZ in the elderly. Results from a pharmacokinetic study of immediate-release sodium oxybate (n=20) in another studied population indicate that the pharmacokinetic characteristics of GHB are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Male and Female Patients

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of GHB following an immediate-release 4.5 g oral dose of sodium oxybate.

Racial or Ethnic Groups

There are insufficient data to evaluate any pharmacokinetic differences among races.

Patients with Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Patients with Hepatic Impairment

The pharmacokinetics of GHB in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function, after a single sodium oxybate oral dose of 25 mg/kg. AUC values were doubled in cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 minutes and 32 minutes, respectively, versus 22 minutes in control patients). LUMRYZ should not be initiated in patients with liver impairment *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In vitro studies with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A, up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with the maximum recommended dose.

A drug interaction study in healthy adults (age 18 to 55 years) was conducted with LUMRYZ and divalproex sodium. Co-administration of a single dose of LUMRYZ (6 g) with divalproex sodium ER at steady state resulted in an approximate 18% increase in AUC (90% CI ratio range of 112%-123%), which is not expected to be clinically meaningful, while C_{max} was comparable. A single dose of LUMRYZ (6 g) did not appear to affect the pharmacokinetics of divalproex sodium. However, a pharmacodynamic interaction between LUMRYZ and divalproex sodium, a sedative antiepileptic drug, cannot be ruled out *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with immediate-release sodium oxybate and diclofenac and ibuprofen:

- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant changes in systemic exposure to GHB. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to GHB, as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between immediate-release sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the pharmacokinetics of GHB. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between immediate-release sodium oxybate and duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommended human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo,* showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m^2 basis.

14 CLINICAL STUDIES

The effectiveness of LUMRYZ for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy has been established based on a double-blind, randomized, placebo-controlled, two-arm multi-center study to assess the efficacy and safety of a once nightly administration of LUMRYZ in patients with narcolepsy (Study 1; NCT02720744).

A total of 212 patients were randomized to receive LUMRYZ or placebo in a 1:1 ratio and received at least one dose of study drug. The study was divided into four sequential study periods, and incorporated dose titration to stabilized dose administration of LUMRYZ (4.5 g, 6 g, 7.5 g, and 9 g). There was a three-week screening period, a 13-week treatment period including up-titration over a period of eight weeks, five weeks of stable dosing at 9 g/night, and a one-week follow-up period. Patients could be on concomitant stimulant as long as dosage was stable for 3 weeks prior to study start.

The three co-primary endpoints were the Maintenance of Wakefulness Test (MWT), Clinical Global Impression-Improvement (CGI-I), and mean change in weekly cataplexy attacks. The MWT measures latency to sleep onset (in minutes), averaged over five sessions at 2-hour intervals following nocturnal polysomnography. For each test session, patients were instructed to remain awake for as long as possible during 30-minute test sessions, and sleep latency was determined as the number of minutes patients could remain awake. The overall score was the mean sleep latency for the 5 sessions. The CGI-I was evaluated on a 7-point scale, centered at *No Change,* and ranging from *Very Much Worse* to *Very Much Improved*. Patients were rated by evaluators who based their assessments on the severity of narcolepsy at Baseline.

Demographic and mean baseline characteristics were similar for the LUMRYZ and placebo groups. A total of 76% were narcolepsy type 1 (NT1; with both symptoms of EDS and cataplexy) patients, and 24% were narcolepsy type 2 (NT2; with symptoms of EDS and without cataplexy) patients. The mean age was 31 years, and 68% were female. Approximately 63% of patients were on concomitant stimulant use. The mean MWT at baseline was 5 minutes for the LUMRYZ group, and 4.7 minutes for the placebo group. The mean number of cataplexy attacks per week at baseline was 18.9 in the LUMRYZ group and 19.8 in the placebo group. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of LUMRYZ, compared to the placebo group (see Table 3, Table 4, and Table 5).

Table 3: Change from Baseline in the Maintenance of Wakefulness Test

Dose	Treatment Group (N)	Change from Baseline (Minutes)*	Difference from Placebo [95% CI]	p-value
6 g (Week 3)	LUMRYZ (87)	8.1	5.0 [2.90;7.05]	<0.001
	Placebo (88)	3.1		
7.5 g (Week 8)	LUMRYZ (76)	9.6	6.2 [3.84;8.58]	<0.001

Dose	Treatment Group (N)	Change from Baseline (Minutes)*	Difference from Placebo [95% CI]	p-value
	Placebo (78)	3.3		
9 g (Week 13)	LUMRYZ (68)	10.8	6.1 [3.52;8.75]	<0.001
	Placebo (78)	4.7		

*Mean MWT at baseline was 5.0 minutes for the LUMRYZ group and 4.7 minutes for the placebo group

Table 4: Proportion of Patients with a Very Much or Much Improved Clinical Global Impression-Improvement

Dose	Treatment Group (N)	Percentage of Responders (Much or Very Much Improved)	Odds Ratio [95% CI]	p-value
6 g (Week 3)	LUMRYZ (87)	40	10.3 [3.93;26.92]	<0.001
	Placebo (87)	6	-	-
7.5 g (Week 8)	LUMRYZ (75)	64	5.7 [2.82;11.40]	<0.001
	Placebo (81)	22	-	-
9 g (Week 13)	LUMRYZ (69)	73	5.6 [2.76;11.23]	<0.001
	Placebo (79)	32	-	-

Table 5: Change from Baseline in the Mean Cataplexy Attacks Per Week in NT1 Patients

Dose	Treatment Group (N)	Change from Baseline*	Difference from Placebo [95% CI]	p-value
6 g (Week 3)	LUMRYZ (73)	-7.4	-4.8 [-7.03;-2.62]	<0.001
	Placebo (72)	-2.6	-	-
7.5 g (Week 8)	LUMRYZ (66)	-10.0	-6.3 [-8.74;-3.80]	<0.001
	Placebo (69)	-3.7	-	-
9 g (Week 13)	LUMRYZ (55)	-11.5	-6.7 [-9.32;-3.98]	<0.001
	Placebo (62)	-4.9	-	-

*Mean (SD) number of cataplexy attacks per week at baseline was 18.9 (8.7) in the LUMRYZ group and 19.8 (8.9) in the placebo group

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LUMRYZ is a blend of white to off-white granules for extended-release oral suspension in water. Each carton contains either 7 or 30 packets of LUMRYZ, a mixing cup, Prescribing Information and Medication Guide, and Instructions for Use.

Dose packets contain a single dose of LUMRYZ provided in 4.5 g, 6 g, 7.5 g, or 9 g doses.

Strength	Package Size	NDC Number
4.5 g	7 packets	NDC 13551-001-07
	30 packets	NDC 13551-001-30
6 g	7 packets	NDC 13551-002-07
	30 packets	NDC 13551-002-30
7.5 g	7 packets	NDC 13551-003-07
	30 packets	NDC 13551-003-30
9 g	7 packets	NDC 13551-004-07
	30 packets	NDC 13551-004-30

16.2 Storage

Keep out of reach of children.

LUMRYZ should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature).

Suspensions should be consumed within 30 minutes.

16.3 Handling and Disposal

LUMRYZ is a Schedule III drug under the Controlled Substances Act. LUMRYZ should be handled according to state and federal regulations. It is safe to dispose of LUMRYZ down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients that LUMRYZ can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients to not engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking LUMRYZ. Instruct patients to inform their healthcare providers of all the medications they take *[see Warnings and Precautions (5.1)]*.

Abuse and Misuse

Inform patients that the active ingredient of LUMRYZ is gamma-hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse *[see Warnings and Precautions (5.2)]*.

LUMRYZ REMS

LUMRYZ is available only through a restricted program called the LUMRYZ REMS *[see Warnings and Precautions (5.3)]*. Inform the patient of the following notable requirements:

- LUMRYZ is dispensed only by pharmacies that are specially certified
- LUMRYZ will be dispensed and shipped only to patients who are enrolled in the LUMRYZ REMS

LUMRYZ is available only from certified pharmacies participating in the program. Therefore, provide patients with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

Advise patients that alcohol and other sedative hypnotics should not be taken with LUMRYZ *[see Warnings and Precautions (5.1)]*.

Sedation

Inform patients that they are likely to fall asleep quickly after taking LUMRYZ (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization *[see Adverse Reactions (6.2)]*. Instruct patients that they should remain in bed following ingestion of their dose *[see Dosage and Administration (2.2)]*.

Food Effects on LUMRYZ

Inform patients that LUMRYZ should be taken at least 2 hours after eating.

Respiratory Depression and Sleep-Disordered Breathing

Inform patients that LUMRYZ may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea *[see Warnings and Precautions (5.4)]*.

Depression and Suicidality

Instruct patients to contact a healthcare provider immediately if they develop depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or

worthlessness, slowed thinking or impaired concentration, or suicidal ideation *[see Warnings and Precautions (5.5)]*.

Other Behavioral or Psychiatric Adverse Reactions

Inform patients that LUMRYZ can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur *[see Warnings and Precautions (5.6)]*.

Sleepwalking

Instruct patients that LUMRYZ has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs *[see Warnings and Precautions (5.7)]*.

Sodium Intake

Instruct patients that LUMRYZ contains a significant amount of sodium and patients who are sensitive to sodium intake (e.g., those with heart failure, hypertension, or renal impairment) should limit their sodium intake *[see Warnings and Precautions (5.8)]*.

Distributed By:

Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO

Medication Guide
LUMRYZ™ (LOOM rize)
(sodium oxybate)
for extended-release oral suspension, CIII

Read this Medication Guide carefully before you start taking LUMRYZ and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about LUMRYZ?

- LUMRYZ is a central nervous system (CNS) depressant. Taking LUMRYZ with other CNS depressants such as medicines used to make you fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including:
  - trouble breathing (respiratory depression)
  - low blood pressure (hypotension)
  - changes in alertness (drowsiness)
  - fainting (syncope)
  - death

  Ask your doctor if you are not sure if you are taking a medicine listed above.
- LUMRYZ is a federal controlled substance (CIII). The active ingredient of LUMRYZ is a form of gamma-hydroxybutyrate (GHB) that is also a federal controlled substance (CI). Abuse of illegal GHB, either alone or with other CNS depressants may cause serious medical problems, including:
  - seizure
  - trouble breathing (respiratory depression)
  - changes in alertness (drowsiness)
  - coma
  - death

  Call your doctor right away if you have any of these serious side effects.
- Anyone who takes LUMRYZ should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking LUMRYZ. Those activities should not be done until you know how LUMRYZ affects you.
- Keep LUMRYZ in a safe place to prevent abuse and misuse. Selling or giving away LUMRYZ may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.
- Because of the risk of CNS depression, abuse, and misuse, LUMRYZ is available only by prescription and filled through certified pharmacies in the LUMRYZ REMS. You must be enrolled in the LUMRYZ REMS to receive LUMRYZ. For more information on how to receive LUMRYZ, visit www.LUMRYZREMS.com. Before you receive LUMRYZ, your doctor or pharmacist will make sure that you understand how to use LUMRYZ safely and effectively. If you have any questions about LUMRYZ, ask your doctor or call the LUMRYZ REMS at 1-877-453-1029.

What is LUMRYZ?

LUMRYZ is a prescription medicine used to treat the following symptoms in adults with narcolepsy:

- sudden onset of weak or paralyzed muscles (cataplexy), or
- excessive daytime sleepiness (EDS)

It is not known if LUMRYZ is safe and effective in children.

Do not take LUMRYZ if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before taking LUMRYZ, tell your doctor about all medical conditions, including if you:

- have a history of drug abuse.
- have short periods of not breathing while sleeping (sleep apnea).
- have trouble breathing or have lung problems. You may have a higher chance of having serious breathing problems when taking LUMRYZ.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.

- have or had behavior or other psychiatric problems such as:
  - anxiety
  - seeing or hearing things that are not real (hallucinations)
  - feeling more suspicious (paranoia)
  - being out of touch with reality (psychosis)
  - acting aggressive
  - agitation
- have liver problems.
- are on a salt-restricted diet. LUMRYZ contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure.
- have heart failure.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if LUMRYZ can harm your unborn baby.
- are breastfeeding or plan to breastfeed. LUMRYZ passes into breast milk. You and your doctor should decide if you will take LUMRYZ or breastfeed.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives) or that may make you sleepy, such as some medicines to treat pain, anxiety, depression, or seizures. Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take LUMRYZ?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take LUMRYZ.
- Take LUMRYZ exactly as your doctor tells you to take it.
- LUMRYZ is taken by mouth 1 time at bedtime.
- Wait at least 2 hours after eating before taking LUMYRZ.
- After mixing LUMRYZ, take it within 30 minutes. Do not mix LUMRYZ with hot water.
- Take LUMRYZ at bedtime while you are in bed and lie down immediately. You should remain in bed after taking LUMRYZ.
- LUMRYZ can cause physical dependence and craving for the medicine when it is not taken as directed.
- Never change the LUMRYZ dose without talking to your doctor.
- LUMRYZ can cause sleep very quickly without feeling drowsy. Some people fall asleep within 5 minutes and most fall asleep within 15 minutes. The time it takes to fall asleep might be different from night to night.
- Falling asleep quickly, including while standing or while getting up from the bed, has led to falls with injuries that have required some people to be hospitalized.
- If you take too much LUMRYZ, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of LUMRYZ?

LUMRYZ can cause serious side effects, including:

- See **"What is the most important information I should know about LUMRYZ?"**
- **breathing problems, including:**
  - slower breathing.
  - trouble breathing.
  - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use LUMRYZ.
- **mental health problems, including:**
  - confusion
  - seeing or hearing things that are not real (hallucinations)
  - unusual or disturbing thoughts (abnormal thinking)
  - feeling anxious or upset
  - depression
  - thoughts of killing yourself or trying to kill yourself

- increased tiredness
- feelings of guilt or worthlessness
- difficulty concentrating

Call your doctor right away if you have symptoms of mental health problems, or a change in weight or appetite.

- **sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of LUMRYZ in adults include:

- nausea
- dizziness
- bedwetting
- headache
- vomiting

Side effects may increase when taking higher doses of LUMRYZ.

These are not all the possible side effects of LUMRYZ. **For more information, ask your doctor or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

How should I store LUMRYZ?

- Store LUMRYZ in the original packet prior to mixing with water. After mixing with water, store LUMRYZ in the mixing cup provided in each kit.
- Store LUMRYZ at room temperature between 68°F to 77°F (20°C to 25°C).
- LUMRYZ suspension should be taken within 30 minutes of preparation.
- When you have finished using the LUMRYZ packet, throw it away (dispose of it) in the trash.

LUMRYZ comes in a child-resistant package. **Keep LUMRYZ and all medicines out of the reach of children and pets.**

General information about the safe and effective use of LUMRYZ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LUMRYZ for a condition for which it was not prescribed. Do not give LUMRYZ to other people, even if they have the same symptoms. It may harm them.

You can ask your pharmacist or doctor for information about LUMRYZ that is written for health professionals.

What are the ingredients in LUMRYZ?

Active ingredients: sodium oxybate

Inactive ingredients: carrageenan, hydrogenated vegetable oil, hydroxyethyl cellulose, magnesium stearate, malic acid, methacrylic acid copolymer, microcrystalline cellulose, povidone, xanthan gum.

Distributed By:

Avadel CNS Pharmaceuticals, LLC Chesterfield, MO 63005

For more information, go to www.LUMRYZREMS.com or call the LUMRYZ REMS at 1-877-453-1029.

This Medication Guide has been approved by the U.S. Food and Drug Administration Approved: MM/YYYY

Instructions for Use
Instructions for use

Avadel

Lumryz (sodium oxybate) for extended-release oral suspension, CIII 1 packet per dose

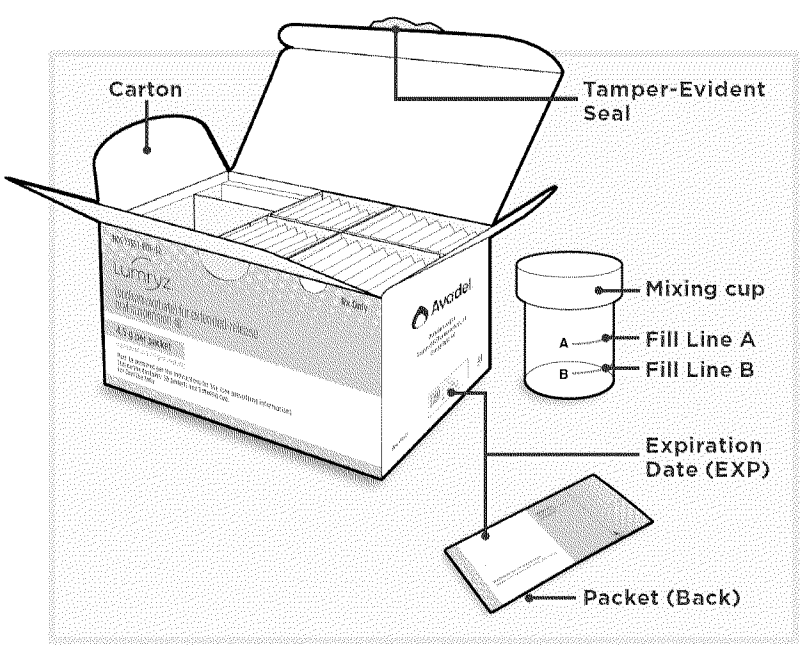
This Instructions for Use contains information on how to take LUMRYZ. Read this Instructions for Use before taking LUMRYZ and each time you get a refill. There may be new information.

This information does not take the place of talking to your doctor about your medical condition or your treatment. **If you have questions, please talk with your doctor.**

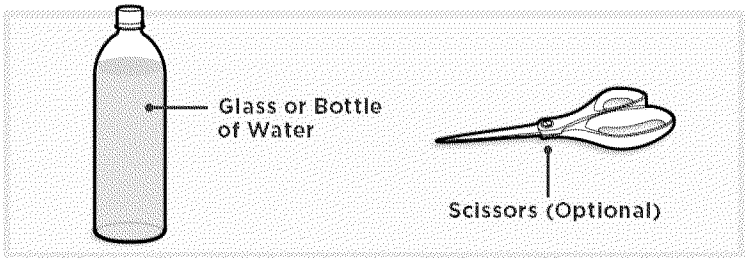
Important information when taking LUMRYZ

- Take 1 packet of LUMRYZ each day at bedtime.
- Avoid getting out of your bed after taking LUMRYZ. Some people fall asleep within 5 minutes of taking LUMRYZ and most will fall asleep within 15 minutes. The time it takes you to fall asleep might be different from night to night.
- Medicines that cause sleepiness should not be used while taking LUMRYZ. .
- **Do not** use LUMRYZ with alcohol.
- **Do not** drive or operate heavy machinery within 6 hours of taking LUMRYZ.
- Mix and take LUMRYZ within 30 minutes. If not taken within 30 minutes of mixing, throw it away (dispose of it) and prepare a new dose.

LUMRYZ carton and contents



Additional supplies needed



How should I store LUMRYZ?

- Store LUMRYZ and all medicines out of the reach of children.
- Store LUMRYZ at room temperature, between 68°F to 77°F (20°C to 25°C).
- Store LUMRYZ in a clean and dry place.

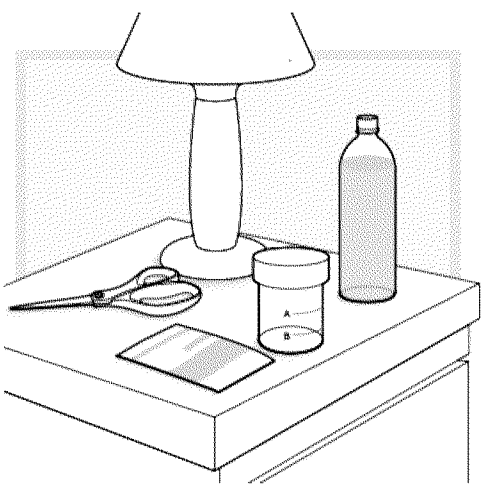
Before using LUMRYZ

- Before using a new LUMRYZ carton, check the tamper-evident seal on the carton lid to make sure it is not missing or broken.
- **Do not** use if the tamper-evident seal is missing or broken.
- Check the expiration date (EXP) on the LUMRYZ carton.
- **Do not** use LUMRYZ after the expiration date (EXP) on the label has passed.
- Open the LUMRYZ carton by tearing the tamper-evident seal with your hands or by using a pair of scissors.

Before each use

- Clean the mixing cup by rinsing it with water and letting it dry before each use.
- **Do not** use a measuring device other than the mixing cup that comes in your LUMRYZ carton to measure and take a dose of LUMRYZ.
- Check the expiration date (EXP) on the packet label. **Do not** use the LUMRYZ packet after the expiration date (EXP) has passed.

Important: Make sure to prepare LUMRYZ at bedside.



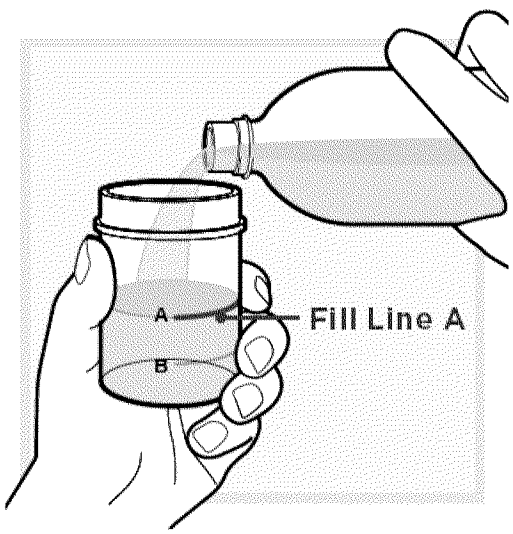
Gather the following supplies and place them on a flat surface at your bedside:

- 1 bottle or glass of water (1/3 cup). Do not use hot water.
- 1 LUMRYZ packet
- 1 clean mixing cup
- 1 pair of scissors (optional)

Mix the LUMRYZ solution at your bedside

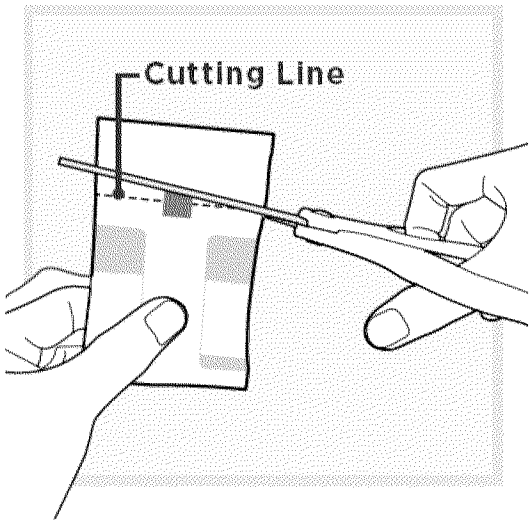
1.) At your bedside, open the mixing cup by twisting the cap to the left (counter-clockwise) to remove it.

2.) Fill the mixing cup with water up to **Fill Line A** (top line) and set the mixing cup down on a flat surface.



3.) Open 1 packet:

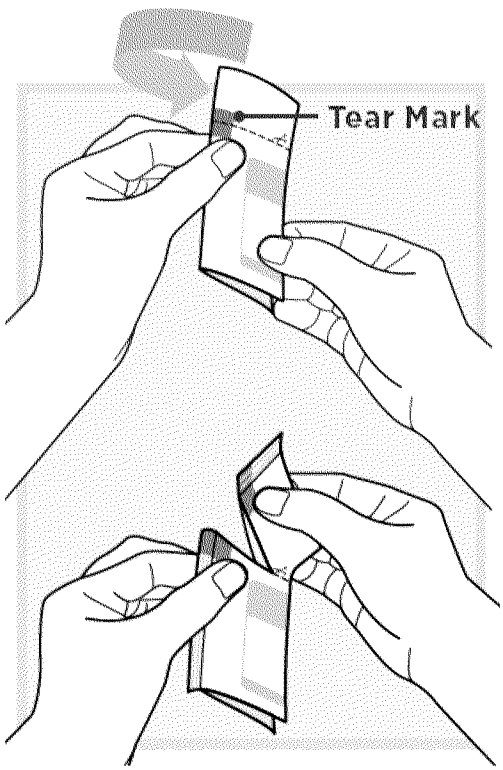
Use scissors to cut open the packet along the **Cutting Line**, located on the back of the packet.



-or-

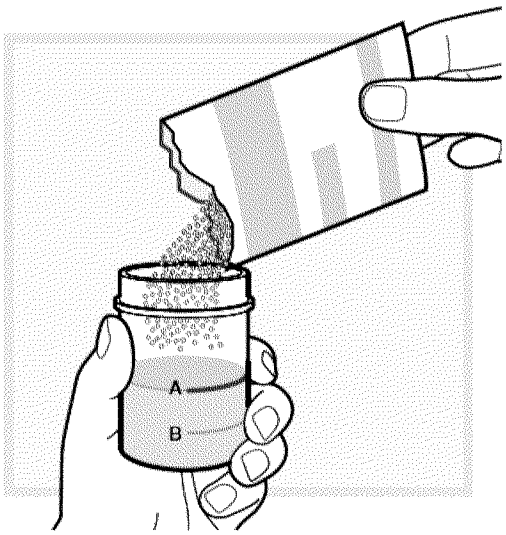
Fold the packet in half at the gray **Tear Mark** located on the back of the packet.

Tear the packet open with your hands.

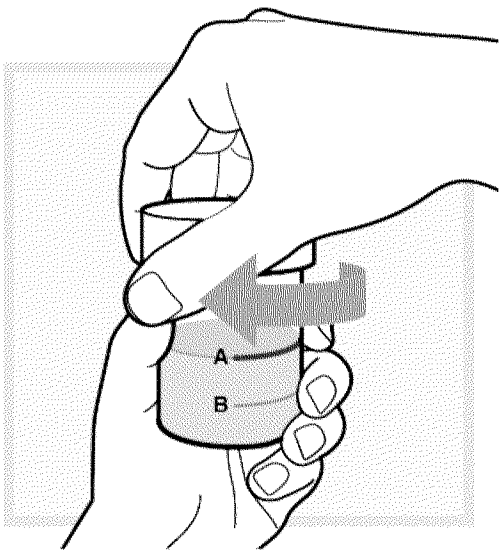


4.) Pour the entire content from the packet into the water-filled mixing cup.

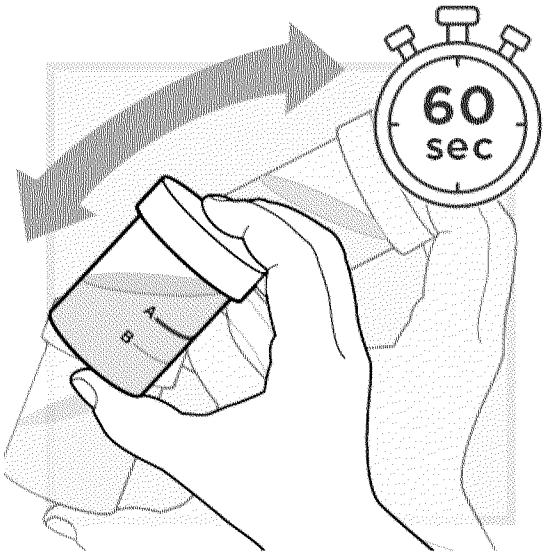
Make sure there is no powder left in the packet.



5.) Close the mixing cup by twisting the cap to the right (clockwise) until firmly closed.

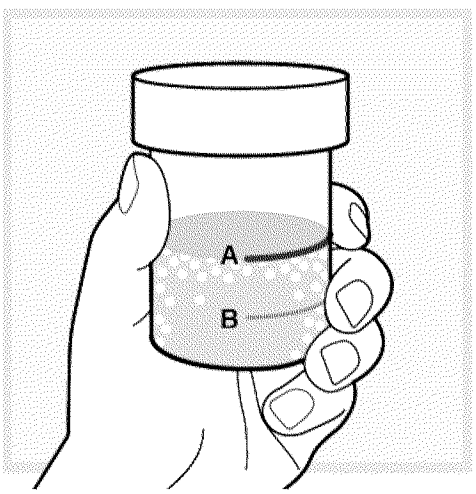


6.) Mix the water and powder solution by shaking the closed mixing cup well for at least **60 seconds (1 minute)**.



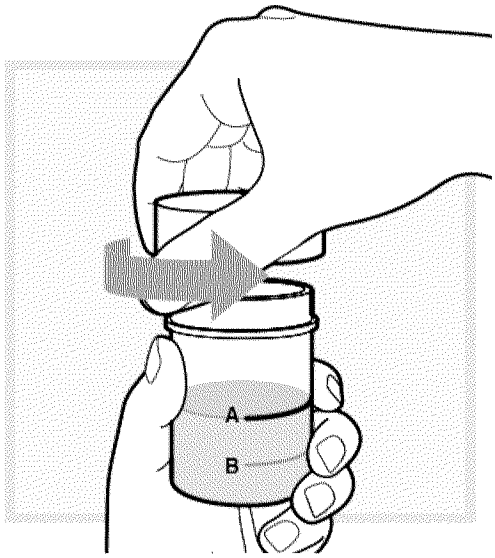
7.) Make sure the solution is mixed thoroughly.

The mixed solution will appear slightly milky with some lumps.



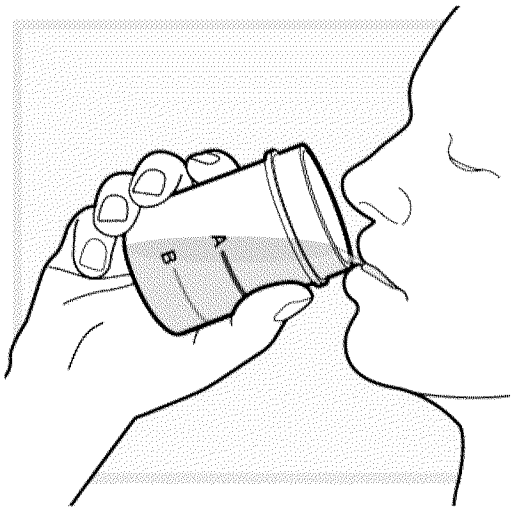
Take the LUMRYZ solution at your bedside

8.) Open the mixing cup by twisting the cap to the left (counter-clockwise) and remove it.



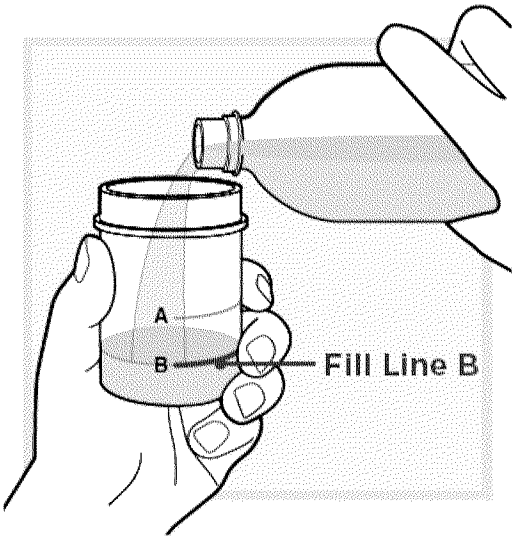
9.) While sitting in bed drink the mixed solution within **30 minutes** of mixing.

Make sure to drink all the mixed solution in the mixing cup.

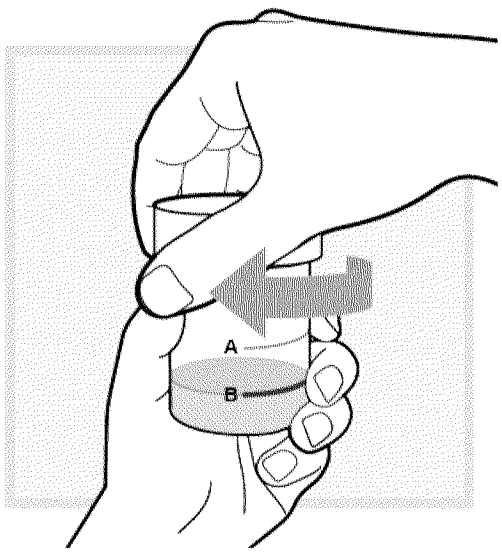


10.) Immediately refill your mixing cup with water up to **Fill Line B** (lower line) to mix in any medicine left in the mixing cup.

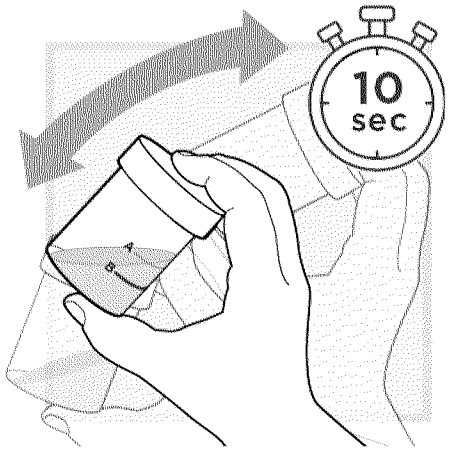
Do not open another packet of LUMRYZ. Take only 1 packet each day at bedtime.



11.) Close the mixing cup by twisting the cap to the right (clockwise) until firmly closed.



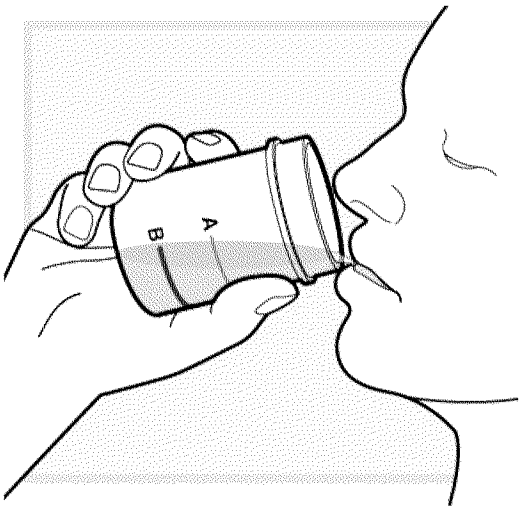
12.) Shake well again for **10 seconds**.



13.) Open the mixing cup by twisting the cap to the left (counter-clockwise) and remove it.

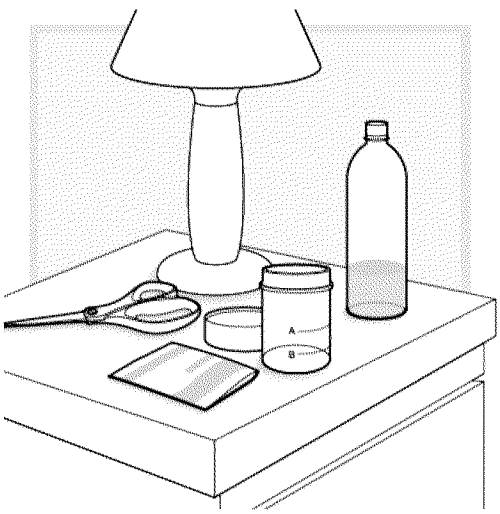
14.) Drink the mixed solution immediately after mixing.

Make sure to drink all the mixed solution in the mixing cup.



15.) Leave the empty mixing cup at your bedside and immediately lie down to go to sleep.

Avoid getting out of your bed after taking your dose.

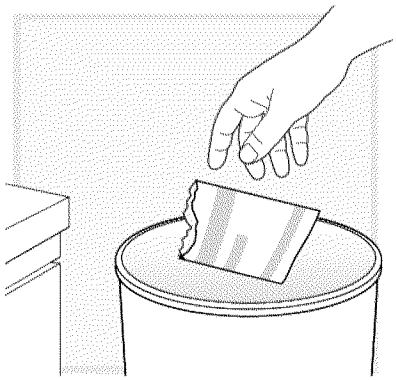


Continue to Step 16

How do I throw away (dispose of) LUMRYZ?

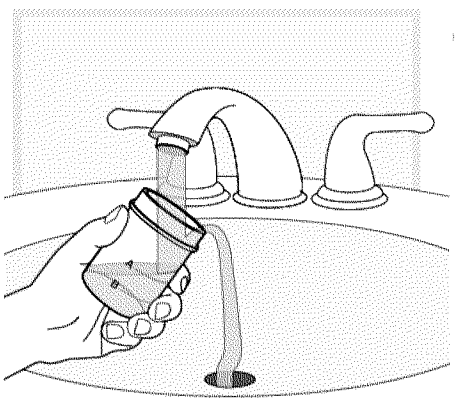
16.) The next day, place the empty LUMRYZ packet in the trash.

If any LUMRYZ remains in the packet, rinse it down the sink prior to disposal.



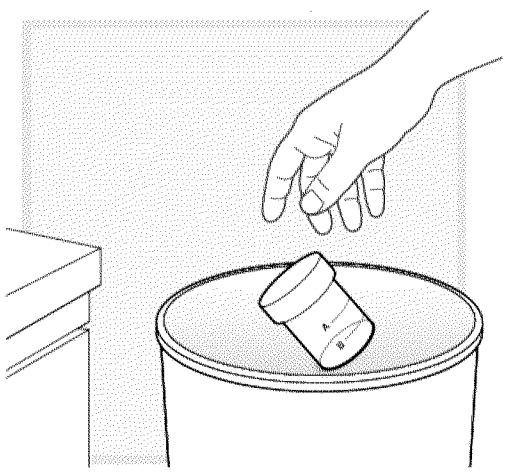
17.) Empty any unused LUMRYZ down the sink drain the next day.

Clean the mixing cup by rinsing it with water and letting it dry before each use.



After you finish all of the packets in your LUMRYZ carton

After you have finished your last packet in the carton, throw away the rinsed mixing cup in the trash.



If you have additional questions about LUMRYZ, talk with your doctor.

You can also contact:
Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO 63005 USA

For more information on LUMRYZ,
visit www.lumryz.com or call
888-8AVADEL (888-828-2335).

Lumryz™ (sodium oxybate) for extended-release oral suspension ℂ **1 packet per dose**

Manufactured for:
Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO 63005 USA

Avadel™

This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Approved: ##-####

EXHIBIT 6

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

OPENING EXPERT REPORT OF ALEXANDER M. KLIBANOV, PH.D.

I. QUALIFICATIONS

1. I, Alexander M. Klibanov, Ph.D., expect to testify on behalf of the Defendant Avadel CNS Pharmaceuticals, LLC ("Avadel") in the above-captioned litigation against Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (together, "Jazz") as an expert witness regarding the validity of certain claims of U.S. Patent Nos. 11,077,079 (the "'079 Patent") and 11,147,782 (the "'782 Patent").

2. I am currently a Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology ("M.I.T."), where I taught and conducted research for over 40 years. From 2014 to 2019 (and also from 2007 to 2012), I held the Novartis Endowed Chair Professorship at M.I.T. From 2012 to 2014, I held the Roger and Georges Firmenich Endowed Chair Professorship in Chemistry. Prior to that, I was a Professor of Chemistry and a Professor of Bioengineering at M.I.T., positions I held from 1988 and 2000, respectively. From 1979 to 1988, I was an Assistant Professor, then Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences (formerly the Department of Nutrition and Food Science) at M.I.T.

3. I obtained my M.S. degree in Chemistry from Moscow University in Russia in 1971 and my Ph.D. in Chemical Enzymology from the same University in 1974. Thereafter, I was a Research Chemist at Moscow University's Department of Chemistry for three years. From 1977 to 1979, following my immigration to the United States, I was a Post-Doctoral Associate at the Department of Chemistry, University of California in San Diego.

4. Over the last 50+ years as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of chemistry, including biological, pharmaceutical formulation, general, and medicinal.

5. During my career, I have earned numerous prestigious professional awards and distinctions for my work. For example, I was elected to the U.S. National Academy of Sciences (considered among the highest honors that can be given to an American scientist) and also to the U.S. National Academy of Engineering (considered among the highest honors that can be given to an American engineer). I am also a Founding Fellow of the American Institute for Medical and Biological Engineering and a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters). In addition, I have received the Arthur C. Cope Scholar Award, the Marvin J. Johnson Award, the Ipatieff Prize, and the Leo Friend Award, all from the American Chemical Society, as well as the International Enzyme Engineering Prize.

6. I currently serve on the Editorial Boards of a dozen scientific journals, including "Open Journal of Pharmacology," "Applied Biochemistry and Biotechnology," "Nanocarriers," "Open Access Academic Books in Chemistry," "Biotechnology and Bioengineering," "Journal of Biological Chemistry and Molecular Pharmacology," "Recent Patents in Biotechnology," "Current Pharmaceutical Biotechnology," "Archives of Medical Biotechnology," and "International Journal of Drug Design, Delivery, and Safety."

7. I have published over 315 scientific papers in various areas of chemistry and am also a named inventor of 32 issued United States patents plus many pending ones. I have given over 370 invited lectures at professional conferences, universities, and corporations all over the world, many dealing with pharmaceutical formulations and medicinal chemistry. Of particular relevance to the technical issues in the present litigations is my extensive experience with oral dosage forms of various drugs, including their both immediate and modified release formulations. According to a recent Stanford University-led study, the overall impact of my published work, places me in the top 0.01% of all scientists in the world.

8. In addition to my research and teaching activities at M.I.T., I have consulted for numerous pharmaceutical, medical device, and biotechnology companies. I have also founded six pharmaceutical companies and have been on the scientific advisory boards and/or boards of directors of those companies and of many others. A number of these industrial and corporate activities have dealt specifically with oral dosage forms and/or controlled release pharmaceutical formulations.

9. My curriculum vitae, attached hereto as Exhibit 1, summarizes my education and professional experience. Included in it is a list of my publications and patents.

10. Exhibit 2 is a list of all other lawsuits in which, during the previous five years, I testified as an expert at trial and/or by deposition.

11. I am being compensated at the rate of $975 per hour for time spent working on this engagement. Neither the amount of my compensation nor the fact that I am being compensated for my time has affected the opinions that I have given in this expert report. My compensation is in no way dependent on the outcome of these litigations.

II. SUMMARY OF OPINIONS

12. Counsel for Avadel ("Counsel") has asked me to form and provide opinions regarding the validity of the asserted claims of the '079 and '782 Patents (collectively, the "Resinate Patents"). Specifically, I have been asked to analyze the issue of obviousness of those asserted claims. Jazz addressed the following claims in its Final Infringement Contentions for the Resinate Patents: claims 1-3, 5-12, and 14-18 of the '079 Patent, and claims 1-24 of the '782 Patent (collectively, the "Asserted Claims of the Resinate Patents.").

13. The opinions presented herein have been formed by me to a reasonable degree of scientific certainty based on my education, training, and professional knowledge and experience,

30. I understand from Counsel that Jazz has asserted claims 1-3, 5-12, and 14-18 of the '079 Patent against Avadel ("Asserted Claims of the '079 Patent"). Claims 1 and 10 of the '079 Patent are independent. Claims 2-3, 5-9, 11-12, and 14-18 depend on claim 1 or claim 10.

31. Claim 1 is:

> "A method of treating narcolepsy in a patient in need thereof, the method comprising:
>
> (a) administering a single daily dose to the patient,
>
> (b) the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate,
>
> (c) wherein the administering comprises: opening a sachet containing a solid oxybate formulation,
>
> (d) mixing the formulation with water, and orally administering the mixture to the patient,
>
> (e) wherein the oxybate formulation comprises an immediate release component and a controlled release component."

32. Claim 10 is:

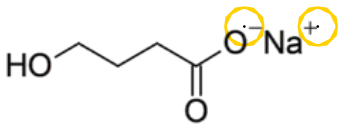
> "A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:
>
> administering a single daily dose to the patient,
>
> the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate,
>
> wherein the administering comprises: opening a sachet containing a solid oxybate formulation, mixing the formulation with water, and orally administering the mixture to the patient,
>
> wherein the oxybate formulation comprises an immediate release component and a controlled release component."

A. Scope and Content of the Prior Art

33. As stated in the legal section above, I understand from Counsel that prior art may be in the form of, among other things, a patent or patent application, a journal publication, a public

statement, or a product. The references below are pertinent prior art because they are within the field of endeavor of the Resinate Patents and, as described in detail below, the Liang 2006, Lebon 2013, and Allphin 2012 references address the problem facing the inventors of the '079 Patent, which was to have a single nightly dose of GHB that would include "a sufficient amount of GHB [] present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration." '079 Patent at col. 4, ll. 20-24.

34. A POSA would have known at the time of the '079 Patent's priority date that Xyrem [i.e., sodium gamma-hydroxybutyrate or Na GHB, whose chemical structure is depicted at the end of this paragraph] was the only sodium oxybate drug approved by the United States Food and Drug Administration ("FDA") for the treatment for cataplexy and excessive daytime sleepiness (EDS) in narcolepsy. Xyrem is a sodium oxybate aqueous solution to be administered orally twice nightly. XYREM® (sodium oxybate) oral solution label was revised in April 2014 ("Xyrem 2014 Label"). However, a POSA would also have been aware of additional prior art references that discuss formulating sodium oxybate, or oxybate salts in general, some in a single daily dose, as discussed below.



1. Liang 2006

35. Liang 2006 is U.S. Patent Application Publication 2006/0210630 titled "Controlled Release Compositions of Gamma-Hydroxybutyrate." The publication is cited on the face of the '079 Patent. In Liang 2006, the inventors Likan Liang et al. report on the results from altering the delivery profile of GHB to provide for a "convenient once nightly or once daily dosing regiment

[sic] for the oral delivery of one or more gamma-hydroxybutyric acid salts to an animal." Liang 2006 at ¶ 12.

36. Liang 2006 discusses a variety of challenges known to affect GHB formulation. It states that "[s]odium gamma-hydroxybutyrate is highly [water-]soluble, hygroscopic, and strongly alkaline." *Id.* at ¶ 5. It also states that "the therapeutic dose [of Na GBH] is normally very high," "[f]or example, a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients." *Id.* Liang 2006 also states that the current twice-nightly dosing regimen requires patients to "take an initial dose of sodium gamma-hydroxybutyrate around bedtime and [] wake up four hours later to take a second dose. Such a dose regimen is rather inconvenient." *Id.* at ¶ 3.

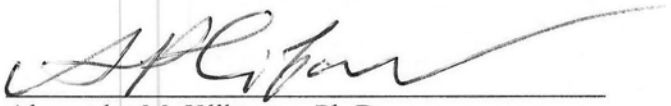
37. Liang 2006 discloses that "[i]n one of the preferred embodiments, the composition comprises multiple delayed release pellets or beads (used interchangeably herein) and an immediate release component." *Id.* at ¶ 29. An immediate release component combined with pH sensitive delayed/controlled release particles "can conveniently replace the nightly multidose regimen of the existing commercial product," which eliminates the need for a patient "to wake up and take a second dose during the night." *Id.* at ¶ 36. The immediate release component can be in the form of, for example, "a sachet." *Id.* at ¶ 45. The immediate release and controlled release components can also be pre-mixed. *Id.* at ¶ 47 ("[T]he immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed/controlled release particles"); *id.* at ¶ 48 ("[T]he immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion.").

2. Lebon 2013

38. Lebon 2013 is U.S. Patent No. 8,529,954, titled "Composition based on gamma-hydroxybutyric acid." In Lebon 2013, the inventors Christophe Lebon and Pascal Suplie describe granules of "gamma-hydroxybutyric acid" or "its pharmaceutically acceptable salt[]." Lebon

315. Finally, with respect to any of the Asserted Claims of the Resinate Patents, I am aware of no objective indicia of non-obviousness to affect my foregoing obviousness conclusions.

Dated: January 17, 2023



Alexander M. Klibanov, Ph.D.

EXHIBIT 7

Hornykiewicz, O. (1963). Die topische logalization und des Verhalten von Noradrenalin und Dopamin (3-Hydroxytyramin) in der Substantia nigra der normalen und Parkinsonkranken Menschen. *Wien. Klin. Wochschr.* 75: 309.
Huntington, G. (1872). On chorea. *The Medical and Surgical Reporter* 26: 317.
Jacobson, G., Baldessarini, R. J., and Manschreck, T. (1974). Tardive and withdrawal dyskinesia associated with haloperidol. *Am. J. Psychiat.* 131: 910.
Kazamatsuri, H., Chien, C., and Cole, J. L. (1973). Long-term treatment of tardive dyskinesia with haloperidol and tetrabenazine. *Am. J. Psychiat.* 130: 479.
Klawans, H. L., Jr. (1973). The pharmacology of tardive dyskinesia. *Am. J. Psychiat.* 130: 82.
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The Effects of γ-Hydroxybutyrate on Sleep

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Sodium γ-hydroxybutyrate (GHB) is a remarkably safe and nontoxic hypnotic agent which is reported to be free of addicting properties. It is also a normal metabolite of the mammalian nervous system. We examined its effects on the sleep-EEG of eight patients with histories of impaired sleep, as a prelude to a more detailed study of its clinical potential. Sleep induced with GHB was indistinguishable subjectively from natural sleep as well as by behavioral and electroencephalographic criteria. Unlike most synthetic hypnotics, GHB increased delta sleep and did not suppress REM sleep. It shortened the REM sleep latency and shifted REM sleep into the first third of the night. On one occasion it induced a sleep onset REM period which was experienced as an attack of sleep paralysis. Withdrawal was simple; there was no REM sleep rebound and sleep patterns immediately returned to their pre-drug form. Its major clinical drawback was its short duration of action: its hypnotic effect lasting only 2 to 3 hr. We suggest that GHB may serve as the prototype for a new class of hypnotic compounds derived from natural sources and capable of activating the neurological mechanisms of normal human sleep.

INTRODUCTION

This study was undertaken to explore the usefulness of sodium γ-hydroxybutyrate in the treatment of insomnia. γ-Hydroxybutyrate (GHB) is a naturally occurring soporific; it is a normal constituent of the mammalian nervous system where it is concentrated in the midbrain and hippocampal areas (Roth, 1970). Its metabolic origin is uncertain, but it may be derived from γ-aminobutyric acid (Roth and Giarman, 1969).

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GHB's attractiveness as a potential clinical hypnotic is based on a number of factors. First, it is a remarkably safe and nontoxic substance (Vickers, 1969). Its LD_{50} is 5 to 15 times the coma-inducing dose, and death, when it occurs, is thought due to sodium intoxication rather than to the active principle. Second, development of tolerance to its hypnotic effect has not been demonstrated in long-term animal studies (Vickers, 1969). Finally, in doses of approximately 30 mg/kg, it induces the natural stages of sleep (Yamada *et al.*, 1976). When given to healthy human subjects at bedtime, the normal sequence of NREM and REM sleep occurs; delta sleep tends to be prolonged, and REM sleep appears after a normal latency.

In contrast, the usefulness of most synthetic hypnotics is limited by the development of tolerance and by their high potential for abuse and self-poisoning. REM and delta sleep are usually suppressed, and the rebound of REM sleep upon drug withdrawal is associated with disturbed, nightmarish sleep – a factor which likely discourages attempts to discontinue the use of these drugs (Oswald and Priest, 1965).

These potential clinical advantages led us to study the effects of GHB in a heterogenous group of eight patients with long-standing histories of impaired sleep. Each patient was studied by means of subjective sleep reports and consecutive all night EEG-sleep recordings. Our study was designed as a preliminary to a more detailed evaluation of the effectiveness of GHB in the treatment of the individual forms of insomnia.

METHODS

Five men and 3 women, ranging in age from 34 to 60 years (mean age = 51 years), were studied. A resume of each subject's clinical history is given in the section on results. All had previously been treated for insomnia, but with the exception of one narcoleptic subject who continued on 10 mg t.i.d. of *d*-amphetamine, all were drug-free for at least 3 weeks before they were studied. Informed consent was obtained from each subject after the nature of the procedure had been fully explained.

Each patient was studied for eight or nine consecutive nights in the sleep laboratory with all-night recordings of the EEG, EOG, EMG, and EKG. The patients were asked not to sleep during the day and to refrain from all alcoholic beverages during the study. The first 3 nights were placebo nights. On the following 3 or 4 nights, each patient was given 1.0 to 4.5 g of γ-hydroxybutyrate orally (15.0-55.0 mg/kg). The last 2 nights were again placebo nights. Most often, on the first drug night, a 3-g dose was given, and depending on the electroencephalographic response, the dose of the drug was varied on the following nights. Our objective was to induce sleep as defined by the appearance of normal EEG-sleep patterns and to minimize the duration of the moderate to high-

voltage theta and delta rhythms induced by high doses of GHB (see Fig. 1). These slow-wave patterns have been previously described (Schneider *et al.*, 1963; Metcalf *et al.*, 1966; Ohye *et al.*, 1966). We arbitrarily scored these EEG patterns as stages X, Y, or Z depending upon the abundance of theta or delta frequency activity exceeding 75 μv (C_4-ear). In stage X, 50% or more of each epoch was occupied by moderate to high-voltage theta rhythms. This merged with stage Y in which the theta waves were progressively replaced by moderate to high-voltage delta waves. When more than 20% of each epoch, but less than 50% was occupied by such moderate to high-voltage delta waves, the epoch was scored as stage Y. When more than 50% of each epoch was occupied by moderate to high-voltage delta waves, the epoch was scored as stage Z. Stage Z was scored only when it occurred in the sequence X, Y, and Z. Otherwise it was often difficult to distinguish it from stage 4. Scoring according to international criteria (Rechtschaffen and Kales, 1968) commenced when well-formed sleep spindles or REM sleep appeared.

The drug or placebo was given at lights out, usually about 11.00 PM, and sleep was recorded continuously until 7.00 AM. The patients were not told on which nights they were given the drug. γ-Hydroxybutyrate was obtained from Laboratoire Egic of Paris, France, who market this drug as a banana flavored syrup, Gamma-OH, for oral use. The placebo consisted of 5 cc of banana flavoring in water.

About ½ hr after awakening, each patient was asked to assess the quality of his previous night's sleep. The sleep self-rating scale of Platman and Fieve (1970) was used. The quality of sleep was rated on a scale of zero to six: zero indicated a very poor night of sleep and six a very good night. Each patient was also asked to guess if his sleep had been drug induced.

Recordings were done with a Grass Model 6 electroencephalograph. Paper speed was 15 mm/sec and scoring was done on each 20-sec epoch. The total recording time was measured from the time the drug or placebo was given, i.e., lights out, until 7.00 AM. The total sleep time was calculated by subtracting the period of wakefulness from the total recording time. Sleep latency was calculated as the time from lights out until initial stage 2 of 1 min or more in duration. REM latency was from initial stage 2 until the first REM sleep period of 1 min or more in duration. On some drug nights REM sleep occurred before stage 2. On these nights, sleep latency was measured from lights out until the beginning of the first REM sleep period of 1 min or more in duration. The sleep latency was not measured in the narcoleptic patient who often fell asleep as the electrodes were being applied. The sleep latency could also not be measured accurately on one night in another subject after a 3-g dose of GHB obscured the normal EEG-sleep patterns (Fig. 1, night 4). REM density was measured as the percentage of 20-sec REM sleep epochs containing one or more rapid eye movements. Delta sleep was calculated by summing stage 3 and 4 sleep. The time spent in each sleep stage in each third of the night was measured after first dividing the total recording time into three equal periods.

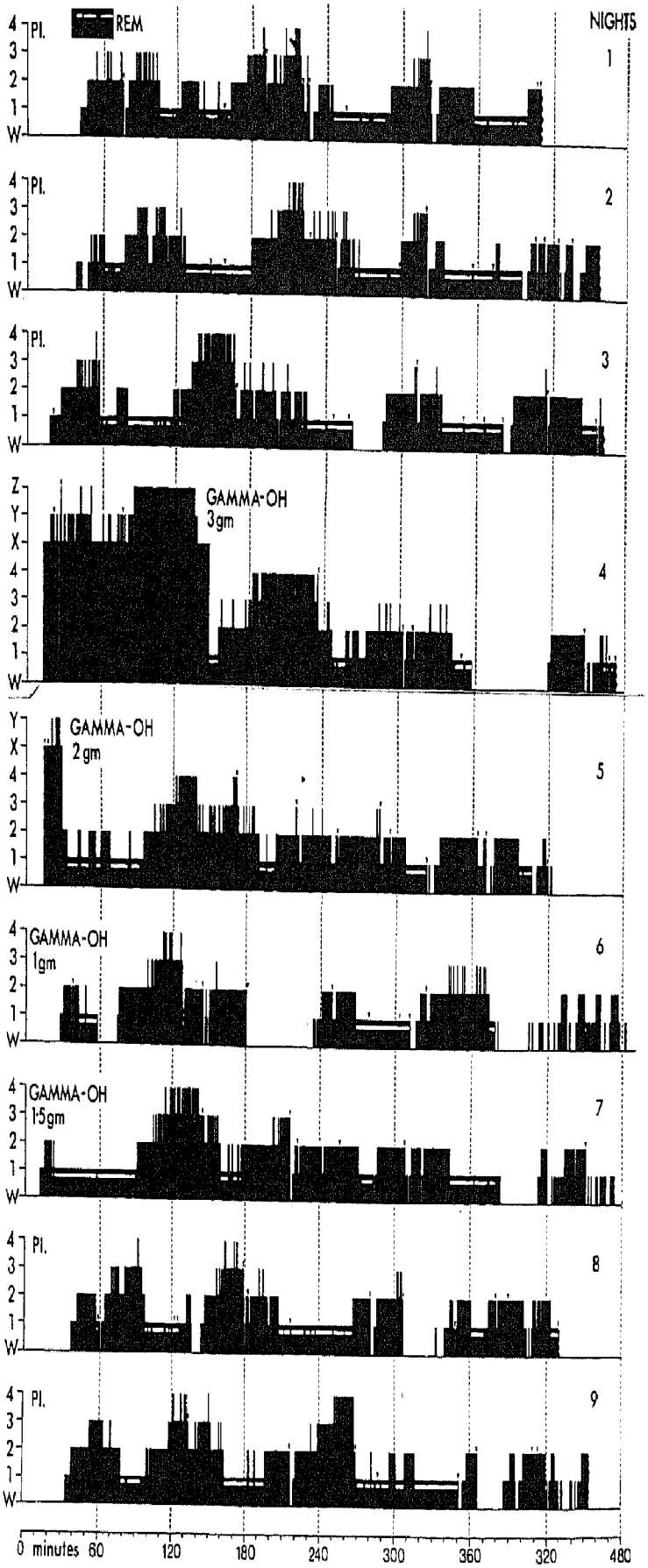

Fig. 1. Case I sleep patterns. In Figs. 1 and 2 the vertical axes indicate the stages of sleep. The horizontal white bars at the level of stage 1 indicate REM sleep and arrows above each night's sleep pattern indicate movement arousals. Consecutive nights of sleep are shown in decending order.

RESULTS

A. Clinical Data

Case I

A 34-year-old woman with an 8-year history of recurrent depressions. For these she had received ECT, tricyclic antidepressants, neuroleptics, and numerous hypnotics. She was withdrawn from daily doses of chlorprothixene (200 mg), methyprylon (300 mg), and flurazepam (30 mg) 25 days before the sleep study. Her mood at the time of the study was normal. Her sleep patterns during the study are shown in Fig. 1. In the data given below, P indicates placebo.

Night	1	2	3	4	5	6	7	8	9
Dose (mg/kg)	P	P	P	47.09	31.39	15.69	24.54	P	P
Was sleep drug induced?	yes	yes	yes	yes	yes	no	yes	no	no
Sleep Quality	3	4	3	4	4	2	4	2	3

Case II

A 60-year-old woman with a 16-year history of manic-depressive psychosis. At the time of the study she had been off all drugs for more than 5 months and her mood was normal. Her sleep patterns during the study are shown in Fig. 2.

Night	1	2	3	4	5	6	7	8
Dose (mg/kg)	P	P	P	45.45	45.45	45.45	P	P
Was sleep drug induced?	no	no	no	no	yes	yes	no	no
Sleep quality	3	3	3	4	5	5	3	5

Case III

A 60-year-old man with a long-standing history of chronic anxiety and alcoholism. He had been treated with a wide variety of anxiolytics, antidepressants, and hypnotics with only moderate success. At the time of the study he had been off all drugs, including ethanol, for more than 1 month and was mildly anxious.

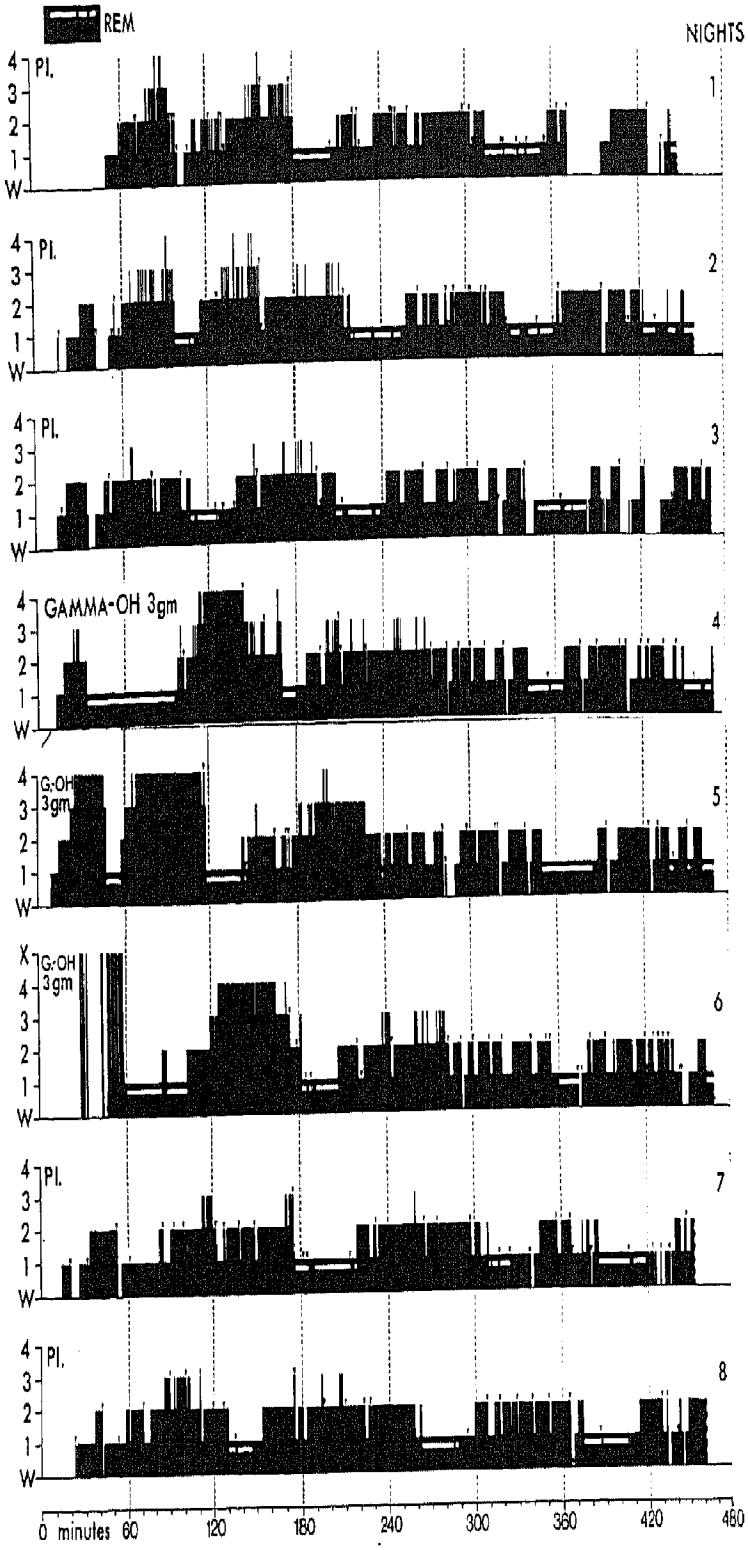

Fig. 2. Case II sleep patterns. See caption to Fig. 1.

Night	1	2	3	4	5	6	7	8
Dose (mg/kg)	P	P	P	50.00	50.00	50.00	P	P
Was sleep drug induced?	no	no	yes	yes	yes	no	yes	yes
Sleep quality	3	3	4	4	5	5	4	4

Case IV

A 50-year-old woman with a 12-year history of recurrent depressions for which she had been treated with ECT and tricyclic antidepressants. At the time of the study she had been off all drugs for 3 weeks and was complaining of depression and fatigue.

Night	1	2	3	4	5	6	7	8
Dose (mg/kg)	P	P	P	52.08	26.04	17.36	P	P
Was sleep drug induced?	no	no	no	yes	yes	yes	yes	yes
Sleep quality	5	4	5	3	3	4	4	4

Case V

A 57-year-old man with a 6-year history of mild bipolar mood swings now effectively controlled by lithium. At the time of the study he had been off all drugs for more than 1 month and his mood was normal.

Night	1	2	3	4	5	6	7	8	9
Dose (mg/kg)	P	P	P	36.23	54.34	36.23	36.23	P	P
Was sleep drug induced?	no	yes	yes	no	yes	no	no	no	yes
Sleep quality	2	4	5	4	3	5	5	4	4

Case VI

A 53-year-old man with a long-standing history of manic and depressive mood swings. These are well controlled by lithium. At the time of the study he had been off all drugs for more than 2 months and his mood was normal.

Night	1	2	3	4	5	6	7	8
Dose (mg/kg)	P	P	P	32.96	32.96	32.96	P	P
Was sleep drug induced?	no	yes	no	yes	yes	no	no	yes
Sleep quality	3	5	4	4	5	4	4	6

Case VII

A 59-year-old man with a long-standing history of chronic anxiety and depression. He has been treated with a wide variety of anxiolytics, antidepressants, and hypnotics without success. At the time of the study he had been off all drugs for more than 3 months and was complaining of anxiety and mild depression.

Night	1	2	3	4	5	6	7	8
Dose (mg/kg)	P	P	P	29.60	19.73	39.41	P	P
Was sleep drug induced	no	yes	yes	yes	no	yes	no	no
Sleep quality	3	2	4	4	4	4	3	4

Case VIII

A 37-year-old man with a 24-year history of narcolepsy. He suffers from attacks of narcolepsy and cataplexy, from sleep paralysis, hypnogogic and hypnopompic hallucinations, and nocturnal dysomnia. At the time of the study he was under adequate control on *d*-amphetamine 10 mg t.i.d.

Night	1	2	3	4	5	6	7	8
Dose (mg/kg)	P	P	P	44.77	22.38	14.92	P	P
Was sleep drug induced	no	no	no	no	yes	no	yes	yes
Sleep quality	2	5	3	4	4	4	4	4

Sleep-induction with GHB was indistinguishable on the whole from the normal process of falling asleep. The patients were unable to guess any better than chance whether or not they had received the drug ($p > 0.05$, ns). With higher doses, patients reported feeling dizzy, light-headed, and somewhat inebriated before falling asleep. Other patients reported feeling very weak before losing consciousness. One patient (Case II) a 60-year-old manic-depressive woman, actually reported being unable to move one night while still awake. Her sleep tracing revealed a progression from wakefulness through stage X to REM sleep (Fig. 2, night 6). Since patients may be conscious during stage X (Yamada *et al.*, 1967), the reported paralysis coupled with the sleep onset REM period suggests a GHB-induced attack similar to hypnagogic sleep paralysis seen with dissociative sleep onset REM periods in cases of compound narcolepsy (Rechtschaffen and Dement, 1967).

The quality of sleep was no different with GHB than it was on the pre-drug night or combined placebo nights ($p > 0.05$, ns). There were no hangovers on awakening.

B. Sleep-EEG Data

Each patient responded to GHB in a somewhat different manner. Nevertheless, an overall response pattern emerged. The earliest electroencephalographic effects were seen about 15 min after the oral administration of GHB. At this time, bursts of high-voltage theta waves appeared. The patients were still conscious, though often drowsy, during this period. The theta bursts frequently became continuous and then merged with NREM sleep. The first REM sleep period usually appeared after a short latency and was often prolonged in duration. REM periods lasting 45 min or longer were not uncommon. REM sleep was shifted to the first third of the night, but the total duration of REM sleep per night was not changed. GHB increased the duration of delta sleep, and typically a period of delta sleep followed a prolonged initial REM period (Figs. 1 and 2).

With higher doses, EEG patterns emerged which were different from those of normal sleep. These were scored as stages X, Y, and Z as described earlier. These stages were devoid of well-formed sleep spindles. It was usually possible to minimize the appearance of these EEG patterns by giving less drug. However, transitional patterns, especially between stages X, 1, 2, and REM did occur. At times, even lengthy periods of normal EEG sleep on drug nights would be interrupted by short intervals or bursts of moderate- to high-voltage theta or delta rhythms. This was most likely to occur at moments of arousal or preceding the shift to a lighter stage of sleep. For example, in a shift from stage 2 to stage 1 or wakefulness, a burst or an epoch or two of moderate to high-voltage theta and delta rhythms might intervene. At these times, the record was scored according to the EEG pattern which dominated 50% or more of the epoch.

The Mann-Whitney U-test was used to evaluate the data. For each sleep parameter, two different comparisons were made. First, night 3, the last pre-drug night, was ranked against the drug nights. Second, night 3 and the last two nights of each study, i.e., the combined placebo nights, were ranked against the drug nights. The first two nights of each study were considered adaptation nights. Since the eight patients represent a clinically heterogenous group, each sleep parameter was ranked separately for each patient. For the sake of comparison with other data in the sleep literature, the mean value and standard deviation of each sleep parameter averaged for all patients is also given (Table I).

1. *Total sleep time*

(a) drug nights *vs.* pre-drug night: $p > 0.05$, ns
(b) drug nights *vs.* combined placebo nights: $p > 0.05$, ns

Table I. Mean Value and Standard Deviation of Each Sleep Parameter

	Pre-drug night	Drug nights	Combined placebo nights
1. Total sleep time	396.08 ± 21.39 min (N = 8)	398.55 ± 34.04 min (N = 26)	384.12 ± 57.24 min (N = 24)
2. Sleep latency (based on 7 patients excluding the narcoleptic)	38.14 ± 25.59 min (N = 7)	28.07 ± 15.69 min (N = 22)	35.39 ± 19.28 min (N = 21)
3. Delta sleep	14.41 ± 17.45 min (N = 8)	34.14 ± 24.28 min (N = 26)	16.46 ± 18.90 min (N = 24)
4. Delta sleep in first third of night	5.66 ± 9.75 min (N = 8)	19.08 ± 17.69 min (N = 26)	5.94 ± 7.85 min (N = 24)
5. REM sleep	89.32 ± 32.14 min (N = 8)	75.58 ± 23.88 min (N = 26)	79.10 ± 24.69 min (N = 24)
6. REM percent in first third of night	23.11 ± 12.47% (N = 8)	37.40 ± 18.51% (N = 26)	26.54 ± 15.82% (N = 24)
7. REM latency (based on 7 patients excluding the narcoleptic)	65.81 ± 40.66 min (N = 7)	32.28 ± 34.36 min (N = 23)	66.79 ± 36.38 min (N = 21)
8. REM density	63.17 ± 8.77% (N = 8)	59.33 ± 12.73% (N = 26)	66.15 ± 7.40 min (N = 24)
9. REM density in first third of night	66.27 ± 12.11% (N = 7)	50.42 ± 20.09% (N = 25)	66.13 ± 12.51% (N = 22)
10. Movement time in first third of night	2.71 ± 2.19 min (N = 8)	1.87 ± 1.32 min (N = 26)	2.87 ± 2.11 min (N = 24)

2. *Sleep Latency* (based on 7 patients, excluding the narcoleptic)

(a) drug nights < pre-drug night: $p < 0.05$
(b) drug nights < combined placebo nights: $p < 0.05$

3. *Delta Sleep*

(a) drug nights > pre-drug night: $p < 0.01$
(b) drug nights > combined placebo nights: $p < 0.01$

4. *Delta Sleep in first third of night*

(a) drug nights > pre-drug night: $p < 0.01$
(b) drug nights > combined placebo nights: $p < 0.01$

5. *REM Sleep*

(a) drug nights *vs.* pre-drug night: $p > 0.05$, ns
(b) drug nights *vs.* combined placebo nights: $p > 0.05$, ns
(c) pre-drug night *vs.* first post-drug night: $p > 0.05$, ns
(d) pre-drug night *vs.* post-drug nights: $p > 0.05$, ns

6. *REM Percent in first third of night*

(a) drug nights > pre-drug night: $p < 0.01$
(b) drug nights > combined placebo nights: $p < 0.02$

7. *REM Sleep latency* (based on 7 patients, excluding the narcoleptic)

(a) drug nights < pre-drug night: $p < 0.01$
(b) drug nights < combined placebo nights: $p < 0.01$

8. *REM Density*

(a) drug nights *vs.* pre-drug night: $p > 0.05$, ns
(b) drug nights *vs.* combined placebo nights: $p > 0.05$, ns

9. *REM Density in first third of night*

(a) drug nights < pre-drug night: $p < 0.05$
(b) drug nights < combined placebo nights: $p < 0.05$

10. *Movement time in first third of night*

(a) drug nights *vs.* pre-drug night: $p > 0.05$, ns
(b) drug nights *vs.* combined placebo nights: $p > 0.05$, ns

DISCUSSION

The pharmacological properties of GHB, including its hypnotic and anesthetic actions, were first studied by Laborit and his collaborators (Laborit, 1964). Earlier, Sampson, Dahl, and White had demonstrated the soporific action of other short chain fatty acids (Sampson and Dahl, 1955; White and Sampson, 1956). With the advent of EEG sleep studies, Jouvet *et al.* (1961) and later Matsuzaki *et al.* (1964) found that short chain fatty acids such as butyrate, isovalerate, caproate, and GHB and its lactone induced both NREM and REM sleep in the cat and that prolonged periods of REM sleep often appeared after a short latency. Interest in GHB heightened when it was isolated from the mammalian nervous system and its derivation from γ-aminobutyric acid (GABA) was

experimentally demonstrated (Roth and Giarman, 1969). However, the normal rate of formation of GHB in the nervous system is not known. The liver, which can also synthesize GHB, has been considered as an alternate source (Roth, 1970).

The behavioral and electroencephalographic effects in GHB in humans have been described by a number of workers (Schneider *et al.*, 1963; Metcalf *et al.*, 1966; Ohye *et al.*, 1966; Yamada *et al.*, 1967). The paradoxical presence of theta and delta rhythms in waking subjects has been a consistent finding. In doses of 60-70 mg/kg, GHB produces coma lasting 1 to 2-hr (Vickers, 1969). No specific electroencephalographic changes mark the transition from wakefulness to coma and the EEG shows continuous irregular medium and high-voltage theta and delta rhythms at this time (Metcalf *et al.*, 1966). Lower doses produce a reversible somnolent state (Vickers, 1969).

In our hands, this somnolent state was readily reversed by such external stimuli as the call to wake up and such internal stimuli as a full bladder. The EEG showed the typical electrical patterns of NREM and REM sleep, and in distinction to the EEG patterns observed with other hypnotics (Kales *et al.*, 1970), delta sleep was prolonged and REM sleep was not suppressed. In fact, on many nights, GHB specifically activated the process of REM sleep. The state induced by GHB, then, closely resembles true sleep as defined by behavioral and electroencephalographic criteria (Dement, 1967).

GHB and REM Sleep

REM sleep rarely appears when GHB is given during the day and even when the drug is given at bedtime to healthy young adults, REM sleep appears only after a normal latency (Yamada *et al.*, 1967). This is in contrast to its effect in our patients in whom REM sleep was usually induced after an abnormally short latency (Figs. 1 and 2). Many of our patients, however, had nights with short REM sleep latencies even in the absence of the drug. An early REM sleep period, however, was a more consistent finding following GHB, and the average REM sleep latency fell from 65.81 min on placebo nights to 32.28 min with GHB.

Our patients all had histories of mental depression, recent drug withdrawal, or narcolepsy, conditions in which abnormally short REM latencies have previously been described (Kupfer and Foster, 1972; Oswald, 1968, 1971; Rechtschaffen and Dement, 1967). Since the first REM sleep period in man does not usually appear until about 90 min after the onset of sleep, the early REM sleep periods in these disorders have been attributed to abnormally low REM sleep thresholds caused by increased REM pressure or to ineffective REM inhibitory mechanisms.

It is noteworthy that clinical conditions with persistent overt early REM sleep periods are characterized by emotional lability, vulnerability to stress, and

disturbances in personality functioning. This is so for schizophrenia (Snyder, 1972), depression, narcolepsy, and withdrawal from centrally active drugs, particularly sedative drugs. The personality disturbances in narcolepsy, notably the high incidence of depression, have been emphasized recently by a number of workers (Broughton and Ghanem, 1975; Roth and Nevsimalova, 1975). In fact, Kupfer (1976) has recently proposed that persistent overt early REM periods are biological markers for primary depressive illness.

We suggest that GHB may be used to probe the REM threshold and that the early induction of a REM sleep period following the administration of GHB at bedtime is indicative of an abnormally low REM sleep threshold. This, in turn, implies a fault in the neurological mechanism controlling REM sleep. We suggest that this fault or defect expresses itself in a vulnerability to stress and that it is one of the abnormalities persisting in depressed patients following clinical recovery which predisposes them to a recurrence of their illness (Mendels and Chernik, 1975). For example, in the case illustrated in Fig. 2, GHB was given to a 60-year-old woman with a long-standing history of manic-depressive illness. At the time of the study she appeared clinically well and had been off all drugs for 5 months. Her REM sleep latency on placebo nights was within normal limits (average sleep latency: 106 mins). GHB markedly reduced the REM sleep latency and on one night even induced a sleep onset REM period. We would have predicted from this that she was not entirely well, and indeed a few months later, continuing off all medications, she became manic.

Narcolepsy and GHB

The induction with GHB of sleep paralysis in conjuction with a sleep-onset REM period was of considerable interest. This phenomenon has been uncommon but we have had a number of reports of sleep paralysis following the administration of GHB. These episodes are comparable to those occurring naturally in compound narcolepsy (Rechtschaffen and Dement, 1967) and encourage speculation that a disorder of GHB metabolism or of a pharmacologically analogous compound exists in narcolepsy.

Jouvet (1969) proposed that acetylcholine and a deaminated catabolite of serotonin trigger the noradrenergic mechanisms of REM sleep. Cholinergic mechanisms have been implicated specifically in the tonic events of REM sleep, the activation of the EEG and the decrease in muscle tone (Jouvet, 1972). GHB both increases the concentration of brain acetylcholine (Giarman and Schmidt, 1963) and shares structural features with it (Feldstein *et al.*, 1970). It is conceivable, then, that GHB acts by increasing acetylcholine levels at critical receptor sites within the nervous system or acts directly on these receptor sites themselves. GHB also shares structural features with the two serotonin catabolites reputed to have soporific properties: 5-hydroxytryptophol and 5-hydroxy

indoleacetaldehyde (Feldstein *et al.*, 1970). The aldehyde, in particular, has been mooted as the active sleep-inducing metabolite (Feldstein *et al.*, 1970; Sabelli and Giardina, 1970). However, GHB's structural similarity to these compounds may be less meaningful since neither actually has been shown to induce REM sleep and their exact role in sleep physiology remains undefined (Rechtschaffen *et al.*, 1968; Feldstein, 1973; Morgane and Stern, 1973).

THERAPEUTIC APPLICATIONS OF GHB

GHB's major clinical disadvantage is its short duration of action. In cases of severe insomnia we have had to repeat the drug two or three times during the night to maintain sleep. Although GHB shortened the sleep latency, the practical significance of this is not clear since our subjects fell asleep after about ½-hr even without the drug. GHB, however, did not suppress REM sleep, and there was no REM sleep rebound after its withdrawal. The absence of a REM rebound on withdrawal likely makes it a less habituating hypnotic than other drugs (Oswald and Priest, 1965). We see it as potentially useful for the large number of patients who have difficulty falling asleep but who once asleep are able to remain so.

GHB may also be useful for certain disorders complicated by specific types of insomnia. For example, we used GHB to treat the insomnia of a small group of narcoleptic patients (Broughton and Mamelak 1975). We were interested in the relationship between their impaired nocturnal sleep (Rechtschaffen *et al.*, 1963) and their daytime symptomatology. We gave the drug in repeated doses during the night. GHB increased the total nocturnal sleep time and the total duration of nocturnal REM sleep. The incidence of daytime attacks of cataplexy declined and daytime functioning improved. This unique therapeutic effect distinguishes GHB from the synthetic hypnotics (Daniels, 1934).

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Can Callosal Speed of Transmission be Inferred from Verbal Reaction Times?

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Filbey and Gazzaniga (1969) found that verbal reaction times were shorter to right than to left visual field stimuli. They interpreted this reaction time difference (30 to 40 msec) to reflect callosal transmission time, i.e., the delay required for information received in the right hemisphere to be acted upon by the verbal left hemisphere. We have performed four verbal reaction time experiments with normal subjects, utilizing differing hemifield stimulus presentations and task requirements. Stimuli were: small lights (light-emitting diodes); checkerboard pattern briefly flashed; small circles; consonant-vowel-consonant triads, either meaningful or nonsense. Contrary to Filbey and Gazzaniga's observations, we found no difference between verbal reaction times to left and right half-field presentations, or a significantly shorter reaction time with left-field presentations, depending upon experimental conditions. Faster reaction times with left-field stimuli were found in left-handed as well as right-handed subjects. Our data indicate that it may be premature to infer callosal speed of transmission from verbal reaction times to half-field stimuli. The paradoxical finding of faster verbal reactions to right hemisphere visual inputs does not appear to be related to handedness, and it occurs with meaningful stimuli; this finding remains unexplained.

INTRODUCTION

Filbey and Gazzaniga (1969) employed a verbal reaction time (VRT) procedure to obtain an estimate of callosal transmission time. In two simple RT experiments, they presented, tachistoscopically, flashes which were either blank or contained a dot to the right or left of central fixation. VRTs to the

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EXHIBIT 8

37

Gamma-Hydroxy-Butyrate in the Treatment of Narcolepsy: a Preliminary Report

ROGER BROUGHTON
MORTIMER MAMELAK

Although in recent years narcolepsy has generally been interpreted as a disturbance of the 24-hour integration of sleep-waking mechanisms, it has also at times been questioned whether the daytime symptoms might not simply be a consequence of the marked disturbance of nocturnal sleep in these patients first described by Rechtschaffen et al. (1963). There is considerable evidence to support the possible primacy of the nocturnal sleep disturbance as one etiologic factor in genetically predisposed individuals. Mitchell and Dement (1968) found that 85% of individuals developing the syndrome of narcolepsy-cataplexy had a history of previous irregular sleep habits or severe sleep deprivation. Broughton and Ghanem (Chapter 13) have recently confirmed this association, although with the somewhat lower incidence of 51.2%. Narcolepsy has also been found to be more common in vocations such as medicine and nursing, which have imposed irregular sleep hours. Finally, the sensitivity of narcoleptics to shift-work (Broughton, 1971) and to sleep deprivation (Berti-Ceroni et al., 1970) has been recognized and has been further confirmed in the questionnaire study of Broughton and Ghanem (Chapter 13). Attention to sleep disturbing factors and to sleep hygiene has also been emphasized in the management of these patients (Zarcone, 1973).

We have been attempting to normalize sleep with gamma-hydroxy-butyrate (GHB) in patients who are otherwise untreated and to study the effects of this procedure upon daytime symptomatology. The pharmacological properties of

GHB at low doses include soporific, and at higher does, anesthetic effects (Laborit, 1964). In contrast with most synthetic hypnotics, GHB does not contribute to nocturnal dyssomnia by suppressing REM sleep (Mamelak et al., 1973). In fact, low doses of GHB induce both REM and NREM sleep (Jouvet, 1967; Matsuzaki et al., 1964). GHB is extremely nontoxic and is completely metabolized within 3 to 4 hours (Roth and Giarman, 1966). In man, a single oral does of 1.5 to 3.0 gm induces two to three hours of sleep. Furthermore, GHB was chosen for trial because it is a normal constituent of the mammalian nervous system (Roth, 1970) and a precursor of gamma-aminobutyric acid (GABA) (Roth and Giarman, 1969), a substance which is probably the main inhibitory transmitter diffusely present in the brain. It was hypothesized that GHB might facilitate GABA formation and thereby alleviate fragmentation of sleep.

METHODS

Four patients with long-standing histories of idiopathic narcolepsy with cataplexy have been studied to date. All were female, their mean age was 38.2 years, and all had been withdrawn from medication a number of weeks before they were investigated. Two were very severe cases who could not be controlled by the combination of methylphenidate and various tricyclic antidepressants. Daytime symptomatology was assessed with the Stanford Sleepiness Scale (Hoddes et al., 1973), which was completed daily by each patient during the study period. All-night sleep recordings were performed in the laboratory on two of the patients, and ambulatory recordings out of the laboratory were made on the other two with a portable 4-channel Medilog system (Oxford Instruments Company). Baseline 48-hour sleep recordings in the sleep laboratory were interrupted only for meals and bathroom visits; the portable recordings were continuous. Sleep records were scored according to international criteria (Rechtschaffen and Kales, 1968), and REM density according to the method described by Snyder (1968).

Each recording series consisted of two to three placebo or baseline nights, followed by a week or more of treatment with GHB, and then two or more placebo nights. GHB was given orally at bedtime in an initial dose of 2.25 gm (15 ml) and repeated in doses of 1.5 gm (10 ml) whenever the patient awoke, if this was two or more hours from the previous dose. Up to three or four doses of GHB (5.25 to 6.75 gm) were given each night in order to maintain as continuous a sleep as was possible. Similarly, three or four doses of placebo were given at intervals of two to three hours on placebo nights. GHB was obtained as a banana-flavored syrup, GAMMA-OH*; the placebo consisted of banana flavoring in water.

*Courtesy of Laboratoire Egic of Paris.

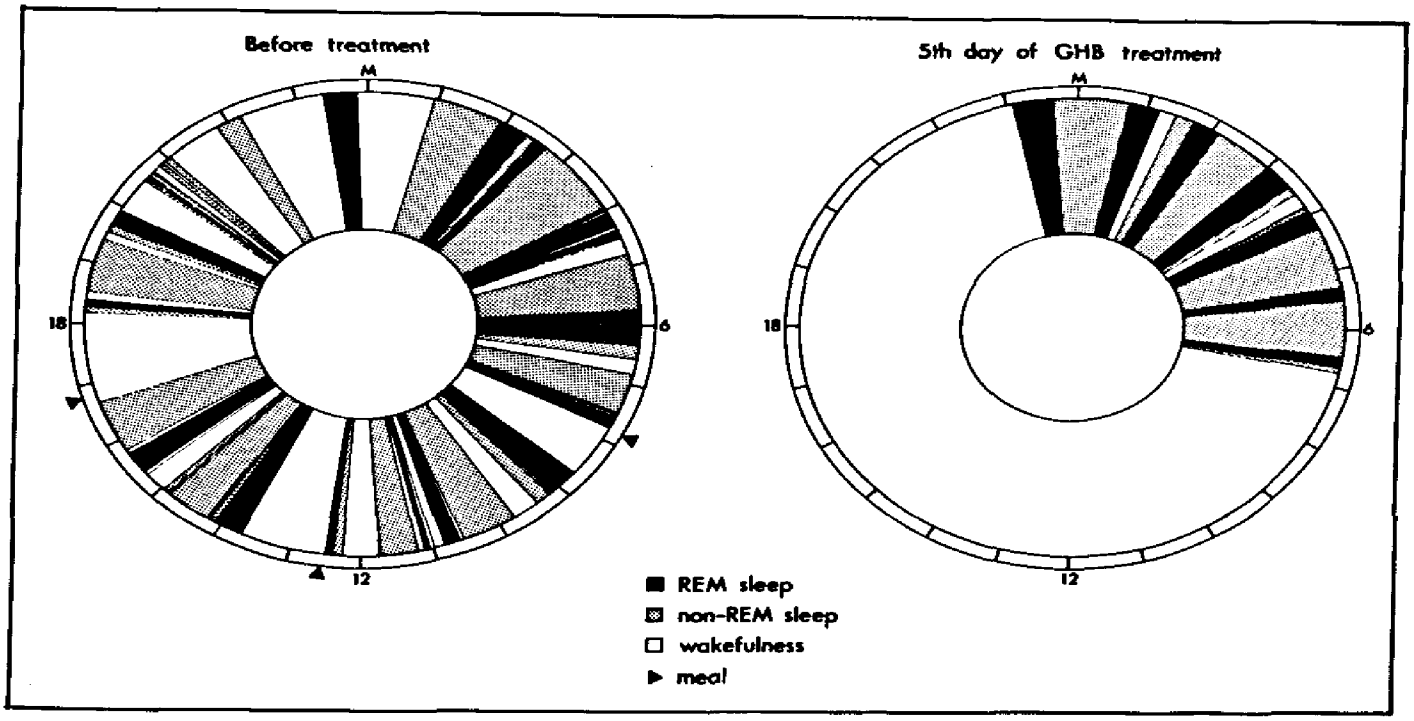

Figure 1. The 24-hour sleep-wakefulness patterns before and after gamma-hydroxy-butyrate.

RESULTS

The polygraphic recordings confirmed the diagnosis of narcolepsy in each of the patients. All had numerous sleep-onset REM periods. Clinical changes became apparent after three or four nights of treatment with GHB. Diurnal irrestible sleep attacks and cataplexy disappeared, the patients were better able to cope with daily chores, and their mood improved. Daytime vigilance as assessed by SSS scores, however, remained impaired, and they continued to show signs of diurnal sleepiness. In one patient the dosage was reduced after several days to a single dose of 2.25 gm at bedtime and the therapeutic effect was sustained for 16 weeks. Nocturnal dyssomnia returned as soon as GHB was discontinued, and diurnal sleep attacks and cataplexy reappeared within one to three days. There were no serious clinical side effects from treatment with GHB, although subjects often felt groggy, as though they had overslept, and they described ocular discomfort the first few days on the drug.

GHB increased total nocturnal sleep time, decreased nocturnal wakefulness, and increased delta sleep (Figures 1 and 2, and Table I). GHB also increased the duration and proportion of nocturnal REM sleep, and decreased REM density. The average nightly REM density fell from 335.1 ± 94.7 in untreated patients to 195.0 ± 78.9 with GHB. Eight normal control subjects in a similar age range had an average nightly REM density of 126.0 ± 39.9. The comparable levels of

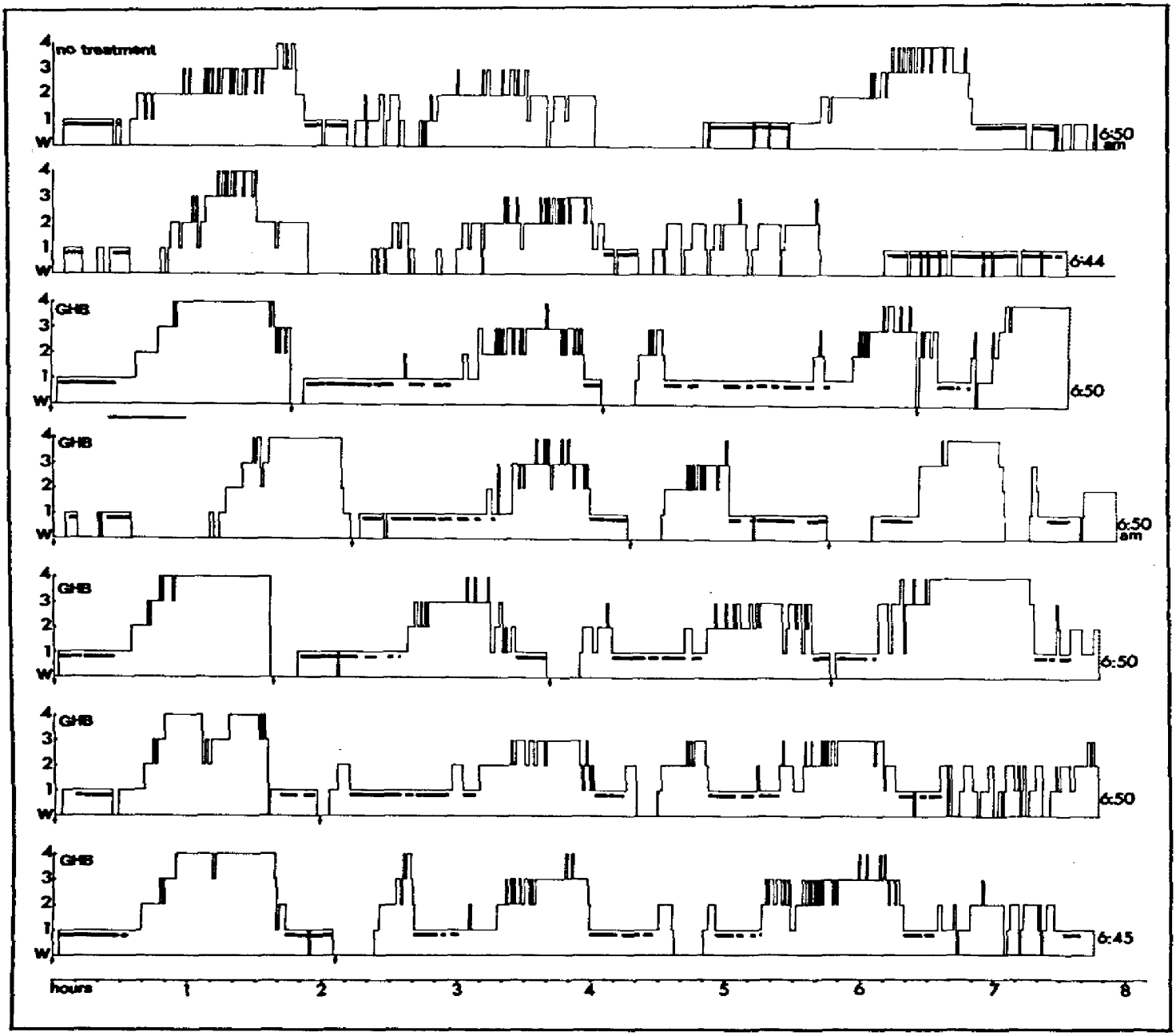

Figure 2. The effect of gamma-hydroxy-butyrate on nocturnal sleep in narcolepsy. The vertical axis indicates the stages of sleep. The horizontal axis is time in hours. REM sleep is indicated by the black bars at the level of stage 1. The arrows beneath the horizontal axis indicate drug administration. The placebo nights are consecutive, as are the nights on GHB. A hiatus of two nights separates the last placebo night from the first drug night.

REM percent for eye movements in 5 second "mini-epochs" would be about 35% under baseline conditions and 25% after GHB in patients, in comparison with 22% in the control group.

DISCUSSION

The improvement in these patients may have been due in part to the increase in nocturnal sleep alone. Nocturnal sleep was not totally normalized, however, in that the evening sleep-onset REM periods persisted, REM densities still

TABLE I

	Wakefulness	Stage 1	Stage 2	Stage 3	Stage 4	Stage REM	Movement time	Total sleep time	REM density
Pre GHB (24 hr recording)	666.7	214.7	247.7	54.3	31.0	201.3	20.3	759.3	404.1
Pre GHB (average of 3 nights)	128.2	70.3	127.7	34.7	24.5	63.7	7.2	328.1	335.1
GHB (average of 5 nights)	47.1	74.0	90.6	67.1	54.7	127.1	5.8	419.3	195.0

All mean data in minutes.

appeared to be above normal, and some of the increased delta activity was drug-induced, similar to the type described by Metcalf et al. (1966). Another interpretation is that the regularization of sleep cycles which occurred with GHB (cf. Figure 2), and particularly its effect during the first few hours of the night, may have resynchronized a number of circadian and ultradian rhythms towards more normal phase relationships to each other. It is noteworthy that maintenance of a reasonable sleep hygiene during the drug trial was important in the control of daytime symptoms and that the compound did not cause a reduction of libido.

Although the original purpose of the study was to increase CNS GABA levels during the first hours of sleep and at times of sleep fragmentation, it is quite possible that other neurochemical mechanisms were also affected. The precise neurochemical effect of GHB in animals remains unknown. There is, however, experimental evidence from various species that it alters CNS dopamine (DA) mechanisms by stimulating dopamine synthesis from tyrosine (Roth and Suhr, 1970) and thus increasing cerebral DA concentration (Gessa et al., 1966; Roth and Suhr, 1970). GHB also leads to increased ACh concentrations in rat and mouse cortex and in brain stem colliculi and adjacent reticular areas (Giarman and Schmidt, 1963). Finally, Spano et al. (1970) have reported increases in cerebral serotonin levels after GHB administration. In fact, the only major amine system which apparently does not show changes with GHB is the norepinephrine one. As dopaminergic, GABA, cholinergic, and serotonergic mechanisms have all been implicated in various aspects of sleep physiology, the precise means by which GHB affects sleep is unclear (see also, de la Mora and Tapia, 1970). For this reason, the mechanisms of the apparent therapeutic effect of GHB in human narcolepsy-cataplexy remain obscure.

We hypothesize that GHB may have had a unique therapeutic effect by releasing phasic activity. Our pretreatment data show that narcolepsy may be characterized by a chronic increased "pressure" for phasic activity. Similar findings have been independently reported by Meier-Ewert et al. (1975a, 1975b), who, in addition, found highest REM densities in the sleep-onset REM period. Measured values of REM density were considerably higher in our narcoleptics than in normal controls. This pressure for phasic REM discharge could, at least in part, explain a number of features: the sleep-onset REM periods in the evenings, in the middle of the night, and in sleep attacks; the multiple awakenings in REM sleep observed in our own baseline records and in the data of other workers (Passouant et al., 1967; Schwartz, 1971); the terrifying dreams often described in narcoleptics; and, if pressure for phasic motor inhibitory phenomena is also assumed, perhaps the dissociated attacks themselves. It is possible that this postulated, long-standing pressure for phasic activity is a consequence of an initial period of sleep deprivation, or irregular sleep habits, or in symptomatic cases, of a cerebral insult which results in continuous hyperactivity of the vestibular nuclei that purportedly generate some phasic phenomena of

REM sleep (Pompeiano and Morrison, 1965). The repeated REM reawakenings could produce chronic self-deprivation of phasic activity and so perpetuate the symptoms.

The main effect of GHB was to maintain and prolong REM periods, which may have permitted some of the postulated phasic REM pressure to dissipate during nocturnal sleep. The pressure for diurnal REM sleep would thereby have been reduced. The effects of other drugs may also be related to their interactions with the REM phasic event system. Synthetic hypnotics, for example, are ineffective in the treatment of narcolepsy and (Daniels, 1934) tend to increase daytime drowsiness. These actions may be due to their suppression of nocturnal REM, which might lead to a subsequent diurnal rebound of REM sleep per se (Kales et al., 1970), and, in particular, of the *phasic* REM components. Finally, antidepressants may alleviate certain narcoleptic symptoms by continuous suppression of this phasic activity pressure, rather than of the tonic REM sleep state itself.

Theoretical issues aside, it is tentatively concluded from these preliminary observations that GHB favorably modifies the course of compound narcolepsy and that the daytime symptoms are in large part secondary to the nocturnal sleep disturbance.

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Discussion

Dr. Pompeiano: It is known that GABA is a cerebellar neurotransmitter, and it is known that cerebellar stimulations produce a tremendous suppression of postural activity as well as monosynaptic inhibition of neurons of the vestibulo-ocular reflex arc. Is it possible to

speculate that gamma-hydroxy-butyrate may simply interact at the cerebellum level, inhibiting the vestibulo-spinal and vestibulo-ocular pathway?

Dr. Broughton: This is a very interesting possible mechanism; however, the phasic activity, at least in the pons, is shown fairly definitively to be cholinergic. Another mechanism of action could be related to the anticholinergic effect of gamma-hydroxy-butyrate (gamma-OH). There is also the question whether gamma-OH is a precursor or subsequent metabolite of GABA (gamma amino-butyric acid), which then returns into the GABA pathway.

Dr. Guilleminault: I have a problem with the GABA-like action of gamma-OH and its possible therapeutic action in narcolepsy. We have recently tried a drug, Baclofen or Lioresal, which is supposedly also a "GABA-like" medication. We administered it to two narcoleptic patients. The results were opposite to those reported here. We saw an increase in daytime sleepiness without any great improvement of disturbed nocturnal sleep. This is against a direct action through a "GABA system." The most obvious action of Baclofen was a decrease of muscle tone during the night.

Dr. Broughton: The problem is very complex, and I am not sure that we have to involve the GABA system to explain these contradictory results. All these butyrate-related drugs, although they do not differ very much in their molecular structure, had very different physiological effects. I would myself much more believe in cholinergic mechanisms reducing phasic activity to explain the therapeutic effects. I think that the hypersomnolence which is left is an NREM sleep type—in fact, it is a *subwakefulness* syndrome, if you prefer.

EXHIBIT 9

The Treatment of Narcolepsy-Cataplexy with Nocturnal Gamma-Hydroxybutyrate

ROGER BROUGHTON AND MORTIMER MAMELAK

SUMMARY: *Sixteen patients with narcolepsy and cataplexy were treated with gamma-hydroxybutyrate (GHB) given at night and tailored to achieve as continuous a night's sleep as possible. The dosage usually consisted of 1.5-2.25 gm orally at bedtime and then one or two further 1.0-1.5 gm doses with awakenings during the night, and totaled about 50 mg/kg. Apart from one patient who took only the bedtime dose, the subjective quality of night sleep improved in all patients and the number of irresistable daytime attacks of sleep and cataplexy substantially diminished. Some residual daytime drowsiness remained and this usually responded well to low doses of methylphenidate. Improvement has been maintained for up to 20 months without the development of tolerance. Two patients experienced adverse side effects necessitating withdrawal of GHB treatment, but no serious toxic effects have occurred.*

RÉSUMÉ: *Seize malades qui présentaient des épisodes de narcolepsie et de cataplexie ont été traités la nuit avec hydroxybutyrate-gamma. Il était dosé pour donner un sommeil nocturne le plus continuel possible. Le dosage normal était de 1.5-2.25 gm. par voie orale avant le coucher suivi par un ou deux autres dosages de 1.0-1.5 gm. pour les réveils nocturnes. Le dosage total était approximativement de 50 mg/kg. Le sommeil nocturne de tous les malades s'est amélioré, sauf pour un seul qui ne prenait que le dosage avant le coucher, et le nombre d'épisodes de sommeil diurne irrésistible et de cataplexie étaient très diminués. Une somnolence résiduelle et diurne persistait, ce qui habituellement répondait bien au dosage minime de methulphenidate. L'amélioration clinique a été maintenue jusqu'à 20 mois sans l'apparition de tolérance. Deux malades ont eu des effets secondaires qui nécessitaient l'arrêt du traitement, mais aucun effet toxique sérieux n'a eu lieu.*

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INTRODUCTION

The prevalence of narcolepsy has been shown in epidemiological studies to be about 0.1% (Roth, 1962; Dement et al., 1973). Therefore it is more frequent than a number of much better known chronic neurological conditions, such as multiple sclerosis. Moreover, as it generally begins in young adulthood and remains for the patients' lifetime, and as it has marked detrimental effects involving employment, education, recreation, interpersonal relations, driving, accidents in general and other parameters of everyday life (Broughton and Ghanem, 1976), the condition can be truly debilitating. The investigation of narcolepsy by modern polysomnographic techniques has shown that of the classical so-called 'tetrad' of Daly and Yoss (1960), the auxillary symptoms (i.e. those other than sleep attacks) of cataplexy, sleep paralysis, and vivid hypnogogic hallucinations are all based upon abnormal rapid-eye-movement (REM) sleep mechanisms, and that the sleep attacks of patients with narcolepsy-cataplexy begin in REM sleep in 50-100% of attacks (Broughton, 1971; Zarcone, 1973), depending upon the author. These findings have led to the addition of drugs which suppress REM sleep, i.e. tricyclic antidepressants (imipramine, chlorimipramine, and desipramine) or less frequently MAO inhibitors (phenelzine) to traditional stimulant medication, usually methylphenidate. The antidepressants have been largely effective in reducing the auxillary symptoms of cataplexy, sleep paralysis and hypnogogic hallucinations, whereas methylphenidate has been most useful for the sleep attacks and for the more or less continuous daytime drowsiness

presented by these patients (Zarcone, 1973). Despite these therapeutic improvements over stimulants alone, the treatment of narcolepsy still remains unsatisfactory. In many patients control of symptoms is far from complete. Others show undesirable side effects discussed later.

This situation led us to use a somewhat different therapeutic strategy. Rather than concentrating upon suppressing the daytime symptoms, we decided to attempt to improve their night-time sleep, which is characterized by early or direct entry into REM sleep (Rechtschaffen et al., 1963), much sleep fragmentation with particular inability to sustain periods of REM sleep (Montplaisir, 1976), and by other features, in the hope that daytime pressure for sleep-related symptoms would be reduced. There were at least two reasons for suggesting that disturbed nocturnal sleep might be central to the physiopathogenesis of narcolepsy with cataplexy. First, prolonged periods of sleep deprivation or of irregular sleep precede the onset of major symptoms of the disease in 50-75% of patients (Mitchell and Dement, 1968; Broughton and Ghanem, 1976) with idiopathic narcolepsy. Secondly, narcoleptics are known to be very vulnerable to the effects of shift work, and therefore to alteration in their circadian sleep-wakefulness rhythms. Such disturbances regularly aggravate their symptoms (Broughton, 1971).

We chose the sodium salt of gamma-hydroxybutyrate (GHB) (Laborit, 1964; Muzard and Laborit, 1977; Snead, 1977) in our attempt to "normalize" the nocturnal sleep patterns of patients with narcolepsy and cataplexy. This short chain fatty acid is a normal constituent of the human nervous system (Doherty and Roth, 1976). It possesses definite hypnotic properties. But in distinction to the commonly used synthetic hypnotics, it promotes sleep which more closely approximates that of normal sleep than do other hypnotics, since it does not inhibit either REM or NREM sleep (Jouvet et al., 1961; Matsuzaki et al., 1964; Mamelak et al., 1977; Muzard and Laborit, 1977). GHB also has an additional possible advantage over the synthetic hypnotics in that animal studies had failed to demonstrate the development of tolerance to its hypnotic effects with prolonged use (Vickers, 1969). To date we have treated 16 patients with nocturnal GHB. Preliminary results in our first four patients have already been reported (Broughton and Mamelak, 1976).

PATIENTS AND METHODS

The sixteen patients, 8 men and 8 women, ranged in age from 21-58 years (Mean = 41.8, s.d. 13.6; Table 1). All had histories of diurnal drowsiness, irresistible sleep attacks, and cataplexy. The other main symptoms of the disease were also present in individual patients to varying degrees. In four patients, the symptoms had been particularly debilitating in spite of treatment with the usual combination of methylphenidate and tricyclic antidepressant drugs. The entire protocol and the investigative nature of the study were carefully explained to each patient and consent forms were signed. In all patients, a sleep onset REM period was observed during at least one daytime polysomnographic recording. Before starting treatment with GHB, all previous drug treatment for narcolepsy was discontinued for at least 14 days. A history and physical were performed and the following laboratory tests completed: hemogram, liver survey, renal survey, chest x-ray, EEG and ECG. Each patient was also given a psychological examination and the Minnesota Multiphasic Personality Inventory.

Polysomnographic assessment of sleep-waking patterns was done for at least 48 continuous hours in the baseline state and then at regular intervals while on GHB. In the Ottawa patients (N = 9) recordings were performed without hospitalization using a portable 4-channel apparatus which permitted the monitoring of patients at their habitual activity levels in the normal home or work environment. In the Toronto studies, patients (N = 7) were hospitalized during the recording periods and the usual polysomnographic techniques were employed. None of the patients had histories of loud snoring or of the peculiar gutteral inspiratory snoring which characterizes sleep apnea. Moreover, this symptom was formally excluded by respiratory monitoring (nasal thermistor and abdominal belt transducer) in Toronto studies, where sufficient recording channels made this possible. The Stanford Sleepiness Scale (Hoddes et al., 1973), which is a self-assessed 1 to 7 scale of alertness, was filled in every 30 minutes over at least 3 consecutive days during wakefulness in the pre-GHB baseline period, and during reassessments while on the drug.

Treatment with GHB was started once the initial baseline data was gathered. The treatment schedule was tailored to achieve as continuous a night's sleep as possible. The patient's body weight and his polysomnographic response to GHB were used as guides. Since each sleep inducing oral dose of GHB lasts only two or three hours (Mamelak et al., 1977) — indeed the substance is only detectable in blood that long (Helrich et al., 1964) — and because our aim was to maximize the duration of sleep produced by the drug while minimizing its anaesthetic effects, multiple doses were used. The usual initial dose was 1.5-2.25 gm (10-15 ml) hs, followed by further multiple 1.0-1.5 gm doses during the night with each major reawakening, if at least 2.5 hours had passed since the previous dose. Usually only 2 or 3 doses per night were necessary. Each dose was about 30 mg/kg, but the total quantity of GHB given each night ranged from 3.75 to 6.25 gms, corresponding to approximately 50 mg/kg.

After seven to ten nights on GHB, the 48 hour polysomnographic recording was repeated with the patient continuing to use the drug according to the optimal dose schedule previously established. Major reassessments were again performed after at least one month, six months and 12 months on GHB. On each of these occasions, the clinical effects of the treatment were assessed, the blood and urine studies, chest x-ray and ECG were repeated, and any adverse reactions to the drug noted and investigated.

GHB was obtained from Laboratoire Egic in France, who market this drug in syrup form under the trade

TABLE 1.

Patients' Symptoms, Previous Treatment and Response to Nocturnal Gamma Hydroxy Butyrate

Patient	Age	Sex	Major Symptoms	Duration of Illness	Previous Medication	Usual GHB Dosage gm/night	Response	Toxicity	Comments
1	21	F	N,SP,HH rare C	6 years	diazepam hs	3.0	+++	none	—
2	22	M	N,C,SP,HH	4 years	diazepam sed[n]	3.75	+	none	—
3	23	F	N,C,SP,HH	3 years	none	3.75	+++	none	—
4	25	F	N,C,SP	5 years	benzedrine	2.25	0	none	Took only hs dose
5	32	F	N,C,SP,HH	14 years	dexedrine	5.25	+++	none	Sister of pat. 4
6	38	F	N,C,SP,HH	15 years	dexedrine methylphenidate chlorimipramine	3.75	+++	none	Old gastrectomy
7	40	M	N,C,SP,HH	28 years	dexedrine methylphenidate imipramine chlorimipramine phenelzine	4.50	+++	none	—
8	43	F	N,C,SP,HH	13 years	dexedrine methylphenidate imipramine chlorimipramine phenelzine phenytoin carbamazepine	4.50	++	abdominal pain, muscle weakness	No evidence for epilepsy
9	45	F	N,C,SP	23 years	dexedrine	6.25	+	none	—
10	45	M	N,C,SP,HH	3 years	methylphenidate	4.50	+++	temporary muscle weakness	—
11	52	M	N,C,SP	14 years	desoxyn	3.75	+++	none	Impotence on previous R
12	55	M	N,C	30 years	methylphenidate	3.75	+++	none	—
13	56	M	N,C,SP	31 years	methylphenidate	3.75	+++	dysthesiae left hand	Post-traumatic epilepsy
14	57	M	N,C	43 years	ephedrine	4.50	+++	none	—
15	57	M	N,C,SP,HH	33 years	dexedrine	5.25	+++	none	—
16	57	F	N,C,SP,HH	37 years	dexedrine methylphenidate impramine chlorimipramine	3.75	+++	none	—

0 = no effect; +/- = 0-20% improvement; + = 20-40% improvement

++ = 40-70% improvement; +++ = over 75% reduction of symptoms from baseline

N = irrisistible sleep attacks; C = cataplexy; SP = sleep paralysis; HH = vivid hypnagogic hallucinations

name "GammaOH". We found it best to dilute the syrup in milk or juice, in order to reduce the gastrointestinal upset caused in some patients when the drug was given in undiluted form. Dilution also retarded GHB's rate of absorption somewhat, so that sleep induction was experienced as gradual and more normal.

RESULTS

We wish to report our clinical observations here. The polysomnographic and Stanford Sleep Scale data and our psychological findings are still being analyzed and will be presented in a future publication. The patient and clinical results are summarized in Table 1.

CLINICAL RESPONSE

The ameliorating effects of GHB on the major daytime symptoms of narcolepsy appeared gradually. By comparison, the subjective quality of night-time sleep improved very rapidly. Over the first 2 to 5 nights, nocturnal sleep became less restless and nightmares, hallucinations, and attacks of sleep paralysis vanished. Some episodes of intense awakenings at about 2-3 hours after taking the initial doses were encountered. These appeared to represent a drug-related rebound phenomenon. Although dreaming continued, it lost its frightening qualities. All patients found it easier to stay awake during the day and noted that after a number of weeks, the irresistible pressure for diurnal sleep and the attacks of cataplexy virtually disappeared. When cataplexy did occur, the attacks were

usually relatively brief, less intense, and tended to occur late in the day when the individual was very tired. Most patients said that they were much more refreshed after their night sleep and were better able to cope during the daytime. Despite these beneficial effects on the major symptoms of the disease and on the subjective quality of sleep, many patients continued to feel somewhat tired and drowsy during the day. We then added 5 to 10 mg of methylphenidate three times a day to their treatment regimen. It was taken on an empty stomach before breakfast and lunch, and then again in the mid-afternoon. With this addition, the daytime drowsiness and fatique became minimal.

Our patients generally reported that sleep gradually consolidated into a seven to eight hour period. One patient, however, reported that if she slept through the night and failed to take her second dose of GHB, the attacks of narcolepsy and cataplexy recurred on the following day. The single patient (No. 4) who failed to respond at all to GHB treatement, turned out to be taking only the single h.s. dose of the drug. Some patients on their own tried to discontinue GHB treatment and to rely on methylphenidate alone, but they noticed recurrence of their symptoms after a few days.

In patients responding to GHB, the improvement was maintained throughout the trial period. The development of tolerance requiring increasing doses for the same clinical effect on night sleep, sleep attacks or cataplexy has not been encountered. As with traditional forms of treatment, it was found that having patients keep regular hours of retiring and of morning awakening was important for optimal therapeutic effectiveness. At the time of writing, one patient has been on GHB nightly for nearly two years, three others have been on it for over a year, and the remainder have been on it for three months to a year.

SIDE EFFECTS

There have been very few adverse clinical effects with this treatment and no abnormal laboratory findings. Minor side effects of GHB have been seen for the first few days in a number of patients which consisted of a "thick head", ocular discomfort, and other apparent hangover effects, but these were rare after one week. Impotence or reduced libido has never been encountered. We decided to discontinue the drug in two patients. One (patient No. 8) complained of non-specific abdominal pain while using GHB plus muscular weakness in the morning, to the point where she found it difficult to initiate movement. Both of these symptoms disappeared when the drug was stopped. A second patient (No. 13), a male with a post-traumatic narcolepsy and cataplexy, experienced disturbing left arm dysthesiae. He had previously had similar symptoms after the initial head injury. A third patient (No. 10) complained of muscular weakness in the morning, also limited to his left arm. This man had suffered a neck injury a few weeks before starting GHB and his left arm was weak following the event. It had gradually been recovering, but the weakness recurred when he started using the drug. Because his narcolepsy improved so dramatically on GHB, we continued to use the drug in spite of the effect on his arm and the weakness gradually disappeared over a few weeks.

Several patients have also mentioned that GHB caused urinary urgency. On one occasion, enuresis occurred in a patient about an hour after the drug had been given. On the whole, however, urgency has not been a serious problem and our patients report that they void no more frequently during the night on GHB than they did before starting the drug. Another complaint from a number of patients was that GHB produced a dream-like confusional state which could be unpleasant and frightening. This happened when the drug was taken before they were ready for sleep, or when they fought against its sleep promoting actions. This phenomenon is rare if patients cooperate with the drug's hypnotic effects and use it at the minimal dose required for sleep induction and maintenance. No other side-effects were encountered and, in sum, most patients felt they had fewer side-effects and substantially better relief from symptoms on GHB than on any previous medication.

DISCUSSION

The salient finding in this study was the marked clinical improvement produced by nocturnal GHB in patients with narcolepsy-cataplexy. This action was coupled with a paucity of adverse clinical or laboratory findings. When GHB was used at night, and supplemented with small doses of methylphenidate during the day, all the major symptoms of narcolepsy were markedly reduced. The project has involved detailed study of a limited number of patients over substantial periods of time. It is not a double-blind controlled design. But, the therapeutic effects on patients previously uncontrolled by the more traditional drug regimens and the rapid deterioration in those who discontinued the use of the drug on their own for several nights leave little doubt about the compound's effectiveness.

The use of GHB for the treatment of this disease has a number of clear advantages over more conventional therapies. As mentioned, the latter usually use substantial doses of stimulants such as methylphenidate or d-amphetamine, alone, or in combination with tricyclic antidepressants such as imipramine or chlorimipramine. The stimulants, however, cause irritability and anxiety in many patients and more serious side effects in others. One of our patients previously had had a gastrectomy for ulcers attributed to stimulant medication. The antidepressant drugs, on the other hand, may cause dry mouth, sweating, and impotence in males (Zarcone, 1973; Dement et al., 1976). The stimulant-antidepressant combination does not consolidate sleep, and in fact may even further disrupt it. Moreover, tolerance develops in time both to the level of stimulants generally employed and to antidepressants so that after a number of months, many patients complain that their symptoms are again every bit as troublesome as they were to begin with. None of these problems occur with GHB. Nocturnal sleep was restful

and sustained and patients awoke alert and well rested. There were few side effects and, specifically, no impotence or reduced libido. Tolerance to the drug's actions did not develop, nor did it develop to the relatively small doses of methylphenidate taken during the day, when taken in combination with nocturnal GHB.

Some of the therapeutic and side-effects of GHB may be related to its influence on motor mechanisms. It is known to inhibit muscle tone (Vickers, 1969) and to block the H-reflex response (Uspenskii, 1965; Muzard and Laborit, 1977). In narcoleptics, as well as in normals, the H-reflex response can be abolished by GHB and remains somewhat attenuated for some time after the patient awakens (Mamelak, Sowden and Caruso, unpublished observations). The latter may be due to residual effects of small quantities of unmetabolized drug. This effect may account for the weakness experienced by two of our patients upon arising in the morning. The sustained hypotonia throughout sleep may be as important as any effect on sleep patterns in the subjective feeling of having had a deep refreshing night's sleep. As far as the urinary urgency is concerned, this has been noted by some patients even if they empty their bladders before bedtime, but it has not proved to be a treatment problem. It is intriguing to speculate, however, that the combination of profound sleep and enuresis observed in childhood might be related to a higher brain GHB concentration present in the early years of life.

GHB's mechanisms of action in the treatment of the major symptoms of narcolepsy remains uncertain. It has been known for many years that hypnotic drugs can be helpful for at least some narcoleptic patients (Daniels, 1934; Zarcone, 1973). Recent studies have shown that narcoleptics do not sleep more in the 24-hour period than normal individuals (Hishikawa et al., 1976). Thus, consolidating the fragmented sleep of these patients into a seven or eight hour period by means of hypnotic drugs should theorectically decrease the need for daytime sleep. Perhaps this is how ordinary hypnotics benefit these patients. But, it must be noted that some of our narcoleptic patients slept reasonably soundly at night and that in these patients nocturnal sleep in fact became more fragmented after starting GHB, because they had to wake up for the second dose. If they failed to take it their symptoms recurred. Furthermore, a preliminary review of our polysomnographic data indicates that GHB did not substantially increase the overall duration of sleep in the eight hour night-time period. GHB, then, likely has more specific actions on sleep mechanisms than simply increasing the duration of nocturnal sleep or its gross continuity. As yet, basic neurochemical studies offer few real insights into the drug's mechanism of action, although it has been shown that GHB may be derived from GABA (Roth and Giarman, 1969), and may act as a GABA agonist (Roth et al., 1977) and that it alters dopamine (Roth and Suhr, 1970), serotonin (Spano et al., 1970), and acetylcholine (de la Mora et al., 1970) metabolism. The last three, at least, have been implicated in sleep control mechanisms (Jasper and Koyama, 1969; Jouvet, 1969; Cordeau, 1970; Morgane and Stern, 1972).

Whatever its precise mode of action, this essentially non-toxic constituent of the normal brain does appear to have important clinical therapeutic effects even in otherwise refractory cases of narcolepsy. Moreover, its effectiveness, when given in the night-time period, adds strong support for the postulated importance of the quality of night sleep in the genesis of daytime sleep attacks and cataplexy. It gives promise that GHB itself or similar substances (we have also used gamma-butylactone sucessfully) may lead to substantial improvement in the control of this debilitating neurological disease. The main disadvantage at present is its relatively short duration of action. It is hoped that this might be extended by use of slow release capsules or another approach in order to produce a sustained 7-8 hour overnight effect.

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EXHIBIT 10

Effects of Nocturnal Gamma-Hydroxybutyrate on Sleep/Waking Patterns in Narcolepsy-Cataplexy

ROGER BROUGHTON and MORTIMER MAMELAK

SUMMARY: *Continuous 48-hour polygraphic recordings of sleep/waking patterns were performed on 14 patients with narcolepsy-cataplexy before and after 7-10 days of treatment of their nocturnal sleep with gamma-hydroxybutyrate (GBH). GBH improved the quality of night sleep by increasing the amount of slow wave sleep, reducing stage 1, increasing sleep efficiency (percentage of time in bed spent asleep), and reducing the number of periods of short sleep under 15 minutes. Also nighttime REM sleep was reduced in latency and became less fragmented. The daytime period contained less slow wave sleep and REM sleep, and fewer episodes of prolonged sleep. Patients experienced reduction or loss of daytime attacks of irresistible sleep, cataplectic attacks, and other auxiliary symptoms. Residual daytime drowsiness subsequently improved on low doses of methylphenidate. Tolerance did not develop and there were no serious toxic side-effects. Four of the patients had been refractory to previous combinations of antidepresents and high doses of stimulants.*

RÉSUMÉ: *Quatorze malades souffrant de narcolepsie-cataplexie ont eu des enregistrements polygraphiques continus de leur éveil-sommeil avant et 7 à 10 jours après le traitement de leur sommeil nocturne avec l'hydroxybutyrate-gamma. La qualité du sommeil nocturne a été améliorée. Ceci a été expérimenté par une augmentation du sommeil avec des ondes lentes électro-encéphalographiques (les stades 3 et 4) et de l'efficacité du sommeil (le pourcentage du temps nocturne alité avec du sommeil), et par une dimunition du stade 1 (du sommeil très léger ou de la somnolence) et des périodes très brèves (moins que 15 minutes) de sommeil. La latence des périodes avec des mouvements oculaires rapides (REM) a été diminuée et le sommeil REM est devenu moins fragmenté. Le sommeil lent et le sommeil REM étaient moins fréquents pendant le sommeil diurne et les épisodes de sommeil moins prolongées. Au niveau clinique, les malades ont eu une réduction ou une disparition d'accès diurnes de sommeil, d'accès cataplectiques et d'autres symptâmes auxiliaires. Une somnolence résiduelle et diurne a été améliorée avec des dosages mineurs de méthylphenidate. Il n'y a eu ni apparition de tolérance ni effets secondaires toxiques sérieux. Quatre des malades ont été réfractaires aux combinations préalables d'antidéprimants tricycliques et de dosages élevés de produits stimulants.*

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INTRODUCTION

The pathogenesis of the excessive daytime drowsiness and sleep attacks in narcolepsy, and of the auxiliary symptoms of cataplexy, hypnagogic hallucinations, and sleep paralysis remain poorly understood. The disease appears to result from increased pressure for sleep or for sub-components of sleep at unexpected times during the sleep/waking cycle. For these reasons, central nervous system stimulants and other types of sleep suppressing medications have been used to control its manifestations (Zarcone, 1973; Dement et al., 1976). Little is known, however, about how such increased pressure develops. In recent years, investigators have paid increasing attention to the nocturnal insomnia, which so paradoxically is a common complaint in this illness (Daniels, 1934; Zarcone, 1973; Dement et al., 1976). Using modern polysomnographic techniques, it has been shown that restless night sleep, interrupted by movements and periods of wakefulness, is a typical feature of narcolepsy-cataplexy (Rechtschaffen et al., 1962; Broughton and Mamelak, 1976; Montplaisir et al., 1978). As well as being abnormally fragmented, night sleep is often reduced in total duration (Rechtschaffen et al., 1962; Montplaisir et al., 1978; Mamelak, Caruso and Stewart, in press).

Other observations made in a variety of settings, have also suggested an important role for nocturnal dyssomnia in the development of the illness. Sleep patterns similar to those characteristic of such patients have been produced by altered sleep schedules. For example, attempts have been made to establish 90 minute (Carskadon and Dement, 1975;

Carskadon, 1976) or 3 hour (Weitzman et al., 1974) "days" in normal subjects. In the course of these experiments, which have involved the sustained fragmentation of sleep, polysomnographic patterns identical to those found in narcolepsy have rapidly emerged. Sleep onset REM periods and other manifestations of dissociated sleep, such as multiple epochs of so-called "intermediate sleep" (Barros-Ferreira and Lairy, 1976), appeared within a few hours. Although the full clinical syndrome was never elicited, it is conceivable that this might have occurred had it been possible to continue these studies for longer times. Indeed, the clinical and polysomnographic patterns of narcolepsy can develop in pathological conditions such as sleep apnea which are typified by chronic sleep fragmentation (Guilleminault et al., 1976). Narcolepsy also appears to develop preferentially in other individuals in whom sleep is chronically disrupted, for example, in shift workers or in nurses and doctors who must keep irregular hours in the course of their duties (Broughton, 1971). In 50-75% of idiopathic cases of narcolepsy-cataplexy a history of severe sleep deprivation or of irregular sleep habits preceded the onset of the disease, often by many years (Mitchell and Dement, 1968; Broughton and Ghanem, 1976). Moreover, in established narcoleptics the condition characteristically becomes unusually difficult to control when there is any disruption of the sleep/waking rhythms by shift work, jet lag, or poor sleep habits (Broughton, 1971; Zarcone, 1973; Broughton and Ghanem, 1976).

Although evidence therefore exists that preceding nocturnal sleep disturbance may have an important role in the genesis of the condition, and indeed some authors have included ordinary hypnotics as part of their treatment (Daniels, 1934; Zarcone, 1973), the major therapeutic approach has been to suppress the daytime symptoms — sleep attacks and drowsiness with stimulants; and cataplexy (and other REM-based auxiliary symptoms) with tricyclic or MAO inhibitory antidepressants.

We decided to attempt to increase the continuity and duration of nocturnal sleep and to study the effect of this on the symptoms of the condition. To achieve this we have used nocturnal doses of gamma-hydroxybutyrate (GHB), a central short chain fatty acid (Doherty et al., 1976) with hypnotic properties (Laborit, 1964). We chose GHB because it had been shown to promote both REM and slow-wave sleep (Mamelak et al., 1977) in contrast to ordinary hypnotics which often suppress these sleep states (Kales et al., 1970). GHB also possessed an additional major advantage over the usual hypnotics in that animal studies had failed to demonstrate the development of tolerance to the drug's hypnotic effects with prolonged use (Vickers, 1969).

To date, we have treated 16 narcoleptic patients with GHB. In a preliminary communication concerning 4 patients (Broughton and Mamelak, 1976) and in a companion article detailing the clinical aspects of the patients included in the present report (Broughton and Mamelak, 1979), we have shown that GHB markedly improves nocturnal sleep and that nightmares, hallucinations, and attacks of sleep paralysis vanish. During the day, pressure for sleep becomes less imperative and cataplectic attacks become milder and less frequent. In many patients virtually all symptoms of the disease disappear when small repeated daily doses of stimulants are used in combination with GHB at night. No tolerance has developed so far for this drug regimen, nor have there been any serious side effects, and patients generally find this treatment much more palatable than the usual combination of stimulants and tricyclic antidepressant drugs. In this paper, we focus on the effects of GHB upon the recorded sleep/waking patterns of our patients.

PATIENTS AND METHODS

Fourteen of the 16 patients (excluding nos. 2 and 10, for technical reasons), whose histories are summarized in the previous report (Broughton and Mamelak, 1979), have had complete studies of their 24 hour sleep/waking patterns. They consisted of seven males and seven females between the ages of 21 and 57 (mean 41.8 ± 13.6). All showed one or several sleep onset REM sleep periods during the recordings. Nine of the fourteen patients were seriously debilitated by their illness and four had not benefited much from the standard treatments combining stimulants and antidepressant medication. Before starting GHB, all previous treatment for narcolepsy was discontinued for at least two weeks. The pre-trial assessment included a history and physical examination, hematological, renal, and hepatic studies, a chest x-ray, ECG, EEG, and MMPI and a brief psychological assessment, repeated subjective assessment of sleepiness using the Stanford Sleepiness Scale (Hoddes et al., 1973), pupillometry in the Ottawa studies, and baseline polysomnographic recordings. After the investigative and purely voluntary nature of the study was explained, informed and signed consent was obtained from each patient.

The polysomnographic recordings in the Ottawa patients (N=7) were made with portable 4 channel Medilog recorders (Oxford Electrical Instrument Company). This permitted patient monitoring in their normal environment and at their usual activity levels. The derivations used were C_4-A_1, C_3-A_2, a combined horizontal-vertical oculogram and a submental EMG. Twenty-four hours of data could be recorded on one regular C120 cassette. In the Toronto studies, the patients (N=7) were hospitalized and the recordings obtained with a Grass model 78B polygraph. None of the patients had histories of excessive or intense snoring suggestive of sleep apnea, and this symptom was formally excluded in the Toronto studies in which a sufficient number of recording channels made it possible to monitor nasal and thoracic respiration. Continuous 48 hour recordings of the sleep/waking patterns were obtained in all patients in the pre-GHB baseline period and then again after 7 to 10 nights on the drug. During the 48 hour Toronto laboratory recordings, the patients were encouraged to remain in bed except for meals and bathroom breaks.

An initial 1.5 gm to 2.25 gm (10-15 ml) dose of GHB was given orally at bedtime and followed by one or two

further 1.0 gm to 1.5 gm doses during the night with any major awakening, if more than 2.5 hours had passed from the previous dose. The patients were required to feel fully alert and clear headed before taking their next dose. The duration of GHB's hypnotic effect in man is about 2.5 hours (Mamelak et al., 1977), which corresponds closely to that of its detectable presence in the blood (Helrich et al., 1964). In most patients, two or three doses were given each night in accord with our objective of maintaining as continuous a night's sleep as possible. GHB was never given within two hours of the anticipated time of the morning awakening in order to avoid hang-over effects. The total quantity given each night ranged from 3.75 gm to 6.25 gms, corresponding to an average patient dosage of about 50 mg/kg.

The polysomnographic data were analysed according to international criteria (Rechtschaffen and Kales, 1968) and scored using 40 sec epochs as wakefulness, stages 1, 2, 3, 4 and REM sleep, plus movement time (MT, i.e., epochs obscured by movement artifacts for over 50% of their duration with previous and succeeding epochs containing sleep patterns). The night and daytime portions of the recordings were analysed separately. The former was arbitrarily defined as the time between the onset of night sleep to the time of the final awakening for breakfast. Sleep during the remainder of the 24 hours was scored as part of the daytime (Figs. 1 and 2). The time of sleep onset was taken as the beginning of the first continuous 10 min of REM or of NREM sleep, exclusive of stage 1, which corresponded to the patients's subjective appraisal of sleep onset for the night as scored on the SSS forms. Since no formal bedtime existed in the laboratory studies, nor could one be established in the portable studies, the latency from bedtime to sleep onset was not determined. For each recording period, nocturnal and diurnal, we calculated the total sleep times including and excluding stage 1 (which corresponds to drowsiness and, most authors agree, not to actual sleep). Corresponding nocturnal sleep efficiencies refer to the percentages of that portion of the recordings occupied by the relevant sleep patterns. Delta sleep latency was defined as the time from sleep onset to the first continuous 3 or more min of stage 3 or 4 sleep. REM sleep latency was defined as the time from the onset of 3 or more min in duration of stage 2 to the first continuous 3 or more min of REM sleep. If REM sleep occurred before stage 2, its latency was determined by measuring the interval between the beginning of the 3 consecutive min of REM sleep and the preceding 3 consecutive min of wakefulness. REM density refers to the percentage of 2 sec mini-epochs containing one or more rapid eye movements. The values obtained for each REM period were normalized for its duration and an average value for each of the nocturnal and diurnal recording periods was determined.

Two further parameters involving REM sleep were defined in order to measure the degree of REM sleep fragmentation. These were REM sleep efficiencies with and without stage 2, i.e. other patterns of definite sleep. For each REM sleep period, the number of epochs between the first and the last 40 sec REM sleep epoch of that period was determined. This was designated the "total REM sleep period duration". Because of fragmentation, it included epochs of wakefulness, stage 1, MT and, at times, stage 2. REM sleep efficiency without stage 2 refers to the percentage of the REM sleep period duration consisting of REM sleep epochs only. REM sleep efficiency including stage 2 refers to the percentage of the REM sleep period duration consisting of epochs of REM sleep or of stage 2 sleep, i.e., of definite sleep. The two REM sleep efficiency values were normalized for each REM sleep period, and an overall average mean value for each of the nocturnal and diurnal recording periods was obtained. In this study, a REM sleep epoch had to be separated from the closet preceding REM sleep epoch by at least 15 min to be scored as part of a separate REM sleep period. The number of REM sleep periods per night and their cycle duration, i.e., the time from the onset of one REM sleep period to the onset of the next period, were also calculated.

A measure for determining the degree of *overall* fragmentation of night sleep was also developed. We calculated the number of periods of sleep, be these NREM, REM, or combinations of the two, which were separated from one another by one min or more of either MT, wakefulness or stage 1. Depending upon their duration, these nocturnal sleep periods were put into five categories: 15 min or less, 16-30 min, 31-45 min, 46-60 min, and greater than 61 min. In addition, we measured the frequency of stage shifts out of stages 2, 3 and 4 collectively (i.e., out of NREM sleep) and out of REM sleep. The number of shifts out of the former was expressed per 100 min of the sum of stages 2, 3 and 4 per night, and out of the latter per 100 min of REM sleep per night.

During the daytime portions of the recordings, sleep was analysed for the duration of stages 1, 2, 3, 4, REM, and MT; and the total sleep times including and excluding stage 1 were calculated as above. The number of daytime sleep periods was also determined. A sleep period was defined as an episode of recorded sleep containing at least 3 min of stages 2, 3, 4 or REM sleep, and preceded and followed by at least 15 min of wakefulness or stage 1 (drowsiness). These sleep periods were divided into 3 groups, those of 31-45 min, of 46-60 min and of more than 61 min, corresponding to the longer measures of consolidated sleep at night.

In this paper, the 48 hours baseline polysomnographic data for each patient is compared to data after 7 to 10 nights on GHB treatment. The data of each patient for each of the two 24 hour periods before and after GHB treatment were averaged before comparison. The two tailed Student t test was applied to each variable, unless otherwise stated.

RESULTS

The data obtained using either the portable outpatient or the laboratory inpatient recording techniques were similar. The major difference was in the sleep patterns which appeared just before sleep onset at night. The inpatient recordings usually showed a period of more or less sustained wakfulness until sleep onset, which was then followed shortly by a REM

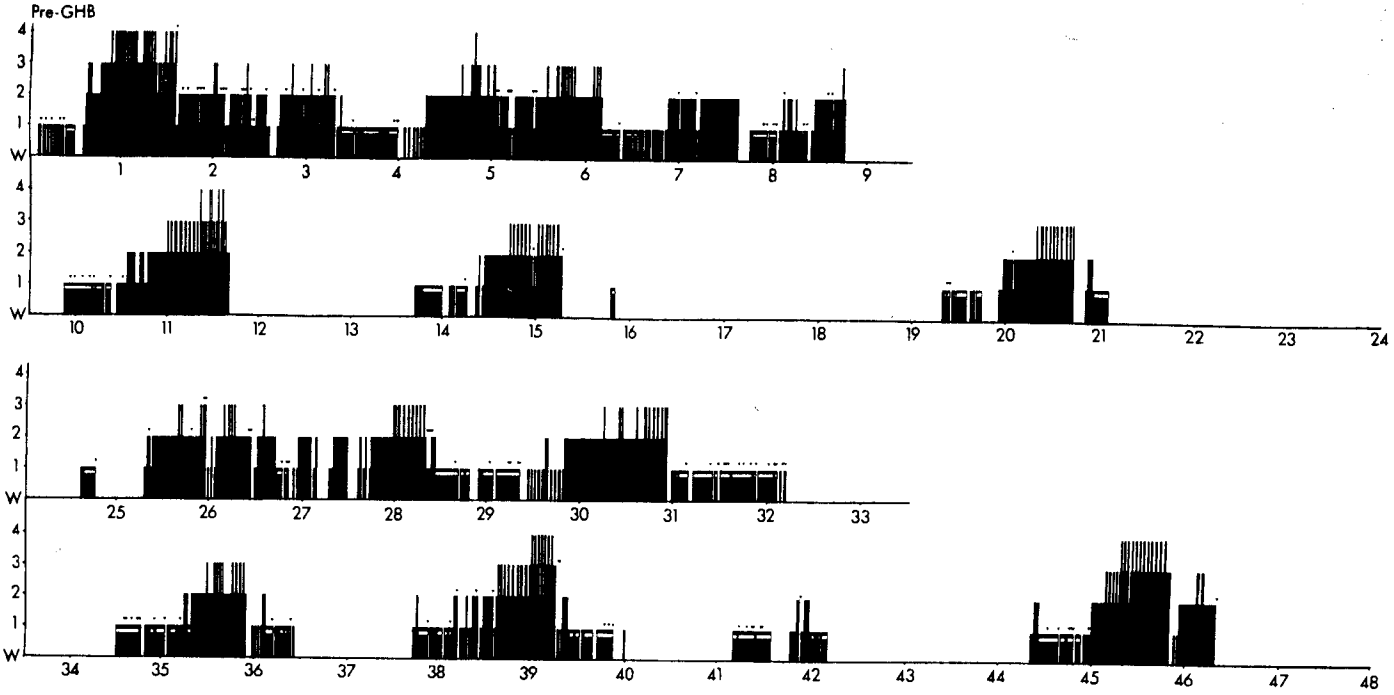

Figure 1 — A 48-hour continuous baseline recording in a typical (hospitalized) patient. It illustrates the frequent awakenings during nocturnal sleep, multiple sleep onset REM periods, fragmentation of REM sleep, and other features of sleep in narcolepsy-cataplexy (note: in Figs. 1 and 2 the vertical axis indicates sleep stages, and the horizontal axis the time in hours. REM sleep is shown as a horizontal white bar at the level of stage 1, and movement by small triangles above the sleep stage line. Time zero hours in both figures was 10:30-11:00 p.m.).

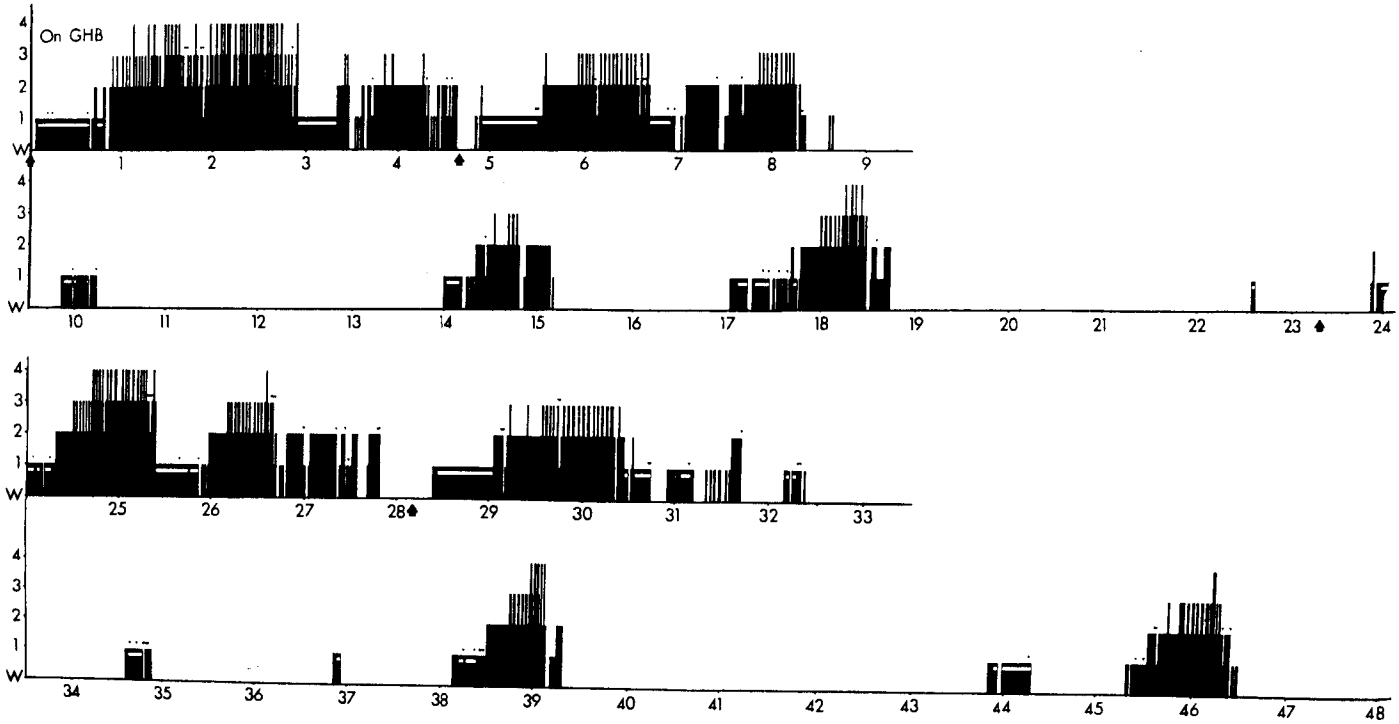

Figure 2 — A 48-hour recording of the same patient on days 9 and 10 of nocturnal GHB. Times of administration are noted by arrows below the horizontal axis. The figure illustrates the increased continuity of nocturnal REM sleep, the decrease in number of nocturnal awakenings, and the reduction of daytime sleep (despite the subjects having remained quietly in the hospital laboratory while on GHB).

TABLE 1

Effects of GHB on Nocturnal Sleep/Waking Patterns

	Baseline	GHB	Sig.
Total sleep (min), incl. S1	415.3 ± 56.5	404.9 ± 77.0	—
Total sleep (min), excl. S1	341.5 ± 62.9	355.1 ± 80.5	—
Nocturnal wakefulness (min)	65.7 ± 38.4	62.4 ± 50.3	—
Stage 1 (min)	73.8 ± 32.6	47.8 ± 26.6	.005
Stage 2 (min)	187.3 ± 59.1	180.3 ± 72.9	—
Stage 3 + 4 (min)	62.8 ± 26.8	82.9 ± 26.4	.005
Stage REM (min)	91.0 ± 20.7	93.3 ± 34.5	—
Movement time (min)	19.3 ± 11.2	15.5 ± 6.8	—
Sleep effic. (%), incl. S1	76.0 ± 11.7	85.1 ± 11.4	.005
Sleep effic. (%), excl. S1	69.0 ± 11.0	75.0 ± 1.6	.01
Delta latency (min)	63.9 ± 86.6	48.0 ± 41.4	—
REM latency (min)	66.7 ± 68.4	16.9 ± 40.8	.005
REM density (min)	23.7 ± 8.9	16.7 ± 6.1	.005
No. REM periods	4.2 ± 1.2	4.1 ± 1.3	—
REM cycle duration (min)	108.2 ± 24.7	116.1 ± 33.7	—
REM sleep effic. (%), incl. S2	82.6 ± 8.6	89.0 ± 7.7	.005
REM sleep effic. (%), excl. S2	80.1 ± 9.6	84.1 ± 11.0	—
Shifts from NREM/100 min NREM	9.8 ± 4.5	9.1 ± 3.4	—
Shifts from REM/100 min REM	23.4 ± 7.5	16.0 ± 7.7	.005
Sleep fragmentation			
< 15 min (no.)	18.4 ± 9.6	11.0 ± 5.9	.025
16-30 min (no.)	3.4 ± 3.1	2.7 ± 1.3	—
31-45 min (no.)	1.3 ± 0.9	1.6 ± 1.6	—
46.60 min (no.)	1.1 ± 1.1	0.9 ± 0.8	—
> 61 min (no.)	1.3 ± 1.2	1.2 ± 1.2	—

TABLE 2

Effects of GHB on Daytime Sleep Variables

	Baseline	GHB	Sig.
Total sleep (min), incl. S1	203.7 ± 90.6	170.1 ± 100.2	—
Total sleep (min), excl. S1	168.8 ± 86.7	117.7 ± 65.7	.025
Stage 1 (min)	35.7 ± 20.9	50.2 ± 54.4	—
Stage 2 (min)	79.0 ± 54.4	69.8 ± 47.3	—
Stage 3 + 4 (min)	38.4 ± 25.1	18.9 ± 16.6	.005
Stage REM (min)	49.4 ± 32.7	28.1 ± 21.3	.01
Movement time (min)	10.1 ± 7.5	9.9 ± 11.6	—
REM density	20.2 ± 8.5	19.5 ± 5.9	—
REM sleep effic. (%), incl. S2	81.0 ± 21.0	80.7 ± 17.0	—
REM sleep effic. (%), excl. S2	80.9 ± 18.0	80.4 ± 17.1	—
Total no. "sleep periods"	4.1 ± 2.5	4.0 ± 2.6	—
No. longer "sleep periods"			
31-45 min	0.6 ± 0.5	0.8 ± 0.7	—
46.60 min	0.7 ± 0.9	0.1 ± 0.3	.025
> 61 min	0.3 ± 0.4	0.0 ± 0.0	.025

sleep period (Fig. 1). Patients recorded at home tended to drift from wakefulness in and out of brief 1-3 min periods of REM sleep or stage 1 for several minutes or even dozens of minutes, before falling into a consolidated sleep period of at least 10 min; and they usually then had much longer or even normal REM sleep latencies. The REM sleep latencies recorded in the outpatient studies were thus significantly longer than in the inpatient studies (Chi squared test, $p < 0.005$). Other REM sleep measures did not differ significantly between the two laboratories.

The nocturnal pre-GHB baseline recordings (Table 1) showed a number of features when compared to published data (Williams et al., 1974), and confirmed the findings of others for this condition (Rechtschaffen et al., 1962; Barros-Ferreira and Lairy, 1976; Montplaisir et al., 1978). These included early or direct sleep onset REM periods, frequent awakenings and periods of relatively prolonged wakefulness, low sleep efficiencies, and frequent stage shifts. In short, night sleep was characterized by marked fragmentation, which was also reflected in our measures showing frequent short (i.e., 15 min or less) periods of sleep and low REM sleep efficiencies (with and without stage 2). The daytime sleep measures before GHB are given in Table 2. Fig. 1 shows a 48-hour pre-GHB recording in a typical patient.

GHB (Table 1, Fig. 2) significantly increased the duration of nocturnal slow wave sleep at the expense of stage 1, increased the sleep efficiency measures, and decreased the number of sleep periods less than 15 min in duration. The total amount of REM sleep was unchanged, but it became less fragmented, as indicated by significantly fewer stage shifts out of REM sleep and by an increase in the REM sleep efficiency. GHB significantly decreased both the latency to REM sleep and the density of the rapid eye movements themselves. The daytime data (Table 2) indicated that nocturnal GHB resulted in a significant decrease in the duration of both diurnal slow wave sleep and REM sleep. Stage 1 patterns, however, increased (non-significantly). Because of this, although the total sleep time (including stage 1 patterns of drowsiness) during the day remained unchanged, actual sleep (excluding stage 1) was decreased and the individual daytime sleep periods became shorter. The overall major effect of the drug, then, was to improve the continuity of nocturnal sleep and to reduce long periods of daytime sleep and diurnal slow wave and REM sleep. Subjectively, the daytime sleep was perceived as being less imperative.

Finally, although there is evidence that GHB can produce EEG and behavioral manifestations similar to petit mal epilepsy in rats (Godschalk et al., 1977) and in cats (Snead et al., 1976), no potentially epileptogenic EEG discharges were present in these very prolonged recordings or in later follow-up recordings, and no clinical seizures have occurred.

DISCUSSION

The clinical and polysomnographic changes produced by GHB during the 7-10 day period followed a parallel course. Clinically, as previously reported (Broughton and Mamelak, 1979), there was reduction both in the duration of daytime sleep and in the incidence and intensity of cataplectic attacks; and, corresponding to this, the daytime portions of polygraphic recordings showed less actual total sleep time, and less time in slow wave sleep and in REM sleep. Subjective drowsiness, however, continued to be a problem. It was reflected in the lack of any significant change in daytime stage 1 sleep, which in fact was somewhat increased. (Drowsiness was subsequently improved with methyl-phenidate.) Night sleep was perceived as being deeper and less restless. There was loss of nightmares and hallucinations, although dreaming, in a more pleasant manner, continued. Correspondingly, the nighttime portion of the recordings showed that sleep was consolidated into longer periods, there were fewer stage shifts and sleep, particularly REM sleep, was more integrated and less fragmented. Although sleep onset REM periods still occurred, and in fact were even more frequent on GHB, these differed from their pre-treatment counterparts in that they were not frightening, they never reached hallucinatory intensity, control over mentation was lost rather than maintained, and the presence of concomitant awareness of ones' surroundings, which can occur in this condition (Hishikawa, 1976; Vogel, 1976), was no longer present.

Like other investigators such as Barros-Ferriera and Lairy (1976) and Montplaisir and colleagues (1978), we were impressed by the marked dissociation and fragmentation of nocturnal (and diurnal) sleep which we found in our patients' baseline recordings. In addition to frequent sleep onset REM sleep periods, there were numerous epochs of "intermediate sleep" (i.e., simultaneous features of stage 2 and REM sleep), multiple brief sleep fragments and prolonged periods with mixed features of sleep and wakefulness. Sleep and its subcomponents appeared to have become dispersed around the 24 hours and the barriers between sleep and wakefulness to have been breached, as exemplified both by the chronic daytime drowsiness and the wakeful awareness during polygraphically monitored REM sleep, especially at sleep onset.

GHB tended to reverse these features. It produced increased consolidation and re-integration of sleep and increasingly synchronized sleep with the nocturnal period. Each dose assured a 2 to 3 hour period of sleep at about the same time each night. In each of these periods, REM sleep usually occurred at sleep onset and was followed by a period of slow wave sleep (Fig. 2). Although the renormalization of night sleep clearly was therefore not complete, each period of drug-induced sleep consisted of sleep which was more continuous, having fewer awakenings and fewer stage shifts. The subjective assessment of patients on medication was that they were truly asleep during each two to three hour drug-induced sleep period and did not experience "twilight" states of mixed sleep and wakefulness. Although the total duration per se of nocturnal sleep was not increased by GHB, the drug's nocturnal effects did alter the duration and organization of daytime sleep. There was significant decrease in the duration of both REM sleep and slow wave

sleep during the day and the individual sleep periods became shorter and more fragmented. This effect might have been more impressive statistically, had not half our patients (the Toronto inpatients) remained in bed during the day.

While on the drug our patients reported that, although they were still drowsy and even slept during the day, they were now better able to resist sleep and could stay awake, when this was necessary. Before starting treatment they averaged about 9 to 10 hours of sleep in a 24 hour period (of which 6 to 7 hours occurred at night). These total figures, which were not changed much by GHB treatment, are not very different from those recorded in ad lib sleep of normals, who will also sleep for about 10 to 12 hours in a 24 hour period, when freely permitted to do so (Hishikawa et al., 1976). Yet, under most circumstances, normals remain fully awake during the day with seven to eight hours of sleep at night or even less (Webb and Cartwright, 1978). What makes this pattern possible for them but not for narcoleptics? We suggest that it is because the night sleep of normals is more integrated than is the sleep of narcoleptics. That is, in normal sleep the component subsystems run their course for the most part in seven to eight consecutive hours usually synchronized with the nocturnal period. In narcoleptic sleep, on the other hand, the dissociation and temporal dispersion of the sleep sub-components prevents this and leads to daytime occurrence of sleep or of chronic drowsiness — a mixture of sleep and wakefulness. At the same time, the nighttime sleep of narcoleptics is rendered shallow and fragmented and loses its stable circadian pattern of deep NREM sleep concentrated in the first third of the night.

It is our thesis that the 6 to 7 hours of sleep facilitated by GHB has greater circadian stability and is a more fully integrated sleep, especially of the REM sleep state, than is that which occurs in narcoleptics in the absence of the drug. As evidence, we can cite the drug-induced decrease in the number of nocturnal sleep stage shifts, as well as the overall improvement in sleep efficiency at night. Nocturnal GHB appears to "glue" together the component subsystems of sleep and to impede their temporal dispersion around the 24-hours. As a result, daytime sleep becomes less consolidated, with stage 1 sleep, i.e., drowsiness, increasing at the expense of slow wave sleep and REM sleep. This accounts for the patients' subjective impression that they are better able to resist sleeping during the day on GHB. When small divided doses (5 to 10 mg t.i.d.) of methylphenidate were later added to the drug regimen during the day, diurnal sleep and drowsiness virtually disappeared in many patients (Broughton and Mamelak, 1979). It can be questioned whether methylphenidate would be necessary at all, if the duration of action of GHB could be extended to integrate sleep at night for a full seven to eight hours.

The decrease in the frequency and intensity of cataplectic attacks is one of the earliest and most impressive clinical benefits of GHB treatment. As the duration of the direct action of GHB (Mamelak et al., 1977) and its detectable presence in the blood (Helrich et al., 1964) last only some 2.5-3.0 hours, the daytime changes must be explained mainly or only by nocturnal effects, when the substance is given. Again, it is suggested that this results from the nocturnal sleep integrating and synchronizing actions of the drug. Cataplexy has been attributed to the dissociated selective activation of the motor inhibitory component of REM sleep (Dement et al., 1976). Our data indicate that nocturnal GHB significantly decreases the total amount of REM sleep during the day: the decline in the number of diurnal cataplectic attacks may be due to this. Other studies, moreover, have shown that daytime administration of GHB in narcolepsy-cataplexy has the apparently unique effect of being able to induce sleep paralysis (Mamelak et al., 1977). This suggests that, in addition to its facilitating or activating effect on REM sleep per se, the drug can also selectively activate the motor inhibitory component of the REM sleep state in such patients. The sensitivity of this motor process to GHB was further demonstrated recently by Mamalek, Sowden and Caruso (in press) in studies on the effect of this drug on monosynaptic transmission in the spinal cord, using the H-reflex technique. Monosynaptic transmission in known to be suppressed during REM sleep (Hodes and Dement, 1964; Hishikawa and Kaneko, 1965) as part of the motor inhibitory process during this sleep state (Pompeiano, 1976). But the studies of Mamelak, Sowden, and Caruso (in press) show that with GHB monosynaptic transmission is blocked during *both* REM and slow wave states following drug administration. Since a refractory period occurs after REM sleep (Jouvet, 1962; Pompeiano, 1976), an analogous state may also prevail after the isolated activation of the motor inhibitory process. The amelioration of daytime cataplexy may be related in this way to prolonged nocturnal activation by the drug of the motor inhibitory mechanisms of REM sleep.

Why do ordinary hypnotic drugs not benefit narcoleptic patients? It should be noted first that at times they can do so. Many narcoleptic patients use such drugs at night to improve their sleep and obtain considerable relief from their diurnal symptoms (Daniels, 1934; Zarcone, 1973). Because of their long duration of action, however, these drugs may increase daytime drowsiness (Daniels, 1934); and, in addition, their consolidating effects on nighttime sleep tend to wane as tolerance develops. Moreover, ordinary hypnotic drugs often suppress both REM sleep and slow wave sleep, and can create increased pressure, at least for REM sleep, later in the night as the drugs wear off (Kales et al., 1970). GHB has none of these disadvantages. It is rapidly metabolized and is cleared from the blood stream after two to three hours (Helrich et al., 1964), tolerance fails to develop to its hypnotic effect (Vickers, 1969), and most important, it does not appear to suppress either REM sleep or slow wave sleep or sub-components of them. In fact, in direct contrast to the synthetic hypnotics, it generally increases the duration of slow wave sleep and facilitates REM sleep (Mamelak et al., 1977).

It must be emphasized, however, that the increase in delta activity produced by GHB may not represent a

true increase in physiological slow wave sleep. GHB can paradoxically induce delta activity with the subject either awake or asleep (Metcalfe et al., 1966; Yamada et al., 1967). The overall increase in delta activity recorded in our subjects may therefore represent a drug effect rather than an increase of physiological slow wave sleep. REM sleep facilitation is a more certain property of the drug. Not only were the psychological attributes of GHB-induced REM sleep similar to those of naturally occurring REM sleep, but its polysomnographic and motor characteristics are similar as well (Mamelak et al., 1977; Mamelak, Sowden, and Caruso (in press). For these reasons, it is intriguing to speculate that GHB acts mainly or perhaps specifically on REM sleep to integrate and synchronize it with the nocturnal period and that, as a result, REM sleep becomes the focus around which the other subsystems of sleep articulate and reintegrate. A corollary of this hypothesis might be that dissociation and fragmentation of nocturnal REM sleep are the primary event in the pathogenesis of narcolepsy-cataplexy.

The results also indicate that narcolepsy symptoms based on REM sleep mechanisms can be treated adequately either by suppressing REM sleep around the 24 hours (tricyclics or MAO inhibitors) or by improving the continuity of nocturnal REM sleep (GHB or similar compounds). The latter approach would appear preferable in that it is more physiological and does not have some of the unpleasant side effects of the former, in particular that of impotence in males.

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EXHIBIT 11

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(54) **CONTROLLED RELEASE COMPOSITIONS OF GAMMA-HYDROXYBUTYRATE**

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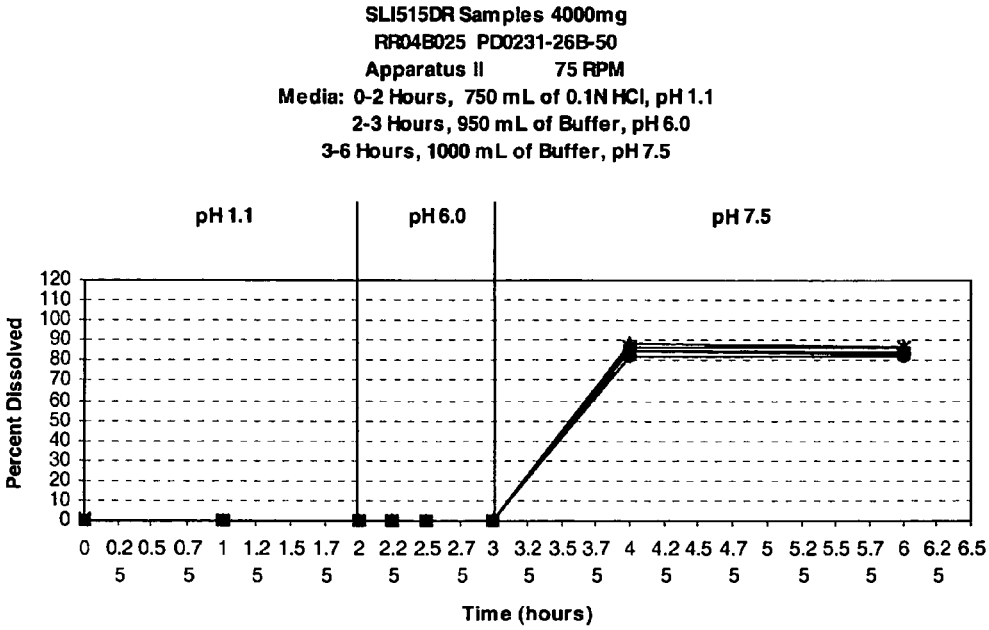
(57) **ABSTRACT**

The present invention is directed to oral pulse-release pharmaceutical dosage form containing an immediate release component of gamma-hydroxybutyric acid, and one or more delayed/controlled release components of gamma-hydroxybutyric acid.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RR04B025 PD0231-26B-50
Apparatus II 75 RPM
Media: 0-2 Hours, 750 mL of 0.1N HCl, pH 1.1
2-3 Hours, 950 mL of Buffer, pH 6.0
3-6 Hours, 1000 mL of Buffer, pH 7.5
pH 1.1
pH 6.0
pH 7.5
Percent Dissolved
120
110
100
90
80
70
60
50
40
30
20
10
0
0 0.25 0.5 0.75 1 1.25 1.5 1.75 2 2.25 2.5 2.75 3 3.25 3.5 3.75 4 4.25 4.5 4.75 5 5.25 5.5 5.75 6 6.25 6.5
Time (hours)

Figure 1

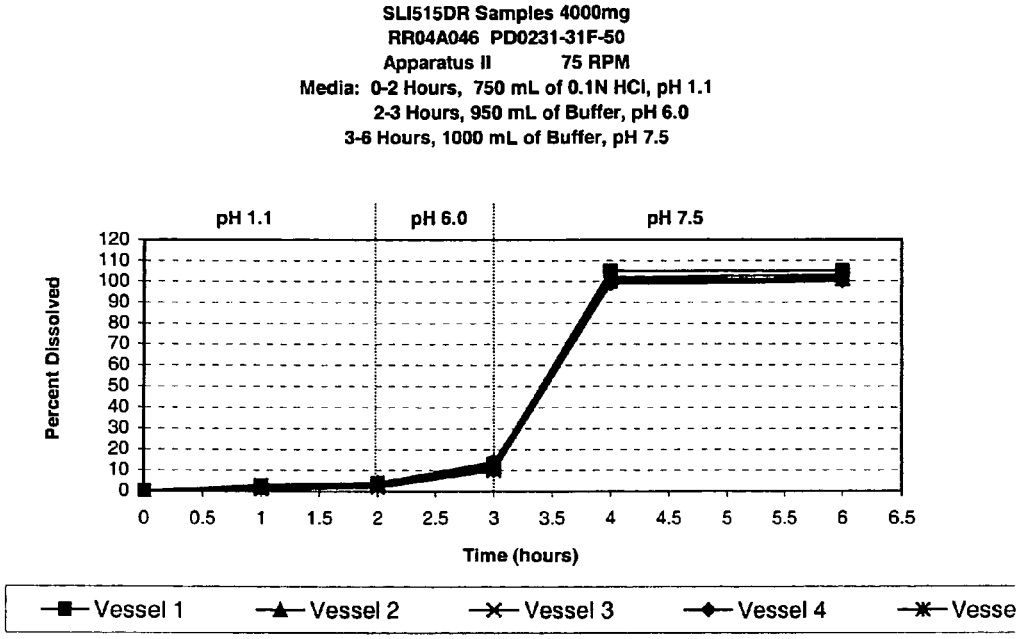

SLI515DR Samples 4000mg
RR04A046 PD0231-31F-50
Apparatus II 75 RPM
Media: 0-2 Hours, 750 mL of 0.1N HCl, pH 1.1
2-3 Hours, 950 mL of Buffer, pH 6.0
3-6 Hours, 1000 mL of Buffer, pH 7.5
pH 1.1
pH 6.0
pH 7.5
Percent Dissolved
120
110
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
Time (hours)
Vessel 1
Vessel 2
Vessel 3
Vessel 4
Vesse

Figure 2

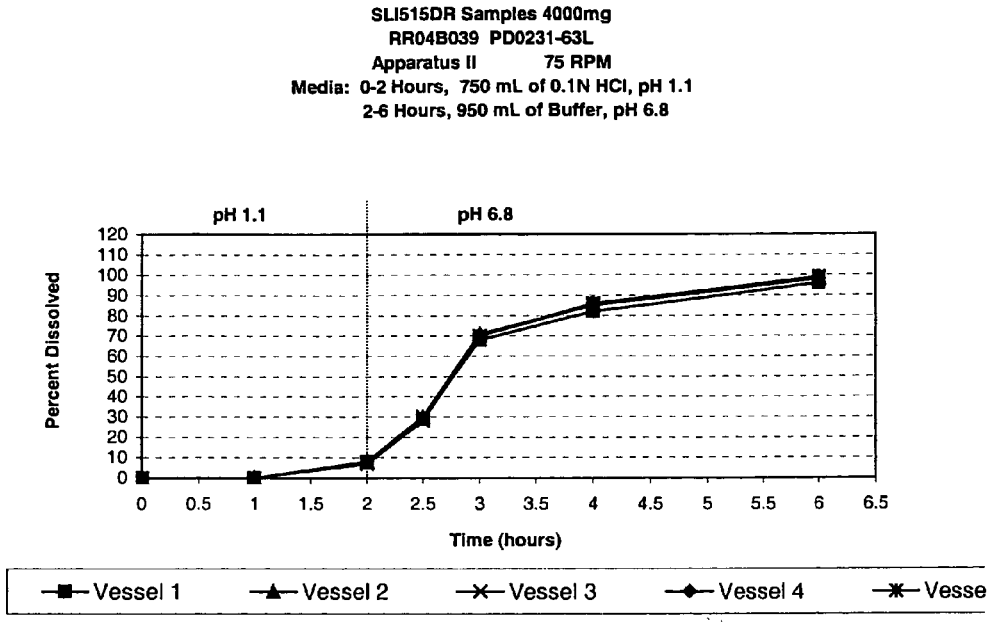

SLI515DR Samples 4000mg
RR04B039 PD0231-63L
Apparatus II 75 RPM
Media: 0-2 Hours, 750 mL of 0.1N HCl, pH 1.1
2-6 Hours, 950 mL of Buffer, pH 6.8
pH 1.1
pH 6.8
Percent Dissolved
120
110
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
Time (hours)
Vessel 1
Vessel 2
Vessel 3
Vessel 4
Vesse

Figure 3

Figure 4. Dissolution profile of an immediate release core at pH 1.1

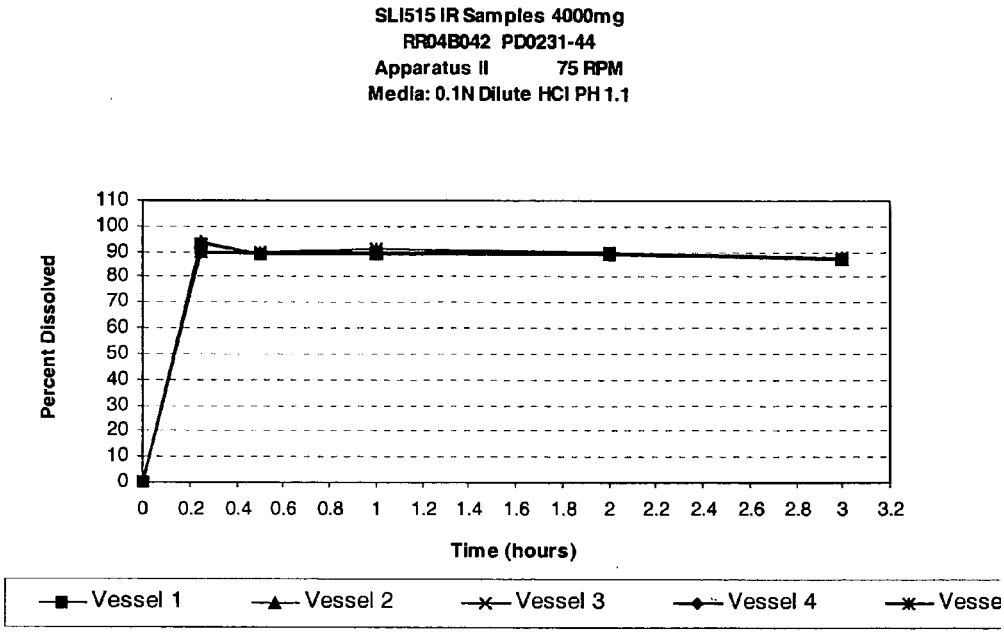


Figure 5. Dissolution profile of an Opadry AMB-coated immediate release core at pH 1.1

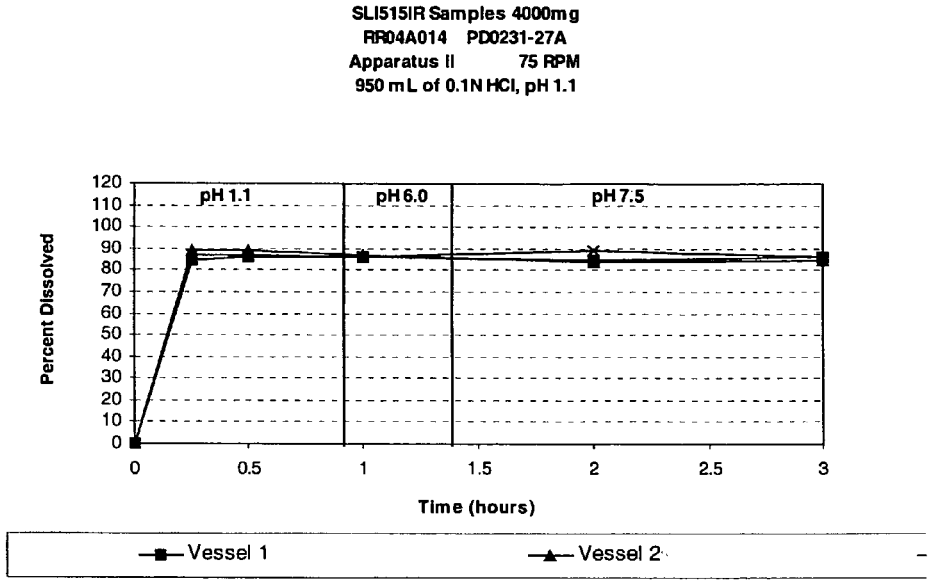
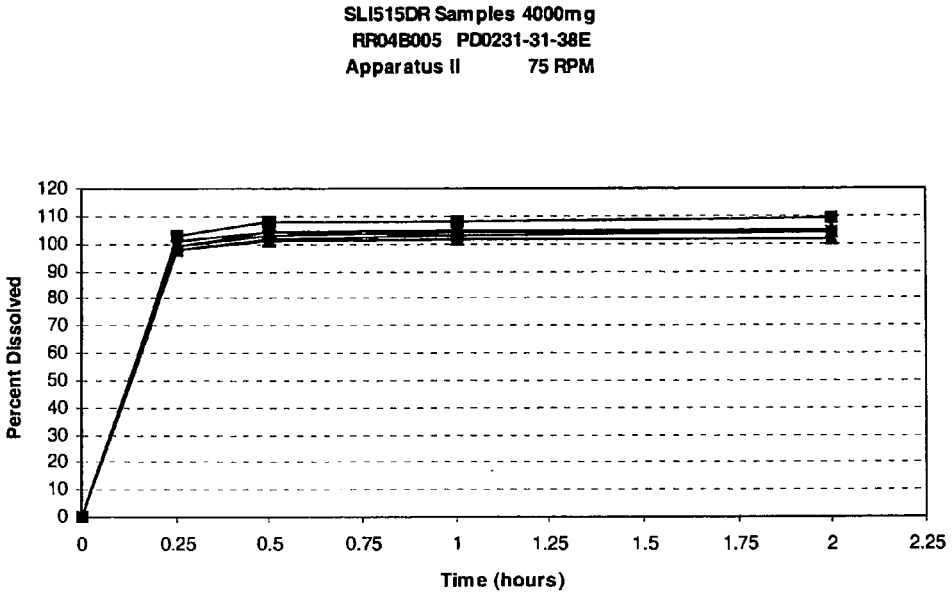


Figure 6. Dissolution profile of an EC-coated immediate release core at pH 1.1



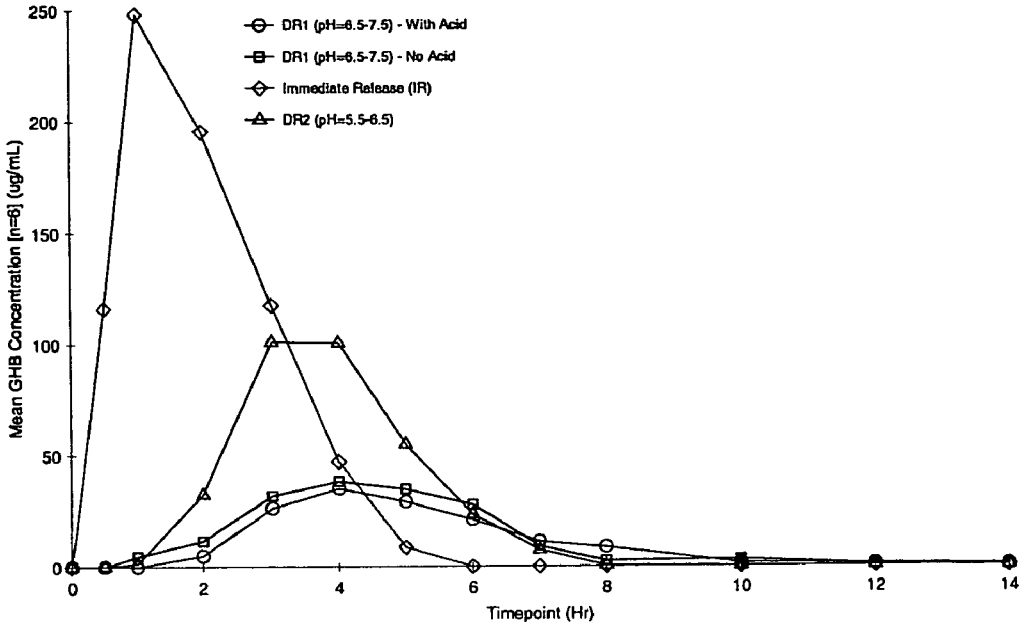

DR1 (pH=6.5-7.5) - With Acid
DR1 (pH=6.5-7.5) - No Acid
Immediate Release (IR)
DR2 (pH=5.5-6.5)
Mean GHB Concentration [n=6] (ug/mL)
250
200
150
100
50
0
0
2
4
6
8
10
12
14
Timepoint (Hr)

Figure 7

CONTROLLED RELEASE COMPOSITIONS OF GAMMA-HYDROXYBUTYRATE

FIELD OF THE INVENTION

[0001] The present invention is directed to pulse-released formulations of oxybate, or gamma-hydroxybutyric acid, salts, which reduce the number of dosages typically required for treatment. For instance, in the treatment of narcolepsy, a twice-nightly dosage regimen can be reduced to a single dose with the compositions of the present invention.

BACKGROUND OF THE INVENTION

[0002] Sodium gamma-hydroxybutyrate (GHB or sodium oxybate) is a naturally occurring metabolite of many mammalian tissues (Fishbein etal, J. Biol Chem. 239:357-61 (1964), Mamelak, Neurosci Biobehav Rev. 13(4):187-98 (1989), Nelson etal, J. Neurochem., 37:1345-48 (1981)) and has broad indications including narcolepsy, cataplexy, sleep paralysis, alcoholism, chronic schizophrenia, catatonic schizophrenia, atypical psychoses, chronic brain syndrome, neurosis, drug addiction and withdrawal, Parkinson's disease and other neuropharmacological illnesses, hypertension, ischemia, circulatory collapse, radiation exposure, cancer, myocardial infarction, anesthesia induction, sedation, growth hormone production, heightened sexual desire, anorectic effects, euphoria, smooth muscle relaxation, muscle mass production, and sleep.

[0003] Currently, sodium gamma-hydroxybutyrate is prescribed for patients with narcolepsy (Xyrem®, Orphan Medical) as a twice-nightly solution. Patients take an initial dose of sodium gamma-hydroxybutyrate around bedtime and must wake up four hours later to take a second dose. Such a dose regimen is rather inconvenient.

[0004] Other dosage forms of sodium gamma-hydroxybutyrate have also been disclosed. For example, U.S. Pat. No. 5,594,030 discloses controlled release pharmaceutical compositions of gamma hydroxybutyric acid salts consisting of a nucleus in the form of granulates or tablets which comprises GHB and a cellulosic matrix, wherein the drug substance is released within 7 to 8 hours.

[0005] Sodium gamma-hydroxybutyrate is highly soluble, hygroscopic, and strongly alkaline, and the therapeutic dose is normally very high. For example, a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients. These characteristics of sodium gamma-hydroxybutyrate have some significant effects on coated particles or tablets comprising GHB. The high solubility of sodium gamma-hydroxybutyrate likely leads to drug migration into the coating layer during the coating process, and dissolves rapidly when the coated articles encounter water or bodily fluids, creating "pores" that allow leakage of the drug from the coated articles. Further, when sodium gamma-hydroxybutyrate penetrates/diffuses into the coating film, it may interfere with the coating material itself. For example, penetrated/diffused sodium gamma-hydroxybutyrate may act as a strong base which reacts with pH sensitive coating polymers, such as Eudragit L30-D55 for instance, weakening the coating layer and lowering the coating efficiency.

[0006] Further, the absorption of sodium gamma-hydroxybutyrate seems to be capacity-limited (Palatini et al, Eur. J Clin Pharmacol. (1993) 45:353-356), but it has been unclear whether the absorption of this drug is region-specific, which would affect the oral delivery of GHB.

[0007] Therefore, a need exists in the art for a more convenient dosing regimen, an effective dosage form of controlled release of gamma-hydroxybutyric acid salts and an efficient way to deliver gamma-hydroxybutyric acid salts to an animal in the gastrointestinal tract. The current invention satisfies these needs.

SUMMARY OF THE INVENTION

[0008] It is an object of the present invention to provide a convenient and effective dosage form of GHB, whereby the number of dosages can be reduced.

[0009] It is another object of the present invention to provide compositions of GHB that have a reduced likelihood of drug migration from the dosage form.

[0010] The present invention takes into account the surprising discovery by the present inventors that the oral absorption of sodium gamma-hydroxybutyrate is region specific in animals, and that the absorption is higher in the upper GI tract than in the lower GI tract.

[0011] The present invention is also directed to methods and compositions for the targeting of the upper GI tract of an animal for improved absorption of sodium gamma-hydroxybutyrate.

[0012] The current invention provides methods and compositions for convenient administration of multiple doses of one or more gamma-hydroxybutyric acid salts to an animal. It provides a convenient once nightly or once daily dose regiment for the oral delivery of one or more gamma-hydroxybutyric acid salts to an animal. With the compositions of the present invention, a patient does not need to wake up at night to take a second dose then go back to sleep.

[0013] The current invention also provides methods and compositions for the effective delayed/controlled release of multiple (i.e., more than one) doses of one or more gamma-hydroxybutyric acid salts. The current invention provides methods and compositions to improve the gastro-stability of delayed/controlled release particulates (e.g. beads, granules, minitabs or pellets) containing gamma-hydroxybutyric acid salts.

[0014] The current invention further provides methods and compositions for the effective delivery of multiple doses of gamma-hydroxybutyric acid salts to one or more specific regions in the gastrointestinal tract of an animal. It provides methods and compositions for the targeting of the upper GI tract of an animal to improve the effectiveness of the absorption of gamma-hydroxybutyric acid salts from the delayed/controlled release particles.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIG. 1**. Dissolution profile of a colon-targeting delayed release prototype with a neutralizing agent in the barrier coat.

[0016] **FIG. 2**. Dissolution profile of a colon-targeting delayed release prototype without a neutralizing agent in the barrier coat.

[0017] **FIG. 3**. Dissolution profile of a duodenum-targeting delayed release prototype without a neutralizing agent in the barrier coat.

[0018] **FIG. 4**. Dissolution profile of an immediate release core of the present invention.

[0019] **FIG. 5**. Dissolution profile of an Opadry AMB-coated immediate release core of the present invention.

[0020] **FIG. 6**. Dissolution profile of an ethylcellulose-coated immediate release core of the present invention.

[0021] **FIG. 7**. Dog pharmacokinetic profiles—demonstrating region of absorption.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The current invention provides methods and compositions for convenient administration of multiple (i.e. more than one, "pulsed") doses of one or more gamma-hydroxybutyric acid salts to an animal.

[0023] It also provides methods and compositions for the effective delayed/controlled release of multiple doses of one or more gamma-hydroxybutyric acid salts.

[0024] The current invention provides methods and compositions to improve the gastro-stability of the delayed/controlled release particles containing gamma-hydroxybutyric acid salts.

[0025] The current invention further provides methods and compositions for the effective delivery of multiple doses of gamma-hydroxybutyric acid salts to one or more specific regions in the gastrointestinal tract of an animal for effective absorption.

[0026] Specifically, at the essence of the present invention is a dosage form comprising one or more pH sensitive delayed/controlled release particles (e.g. beads, granules, minitabs or pellets), wherein each of the pH sensitive delayed/controlled release particles is composed of an immediate release core comprising one or more gamma-hydroxybutyric acid salts and one or more pharmaceutically acceptable excipients, one or more barrier coats surrounding such core (with or without a neutralizing agent), a pH sensitive enteric release coat around said barrier coat, and optionally an overcoat.

[0027] The dosage forms of the current invention comprise an immediate release component in the form of a solid, a semi-solid or a liquid, comprising one or more gamma-hydroxybutyric acid salts and optionally one or more pharmaceutically acceptable excipients, wherein the immediate release component is present together with (or separated contained from) one or more pH sensitive delayed/controlled release particles.

[0028] The dosage forms thus provide, which administered together or sequentially, multiple release pulses of gamma-hydroxybutyric acid salts targeting multiple regions in the gastrointestinal tract of an animal for improved absorption.

[0029] In one of the preferred embodiments, the composition comprises multiple delayed release pellets or beads (used interchangeably herein) and an immediate release component. In a most preferred embodiment, the dosage form comprises a liquid immediate release component, and two delayed/controlled release pellets/beads.

[0030] Each of the pH sensitive delayed/controlled release particles in the current invention is designed to release its contents at a specific region in the gastrointestinal tract of an animal. The one or more pH sensitive delayed/controlled release particles releases the contents at one or more corresponding regions in the gastrointestinal tract of an animal.

[0031] The immediate release component, in the form of a solid, a semi-solid or a liquid, of the current invention releases its contents immediately for absorption upon oral administration. Preferably, due to the high dosage of GHB, the immediate release component is a liquid.

[0032] Combining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete once-nightly or once-daily dose. The term "combining" as used herein means supplying and consuming all components (1) simultaneously in the same presentation or dosage form, or (2) simultaneously in different presentations or dosage forms, or (3) sequentially in the same presentation or dosage forms, or (4) sequentially in different presentations or dosage forms.

[0033] For example, an immediate release component in the form of particles and one or more pH sensitive delayed/controlled release particles are supplied as pre-mixed doses, and are consumed simultaneously at the time of dosing. Or, an immediate release component in the form of particles and one or more pH sensitive delayed/controlled release particles are supplied in separated parts, and are consumed simultaneously at the time of dosing. Alternatively, an immediate release component in the form of a powder and one or more pH sensitive delayed/controlled release particles are supplied in separate parts, and are consumed simultaneously at the time of dosing. In another embodiment, an immediate release component in the form of a solution and one or more pH sensitive delayed/controlled release particles are supplied in separate parts, and are consumed simultaneously at the time of dosing. Or, an immediate release component in the form of a solution and one or more pH sensitive delayed/controlled release particles are supplied in separated parts, and are consumed sequentially at the time of dosing. Other permutations would be apparent in those skilled in the art.

[0034] In one embodiment of the present invention, the delayed/controlled release component(s) is/are administered prior to the immediate release component, which can be administered from several minutes to about a half hour or more later (for practical reason, likely no more than about an hour later because the patient will become somewhat sleepy from the first dose). Thus, in it's most basic form, the present invention is directed to the delayed/controlled release component(s), which have utility as a separately administrable dosage form. These components can be supplied as a separate entity, and preferable used in conjunction with an immediate release dosage form as is currently marketed.

[0035] Multiple (i.e. more than one) delayed releases can be achieved by combining multiple pH sensitive delayed/controlled release particles targeting certain sites of the GI tract of an animal. For example, an immediate release component can be combined with two pH sensitive delayed/controlled release particles that are released at two different sites in the GI tract to provide an immediate release and two other delayed release pulses.

[0036] An immediate release component can be combined with one type of pH sensitive delayed/controlled release particles to provide two pulses of gamma-hydroxybutyric acid salts, which can conveniently replace the nightly multi-dose regimen of the existing commercial product. In this case, a patient does not need to wake up and take a second dose during the night, as described earlier.

[0037] Preferably, an immediate release component is combined with one or more pH sensitive delayed/controlled release particles to provide multiple releases in a period of time. Preferably, an immediate release component is combined with one or more pH sensitive delayed/controlled release particles targeted to the upper GI tract of an animal. The inventors discovered that the absorption of sodium gamma-hydroxybutyrate in the GI tract of an animal is site specific, and that the absorption of sodium gamma-hydroxybutyrate in the upper GI tract is higher than in the lower GI tract. The aforementioned combination therefore provides an initial dose and one or more delayed doses of gamma-hydroxybutyric acid salts, thereby providing an effective and convenient dose regimen for treating a patient.

[0038] More preferably, an immediate release component is combined with a single type of pH sensitive delayed/controlled release particles targeted to the duodenum or the jejunum of an animal to provide a two-pulse regiment to treat a patient.

[0039] The dose ratio of the immediate release component to one or more pH sensitive delayed/controlled release particles is dictated by the type of therapy and readily determined by the clinician, using currently available dosages as a reference. For example, the immediate release dose can be equivalent of, higher than, or lower than, the one or more delayed release doses.

[0040] It is contemplated that the delayed release dose amount, which is used to replace the second nightly dose (currently as a solution) in the current treatment of narcolepsy patients, can be the same as the immediate release dose amount, although the bioavailability is lower further along the GI tract, or even at a reduced dose amount, since the patients do not need to wake up and take a separate second nightly dose then go back to sleep.

[0041] It is also contemplated that the immediate release component can be at a slightly higher than normal dose, and the delayed release dose can be at a normal dose or at a reduced dose.

[0042] It is also contemplated that an immediate release component can be combined with one or more pH sensitive delayed/controlled release particles that are at reduced doses. For example, an immediate release dose can be combined with 0.7 equivalent dose of a duodenum-targeting delayed release component and 0.2 equivalent dose of a colon-targeting delayed release component to give a broader time coverage.

[0043] The immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can be administered to an animal directly, or mixed/sprinkled with fluids, soft foods (i.e. yogurt, applesauce), or pharmaceutically acceptable carriers. For example, an immediate release component in the form of a solution can be mixed with juice and the pH sensitive delayed/controlled release particles can be combined with foods (such as yogurts) for administration. Or, an immediate release component in the form of particles and the pH sensitive delayed/controlled release particles can be sprinkled with drinkable yogurt for dosing.

[0044] The Immediate Release Component

[0045] The dosage forms of the current invention comprise an immediate release component in the form of a solid, a semi-solid or a liquid. It can be a particle, a bead, a pellet, a granulate, a powder, a tablet, a minitablet, a capsule, a caplet, a lozenge, a hard shell or soft shell capsule, a sachet, a cachet, a solid dispersion, a solid solution, a suspension, an emulsion, a lotion, a solution, a liquid drop, an elixir, a syrup, a tincture, a liquid spray, an aerosol, a gel, an ointment, a cream, or the like.

[0046] The immediate release component can be present together with one or more of the pH sensitive delayed/controlled release particles described herein, or separated from the pH sensitive delayed/controlled release particles.

[0047] For example, the immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed/controlled release particles. Or the two components can be provided as separate parts, possibly in a kit, wherein both components can be consumed together, or separately in a sequential manner.

[0048] In another example, the immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion. In this embodiment, the immediate release component is a powder comprising up to 100% of one or more gamma-hydroxybutyric acid salts and optionally one or more pharmaceutically acceptable excipients. Such a powder can be taken as is, or preferably is stirred into a drink or food along with the delayed/controlled release beads/pellets/minitabs.

[0049] In another preferred embodiment, the immediate release component is an aqueous solution (like the current Xyrem® product) of one or more gamma-hydroxybutyric acid salts stabilized with antioxidants, stabilizers, preservatives and neutralizing agents.

[0050] In yet another example, which is preferred because of the very high dosage needed for this drug, the immediate release component can be in the form of a solution that is provided separately from the pH sensitive delayed/controlled release particles, possibly in a kit form. The immediate release component is an aqueous solution (like the current Xyrem®) product) of one or more gamma-hydroxybutyric acid salts stabilized with antioxidants, stabilizers, preservatives and neutralizing agents. Preferably, the delayed release particles are mixed with the liquid and then ingested.

[0051] The immediate release component of the current invention comprises one or more gamma-hydroxybutyric acid salts and optionally one or more pharmaceutically acceptable excipients, wherein the gamma-hydroxybutyric acid salts are selected from gamma-hydroxybutyric acid sodium salt, gamma-hydroxybutyric acid potassium salt, gamma-hydroxybutyric acid tetraammonium salt, or any other pharmaceutically acceptable salt forms of gamma-hydroxybutyric acid.

[0052] The immediate release component comprises from about 20% to about 100% by weight of one or more gamma-hydroxybutyric acid salts and optionally one or more pharmaceutically acceptable excipients.

[0053] The pharmaceutically acceptable excipients in the immediate release component are those known in the art as suitable for use in solid, semi-solid or liquid dosage forms, including but not limited to, binders, lubricants, anti-adherents, glidants, granulating aids, fillers, disintegrants, antioxidants, stabilizers, preservatives, neutralizing agents, buffering agents, tonicifiers, moisture absorbents, colorants, flavorants, sweeteners, sugars, and taste-masking agents, suspending agents, thickening agents, gelling agents, solvents, solubilizers, surfactants, absorption enhancers, emulsifying agents, and combinations thereof.

[0054] The total amount of these pharmaceutically acceptable excipients in the immediate release component is from about 0% to about 80% by weight.

[0055] Examples of these pharmaceutically acceptable excipients in the immediate release component of the current invention include, but are not limited to, binders/fillers: microcrystalline cellulose, silicified microcrystalline cellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, starch, pregelatinized starch, starch paste, lactose, mannitol, sorbitol, xylitol, sucrose, calcium phosphate, calcium carbonate, ethylcellulose, methylcellulose, and Acacia; lubricants/anti-adherents/glidants/granulating aids: talc, sodium lauryl fumarate, fumed silicon dioxide, colloidal silica, titanium dioxide, kaolin, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, and sodium lauryl sulfate; disintegrants: sodium starch glycolate, croscarmellose sodium, cross-linked polyvinylpyrrolidone, and alginic acid; antioxidants/stabilizers/preservatives: riboflavin, tocopherol, vitamin E TPGS, BHT, BHA, cysteine and derivatives, ascorbates, sorbates, benzoates, propionates, bicarbonates, thiosulfates, metabisulfites, EDTA, carrageen, gums and benzyl alcohol; neutralizing agents: acids such as malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, polyacids, acidic ionic resins, and other acidic excipients; suspending agents/thickening agents/gelling agents: mineral oils, vegetable oils, silicon dioxide, various gums such as xanthan gum, locust bean gum, gum Arabic, alginates, Carbopols, polyvinyl alcohols, carrageenan, gelatin, starches; or mixtures thereof.

[0056] Preferably, if the immediate release component is a solid pellet, bead or minitablet or the like, that component is also used as the immediate release core of the pH sensitive delayed/controlled release particles by coating them using materials and methods similar to the barrier coats or the overcoat as described herein.

[0057] Delayed/Controlled Release Particles

[0058] The immediate release core of the pH sensitive delayed/controlled release particles (i.e., beads, pellets, minitabs, granulate, etc.) of the current invention comprises from about 20% to about 99% of one or more gamma-hydroxybutyric acid salts by weight of the core and one or more pharmaceutically acceptable excipients, wherein the gamma-hydroxybutyric acid salts are selected from gamma-hydroxybutyric acid sodium salt, gamma-hydroxybutyric acid potassium salt, gamma-hydroxybutyric acid tetraammonium salt, or any other pharmaceutically acceptable salt forms of gamma-hydroxybutyric acid, or combinations thereof.

[0059] One or more pharmaceutically acceptable excipients in the immediate release core of the pH sensitive delayed/controlled release particles of the current invention are excipients known in the art as suitable for use in particulates, including but not limited to binders, lubricants, anti-adherents, glidants, granulating aids, fillers, disintegrants, antioxidants, stabilizers, preservatives, neutralizing agents, buffering agents, moisture absorbents, colorants, flavorants and task-masking agents.

[0060] The total amount of these pharmaceutically acceptable excipients in the immediate release core is from about 1% to about 80% by weight of the core.

[0061] Examples of these pharmaceutically acceptable excipients in the immediate release core of the current invention include, but are not limited to, binders/fillers: microcrystalline cellulose, silicified microcrystalline cellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, starch, pregelatinized starch, starch paste, lactose, mannitol, sorbitol, xylitol, sucrose, calcium phosphate, calcium carbonate, ethycellulose, methylcellulose, and Acacia; lubricants/anti-adherents/glidants/granulating aids: talc, sodium lauryl fumarate, fumed silicon dioxide, colloidal silica, titanium dioxide, kaolin, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, and sodium lauryl sulfate; disintegrants: sodium starch glycolate, croscarmellose sodium, cross-linked polyvinylpyrrolidone, and alginic acid; antioxidants/stabilizers/preservatives: riboflavin, tocopherol, vitamin E TPGS, BHT, BHA, cysteine and derivatives, ascorbates, sorbates, benzoates, propionates, bicarbonates, thiosulfates, metabisulfites, EDTA, carrageen, gums and benzyl alcohol; neutralizing agents: acids such as malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, polyacids, acidic ionic resins, and other acidic excipients; or mixtures thereof.

[0062] Preferably, the immediate release core of the current invention comprises one or more excipients selected from binders, lubricants, anti-adherents, glidants and neutralizing agents.

[0063] The lubricants/anti-adherents/glidants may be selected from talc, sodium lauryl fumarate, fumed silicon dioxide, magnesium stearate and stearic acid, for instance. Preferably, the lubricants/anti-adherents/glidants are selected from one or both of talc and magnesium stearate.

[0064] In a preferred embodiment, the amount of talc in the immediate release core of the current invention about 1% to about 25% by weight of the core. More preferably, this amount is from about 5% to about 15% by weight of the core.

[0065] If magnesium stearate is used in the core it is present in an amount of from about 0% to about 10% by weight of the core. More preferably, this amount is from about 0.1% to about 5% by weight of the core.

[0066] Preferably, the binders/fillers in the immediate release core are selected from microcrystalline cellulose, silicified microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl cellulose.

[0067] Preferably, the immediate release core comprises microcrystalline cellulose or silicified microcrystalline cellulose at about 1% to about 80%% by weight of the core. More preferably, the immediate release core comprises microcrystalline cellulose or silicified microcrystalline cellulose at about 3% to about 40% by weight of the core.

[0068] Preferably, the immediate release core comprises a neutralizing agent. The uptake of gamma-hydroxybutyric acid salts may be affected by the environmental pH and the ionization state of the salts. Preferably, the immediate release core contains a neutralizing agent to modulate the ionization state of the salt for better absorption in the gastrointestinal tract.

[0069] The immediate release cores in the pH sensitive delayed/controlled release particles of the current invention are made by techniques and equipment known in the art, for example dry blending, milling, dry granulation, wet granulation, pelletization, direct pelletization, extrusion, melt-extrusion, spheronization, drug layering, compaction, compression. Solvents can be used to facilitate the preparation of the immediate release core. These solvents can be removed partially or completely during the preparation of the core. Suitable solvents include, but are not limited to, water, alcohols, ketones and combinations thereof. For example, water and/or alcohols can be used during wet granulation and spheronization, or during direct pelletization, or during drug layering, and the solvents can be removed thereafter.

[0070] Barrier Coat(s)

[0071] One or more barrier coats applied to the pH sensitive delayed/controlled release particles of the current invention provides a barrier, and a neutralization zone when a neutralizing agent is used, between the immediate release core and the enteric coat, and functions to prevent gamma-hydroxybutyric acid salts from entering into or interfering with the enteric coat. The barrier coats can optionally act also as a controlled release coat to control the rate of release of gamma-hydroxybutyric acid salts from the immediate release core.

[0072] The barrier coats in the current invention provide a barrier and optionally a neutralization zone between the immediate release core and the enteric coat to prevent the alkalinic gamma-hydroxybutyric acid salts from migrating into and interfering with the pH sensitive enteric coat. If the highly water-soluble and strongly alkalinic gamma-hydroxybutyric acid salts migrate into the enteric coat, they not only create channels in the enteric coat which act as pore formers, but also react with the functional groups of the coat materials and weaken the enteric coat. By controlling the thickness and/or the permeability of the barrier coats, the migration of gamma-hydroxybutyric acid salts can be minimized. Further, neutralizing agents, mainly acidifiers, can be used in the barrier coat to neutralize gamma-hydroxybutyric acid salts in the barrier layer thus preventing these alkalinic salts from reacting with the enteric coat material.

[0073] Moreover, the barrier coats can optionally act as a controlled release coat to control the rate of release of gamma-hydroxybutyric acid salts from the immediate release core, allowing for site specific and controlled release of gamma-hydroxybutyric acid salts in the GI tract of an animal.

[0074] Suitable coating materials for the barrier coats in the current invention include, but are not limited to, cellulosic polymers such as ethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate, polyvinyl alcohol, or other water-based or solvent-based coating materials.

[0075] Suitable neutralizing agents in the barrier coats of the current invention include, but are not limited to, acids such as malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, polyacids (a polymer with multiple carboxylic acid functional groups or side chains, e.g. polymethacylic acid, or molecules with multiple acid functional groups, e.g. EDTA, ethylenediaminetetraacetic acid), acidic ionic resins, and other acidic excipients, and are used in amounts sufficient to neutralize any migrating gamma-hydroxybutyric acid salts. Preferably, the amount of neutralizing agent in the barrier coat is at about 0.01% to about 10% movmol of the gamma-hydroxybutyric acid salts in the core. More preferably, this amount is at about 1% to about 5% mol/mol of the salts.

[0076] The barrier coats in the current invention can further comprise other additives known in the art, such as pore formers, plasticizers, anti-adherents, glidants, and anti-foam agents. Pore formers suitable for use in the barrier coats of the invention are organic or inorganic agents, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. Examples of the pore formers include, but are not limited to, organic compounds such as saccharides including sucrose, glucose, fructose, mannitol, mannose, galactose, sorbitol, pullulan, dextran; polymers soluble in the environment of use such as water-soluble hydrophilic polymers, hydroxyalkylcelluloses, carboxyalkylcelluloses, hydroxypropylmethylcellulose, cellulose ethers, acrylic resins, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, polyethylene oxide, Carbowaxes, Carbopol, and the like, diols, polyols, polyhydric alcohols, polyalkylene glycols, polyethylene glycols, polypropylene glycols, or block polymers thereof, polyglycols, poly(a-w)alkylenediols; inorganic compounds such as alkali metal salts, lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, suitable calcium salts, and the like. The amount of pore formers used in the barrier coats varies depending on the functions of the barrier coats. For example, if the pH sensitive delayed/controlled release particles are intended for immediate release after entering the targeted site in the GI tract, high amounts of pore formers (e.g. as high as about 50% by weight of the barrier coat) can be used. If the pH sensitive delayed/controlled release particles are for controlled release after entering the targeted site in the GI tract, little or no pore formers are used (e.g. no more than about 25% by weight of the barrier coat).

[0077] The rate of release of gamma-hydroxybutyric acid salts in the pH sensitive delayed/controlled release particles can also be controlled by varying the thickness and/or types of the barrier coats, with or without the use of pore formers. For example, when ethylcellulose is used together with PVP K30 (5%) as the pore former, or when ethylcellulose is used with or without a water-insoluble plasticizer and without the use of any pore formers, or when ethylcellulose is used with a water-soluble plasticizer such as triethyl citrate, the barrier coat can be between about % to about 20% weight gain on the particles in order to obtain different controlled release profiles. Or, when Opadry AMB is used as the barrier coat,

the barrier coat can be from about 2% to about 10% weight gain on the particles, in order to obtain an immediate release profile.

[0078] The barrier coats can also be multiple coats of different coating materials. For example, the barrier coats can have an Opadry AMB initial barrier coat, and an ethylcellulose secondary barrier coat surrounding the initial coat, and optionally an Opadry tertiary barrier coat surrounding the secondary coat.

[0079] The barrier coats can be water-based coatings, or organic solvent-based coatings. Preferably, the barrier coat is organic solvent-based coating such as an alcohol or alcohol-water or ketone based coating.

[0080] Furthermore, the barrier coats of the current invention can provide moisture protection for hygroscopic gamma-hydroxybutyric acid salts inside the barrier coats.

The pH Sensitive Enteric Coat

[0081] The pH sensitive enteric release coat of the current invention enables targeted delivery of the particles to a specific region in the GI tract. It also provides a time delay in the release of the gamma-hydroxybutyric acid salts from the pH sensitive delayed/controlled release particles of the current invention. Combinations of more than one of these pH sensitive delayed/controlled release particles in a dosage form will provide multiple doses of gamma-hydroxybutyric acid salts delivered to multiple sites in the GI tract with multiple delay time periods or pulses. When combined with any controlled release characteristics of the barrier coats, the compositions of the current invention provide a wide spectrum of combined site specific, delayed and controlled release profiles for oral delivery of gamma-hydroxybutyric acid salts to an animal.

[0082] Materials suitable for use in the pH sensitive enteric coat of the current invention are pH sensitive coating materials known in the art. The pH sensitive coating materials include, but are not limited to, methacrylate-based coating materials such as polymers of methacrylic acid and methacrylates (e.g. Eudragit L 100-55, Eudragit L 30-D55, Eudragit L 100, Eudragit S 100, Eudragit FS 30 D), cellulose-based coating materials such as cellulose acetate phthalate, carboxymethyl ethylcellulose, cellulose acetate trimellitate, hydroxypropyl methylcellu lose phthalate, hyd roxypropyl methylcellu lose acetate succinate, Shellac-based coating materials such as Emcoat 1 20N and Marcoat 125, and other enteric coating polymers such as polyvinyl acetate phthalate.

[0083] Other additives such as solvents, plasticizers (e.g. PEG, triethyl citrate, dibutyl secbate), anti-tack agents (e.g. talc), anti-foam agents, colorants, fillers/extenders, flavorants, surfactants (e.g. sodium lauryl sulfate), bases, buffers, and other suitable additives known in the art can also be used together with the pH sensitive enteric coating materials.

[0084] The coating can be organic solvent-based, or aqueous-based, or organic solvent/aqueous based.

[0085] Preferably, the pH sensitive delayed/controlled release particles are prepared by coating the barrier-coated immediate release core with an appropriate pH sensitive coating material targeting to a specific region in the GI tract of an animal. The weight gain of the pH sensitive enteric coating is from about 10% to about 70% of the final enteric-coated particle weight. Preferably, the weight gain of this coating is from about 20% to about 60% of the final enteric-coated particles. More preferably, the weight gain of this coating is about 30% to about 50% of the final enteric-coated particle weight.

[0086] The pH sensitive enteric release coat can target both the upper part and the lower part of the GI tract of an animal. The pH sensitive enteric coat releases/dissolves in one of the stomach, the duodenum, the jejunum, the ileum, or the colon of an animal. Suitable pH sensitive enteric coating materials targeting each of these regions in humans are known in the art, such as Eudragit E 100 or Eudragit E PO (stomach), Eudragit L 30 D-55 and Eudragit L 100-55 (duodenum), Eudragit L 12.5 and Eudragit L 100 (jejunum), Eudragit S 100 (ileum), and Eudragit FS 30 D (colon).

[0087] Preferably, the pH sensitive enteric release coat releases/dissolves in the upper GI tract of an animal, which will allow for better absorption of the drug. In a more preferred embodiment, the pH sensitive enteric coat releases/dissolves in the duodenum or the jejunum of an animal.

[0088] Optionally, acidifiers or bases can be added to the pH enteric coating materials to adjust the target release/dissolution pH or region in the GI tract of an animal. Further, acidifiers in the pH sensitive enteric coat can also counteract the alkaline effect from any migrating gamma-hydroxybutyric acid salts. Suitable acidifiers are organic acids or inorganic acids, acidic excipients, and the aforementioned neutralizing agents.

[0089] The delay in release of gamma-hydroxybutyric acid salts from the particles of the current invention can be achieved by selecting different pH sensitive enteric release coats targeting the desired regions of the GI tract of an animal. Combinations of various particles with different pH sensitive enteric coats thus provide multiple pulses of gamma-hydroxybutyric acid salts with various delayed release times.

Overcoats

[0090] Optionally, the immediate and/or delayed/controlled release solid dosage forms of the current invention can be coated with an overcoat. The overcoat can be a moisture barrier coat, a protection coat, a seal coat, a taste-masking coat, a flavor coat, a polish coat, a color coat, or any other cosmetic coats. Suitable coating materials for such an overcoat are known in the art, including, but are not limited to, cellulosic polymers such as hydroxypropylmethylcellulose, hydroxypropylcellulose, microcrystalline cellulose carrageenan, and ethylcellulose.

[0091] Other additives known in the art can also be used in the overcoat, such as solvents, plasticizers (e.g. PEG, triethyl citrate, dibutyl secbate), anti-tack agents (e.g. Talc), anti-foam agents, colorants, fillers/extenders, flavorants, and surfactants (e.g sodium lauryl sulfate).

[0092] The invention now will be described with respect to the following examples; however, the scope of the present invention is not intended to be limited thereby.

EXAMPLES

Example 1

Compositions of the Immediate Release Core and/or the Immediate Release Component

[0093]

TABLE 1

Ingredients	PD0231-25	PD0231-24A	PD0231-24B	PD0231-24C	PD0231-19	PD0231-17A	PD0231-16	PD0231-15A	PD0231-12	PD0231-10A
Sodium gamma-hydroxybutyrate	80	80	84	80	80	80	80	90	40	80
Avicel PH101	10	15	10	10	20	10	15	10	58	—
Talc	9	5	5	9	—	—	—	—	—	—
Magnesium stearate	1	—	1	1	—	—	—	—	—	—
SMCC 50	—	—	—	—	—	—	—	—	—	15
Emcompress	—	—	—	—	—	10	5	—	—	—
HPMC E5	—	—	—	—	—	—	—	—	2	—
PVP K30	—	—	—	—	—	—	—	—	—	5
Lactose	—	—	—	—	—	—	—	—	—	—
Water	10*	11.3*	11.3*	5.5*	11.3*	15*	15*	12*	10.5*	9*
Ethanol	—	—	—	—	—	—	—	—	—	9*

[0094]

TABLE 2

Ingredients	PD0231-10B	PD0231-10C	PD0231-9B	PD0231-8A
Sodium gamma-hydroxybutyrate	70	65	80	83
Avicel PH101	—	—	—	—
Talc	—	—	—	—
Magnesium stearate	—	—	—	—
SMCC 50	28	35	17	17
Emcompress	—	—	—	—
HPMC E5	2	—	1	—
PVP K30	—	—	—	—
Lactose	—	—	2	—
Water	20*	18*	10.8	9.5
Ethanol	—	—	—	—

Number in parts by weight.
*Removed partially or completely during preparation

Example 2

Preparation of the Immediate Release Core

[0095] The immediate release core can be made by techniques or processes or equipments known in the art, including but are not limited to dry blending, milling, dry granulation, wet granulation, pelletization, direct pelletization, extrusion, melt-extrusion, spheronization, drug layering, as exemplified by the following preparations:

[0096] Dry powders of sodium gamma-hydroxybutyric acid, Avicel PH101, Talc and magnesium stearate were screened and mixed briefly, then charged into a high shear granulator. Water was added to the mixture during the granulation. The granulates were extruded through a screen with a desirable pore size then spheronized to yield pellets. The pellets were dried in an oven for a sufficient time, for example overnight, then screened.

Example 3

Moisture Protection Coat of the Immediate Release Core

[0097] Opadry AMB Coating Solution:

Opadry AMB	25 g
Deionized water	475 g

[0098] Uncoated pellets from Example 2 (600 g) were charged into a fluid bed coater. The Opadry AMB coating solution was sprayed onto the pellets with a product temperature at 39° C. until 3% weight gain was reached to yield an Opadry AMB-coated immediate release core.

Example 4

Barrier Coats of the Immediate Release Core

[0099] Ethylcellulose Coating Solution:

Ethylcellulose	73.9 g
PV7 K90	1.72 g
Triethyl citrate	8.1 g
Isopropyl alcohol	1000 g
Ethyl alcohol	1000 g

[0100] Uncoated pellets from Example 2 (600 g) were charged into a fluid bed coater. The ethylcellulose coating solution was sprayed onto the pellets with a product temperature at 35° C. until 3%, 6% or 9.2% weight gain was reached to yield the EC-coated immediate release core.

[0101] For a slower release core, PVP K90 is used at lower levels or can be omitted.

Example 5

Neutralizing Agent-containing Barrier Coats of the Immediate Release Core

[0102] Neutralizing Agent-containing Barrier Coat Solution:

Opadry White	30 g
Malic acid	30 g
Deionized water	540 g

[0103] The 3% Opadry AMB-coated pellets (Example 3) were further coated with the neutralizing agent-containing barrier coat solution to 10% weight gain. An additional coat of Opadry AMB was also applied to some of the resultant pellets.

Example 6

pH Sensitive Enteric Release Coatings

[0104] Enteric Coating Solution 1 (Duodenum):

Eudragit L 30 D-55	840 g
Triethyl citrate	12 g
Talc	24 g
Deionized water	324 g

[0105] Enteric Coating Solution 2 (Jeiunum):

Eudragit L 100	390 g
Talc	24 g
Triethyl citrate	34 g
Isopropyl alcohol	2460 g
Acetone	377 g
Deionized water	390 g

[0106] Enteric Coating Solution 3 (Colon):

Eudragit FS 30 D	540 g
Triethyl citrate	9 g
Talc	45 g
Deionized water	304 g

[0107] (a) The ethylcellulose (EC)-coated immediate release core from Example 4 was further coated with enteric coating solution (1) to 40%, 45% or 50% weight gains to yield the duodenum-targeting particles.

[0108] (b) The EC-coated immediate release core from Example 4 was further coated with enteric coating solution (2) to 40%, 45%, 50%, or 60% weight gain to yield the jejunum-targeting particles.

[0109] (c) The Opadry AMB coated immediate release core from Example 3 was further coated with enteric coating solution (3) to 40%, 45% or 50% weight gain to yield the colon-targeting particles.

[0110] (d) The core coated with neutralizing agent-containing barrier coats from Example 5 was coated with an additional coat with enteric coating solution (3) to 40%, 45% or 50% weight gain to yield the colon-targeting particles.

Example 7

Dissolution Profiles of Various Prototypes—Gastro-Stability Improvement by the Neutralizing Agent in the Barrier Coats

Delayed/Controlled Release Prototypes

[0111] Colon-targeting prototype having a neutralizing agent (malic acid) in the barrier coat (PD0231-26B-50) does not release any sodium gamma-hydroxybutyrate at pH 1.1 and pH 6.0 for up to 3 hours (**FIG. 1**), whereas the one without the neutralizing agent in the barrier coat (PD0231-31 F-50) releases 3% at pH 1.1 in 2 hours and 12% at pH 6.0 in 1 hour (**FIG. 2**). The neutralizing agent in the barrier coats thus improves the gastro-stability of the prototypes significantly.

[0112] Immediate Release Prototypes

[0113] Immediate release core (PD031-44), Opadry AMB-coated immediate release core (PD0231-27A) and an EC-barrier coated immediate release core (PD0231-38E) all showed an immediate release profile at pH 1.1.

Example 8

Canine PK Study

[0114] Four prototypes were used in the cross-over dog PK study, including an immediate release core (as the immediate release component in the current invention, IR) (see Ex. 2), an Eudragit L 30 D-55 coated delayed release prototype (DR2) (see Ex. 6a), an Eudragit FS 30 D coated delayed release prototype (DR1-no acid) (see Ex. 6c) and an Eudragit FS 30 D coated delayed release prototype with malic acid as the neutralizing agent in the barrier coats (DR1-with acid) (see Ex. 6d). A total of 6 dogs (3 males and 3 females) were given two oral capsules of one of the prototypes containing 1 g of sodium gamma-hydroxybutyrate per capsule. There was a minimum of a 2-day washout between each dose. Blood was collected at the following time points: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 14 Hrs post dose (for atotal of 312 samples). Plasma samples were analyzed using a verified LC/MS/MS method. Relative bioavailability was determined by comparing the AUC from the delayed release prototype group to the AUC of the immediate release prototype group.

[0115] The results show that the lower in the GI, the lower the bioavailability (BA); i.e., absorption is higher at upper GI. The immediate release component has the highest BA, so GHB may be absorbed better in its acid form. The BAs for the delayed release components with or without an

neutralizer in the barrier coat do not very much so the neutralizer helps the coating—in turn the gastro-stability—but does not affect the BA. See Table 3 and **FIG. 7**.

TABLE 3

	Mean GHB Concentrations (ug/mL)			
	Period			
Time Point (Hr)	1 DR1-w/ Acid	2 DR1-No Acid	3 IR	4 DR2
0	0.00	0.00	0.00	0.00
0.5	0.00	0.00	116.04	0.00
1	0.00	4.76	248.27	1.53
2	4.99	11.62	195.51	32.52
3	26.31	31.88	117.56	100.99
4	35.14	38.26	47.21	100.57
5	29.18	34.77	8.74	54.99
6	21.09	27.83	0.00	23.42
7	11.25	9.13	0.00	7.52
8	8.67	2.53	0.00	0.34
10	1.43	3.03	0.00	0.00
12	0.98	0.67	0.00	0.00
14	0.43	0.00	0.00	0.00
Tmax (Hr)	4.2	5.2	1.2	3.7
Cmax (ug/mL)	38.77	58.44	249.5	112.7
AUClast	134.3	162.6	601.0	318.4
Rel BA	22%	27%	100%	53%

What is claimed is:

1. An oral pharmaceutical dosage form, comprising an immediate release component of gamma-hydroxybutyric acid (GHB), and one or more delayed/controlled release components of gamma-hydroxybutyric acid.

2. The oral dosage form of claim 1, wherein said delayed/controlled release components are particles containing GHB as the core, which core is immediately surrounded by a barrier coat to control the migration of GHB from the core, which in turn is surrounded by an enteric release coat that will allow release of the GHB at a predetermined pH after ingestion.

3. The oral dosage form of claim 2, wherein said barrier coat contains a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins.

4. The oral dosage form of claim 3, wherein the neutralizing agent(s) are used in amounts sufficient to neutralize any migrating gamma-hydroxybutyric acid salts.

5. The oral dosage form of claim 4, wherein said neutralizing agent(s) are used in an amount of about 0.01% to about 10% mol/mol of the GHB.

6. The oral dosage form of claim 5, wherein the amount is from about 1% to about 5% mol/mol of the GHB.

7. The oral dosage form of claim 2, wherein the barrier coat is composed of materials selected from ethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate, polyvinyl alcohol, or other water-based or solvent-based coating materials.

8. The oral dosage form of claim 2, wherein more than one barrier coat is applied to the immediate release core.

9. The oral dosage form of claim 8, wherein the immediate release core is coated with Opadry AMB as the primary barrier coat, and a secondary barrier coat surrounding it composed of ethylcellulose, and an Opadry tertiary barrier coat surrounding the secondary coat.

10. The oral dosage for of claim 2, wherein the enteric release coat is a pH sensitive material, which will allow release of GHB at a predetermined pH in the gastrointestinal tract.

11. The oral dosage form of claim 10, wherein the pH sensitive material is comprised of one or more selected from the group consisting of methacrylate-based coating materials, cellulose-based coating materials, shellac-based coating materials such as Emcoat 120N and Marcoat 125, and polyvinyl acetate phthalate.

12. The oral dosage form of claim 11, wherein the methacrylate-based coating materials are polymers of methacrylic acid and methacrylates and are selected from Eudragit E 100, Eudragit E PO, Eudragit L 12.5, Eudragit L 100-55, Eudragit L 30-D55, Eudragit L 100, Eudragit S 100, Eudragit FS 30 D.

13. The oral dosage form of claim 11, wherein the cellulose-based coating materials are selected from cellulose acetate phthalate, carboxymethyl ethylcellulose, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, and hydroxypropylmethylcellulose acetate succinate.

14. The oral dosage form of claim 11, wherein the shellac-based coating materials are selected from Emcoat 120N and Marcoat 125.

15. The oral dosage form of claim 10, wherein the pH sensitive enteric release coat allows the release of GHB in the upper gastrointestinal tract.

16. The oral dosage form of claim 15, wherein the enteric release coat is comprised of Eudragit L 30 D-55, Eudragit L 100-55, Eudragit L 12.5 and Eudragit L 100.

17. The oral dosage form of claim 11, wherein the enteric release coat further comprises acidic materials that will counteract the alkaline effects of GHB.

18. The oral dosage form of claim 1, wherein the immediate release component is a solid, a semi-solid or a liquid.

19. The oral dosage form of claim 18, wherein the immediate release form is a liquid.

20. The oral dosage form of claim 19, wherein there are two delayed release components, which are each targeted to release GHB in different regions of the gastrointestinal tract.

21. The oral dosage form of claim 20, wherein one of the delayed release components release GHB in the duodenum, and the other delayed release component releases GHB in the jejunum.

22. The oral dosage form of claim 21, wherein one of the delayed release components is a bead comprising an immediate release core surrounded by a barrier coat, which is turn is surrounded by an enteric coating comprised of Eudragit L 30 D-55 or Eudragit L 100-55, and the other delayed release component is a bead surrounded by a barrier coat, which in turn is surrounded by a coating comprised of Eudragit L 12.5 or Eudragit L100.

23. An oral pharmaceutical dosage form, comprising an immediate release component in the form of a liquid or a powder, and at least one delayed release component, the delayed release component and the immediate release component being in separate forms.

24. The oral dosage form of claim 23, wherein all of the components are mixed together prior to ingestion.

25. The oral dosage form of claim 23, wherein all of the components are mixed together in the presence of a food, which is then ingested.

26. The oral dosage form of claim 23, wherein the at least one delayed release component is ingested first, followed by ingestion of the immediate release dosage form up to about one hour later.

27. The oral dosage form of claim 2, wherein the core further comprises one or more excipients selected from binders, lubricants, anti-adherents, glidants and neutralizing agents.

28. The oral dosage form of claim 27, wherein the excipients are selected from talc, sodium lauryl fumarate, fumed silicon dioxide, magnesium stearate, and stearic acid.

29. The oral dosage form of claim 27, wherein the excipients are selected from on or both of talc and magnesium stearate.

30. The oral dosage form of claim 29, wherein the talc is present in an amount of about 1% to about 25% by weight of the core.

31. The oral dosage form of claim 30, wherein the amount of talc present is between about 5% and about 15% by weight of the core.

32. The oral dosage form of claim 29, wherein the magnesium stearate is present in an amount of about 0.1% to 10% by weight of the core.

33. The oral dosage form of claim 32, wherein the amount of magnesium stearate is from about 0.1% to about 5% by weight of the core.

34. The oral dosage form of claim 1, wherein the immediate release component is present in an amount that is equivalent to, higher than, or less than the amount of the one or more delayed/controlled release components.

35. The oral dosage form of claim 1, wherein the dose of the delayed/controlled release component(s) is/are less than the dose of the immediate release component.

36. The oral dosage form of claim 35, wherein the immediate release component is combined with a 0.7 equivalent dose of a duodenum-targeting delayed release component, and 0.2 equivalent dose of a colon-targeting delayed release component.

37. An oral pharmaceutical composition, comprising one or more delayed/controlled release components of gamma-hydroxybutyric acid.

38. The composition of claim 37, wherein said delayed/controlled release component(s) are particles containing GHB as the core, which core is immediately surrounded by a barrier coat to control the migration of GHB from the core, which in turn is surrounded by an enteric release coat that will allow release of the GHB at a predetermined pH after ingestion.

39. The composition of claim 38, wherein said barrier coat contains a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins.

40. The composition of claim 39, wherein the neutralizing agent(s) are used in amounts sufficient to neutralize any migrating gamma-hydroxybutyric acid salts.

41. The composition of claim 40, wherein said neutralizing agent(s) are used in an amount of about 0.01% to about 10% mol/mol of the GHB.

42. The composition of claim 41, wherein the amount is from about 1% to about 5% mol/mol of the GHB.

43. The composition of claim 38, wherein the barrier coat is composed of materials selected from ethylcellulose, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, cellulose acetate, cellulose acetate phthalate, polyvinyl alcohol, or other water-based or solvent-based coating materials.

44. The composition of claim 38, wherein more than one barrier coat is applied to the immediate release core.

45. The composition of claim 44, wherein the immediate release core is coated with Opadry AMB as the primary barrier coat, and a secondary barrier coat surrounding it composed of ethylcellulose, and an Opadry tertiary barrier coat surrounding the secondary coat.

46. The composition of claim 38, wherein the enteric release coat is a pH sensitive material, which will allow release of GHB at a predetermined pH in the gastrointestinal tract.

47. The composition of claim 46, wherein the pH sensitive material is comprised of one or more selected from the group consisting of methacrylate-based coating materials, cellulose-based coating materials, shellac-based coating materials such as Emcoat 120N and Marcoat 125, and polyvinyl acetate phthalate.

48. The composition of claim 47, wherein the methacrylate-based coating materials are polymers of methacrylic acid and methacrylates and are selected from Eudragit E 100, Eudragit E PO, Eudragit L 12.5, Eudragit L 100-55, Eudragit L 30-D55, Eudragit L 100, Eudragit S 100, Eudragit FS 30 D.

49. The composition of claim 47, wherein the cellulose-based coating materials are selected from cellulose acetate phthalate, carboxymethyl ethylcellulose, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, and hydroxypropylmethylcellulose acetate succinate.

50. The composition of claim 47, wherein the shellac-based coating materials are selected from Emcoat 120N and Marcoat 125.

51. The composition of claim 46, wherein the pH sensitive enteric release coat allows the release of GHB in the upper gastrointestinal tract.

52. The composition of claim 51, wherein the enteric release coat is comprised of Eudragit L 30 D-55, Eudragit L 100-55, Eudragit L 12.5 and Eudragit L 100.

53. The composition of claim 47, wherein the enteric release coat further comprises acidic materials that will counteract the alkaline effects of GHB.

54. The composition of claim

55. A method for the treatment of a subject in need of the effects of GHB, comprising administering an effective amount of the oral dosage form of claim 1 to the subject.

56. The method of claim 37, wherein the subject is a human.

* * * * *

EXHIBIT 12

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Pharmacokinetics of γ-hydroxybutyric acid in alcohol dependent patients after single and repeated oral doses

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1 The pharmacokinetics of γ-hydroxybutyric acid (GHB) were studied in 10 alcohol dependent subjects after single and repeated therapeutic oral doses (25 mg kg^{-1} every 12 h for 7 days).

2 GHB was readily absorbed and rapidly eliminated (t_{max} = 20–45 min; mean $t_{½z}$ 27 ± 5 s.d. min). Urinary recovery of unchanged GHB was negligible (< 1% of the dose). γ-butyrolactone was not detected in either plasma or urine, indicating that lactonization of GHB does not occur *in vivo*.

3 The multiple-dose regimen resulted neither in accumulation of GHB nor in time-dependent modification of its pharmacokinetics.

4 In five subjects, the data were consistent with nonlinear elimination kinetics of GHB. Administration of a 50 mg kg^{-1} dose to these subjects resulted in significant increases in dose-normalized AUC, $t_{½z}$ and mean residence time.

5 Doubling of the dose also resulted in a significant increase in t_{max} with little change in C_{max}.

6 At the administered doses, GHB did not accumulate in the plasma and caused no serious side effects.

Keywords γ-hydroxybutyric acid pharmacokinetics alcohol dependence

Introduction

γ-hydroxybutyric acid (GHB) is present in the mammalian brain with highest concentrations in the hypothalamus and basal ganglia (Snead & Morley, 1981). It appears to function as a neurotransmitter or a neuromodulator rather than as an incidental metabolite of γ-aminobutyric acid (Vayer *et al.*, 1987). GHB has been used as an intravenous anaesthetic agent (Laborit *et al.*, 1960) and in the treatment of sleep disorders (Mamelak *et al.*, 1986). Following the demonstration of its effectiveness in inhibiting voluntary ethanol consumption and suppressing the ethanol withdrawal syndrome in rats physically dependent on ethanol (Fadda *et al.*, 1983, 1989), GHB has been used in oral, non-hypnotic doses to treat the effects of alcohol withdrawal in man (Gallimberti *et al.*, 1989). Of the various mechanisms proposed for this therapeutic effect, inhibition of dopamine release (Gessa *et al.*, 1966; Walters *et al.*, 1973), increase in acetylcholine release (Stadler *et al.*, 1974), GABAergic actions (Anden & Stock, 1973; Roth & Nowycky, 1977), and interaction with GHB specific receptors (Vayer *et al.*, 1987), none has been established conclusively.

Following intravenous administration of high doses of GHB to dogs, evidence of nonlinear elimination kinetics has been obtained, with apparent half-lives of 1–2 h (Shumate & Snead, 1979; Van der Pol *et al.*, 1975). Both absorption and elimination have been shown to be capacity-limited in rats (Arena & Fung, 1980; Lettieri & Fung, 1979). Few data are available on the pharmacokinetics of GHB in man. Thus, there is an anecdotal report of dose-dependent elimination kinetics ($t_{½}$ = 0.5–5 h) (Vree *et al.*, 1976).

The aim of this study was to characterize the kinetics of GHB after oral administration to alcohol dependent patients and to assess any accumulation or time-dependent changes on multiple dosing.

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Methods

Patients

The study was carried out in 10 male subjects attending the 3rd Medical Division of Padova General Hospital for treatment of alcohol withdrawal syndrome and alcohol dependence. After the protocol of the study was approved by the University of Padova Medical School Ethics Committee, and after the purpose and the procedures of the study were fully explained, all subjects gave informed and written consent to participate.

A complete preliminary clinical examination, routine biochemical and haematological screening, and laboratory tests of kidney and liver functions were performed before the study. All subjects were in good nutritional state, not suffering from decompensated liver diseases or other severe organic illnesses. All patients had normal kidney function as assessed from the levels of serum creatinine (<120 μmol l^{-1}) and blood urea nitrogen (<7.5 mmol l^{-1}). Physical characteristics of the patients, results of liver function tests and concomitant medications are shown in Table 1. Subject 6 suffered from the manic type of manic-depressive psychosis, but was free from psychotic symptoms on admission to the hospital and during the course of the study. Subjects 7 and 8 had biopsy-proven liver cirrhosis in a compensated stage (grade A according to Child's classification; Conn, 1981). Apart from subject 8, all subjects were smokers (6 to 20 cigarettes per day) but they abstained from smoking during the preceding week and the whole period of study.

Study protocol

At 07.00 h after an overnight fast, GHB dissolved in a black cherry syrup (CT, Sanremo, Italy) was administered to each patient at a dose of 25 mg kg^{-1} every 12 h for a minimum of 7 days. Venous blood samples were collected through an indwelling catheter into heparinized plastic tubes at 0, 10, 15, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 12 h after the first dose and after the 13th dose on the seventh day. Urine was collected before dosing and at 0 to 4, 4 to 8 and 8 to 12 h after the 1st and 13th doses. Five of the 10 subjects were given a single 50 mg kg^{-1} dose of GHB on the 10th day and plasma and urine samples were taken as on days 1 and 7. Plasma and urine samples were stored at −40° C for 1 day prior to assay. Preliminary experiments showed the GHB was stable during this time.

Analytical methods

Plasma and urine samples (2 ml) acidified with perchloric acid 0.8 N (plasma) and hydrochloric acid 6 N (urine), were heated at 80° C for 20 min to convert GHB to butyrolactone (GBL) (Lettieri & Fung, 1979; Van der Pol *et al.*, 1975). Omission of this step indicated that no GBL was present in the samples as a metabolite of GHB. After adjusting the pH to 6.5 and adding internal standard (δ-valerolactone), plasma and urine samples were extracted with benzene, centrifuged and concentrated under a stream of nitrogen. Aliquots (3 μl) of the final solutions were injected into a Hewlett Packard (HP) 5790 gas chromatograph coupled to an HP 5970 A Mass Selective Detector (MSD), equipped with an HP ULTRA 1 (Part. N. 1A-101) bonded phase capillary column (12 m × 0.20 mm i.d.; 0.3 μ). Detection was by electron impact mass spectrometry in the Selected Ion Monitoring mode programmed to detect the characteristic ionic species at m/z 41, 42, 56, 86, 100 for GHB and δ-valerolactone.

The assay was linear over the clinically relevant concentration range (2–200 μg ml^{-1}), with correlation coefficients of 0.999 and 0.998 for plasma and urine, respectively. The intra- and inter-assay coefficients of variation ($n = 5$) determined at 5 μg ml^{-1} were always below 5%. The limits of determination were 1 μg ml^{-1} and 0.2 μg ml^{-1} for plasma and urine, respectively.

Pharmacokinetic and statistical analyses

Peak plasma GHB concentrations (C_{max}) and the time of their occurrence (t_{max}) were noted directly from the data. Terminal half-lives ($t_{½z}$) were estimated by log-linear regression of the terminal 2–4 data points. The area under the plasma drug concentration-time curve (AUC) and the area under the first moment of the plasma drug concentration-time curve (AUMC) were

Table 1 Patient demographic data, results of liver function tests and concomitant medication

Patient	*Age (years)*	*Weight (kg)*	*Serum albumin (g l^{-1})*	*Serum bilirubin (μmol l^{-1})*	*Prothrombin level (% normal)*	*AST[a] (iu)*	*ALT (iu)*	*γ-GT (iu)*	*Concomitant medication*
1	53	84	47	9.1	96	22	27	60	1,2,3
2	47	75	45	13.0	92	15	13	10	1,2,3
3	45	72	45	10.5	81	13	19	19	
4	56	92	45	12.5	100	25	26	28	1,2,4,5,6
5	48	74	40	31.3	86	122	74	448	1,2,3,6
6	47	60	43	15.2	99	70	104	34	7,8
7	41	76	48	32.5	63	114	124	629	1
8	34	75	49	13.6	78	90	156	215	1,2,3,6,9,10
9	56	57	54	10.5	100	66	51	180	1,2,3,6
10	39	67	55	9.1	87	138	81	343	1,2,3,6
Normal range			35–55	5–17	70–100	15–45	15–50	3–65	

[a]AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; γ-GT = γ-Glutamyltransferase.
Medication: 1 = thiamine; 2 = pyridoxine; 3 = cyanocobalamin; 4 = cetirizine; 5 = chlorphenamine; 6 = folinic acid; 7 = haloperidol; 8 = orphenadrine; 9 = lactulose; 10 = ranitidine.

estimated using the linear trapezoidal rule, with extrapolation to infinity using $C(\text{last})/\lambda_z$ (Gilbaldi & Perrrier, 1982). The extrapolated portion was always less than 10% of the total area. Mean residence time (MRT) was calculated from AUMC/AUC. Oral clearance (CL_o) was calculated from D/AUC. Urinary recovery was calculated as the cumulative amount excreted within the 12 h collection period and expressed as a percentage of the administered dose. The renal clearance (CL_R) of GHB was calculated from the ratio of the total amount recovered in the urine to the AUC.

The two-tailed Wilcoxon signed rank test was used to compare the parameters obtained after the 1st and 13th doses, as well as the parameters obtained after administration of different doses. The two-tailed Wilcoxon rank-sum test was used to evaluate differences between subgroups of patients. Other statistical analyses are specified in the text. A P value <0.05 was considered statistically significant.

Results

The individual and mean values of the pharmacokinetic parameters of GHB obtained after the 1st and 13th doses are shown in Table 2. Values of t_{max} and $t_{½z}$ suggest that GHB was readily absorbed after oral administration and rapidly eliminated. The drug was essentially removed from plasma by 2 to 4 h after dosage as indicated by values of CL and MRT. GHB was not excreted unchanged to any significant extent. In all cases, urinary recovery was virtually complete within 8 h of any administration. Consistent with the short terminal half-life, no accumulation occurred on repetitive dosing (the mean ratio between the AUC values after the 13th and the 1st administration was 1.03 ± 0.20 s.d). No statistically significant differences were observed between the pharmacokinetic parameters determined after the 1st and the 13th dose.

In five of the 10 subjects examined (patients 1, 2, 3, 4, and 8) the shape of the plasma concentration-time curve of GHB was consistent with first-order elimination kinetics, whereas in the other five subjects the decay phase exhibited a downward curvature suggestive of capacity-limited elimination (Figure 1a, b). In each of the 10 subjects, similar curves were obtained after the 1st and 13th doses. Four of the five subjects exhibiting linear kinetics (patients 1 to 4) had apparently normal liver function (Table 1), whereas in all patients exhibiting nonlinear kinetics, two to five values of the liver function tests were abnormally elevated. Analysis by the Fisher exact probability test showed that the occurrence of nonlinear kinetics was significantly more frequent in patients with abnormal liver function tests ($P = 0.024$). In the group exhibiting nonlinear decay kinetics, values of AUC and MRT were somewhat higher, but the differences did not reach statistical signficance. To confirm capacity-limited elimination of GHB, patients 5, 6, 7, 9 and 10 were given a single dose of 50 mg kg^{-1}

Table 2 Pharmacokinetic parameters of GHB following oral administration of 25 mg kg^{-1} GHB every 12 h to 10 alcohol dependent patients. Data obtained after the 1st and the 13th dose (values in brackets)

Patient	C_{max} ($\mu g\ ml^{-1}$)	t_{max} (*min*)	$t_{½z}$ (*min*)	*MRT* (*min*)	*AUC* ($\mu g\ ml^{-1}\ min$)	CL_o ($ml\ min^{-1}\ kg^{-1}$)	*Urinary recovery* (*% dose*)	CL_R ($ml\ min^{-1}\ kg^{-1}$)
1	51 (72)	20 (20)	22 (19)	37 (34)	2410 (2616)	10.4 (9.6)	0.33 (0.37)	0.04 (0.04)
2	48 (52)	30 (30)	27 (29)	57 (48)	1663 (1984)	15.0 (12.6)	0.85 (1.05)	0.13 (0.13)
3	35 (32)	20 (30)	24 (24)	41 (45)	1577 (1750)	15.8 (14.3)	1.06 (0.63)	0.17 (0.09)
4	65 (54)	45 (20)	33 (29)	65 (50)	4485 (4440)	5.6 (5.6)	0.84 (0.54)	0.05 (0.03)
5	24 (35)	45 (45)	33 (26)	74 (82)	1631 (1701)	15.3 (14.7)	0.09 (0.17)	0.01 (0.02)
6	61 (71)	30 (20)	35 (39)	79 (81)	4363 (4038)	5.7 (6.2)	0.27 (0.31)	0.02 (0.02)
7	76 (72)	20 (30)	20 (23)	48 (54)	3360 (3397)	7.4 (7.4)	1.03 (1.12)	0.08 (0.08)
8	45 (32)	30 (30)	25 (25)	52 (55)	2482 (2708)	10.1 (9.2)	0.42 (0.35)	0.04 (0.03)
9	53 (48)	30 (30)	25 (22)	77 (73)	3950 (3513)	6.3 (7.1)	1.50 (1.45)	0.09 (0.09)
10	88 (85)	30 (30)	23 (29)	60 (54)	5303 (5102)	4.7 (4.9)	0.87 (1.30)	0.04 (0.06)
Mean	54 (55)	30[a] (30)[a]	27 (26)	59 (58)	3122 (3125)	9.6 (9.2)	0.73 (0.73)	0.07 (0.06)
± s.d.	±19 (±19)		±5 (±5)	±15 (± 16)	±1356 (±1171)	±4.4 (±3.6)	±0.44 (±0.46)	±0.05 (±0.04)
P value[b]	NS	NS	NS	NS	NS	NS	NS	NS

[a]Median value.
[b]13th *vs* 1st dose.

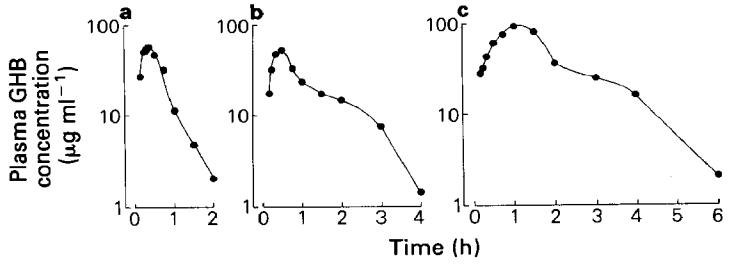

Figure 1 Plasma concentrations of GHB after oral administration of 25 mg kg^{-1} GHB to representative patients exhibiting linear (a) and nonlinear (b) elimination kinetics (subjects 1 and 9, respectively). (c) Plasma GHB concentrations after administration of 50 mg kg^{-1} GHB to subject 9.

Table 3 Dose dependency of GHB pharmacokinetic parameters. Mean values ± s.d. from five patients (5, 6, 7, 9 and 10) after administration of 25 mg kg^{-1} (1st and 13th doses) and 50 mg kg^{-1} GHB, on 1st, 7th and 10th days, respectively, of multiple dose regimen

	Dose (mg kg^{-1})				
	25			P *value*[a]	
	1st dose	*13th dose*	*50*	*1st dose*	*13th dose*
C_{max} (μg ml^{-1})	60 ± 24	62 ± 20	45 ± 17[b]	NS	NS
t_{max} (min)	30 (20–45)[c]	30 (20–45)[c]	45 (30–60)[c]	<0.01	<0.005
$t_{½z}$ (min)	27 ± 6	28 ± 7	35 ± 7	<0.01	<0.05
MRT (min)	68 ± 13	69 ± 14	96 ± 16	<0.05	<0.05
AUC (μg ml^{-1} min)	3721 ± 1366	3550 ± 1234	5419 ± 1637[b]	<0.005	<0.005
CL_o (ml min^{-1} kg^{-1})	7.9 ± 4.3	8.1 ± 4.8	5.3 ± 2.2	<0.05	<0.05
Urinary recovery (% dose)	0.75 ± 0.57	0.87 ± 0.59	1.33 ± 0.62	<0.05	<0.05
CL_R (ml min^{-1} kg^{-1})	0.05 ± 0.04	0.05 ± 0.03	0.08 ± 0.04	NS	<0.05

[a]50 mg kg^{-1} dose *vs* 1st and 13th 25 mg kg^{-1} doses.
[b]Normalised to 25 mg kg^{-1}.
[c]Median value (range).

of GHB on the 10th day. This doubling of the dose resulted in dose-disproportionate increases in AUC and MRT (Table 3, Figure 1b, c).

No side effects were recorded, with the exception of a slight transient drowsiness around the time of peak drug concentration in subjects 3 and 8 after the first 25 mg kg^{-1} dose, and subjects 7 and 9 after administration of the 50 mg kg^{-1} dose. C_{max} values in these subjects (35 to 97 μg ml^{-1}) were similar to those observed in the other subjects at corresponding doses.

Discussion

Bessman & Skolnik (1964) postulated that GBL is formed from exogenously administered GHB and considered the lactone to be the pharmacologically active species. However, subsequent investigations failed to confirm this, since only GHB could be detected in biological fluids and tissues after administration of GHB, GBL or precursors of the former (Giarman & Roth, 1964; Lettieri & Fung, 1978; Snead *et al.*, 1989). Therefore, GBL, rather than GHB, can be classified as a prodrug (Arena & Fung, 1980). Our observations are in accordance with this and confirm that analytical procedures involving preliminary conversion of GHB to GBL can be used to study the pharmacokinetics of GHB.

Our results suggest that both the oral absorption and the elimination of GHB are fast processes, but that clearance becomes capacity-limited as the dose is raised.

The observation that, following administration of the 25 mg kg^{-1} dose, evidence of nonlinear kinetics was apparent exclusively in patients with abnormal values of liver function tests, suggests that a relationship exists between liver function and saturation of the elimination pathway(s) of GHB. Nevertheless, this may be of limited therapeutic relevance, since no accumulation of GHB in plasma was observed at therapeutic doses irrespective of whether there was evidence of nonlinear kinetics.

Oral administration of increasing doses of GHB to rats has been shown to result in a dose-dependent increase in t_{max}, suggestive of a slower rate of absorption. Concomitant increases in C_{max} were much less than expected from first-order absorption kinetics (Lettieri & Fung, 1979). These dose-related effects have been shown to reflect capacity-limited absorption of GHB (Arena & Fung, 1980). Similar results were obtained in this study on doubling the dose (Table 3), suggesting that GHB absorption is capacity-limited also in humans.

Two further findings of clinical relevance have emerged from this study: firstly, the pharmacokinetic parameters of GHB are time-invariant. This suggests that neither GHB nor its metabolites cause auto-induction or auto-inhibition of metabolism. Secondly, GHB is rapidly cleared such that no accumulation occurs in the plasma at the usual maintenance doses. Even after administration of 50 mg kg^{-1} the drug is completely eliminated within 4 to 6 h. On the basis of our clinical observations, a daily dose of 100 mg kg^{-1} of GHB may be needed in certain cases of severe alcohol dependence. In the light of the present results, this daily dosage may be safe if appropriately divided.

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EXHIBIT 13

stimulatory or inhibitory peptides or, conceivably, activate precursor forms by limited cleavage. Alternatively, it could have a protective role by stopping inhibitory factors from gaining access to the luminal cells in the intact tissue. Interestingly, although oxytocin (which has powerful action on myoepithelial cells) can be hydrolysed by endopeptidase-24.11, it is a very poor substrate compared with peptides such as ANP and bradykinin, thus raising some doubts that this hormonal signal is terminated by the surface endopeptidase.

Several new antigens have lately been identified on the myoepithelial cell membrane.[27,28] Our hypothesis would predict that some of these antigens may well be other members of a battery of cell-surface enzymes that control the local milieu. Thus, the overexpression of the c-*erb*B-2 gene product on the lateral and basal membranes of breast carcinoma cells in a high proportion of intraduct carcinomas[29] would be consistent with this molecule's being a receptor for a paracrine growth factor (as yet unidentified) perhaps produced by the myoepithelial cells, or modified by them by means of their endopeptidase activity before its reaction with the tumour cells.

We therefore propose that cell-surface peptidases may have a key role in the control of growth and differentiation of many cellular systems by modulating the activity of peptide factors and regulating their access to adjacent cells. The hypothesis is open to direct experimental investigation since various well-characterised, non-toxic inhibitors,[5] acting specifically on several of these enzymes,[3] are available. These can be tested both in vitro and in vivo for their ability to alter growth and differentiation of different cell types in tissues with cell-surface peptidase activity.

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Clinical Pharmacology

GAMMA-HYDROXYBUTYRIC ACID FOR TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME

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Summary The effect of gamma-hydroxybutyric acid (GHB) on ethanol withdrawal syndrome in alcoholics was investigated in a randomised double-blind study. Patients with withdrawal symptoms were treated either with GHB (orally in a syrup preparation) (11 patients) or with the syrup alone (12). GHB treatment (50 mg/kg) led to a prompt reduction in withdrawal symptoms, such as tremors, sweating, nausea, depression, anxiety, and restlessness. The only side-effect was dizziness. GHB may be useful in the management of alcohol withdrawal syndrome in man.

INTRODUCTION

Gamma-hydroxybutyric acid (GHB), a constituent of the mammalian brain, is found in highest concentrations in the hypothalamus and basal ganglia.[1] Since there are central recognition sites with high affinity for GHB, this compound

A. J. KENNY AND OTHERS: REFERENCES—*continued*

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EFFECT OF GHB ON ALCOHOL WITHDRAWAL SYNDROME

Treatment group (no of patients)	Total score					
	30 min before treatment	After treatment (h)				
		1	2	3	5	7
GHB (11)	12·6 (6·1)	7·2 (3·9)*	4·2 (3·1)†	2·1 (1·6)†	1·5 (1·7)†	2·6 (1·3)†
Control (12)	11·8 (5·7)	11·8 (4·7)‡	11·3 (3·5)	12·6 (9·2)	13·6 (6·5)	14·7 (4·3)*

Values are means (SD).
*$p < 0.05$; †$p < 0.01$ (Pratt's test for comparison of scores before and after treatment).
‡$p < 0.05$ (Mann-Whitney test for comparison of control and GHB groups).

probably functions as a neurotransmitter or as a neuromodulator rather than as an incidental metabolite of gamma-aminobutyric acid (GABA).[2] GHB has been used as an intravenous hypnotic anaesthetic agent,[3] and in the treatment of sleep disturbances.[4] In narcolepsy GHB is given orally, at bedtime, to limit the number of rapid eye movement episodes during the night, and this reduces narcoleptic episodes during the day.[5]

In its lactone form, GHB inhibits voluntary ethanol consumption in rats that have a strong preference for ethanol.[6] GHB also suppresses ethanol withdrawal syndrome in rats that have been rendered physically dependent on ethanol by repeated ethanol administration.[7]

These considerations and the safety of GHB[4] led us to study the effect of this drug on alcohol withdrawal syndrome in alcoholics.

PATIENTS AND METHODS

Patients included in the study were alcoholics who met the DSM III-R criteria of alcohol withdrawal syndrome. Patients gave written consent. Patients were excluded if they had convulsions, delirium tremens, or concurrent severe illness, or if they abused other drugs, or were receiving antiepileptic treatment. On admission, patients were clinically examined and randomly allocated to one of two groups; one received 1 dose of oral GHB (50 mg/kg) dissolved in a black cherry syrup, and the other received a corresponding volume of syrup alone (control group). Both preparations were provided by CT, Sanremo, Italy. The patients did not know whether they were receiving GHB or vehicle. The GHB group consisted of 11 patients (8 men, 3 women) and their ages ranged from 31 to 63 years (mean 43·9). The control group consisted of 12 patients (8 men, 4 women) with a mean age of 43·5 years (range 28–59).

Clinical evaluations were done by the same investigator (G. L.) who was blinded to treatment group. On the morning after admission, each patient was examined 30 min before the dose of GHB was given, and 1, 2, 3, 5, and 7 h later. 6 main withdrawal symptoms were evaluated—ie, tremors, sweating, nausea, depression, anxiety, and restlessness. Each symptom was scored on a 4-point scale as follows: 0, not present; 1, mild; 2, moderate; and 3, severe. The sum of these points gave the total score of symptoms for each patient, the maximum being 18 points. Individual alcohol withdrawal symptoms were not compared because they varied greatly between patients. Instead the sum of the scores for each symptom were added together for each patient and the total score was used as an index of severity of withdrawal. Blood pressure and heart rate were also recorded every day. We used the word fluency test of Borkowski et al[8] to look for a possible sedative effect of GHB. Routine laboratory tests were carried out on admission and were repeated if there were any abnormalities. Standard routine therapy (diazepam, vitamins, and sodium valproate) was available for severe distress in both groups of patients, but this was not needed during the double-blind phase.

The Mann-Whitney U-test was used to test differences between the two treatment groups. A modified Wilcoxon test (Pratt's test) was applied for within-patient comparisons.

RESULTS

The mean scores of the two groups before treatment were similar—ie, 12·6 in the GHB group and 11·8 in the control group. In the GHB patients, there was a rapid decrease in mean score with a significant effect within 1 h. Nearly all withdrawal symptoms disappeared within 2 to 7 h of receiving the dose of GHB. By contrast, withdrawal scores of control patients did not decrease, and even significantly increased after 7 h (table). A small decrease in heart rate (10–13%), but no change in blood pressure, was observed after GHB treatment. There were no significant differences in the word fluency test between GHB patients and controls.

After completion of the double-blind phase of the study, the code was broken and control patients were assigned to a conventional treatment schedule, as indicated by their clinical state. Patients in the GHB group received further doses of the drug every 8 h up to the 3rd day. Subsequently, the total daily dose was reduced by 30% per day until the 7th day when GHB was discontinued. The mean withdrawal score of these patients, recorded in open study each morning before the first daily treatment, remained below 2.

7 of the 11 patients treated with GHB said that they had slight and transient dizziness about 30 min after the first drug administration; these symptoms disappeared spontaneously within 15 min. Dizziness with similar features recurred on the second day in 3 patients after the first morning dose of GHB. None of the control group reported dizziness. No other side-effects attributable to GHB were noted by the observer or the patients. None of the patients reported somnolence after GHB.

DISCUSSION

Despite the small number of patients, the results clearly indicated that GHB is effective for the suppression of withdrawal symptoms in alcoholics. GHB action has a rapid onset and seems to be without serious side-effects. Our findings agree with experimental data in rats: therefore, the mechanisms involved in ethanol dependence in rats may be similar to those in human beings. Thus, study of laboratory animals might help to clarify some of the neurochemical mechanisms of ethanol dependence in man.

The protective action of GHB against ethanol withdrawal in our patients was not due to sedative and hypnotic effects. Moreover, the GHB effect cannot be attributable to other central actions of the compound, such as inhibition of dopamine release[9,10] and increase in acetylcholine release,[11] because the mechanisms of these actions are not yet known. The protective effect of GHB may be due to its GABA-like action:[12,13] drugs which are effective clinically or in experimental ethanol withdrawal (eg, benzodiazepines, barbiturates, muscimol, amino-oxyacetic acid, progabide, and ethanol itself)[14–18] all have a direct or indirect GABA-like

action in the central nervous system, which eventually leads to an increase in the chloride transport across the chloride ion channels in the neuronal membrane (see refs 19, 20). Although the above drugs are known to potentiate transmission at the level of $GABA_A$ receptors, the nature of the GABAergic action of GHB is not clear.[21]

Finally, GHB may exert its protective effect by acting on its specific receptors in the brain. This hypothesis raises the important question of the possible role of such receptors in ethanol dependence.

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Oncology

AGE OF ONSET AND TYPE OF LEUKAEMIA

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INTRODUCTION

LEUKAEMIA is a common cancer in people younger than 50 years old, especially children. Several types are described, including acute lymphoblastic leukaemia (ALL), and acute and chronic myelogenous leukaemia (AML and CML). ALL occurs predominantly in young children and adolescents, whereas CML is uncommon in young people (< 20 years). AML occurs in infants, adolescents, and older people but not usually in young children.[1] Why do different leukaemias predominate at different ages? If specific leukaemogens cause certain types of leukaemia, and if the influence of these factors correlates with age, distinct leukaemias would be age-associated. An alternative hypothesis is that age at leukaemogenesis determines the type of leukaemia, irrespective of the specific leukaemogenic agent.[2] For example, exposure to the same leukaemogenic factor may cause ALL in a child but AML in an adult. These two hypotheses are not mutually exclusive and both might operate with different leukaemogenic factors.

Since the cause of most cases of leukaemia is unknown, it is difficult to decide between these alternatives. However, there are some instances in which either the cause of leukaemia or the host factors that predispose to leukaemia (other than age) are known. We now review the situations that might point to the pathogenesis of leukaemia.

EXOGENOUS AND HOST RISK FACTORS

Known exogenous causes of leukaemia in human beings are ionising radiation, mutagenic drugs and chemicals, and the HTLV-1 retrovirus.[1] There are several examples of radiation-induced leukaemogenesis, including the atomic bomb survivors, people exposed to diagnostic X-rays in utero, and people who have received radiation for malignant or non-malignant conditions.[3] Data about non-ionising radiation are controversial. The leukaemogenic effects of drugs and chemicals are most evident in people with cancer (usually Hodgkin's disease or ovarian cancer) who are receiving chemotherapy,[3] and in those exposed to benzene.[4] HTLV-1 is associated with the development of adult T-cell leukaemia (ATL) predominantly in Japan but also in other areas.[5] In addition, several host factors increase the likelihood that leukaemia will develop, including congenital disorders associated with chromosomal imbalances or instability such as Down syndrome and Fanconi's anaemia.[6,7]

To see whether age is an important determinant of the type of leukaemia that develops in human beings, we will consider the interaction of exogenous and host risk factors (other than age).

Radiation

Atomic bomb survivors[8] can be grouped into those who were exposed after birth and those who were exposed in utero. There is no evidence of an increased risk of leukaemia in the latter,[9] so we will focus on the former. The incidences of ALL, AML, and CML were all greatly increased in people exposed to radiations from the atomic bombs; the relative risks of getting leukaemia were 20 to 25-fold and were highest in those who were the youngest at the time of exposure. Also, young people had the shortest latent period before developing leukaemia. However, these data do not point to any correlation between age at exposure and type of

EXHIBIT 14

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ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

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Gamma-Hydroxybutyric Acid in the Treatment of Alcohol Dependence: A Double-Blind Study

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The effect of gamma-hydroxybutyric acid on alcohol consumption and alcohol craving in alcoholics was investigated in a randomized double-blind study versus placebo. Patients were treated as outpatients during a three month period either with gamma-hydroxybutyric acid (50 mg/kg/day, divided into three daily doses) or with placebo. Of the 82 alcoholics that entered the study, 71 completed it, 36 in the gamma-hydroxybutyric acid and 35 in the placebo group. Alcohol consumption was assessed by the subject's self report. At the 3rd month of treatment, 11 patients in the gamma-hydroxybutyric acid group referred to be abstinent and 15 referred controlled drinking; while in the placebo group only two and six patients referred abstinence and controlled drinking, respectively. Serum-gammaglutamyltransferase activity correlated with the admitted alcohol consumption. Gamma-hydroxybutyric acid treatment decreased alcohol craving during the 3 months of treatment. Transient side effects were noted by six patients on gamma-hydroxybutyric acid and two on placebo. The results suggest that gamma-hydroxybutyric acid may be useful in the treatment of alcohol dependence.

Key Words: GHB, Alcohol Dependence, Craving.

GAMMA-HYDROXYBUTYRIC ACID (GHB), a normal brain constituent originating from GABA metabolism, is considered to play a neurotransmitter and/or neuromodulatory role in the central nervous system (CNS).[1] Systemically administered, GHB exerts hypnotic and anesthetic effects in animals and in man, therefore it was introduced in the clinic as a general anesthetic and hypnotic agent.[2]

The mechanism by which GHB produces its central effect is not known. It has been suggested that GHB enhances GABAergic activity,[3] although evidence for a direct interference of GHB with GABA transmission is not available. Previous results from our laboratory have shown that GHB, in its lactone form, inhibits voluntary ethanol consumption in a rat line selectively bred for high preference for ethanol,[4] and that GHB suppresses ethanol withdrawal syndrome in rats rendered physically dependent on ethanol by forced ethanol administration.[5]

More recently in a double-blind study we found that GHB, given orally in nonhypnotic doses, is highly effective in suppressing the withdrawal symptomatology in alcoholics; the GHB effect has a rapid onset and the compound is devoid of adverse side effects.[6]

The above considerations and the relative safety of GHB led us to study the clinical efficacy of the compound in the treatment of alcohol dependence.

METHODS

Eighty-two alcoholic patients entered the study sequentially over a 1-year period after giving informed consent. Each patient was studied for 3 months in a double-blind versus placebo trial. Patients included in this study had a 5-year or more history of alcoholism defined according to the DMS III-R criteria. They had an average daily ethanol intake in excess of 150 g for the past 2 years or more. Exclusion criteria were a major psychiatric disorder other than alcohol dependence, cirrhosis of the liver, pregnancy, renal or heart failure, epilepsy. Within 8 hr of admission to the day-hospital, each subject underwent a full physical examination by a physician of the team and routine laboratory tests, including serum-gammaglutamyltransferase (S-GT), erythrocyte mean cell volume (E-MCV), and alcoholuria. Thereafter each subject was examined for depression, anxiety, and severity of alcoholism according to the rating scales reported in Table 1; each subject was randomly assigned to the drug or placebo group.

The active medication consisted of GHB dissolved in a black cherry syrup, in the concentration of 250 mg/ml. Placebo consisted of a cherry syrup with the same organoleptic characteristics as the active medication. GHB was administered orally at the dose of 50 mg/kg divided into three daily doses. The placebo group received the same volume of the syrup. Both the active medication and the placebo syrup were supplied by CT Laboratories, Sanremo, Italy.

Patients received the first medical interview and treatment in the day-hospital; thereafter they were followed up as outpatients and seen every day from 8 AM to 5 PM for the first 3 days and then at weekly intervals. Subjects were told by the physician that the goal of the treatment was to assess whether a drug that they were going to receive was able to decrease alcohol withdrawal symptomatology and alcohol craving, that they should try to abstain from alcohol ingestion, but that this was not mandatory for the study. The latter was aimed at assessing the real efficacy of the drug and any possible side effects.

At the weekly visit subjects provided a urine sample for measurement of alcohol concentration[7] and were interviewed by one of the physicians (L.G. or M.F.) about their alcohol intake and the intensity of alcohol craving. A self-reported alcohol intake was recorded as the mean number of standard drinks consumed per day and the percentage of days of abstinence.

Craving for alcohol was defined as the preoccupation with, thought about, and urge for alcohol. The intensity of alcohol craving was assessed with a questionnaire derived, with proper modifications, from Stunkard and Messick's questionnaire to measure dietary restraint, disinhibition, and hunger.[8] The questionnaire contained 11 items, each of which required a yes or no answer, corresponding to 1 or 0 points, respectively; therefore, the maximum craving score was 11 points.[9]

The self-reported alcohol consumption was correlated with the weekly measurements of alcoholuria and by any possible information obtained

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from collaterals of the patients. Other laboratory tests were repeated at monthly intervals.

Physicians who performed treatments and medical interviews were unaware of the treatment administered.

RESULTS

Of the 82 subjects that entered the study, 71 completed the course. Of the 11 subjects who withdrew from the study, four did so for lack of compliance (in failing to report at one weekly visit: three in the placebo and one in the GHB group), three for dizziness and vertigo and one for headache (in the GHB group), one for gastric ulcer exacerbation, one for refusal to take the treatment, and one for nausea (in the placebo group). The relatively high percentage of subjects remaining in the study may be attributed to the intensive follow-ups. The placebo group consisted of 35 subjects, 24 men and 11 women; while the GHB group numbered 36 subjects, 23 men and 13 women. The two groups did not differ in age, initial S-GT, and E-MCV. In fact, the GHB group was aged 41 ± 15 years, S-GT 115 ± 108, E-MCV 97 ± 8 fl; while the placebo group was aged 40 ± 13 years, S-GT 118 ± 112, E-MCV 98 ± 6 fl (means ± SD).

As shown in Tables 1 and 2, subjects in the two groups did not differ for severity of alcoholism or alcohol intake, they were not depressed and their level of anxiety was relatively low.

Table 1. Characteristics of Subjects Undergoing Treatment with Placebo or Gamma-Hydroxybutyric Acid (GHB)

Variable (mean ± SD)	Subjects to receive		p
	Placebo	GHB	
Males	24	23	
Females	11	13	
Age	36.8 ± 15.6	38.1 ± 13.4	NS*
Years of alcoholism (DMS-III-R)	6.7 ± 4.9	7.1 ± 5.1	NS
VAST score†	26.4 ± 11.3	28.2 ± 14.7	NS
Anxiety score‡			
State	43.6 ± 11.4	48.4 ± 16.3	NS
Trait	45.3 ± 13.1	46.9 ± 10.2	NS
Depression score§	6.1 ± 5.8	5.3 ± 6.1	NS

p, Student's *t* test.

* NS, not significant.

† VAST, Veterans Alcoholism Screening Test.[16] The scores reported are referred to the past year.

‡ Spielberger's State and Trait Anxiety Scale scores range from 20 = no anxiety to 80 = extreme anxiety.[17]

§ Hamilton Depression Scale scores range from 0 = no depression to 60 = extreme depression.[18]

Table 2 shows the effect of GHB treatment on ethanol consumption, assessed as the mean number of drinks consumed per day and the percentage of days of abstinence. During the 3-month treatment period, in the placebo group there were no significant variations in both the number of daily drinks and in the abstinent days. On the other hand, the GHB-treated patients showed a decrease to about one half in the number of daily drinks and a 3-fold increase in the number of abstinent days.

As Table 3 shows, GHB significantly reduced alcohol craving. This effect was present within the 1st month of treatment and persisted throughout the treatment period. Placebo treatment produced a modest reduction in craving during the 1st month of treatment.

At the end of the 3rd month of treatment, on the basis of the self-reported ethanol consumption during the previous month, the subjects were assigned to one of three categories: abstinence, controlled drinking, and excessive drinking. Controlled drinking and excessive drinking were defined when the subject admitted ethanol consumption of less and more than 40 g/day, respectively.

As shown in Table 4, 11 and 15 out of the 36 subjects reported abstinence and controlled drinking in the GHB-treated group. On the other hand, in the placebo-treated group only two and six out of the 35 subjects showed abstinence and controlled drinking, respectively, while 27 subjects reported excessive drinking.

As Table 3 shows, S-GT values correlated with the admitted alcohol consumption. On the other hand no significant differences were observed in the E-MCV values before treatment and in the follow-up within groups as well as between the two groups. The alcoholuria correlated with the admitted alcohol consumption (data not shown) and the validity of the self report of alcohol intake was confirmed by information obtained from the patient's collaterals.

Adverse side effects were investigated using a standard questionnaire. Four of the patients on GHB and one on placebo complained of dizziness and vertigo after the first morning dose on the first 3 days of treatment, the symptomatology was transient, disappearing within 6 hr. Two patients on GHB and one on placebo complained of headache after the first morning dosage persisting for 3 to 4 hr. This symptomatology disappeared following the 3rd day of treatment.

No subject showed alterations in the renal, blood, and

Table 2. Effect of Gamma-Hydroxybutyric acid (GHB) on Ethanol Consumption in Alcoholics

Response	During the 3 months before treatment		p	During the 3 months of treatment period		p
	Placebo	GHB		Placebo	GHB	
Daily drinks (mean ± SEM)	11.4 ± 0.6	12.1 ± 0.5	NS	9.3 ± 0.7	4.7 ± 0.4	<0.01
% of abstinent days (mean ± SEM)	4.9 ± 0.4	5.6 ± 0.5	NS	8.4 ± 1.6	25.9 ± 3.1	<0.001

Each value is the mean ± SEM from 35 placebo and 36 GHB treated subjects. Values of alcohol intake prior to treatment were based on a single interview, while those during treatment were obtained by weekly interviews (means ± SEM). Therefore, the statistical significance of the results was calculated by comparing the values of GHB versus placebo, during the 3-month treatment period (Student's *t* test).

Table 3. Effect of Gamma-Hydroxybutyric Acid on Ethanol Craving

Month of treatment	Craving score	
	Placebo	GHB
Prior to treatment	8.5 ± 0.3	8.9 ± 0.5
1st month	5.1 ± 0.6†	2.1 ± 0.1†
2nd month	7.5 ± 0.4	3.3 ± 0.4*,†
3rd month	7.6 ± 0.3	3.1 ± 0.6*,†

Data are the means ± SEM obtained by averaging the scores of the 4 weekly interviews during each month. Baseline scores were those of the first visit prior to treatment (maximum score 11). * $p < 0.001$ with respect to placebo value, † $p < 0.001$ with respect to basal value by Student's t test.

In consideration of the multiple comparisons, in order to protect against false-positive results, level of significance was fixed as follows $/n = 0.05/9 = 0.0055$; therefore, vaues of $p > 0.0054$ were considered statistically not significant.

Table 4. Correlation of Gamma-Hydroxybutyric Acid Effect on Alcohol Consumption, Serum Gamma-Glutamyltransferase (S-GT) and Erythrocyte Mean Cell Volume (E-MCV)

Condition of patients	Placebo			GHB		
	N	S-GT (I.U./L)	E-MCV (fl)	*N*	S-GT (I.U./L)	E-MCV (fl)
Before treatment						
Excessive drinking	35	118 ± 112	98 ± 6	36	115 ± 108	97 ± 8
Last month of treatment						
Abstinence	2	33, 48	97 ± 4	11	31 ± 38*	94 ± 4
Controlled drinking	6	53 ± 41*	98 ± 7	15	48 ± 61*	90 ± 8
Excessive drinking	27	118 ± 110	103 ± 6	10	113 ± 131	98 ± 7

Values are means ± SD.

Controlled and excessive drinking: admitted ethanol consumption during the preceding month period of less and more than 40 g/day, respectively. *N*, number of patients.

* $p < 0.01$ with respect to pretreatment value (Student's t test).

liver tests. Blood pressure and pulse rate did not change significantly after either placebo or GHB treatment. Scores for depression and anxiety did not change significantly either in the placebo or GHB-treated patients during the 3-month treatment period (results not shown).

COMMENT

The present study shows that GHB is effective in reducing ethanol consumption and ethanol craving in alcoholics. Ethanol consumption was assessed as the patient's self report and the reduction was measured as a reduction both in the number of drinks per day and in the percentage of days of abstinence during the 3-month treatment period.

Moreover, the combination of the number of patients reporting abstinence and those reporting controlled drinking was considered to be an indicator of the treatment's success. According to this parameter, the success score with GHB was higher than 70% of the subjects at the end of the 3rd month of treatment, while it was about 20% with placebo. The validity of self-reported data was supported by laboratory tests (S-GT) and weekly urine analyses for alcohol.

It is likely that GHB-induced reduction in ethanol consumption is the consequence of its reducing effect on alcohol craving. The latter effect is consistent with previous observations showing that the compound is effective in suppressing the ethanol withdrawal syndrome in alcoholics[6]; craving being considered a symptom of protracted abstinence[10] and the major stimulus for relapses into ethanol abuse. The finding that GHB inhibits ethanol craving suggests a possible association of the drug with disulfiram, which is known to prevent ethanol consumption by a negative reaction but fails to reduce craving.

As mentioned above, we found that GHB suppresses voluntary ethanol consumption in rats selected for high ethanol preference[4] and reduces ethanol withdrawal syndrome in rats physically dependent on ethanol.[5] Therefore, our clinical results are not only of practical, but also of general theoretical interest, since they stress the predictive relevance of the experimental model for clinical research.

Experimental studies suggest that GHB administration interferes with the activity of dopamine,[11] serotonin,[12] acetylcholine,[13] opioids,[14] and GABA.[15] At present it is unknown which of these interactions bears some relevance for the suppressant effect on ethanol consumption and craving.

Moreover, since GHB is a normal brain constituent and has many of the characteristics of neurotransmitter and/or neuromodulator,[1] the possible relevance of changes in the content and activity of endogenous GHB in the pathogenesis of alcoholism might be considered.

Finally, the possibility exists that GHB might act by mimicking the central effects of ethanol. Indeed, ethanol moiety is present in the structure of GHB and the latter shares with ethanol different pharmacological and neurochemical characteristics. Moreover tolerance to ethanol is extended to GHB.[5] Should the latter hypothesis be validated, the rationale for using GHB in the treatment of alcoholism would be the same as that of using methadone in heroin addiction.

Whatever the exact mechanism of action of GHB, our results indicate that GHB deserves more extensive investigation as a clinically useful drug in the treatment of alcoholism.

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ANNOUNCEMENT

OCTOBER 8–9, 1992. **Symposium on Alcohol and Aggression** will be held at Rutgers University. Internationally prominent scientists will present their latest findings, focus on critical issues, and set future research directions in this field. For further information and registration on this interdisciplinary Symposium contact: Patricia Castellano, Symposium on Alcohol and Aggression, Rutgers Center of Alcohol Studies, PO Box 969, Piscataway, NJ 08855. Telephone: 908–932–3510. FAX: 908–932–5944.

EXHIBIT 15

after imposed abstinence (Kornet et al., 1991). Naltrexone was administered under two conditions: (a) continuous access to alcohol and water and (b) after abstinence that was imposed by interrupting the alcohol supply for 2 days. Naltrexone reduced total net ethanol intake in a graded dose dependent manner. The effect of naltrexone was apparent shortly after injection and lasted until the following day. After imposed abstinence which resulted in an increased alcohol consumption in the first hours after renewed access, the monkeys were more sensitive to naltrexone with respect to its decreasing effect on ethanol consumption. The data may further support the idea that endorphins are involved in alcohol drinking behavior, and particularly in the so-called catch up phenomenon after a period of abstinence, which may be an important factor in relapse. Of interest in this respect are the recent clinical observations, showing that chronic oral treatment of alcoholics with naltrexone decreased the craving for alcohol and resulted in a diminished relapse rate. In line with the monkeys studies is the finding that drinking alcohol under naltrexone led less frequently to relapse than under placebo treatment (Volpicelli et al., 1992; O'Malley et al., 1992).

Concluding remarks

The modulatory role of endorphins in brain reward may be pertinent to the initiation of drug taking behavior and may contribute to the individual variation in susceptibility to addictive drugs and habits. The postulate emerges that endorphins play a role in the craving for drugs, a characteristic feature of drug addiction and probably an important and critical factor in relapse. Relapse is the major problem in addiction and therapeutic intervention should be directed to decrease relapse. In this respect the recent naltrexone trials in alcoholics are encouraging and worthwhile to continue and to extend to other forms of addiction.

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S-8-5

Gamma-hydroxybutyric acid (GHB) for treatment of ethanol dependence

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Key words: Gamma-hydroxybutyric acid; Ethanol dependence

Gamma-hydroxybutyric acid (GHB) is a normal constituent of the mammalian brain (Roth, 1970). Although for many years it was considered a product of the metabolism of GABA it has now been proposed as a neurotransmitter or a neuromodulator (Vayer et al., 1987). Accordingly, GHB has been shown to be released by chemical and electrical stimulation of brain slices (Vayer and Maitre, 1988), to be present in the brain in discrete areas such as the neostriatum and hippocampus (Hechler et al., 1987) and its specific receptors in the brain have been described (Benavides et al., 1982). Chemically, GHB

possess an alcoholic residue in its molecule and pharmacologically mimics many of the effects of ethanol. Indeed, GHB has been used in humans to treat narcolepsy for its hypnotic properties and, in higher doses, as a general anesthetic (Mamelak et al., 1986).

For these reasons we administered GHB in low doses to ethanol-preferring rats (Sp), to test whether GHB might alter spontaneous ethanol self-administration. We also tested its activity in rats made dependent on ethanol to verify if it might reduce ethanol withdrawal symptomatology.

GHB, administered intraperitoneally as its lactone precursor gamma-butyrolactone (GBL) at a dose of 200 mg/kg, drastically reduced spontaneous ethanol intake in Sp rats without affecting fluid intake (Fadda et al., 1983). Further, when GHB (0.25–1.0 g/kg/i.p.) was administered to ethanol-withdrawn rats, it dose-dependently reduced audiogenic seizures and tremors, two signs typical of the ethanol withdrawal syndrome symptomatology (Fadda et al., 1989).

Since ethanol is known to stimulate mesolimbic dopaminergic firing (Gessa et al., 1985) and to inhibit pars reticulata electrical activity (Mereu and Gessa, 1985) we tested GHB on these two parameters. While GHB (0.05–0.2 g/kg i.v.) increased dopaminergic firing (Diana et al., 1991), at the same dose regimen, it produced heterogeneous responses on pars reticulata neuronal activity (Diana et al., 1993) providing an example of dissimilarity between ethanol and GHB. Consistently GHB, unlike ethanol, failed to alter ^{36}Cl uptake and [^{35}S]TBPS binding further suggesting a lack of action of GHB on GABA-A receptor function (Serra et al., 1991).

The effect of GHB on alcohol consumption and alcohol craving was investigated in a randomized double-blind study versus placebo. Patients were treated as outpatients during a 3-month period either with GHB (50 mg/kg/day, divided into three daily doses) or with placebo. GHB produced a significant decrease in the number of daily drinks and a marked increase in the number of abstinent days. Moreover, GHB significantly reduced ethanol craving (Gallimberti et al., 1989).

Since GHB suppresses voluntary ethanol consumption in our rat line selected for high ethanol preference and reduces the ethanol withdrawal syndrome in rats physically dependent on ethanol, our clinical results are not only of practical, but also of general theoretical interest, as they stress the predictive value of the experimental model for clinical research. As far as the mechanism of action is concerned, the failure of GHB in reducing pars reticulata neuronal activity suggests a difference in its action as compared with ethanol.

Preliminary experiments, however, indicate that GHB (10^{-3}, 10^{-4} M) inhibits ^{3}H[MK-801] binding in brain membranes (Tagliamonte et al., in preparation) suggesting that this compound might share with alcohol the ability to interact with NMDA receptors.

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EXHIBIT 16

GAMMA-HYDROXYBUTYRIC ACID IN THE TREATMENT OF ALCOHOL DEPENDENCE

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Gamma-hydroxybutyric acid (GHB), a normal brain constituent originating from GABA metabolism, is considered to play a neurotransmitter and/or neuromodulatory role in the CNS.[1] Systemically administered, GHB exerts hypnotic and anesthetic effects in animals and in man, therefore it was introduced in the clinic as a general anesthetic and hypnotic agent.[2]

Previous results from our laboratory have shown that GHB, in its lactone form, inhibits voluntary ethanol consumption in a rat line selectively bred for high preference for ethanol,[3] and that GHB suppresses ethanol withdrawal syndrome in rats rendered physically dependent on ethanol by forced ethanol administration.[4]

More recently in a double blind study we found that GHB, given orally in non hypnotic doses, is highly effective in suppressing the withdrawal symptomatology in alcoholics; the GHB effect has a rapid onset and the compound is devoid of adverse side effects.[5]

The above considerations and the relative safety of GHB led us to study the clinical efficacy of the compound in the treatment of alcohol dependence.

We investigated the effect of gamma-hydroxybutyric acid on alcohol consumption and alcohol craving in alcoholics in a randomized double-blind study versus placebo. Alcohol consumption was assessed by the subject's self report. Patients were treated as outpatients during a three month period either with gamma-hydroxybutyric acid (50 mg/kg/day, divided into three daily doses) or with placebo. Of the 82 alcoholics that entered the study 71 completed it; 36 in the gamma-hydroxybutyric acid and 35 in the placebo group. At the 3rd month of treatment 11 patients in the gamma-hydroxybutyric acid group referred to be abstinent and 15 referred controlled drinking; while in the placebo group only 2 and 6 patients referred abstinence and controlled drinking, respectively. Serum-gammaglutamyltransferase activity correlated with the admitted alcohol consumption. Gamma-hydroxybutyric acid treatment decreased alcohol craving during the 3 months of treatment. Transient side effects were noted by 6 patients on gamma-hydroxybutyric acid and 2 on placebo.

Experimental studies suggest that GHB administration interferes with the activity of dopamine,[6] serotonin,[7] acetylcholine,[8] opioids[9] and GABA.[10] At present it is unknown which of these interactions bears some relevance for the suppressant effect on ethanol consumption and craving.

Moreover, since GHB is a normal brain constituent and has many of the characteristics of neurotransmitter and/or neuromodulator,[1] the possible relevance of changes in the content and activity of endogenous GHB in the pathogenesis of alcoholism might be considered.

Finally, the possibility exists that GHB might act by mimicking the central effects of ethanol. Indeed, ethanol moiety is present in the structure of GHB and the latter shares with ethanol different pharmacological and neurochemical characteristics. Moreover tolerance to ethanol is extended to GHB.[4] Should the latter hypothesis be validated, the rationale for using GHB in the treatment of alcoholism would be the same as that of using methadone in heroin addiction.

Whatever the exact mechanism of action of GHB, our results indicate that GHB deserves more extensive investigation as a clinically useful drug in the treatment of alcoholism.

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EXHIBIT 17

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European Journal of Clinical Pharmacology

Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers

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Summary. Gamma-hydroxybutyric acid (GHB) is effective in treatment of the alcohol and opiate withdrawal syndromes. Its absorption and disposition kinetics have been studied in 8 healthy male volunteers following oral administration of single doses of 12.5, 25 and 50 mg kg^{-1}.

The AUC increased disproportionately with the dose and so the apparent oral clearance decreased significantly as the dose was increased, whereas the terminal half-life and mean residence time increased. The peak plasma concentrations normalised to the lowest dose fell significantly with increasing doses, whilst the corresponding peak times increased.

These findings suggest that both the oral absorption and the elimination of GHB are capacity-limited processes. GHB did not bind to significant extent to plasma proteins over the therapeutic concentration range.

The pharmacokinetic parameters in healthy volunteers were not significantly different from those previously observed in alcohol-dependent patients with compensated alcoholic liver disease.

Key words: Gamma-hydroxybutyric acid; pharmacokinetics, dose-proportionality

Gamma-hydroxybutyric acid (GHB) is an endogenous constituent of the mammalian brain, where it is synthesized from gamma-aminobutyric acid (GABA) [1, 2]. Evidence has accumulated that GHB is not just a metabolite of GABA and that it plays a role as a central neurotransmitter or neuromodulator (see 3 for review). GHB was formerly used as an intravenous anaesthetic agent [4] and in the treatment of narcolepsy [5]. It has recently been reintroduced into therapeutics for the treatment of alcohol dependence [6]. Given daily in oral doses of 50 to 100 mg kg^{-1}, GHB rapidly suppresses alcohol withdrawal symptoms, and reduces alcohol comsumption and craving without causing any serious side-effects [6, 7]. A pharmacokinetic study has recently been conducted in alcohol-dependent patients [8]. Consistent with the rapid onset and short duration of the effect of GHB, the study showed that GHB absorption and elimination were fast processes. Virtually no unchanged drug could be recovered in the urine, in accordance with previous animal studies, which indicated that GHB was almost exclusively cleared by hepatic biotransformation [3]. Preliminary indications have also been obtained of non-linear kinetic behaviour.

The present study had three main purposes:

1. To determine the pharmacokinetic parameters of GHB in healthy volunteers, since no information was available from normal subjects. It is known that long-term alcohol abuse may enhance or decrease hepatic drug metabolism as a consequence of enzyme induction or hepatocyte dysfunction [9]. Thus, pharmacokinetic information obtained in alcohol abusers may not be relevant to normal subjects. Pharmacokinetic information in non-alcoholics is necessary because of recent clinical observations that GHB is not only useful in alcohol dependence, but it is also effective in preventing and suppressing opiate withdrawal symptomatology [10].
2. To examine the dose-proportionality of GHB after administration of ascending therapeutic oral doses.
3. To assess the plasma protein binding of GHB and its possible concentration dependence.

Subjects and methods

Subjects

Eight, healthy, nonsmoking male volunteers, aged 22 to 26 y, and weighing 66 to 85 kg (mean 79.2 kg, SD 7.5 kg), gave informed written consent to participation in the study, which was approved by the University of Padova Medical School Ethics Committee. All participants were diagnosed as healthy by means of a thorough clinical examination, including medical history, physical examination, complete blood count and laboratory tests, indicating normal function of the kidney (serum creatinine and blood urea nitrogen) and liver (direct and total serum bilirubin, serum protein and albumin, alanine and aspartate aminotransferases, gamma-glutamyltransferase, prothrombin time). The subjects were instructed to avoid any other drugs, including alcohol, for 2 weeks before the study and during the entire period of investigation.

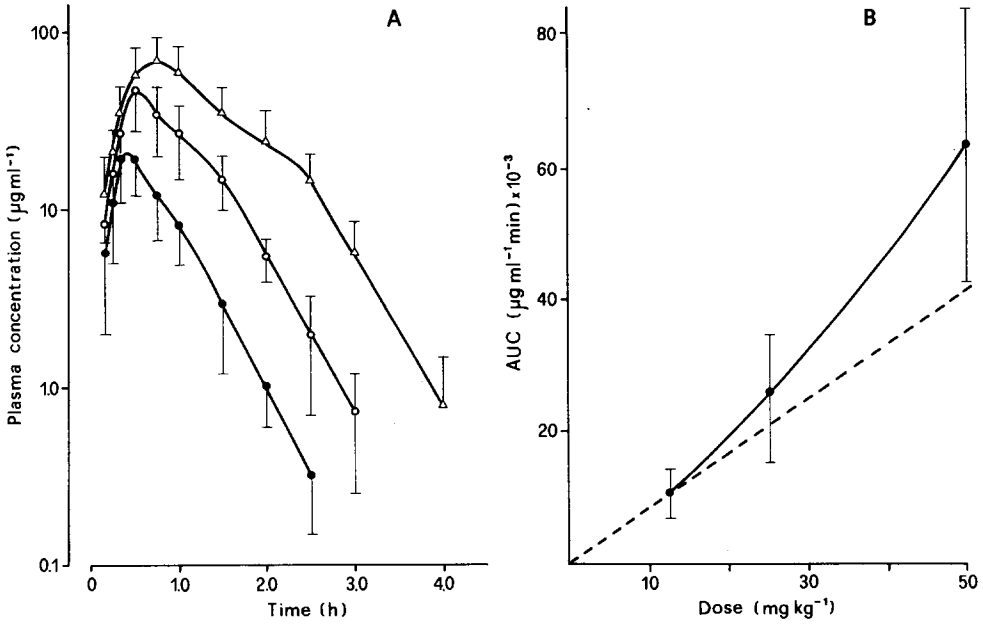

Fig. 1. A. Semilogarithmic plots of mean (SD) plasma concentrations of GHB following oral administration of 12.5 (●), 25 (○) and 50 (△) mg kg^{-1}.
B shows the relationship between AUC and dose of GHB. The *dotted line* is the relationship anticipated from the lowest AUC-dose data pair on the basis of linear kinetics

Study design

At 08.00 h, after an overnight fast, GHB dissolved in a black cherry syrup (CT, Sanremo, Italy) was given orally to the 8 volunteers in doses of 12.5, 25 and 50 mg kg^{-1}. The different doses were given in a random order, with a washout period of 3 days between each dose. The appropriate volumes of syrup were diluted to 100 ml with water and the cup containing GHB was rinsed with a further 50 ml water, so that the total fluid intake was 150 ml for all doses. The volunteers remained sitting for the first 2 h after dosing, after which, they were allowed a further drink of water and were permitted to walk in the ward. A light standard meal was provided after 4 h.

Blood samples were collected through an indwelling catheter into heparinised plastic tubes at 0 (predose), 10, 15, 20, 30, 45 min and 1, 1.5, 2, 2.5, 3, 4 and 6 h after dosing. All subjects were closely monitored for possible adverse effects during the entire course of the study.

Analytical methods

Plasma GHB was determined by a gas chromatographic/mass spectrometric method [8, 11]. The assay was linear over the clinically relevant concentration range (2–200 μg ml^{-1}) with a correlation coefficient of 0.999. The detection limit was 0.2 μg ml^{-1}. The intra- and inter-assay coefficients of variation (n = 5) at 5 and 100 μg ml^{-1} were below 5%.

The plasma protein binding of GHB at 37° was determined in duplicate by equilibrium dialysis, using a Dianorm® equilibrium dialyser (Diachema AG, Switzerland) equipped with 1 ml cells and semipermeable membranes with a molecular weight cut-off of 5.000 D. Preliminary experiments established that equilibrium was attained within 1 h and that there was no difference in binding between plasma and serum. The possible concentration dependence of GHB protein binding was evaluated in the plasma of a single volunteer at predialysis concentrations of 3, 10, 20, 100, 200, 300 μg ml^{-1}. As no concentration-dependent binding was observed, the plasma protein binding in each subject was determined at a single GHB concentration. GHB was added to 0.9 ml of a predose plasma sample to produce a concentration of 25 μg ml^{-1}, and the pH was adjusted to 7.4 with 0.3 M phosphoric acid. The plasma was dialysed against an equal volume of 0.13 mol · l^{-1} phosphate buffer pH 7.4 for 1 h and the GHB concentration was then determined in aliquots taken from both chambers. The fraction of unbound drug (f_u) was calculated as the ratio of the concentration in buffer to that in plasma. Allowance was not made for volume shift (< 10%), since the error introduced by ignoring it was negligible at the observed degree of binding [12].

Pharmacokinetic and statistical analyses

Pharmacokinetic parameters were estimated by standard non-compartmental methods. The peak plasma GHB concentration (C_{max}) and the time of its occurrence (t_{max}) were the observed values. Terminal half-life ($t_{1/2z}$) was obtained by log-linear regression analysis of the terminal phase of the concentration-time curves. The areas under the plasma drug concentration-time curves (AUC) and under the first moment of the plasma drug concentration-time curves (AUMC) were calculated by the linear trapezoidal rule up to the last determined concentration, and were extrapolated to infinity by standard methods [13]. The extrapolated portion was always less than 10% of the total area. Mean residence time (MRT) was calculated as AUMC/AUC and apparent oral clearance (CL_o) as dose/AUC.

Pharmacokinetic parameters are expressed as means (SD), with the exception of t_{max}, for which the median value (range) is reported. Statistical comparisons were made by two-way analysis of variance (ANOVA) using the general linear model (GLM) procedure of the statistical analysis system (SAS® (1988) Release 6.03. SAS Institute, Cary, NC, USA). Wilcoxon's signed rank test was used as the non-parametric test of differences in t_{max}. A $P < 0.05$ was considered statistically significant.

Results

The time course of the plasma GHB levels after administration of 12.5, 25 and 50 mg kg^{-1} is shown in Fig. 1 A. After each dose, the semilogarithmic plot of concentration-time data exhibited a biphasic decay phase: an initial rapid decline followed by a convex concentration-time profile, which became increasingly prominent as the dose was raised. Such a decay pattern is typical of drugs with a pronounced distributive phase and non-linear elimination kinetics [13]. Increasing the dose caused a disproportion-

Table 1. Mean (SD) pharmacokinetic parameters of GHB after administration of different doses to 8 healthy volunteers

Parameter	Dose ($mg\,kg^{-1}$)		
	12.5	25	50
AUC ($\mu g\,ml^{-1}\,min$)	905 (443)	1271 (560)[a]**	1565 (548)[a]**
CL_o ($ml\,min^{-1}\,kg^{-1}$)	14 (6)	9 (4)*	7 (3)**
MRT (min)	45 (10)	53 (9)**	70 (12)**
$t_{1/2z}$ (min)	20 (2)	22 (3)	23 (3)*
c_{max} ($\mu g\,ml^{-1}$)	23 (9)	23 (11)[a]	20 (7)[a]*
t_{max} (min)	25 (20–30)[b]	30 (20–45)[b]*	45 (30–60)[b]**
f_u	0.99 (0.03)[c]		

[a] Normalized to 12.5 $mg\,kg^{-1}$; [b] Median value (range); [c] Determined at a predialysis concentration of 25 $\mu g\,ml^{-1}$ (see Methods); * $P < 0.05$ and ** $P < 0.01$ relative to values in the 12.5 $mg\,kg^{-1}$ dose group

ate increase in AUC (Fig. 1B), thereby confirming the nonlinearity of GHB elimination kinetics. Accordingly, there was a significant and progressive increase in dose-normalised AUC as the dose was raised (Table 1). As a consequence, large variations were recorded in CL_o and MRT. However, $t_{1/2z}$ changed to a much more limited extent. Increasing the dose did produce a significant increase in t_{max} with a concomitant decrease in dose-normalised C_{max} (Table 1). This suggests that the absorption of GHB is capacity-limited in the therapeutic dose range. It can also be appreciated that the free fraction of GHB in plasma approached 1, indicating no significant protein binding of the drug.

Statistical comparison of the present results with data previously obtained in alcohol-dependent-subjects [8] revealed that, at equal doses, the pharmacokinetic parameters did not differ significantly between the two groups ($P > 0.05$ for all parameters).

After the 12.5 $mg\,kg^{-1}$ dose, three subjects reported slight dizziness, which occurred around t_{max} and lasted about 15 min. After the doses of 25 and 50 $mg\,kg^{-1}$ all volunteers complained of dizziness and/or drowsiness. The symptoms were still mild and subsided completely within 20 to 60 min, with the exception of three subjects, who, after the 50 $mg\,kg^{-1}$ dose, also complained of nausea for 60 to 90 min. The peak concentrations in those subjects (56 to 98 $\mu g\,ml^{-1}$) were similar to those observed in the other subjects.

Discussion

Previous studies have shown that the elimination kinetics of GHB is non-linear in animals [15–18]. The results of the present investigation indicate that GHB elimination kinetics is also non-linear in normal human subjects over the therapeutic dose range. A plasma decay profile quite similar to that observed here was obtained by van der Pol et al. following IV administration of 60 $mg\,kg^{-1}$ GHB (unpublished data reported in Ref. 19). Such a decay pattern was interpreted as reflecting the presence of parallel first-order and capacity-limited alimination pathways [19; see also 13, pp. 282–4]. As GHB is not excreted by the kidneys [8], the most likely explanation for the observed non-linearity is saturation of one or more of its as yet poorly defined metabolic pathways [3]. However, it cannot be excluded that saturable cellular uptake may be responsible for the dose-dependent kinetics of GHB, since active transport of the drug has been documented in the rat [18].

In apparent contrast to the large reduction in CL_o, which was halved upon increasing the dose from 12.5 to 50 $mg\,kg^{-1}$, $t_{1/2z}$ increased by only 15%. This cannot be ascribed to variation in the apparent volume of distribution, since GHB does not bind to plasma proteins; the apparent volume of distribution of GHB in rats was shown to be invariant with dose [17]. The most likely explanation for this apparent discrepancy is that $t_{1/2z}$ reflects the slope of the terminal portion of the curve, which is essentially independent of the dose, since the drug concentration was no longer saturating.

Oral administration of ascending doses of GHB resulted in an increase in t_{max} and a decrease in normalised c_{max}, suggesting capacity-limited absorption of GHB. The fact that the modification of c_{max} was not as prominent as that of t_{max} may have been due to the concomitant saturation of the elimination process, which made c_{max} values higher than expected from linear elimination kinetics, thereby masking the effect of saturable absorption. A quite similar dose-related absorption pattern has been observed in the rat, where saturable transport across the intestinal mucosa has been demonstrated [17, 18].

The pharmacokinetic parameters of GHB observed here in healthy volunteers proved to be very similar to those previously obtained from a group of alcohol-dependent patients with compensated alcoholic liver disease [8]. Thus, as long as hepatic function remains in a compensated state, alcohol abuse does not appear to affect GHB elimination. In spite of similar peak plasma concentrations, the frequency of concentration-related side-effects was higher in healthy volunteers than in alcohol-dependent patients (only 20% of the latter subjects complained of dizziness or drownsiness; 8). However, tolerance to these symptoms readily develops [6, 7].

On the basis of the present results, it may be concluded that the same dosing regimen can be used for alcoholic and non-alcoholic subjects. However, a greater fractionation of the daily dose of GHB appears preferable for the latter subjects, in order to avoid concentration-related adverse effects during the early phase of therapy.

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EXHIBIT 18

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γ-BUTYROLACTONE AND γ-HYDROXYBUTYRIC ACID—II. THE PHARMACOLOGICALLY ACTIVE FORM*

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(*Accepted* 5 *August* 1966)

Summary—Three lines of evidence are presented to establish γ-hydroxybutyric acid (GHB) as the pharmacologically active form of γ-butyrolactone (GBL). A greater delay in the onset of blockade of transmission in the superior cervical ganglion of the cat was seen with GBL than with GHB, suggesting that the lactone must be converted to the acid before pharmacologic activity can be observed. Only GHB was active in depressing the rat by the intra-cisternal route of administration. When administered by micro-injection into the thalamus and hippocampus of unanesthetized monkeys, GHB produced slow-wave, high amplitude activity in the electroencephalogram, while GBL was without effect. GHB administered directly into the brain produced these effects almost immediately.

INTRODUCTION

γ-BUTYROLACTONE (GBL) and its hydrolytic cleavage product, γ-hydroxybutyric acid (GHB), are interconvertible *in vitro* (HENRY, 1892), and GBL is rapidly hydrolysed to GHB *in vivo*, a reaction catalysed by an enzyme in blood and liver (ROTH and GIARMAN, 1965). Each of these substances can produce a similar depression of the central nervous system in a variety of mammals (BENDA and PERLES, 1960), but there is some controversy about which of the pair is responsible for the action *in vivo*. BESSMAN and SKOLNIK (1964) claimed that GBL is the form in the brain of the rat that is correlated with depression of the CNS; while GIARMAN and ROTH (1964), using a gas chromatographic method for the differential assay of GBL and GHB, showed that the onset and offset of depression of the CNS is dependent entirely upon the level of GHB in the brain of the rat.

The purpose of this communication is to marshall more evidence in favor of the contention that the acid and not the lactone is responsible for the effects of these substances on the nervous system.

METHODS

In the series of experiments in which effects on ganglionic transmission were studied, mature cats of either sex, weighing at least 2 kg, were used. In most of the experiments

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anesthesia was initially induced with ether, and then spinal preparations were accomplished according to BURN (1952). After the beginning of the spinalization procedure, the cats were maintained on artificial respiration through a tracheal cannula. When appropriate, the right superior cervical ganglion and nictitating membrane were prepared for close intra-arterial injection *in situ* in accordance with the method described by TRENDELENBURG (1957). The preganglionic sympathetic nerve trunk was dissected free of the vagus and transected. When required, the preganglionic sympathetic nerve was stimulated by means of a bipolar platinum electrode submerged in warm mineral oil, which served as an efficient insulator as well as a means of preventing drying of exposed tissue. The stimulus parameters used were as follows:

(1) For supramaximal stimulation, square wave stimuli with an intensity of 10 V, 0·7 msec duration and a frequency of 20 c/s were applied to the preganglionic nerve for 5 sec every 2½ min.

(2) For submaximal stimulation, square wave stimuli with an intensity of 10 V, 0·7 msec duration and frequency of 0·5 c/s were applied to the preganglionic nerve for 5 sec every 2½ min.

For recording contractions of the nictitating membrane, the cat's head was rigidly held in position by fixing its jaws tightly around a transverse rod attached to the edges of the operating table. The membrane was held clear of the eyeball and arranged to pull in a direction which approximated that of its physiological orientation at rest. This was controlled by interposing a small, almost frictionless pulley in the path of a No. 4–0 silk thread which was sewn through the middle of the border of the nictitating membrane cartilage and attached at its other end to a force displacement transducer (Grass FT-03) coupled to a Grass model 5 polygraph. After an initial tension load of 5 g was placed on the nictitating membrane the preparation was allowed to equilibrate for about 30 min. When equilibrium was attained, the basal tension was approximately 3 g and the baseline was stable. Concomitantly with contractions of the nictitating membrane, mean arterial blood pressure was recorded from the cannulated right femoral artery by means of a Statham (P23 AC) pressure transducer. For intravenous injections, the left saphenous vein was cannulated.

Intracisternal punctures were made by a procedure previously described by JEFFERS and GRIFFITH (1949). Adult male rats, weighing 350 to 400 g, were lightly anesthetized with ether and the hair shaved off the back of the neck. The animals were placed in a prone position with the head elevated so that the long axis of the body lay at about a 45 degree angle to the horizontal axis. The fore and hind legs were fastened in place with rubber bands to maintain this position, in which the head extends over the upper portion of the stand and is freely movable. When the head is flexed acutely, the external occipital protuberance can be felt with the index finger. Directly caudal to this protuberance is a depression between it and the spine of the atlas. A 27 gauge 5/8 in. needle was carefully inserted into the center of this depression with a circular motion. As the needle enters the cisterna magna, a sudden decrease of resistance is felt and a small amount of cerebral spinal fluid (CSF) will flow into the syringe. Routinely, 0·05 ml of CSF was withdrawn and 0·05 ml of drug solution injected.

The infusion of drugs into discrete nuclear masses of the brain of unanesthetized, restrained monkeys was performed according to the procedure of DELGADO and RUBENSTEIN (1964); and DELGADO (1965). Two monkeys were used in these experiments with a

"cross-over" design. A modified "chemitrode" assembly consisting of a permanently implanted micro-cannula and an array of six contacts in the thalamic region of the brain of one monkey and in the hippocampus of another was employed in these experiments. A total of 6 experiments were carried out with an interval of at least 4 days between experiments. Each monkey received GHB in one experiment and after the appropriate time-lapse, each received GBL. When these animals were sacrificed histological examination of the brain indicated that the tip of the chemitrode in one monkey lay in the hippocampus at coordinates A–10 and R–9 of the SCHNEIDER and LEE map (1961), while that in the other monkey (whose EEG is shown in Fig. 4) lay in the posterior inferior *nucleus ventralis* of the thalamus bordering on the *substantia nigra* at coordinates A–6 and L–3 of the Schneider and Lee map.

RESULTS

(1) *Actions on the superior cervical ganglion (SCG)*

In an attempt to find an easily explorable neural system in which GBL and GHB might exert depressant effects, the actions of these agents on transmission in the superior cervical ganglion of the cat were examined.

Close intra-arterial injection of either GBL or GHB (even in high doses of 1–10 mg) through the SCG had little influence on the response of the nictitating membrane to submaximal stimulation or to administration of acetylcholine directed to the ganglion by close intra-arterial injection. In contrast to these unimpressive results, it was found that when the compounds were administered (20% solutions in distilled water) intravenously in anesthetic doses, both the lactone (345 mg/kg) and the acid (sodium salt, 500 mg/kg) could depress transmission in the SCG of the cat elicited by submaximal stimulation of the preganglionic nerve trunk. This action was localized primarily to the ganglion by comparing the effects of both substances on the response to preganglionic and postganglionic stimulation of the cervical sympathetic nerve trunk, but some slight depression at the neuroeffector junction could not be ruled out.

The data obtained in this system indicated that the inhibitory activity was correlated with the presence of the acid and not with the lactone. Figure 1 shows a tracing obtained

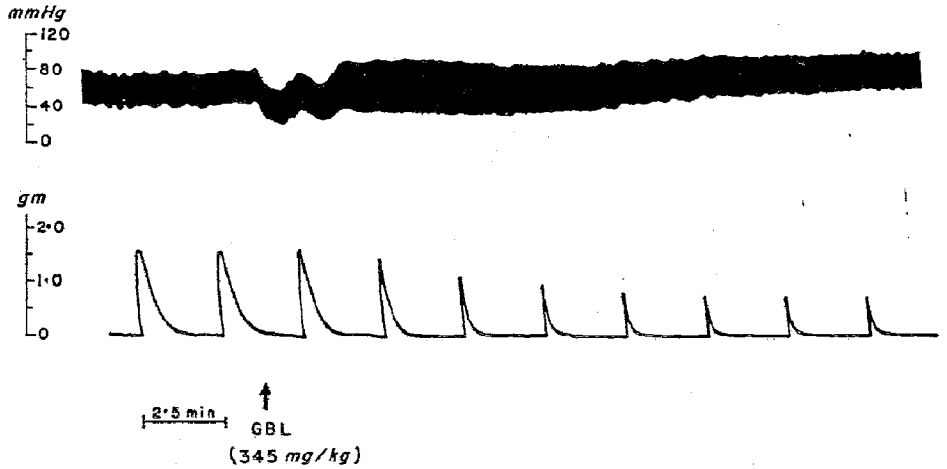

FIG. 1. Effect of GBL upon blood pressure (upper tracing) and contractions of the nictitating membrane (lower record) elicited by submaximal preganglionic stimulation at 2·5 min intervals. At the arrow GBL was administered into saphenous vein in the dose shown over a period of 1 min.

from a spinal cat given an anesthetic dose of GBL (345 mg/kg) administered via the saphenous vein 1·5 min before the next stimulation of the preganglionic nerve trunk (dose given in a 1 min infusion). From this figure it can be observed that there is a definite delay before the lactone begins to depress transmission. Forty per cent inhibition is seen within about 8 min. However, when an equivalent amount of GHB was administered under identical conditions, a much shorter delay was observed (Fig. 2). In this experiment 40%

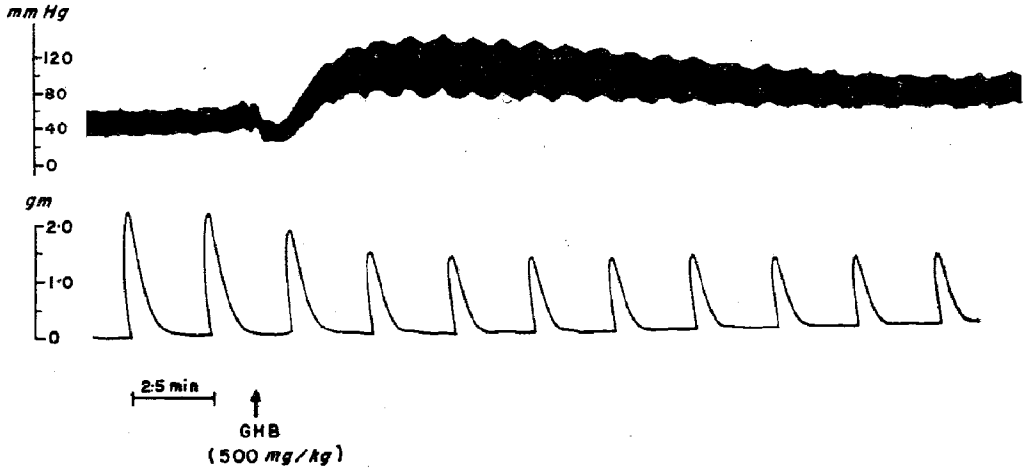

FIG. 2. Effect of GHB upon blood pressure (upper tracing) and contractions of the nictitating membrane (lower record) elicited by submaximal preganglionic stimulation at 2·5 min intervals. At the arrow GHB was administered into saphenous vein in the dose shown over a period of 1 min.

inhibition is seen in 3 min. The relatively longer delay was routinely seen with the lactone in all similar experiments; and it is now believed that the delay can be attributed to the time it takes the lactonase in serum and liver (ROTH and GIARMAN, 1965) to hydrolyze the lactone to GHB.

The possibilities that GBL and GHB might exert this depressant action through an active metabolite or through the release of catecholamines from the adrenal medulla were considered. Experiments in eviscerated or acutely adrenalectomized cats, however, proved that neither the visceral organs nor the adrenal glands were necessary for the blocking action of GHB and GBL on transmission in the SCG.

Effects on blood pressure varied, but in most experiments GBL produced a pressor response after a few minutes delay.

(2) *Effects elicited by intracisternal administration of GHB and GBL*

The fact that neither brain nor cerebral spinal fluid contained any appreciable lactonase activity (ROTH and GIARMAN, 1965) suggested the possibility of depositing GBL in brain tissue directly without allowing it to be subjected to hydrolysis by the plasma or liver lactonase. This was accomplished easily by intracisternal administration of the lactone and the results are shown in Table 1. It was found that when 115 to 230 μmole of GBL were administered in this manner, it was virtually devoid of any CNS depressant activity. However, when GHB (sodium salt) was administered in equimolar amounts, profound and lasting central nervous system depression resulted. In fact, with the high dose, GHB

TABLE 1. EFFECTS IN THE RAT ELICITED BY THE INTRA-CISTERNAL ADMINISTRATION OF GHB AND GBL

Drug*	Dose	Return of RR† (min)	Complete recovery (min)	Remarks
Isotonic sodium chloride	0·05 ml	6	18	
Isotonic sodium chloride	0·10 ml	5	18	
GBL	20 mg (230 μmole)	6	20	
GBL	20 mg (230 μmole)	6	19	
GHB (sodium salt)	29 mg (230 μmole)	—	—	Died of respiratory paralysis 18 and 19 min after injection
GHB	29 mg (230 μmole)	—	—	
GHB	29 mg (230 μmole)	55	90	
GBL	10 mg (115 μmole)	4	14	Recovery not complete—brain damage
GBL	10 mg (115 μmole)	12	19	
GBL	10 mg (115 μmole)	7	21	
GHB	15 mg (115 μmole)	48	75	
GHB	15 mg (115 μmole)	—	—	Died of respiratory paralysis 10 min after injection
GHB	15 mg (115 μmole)	65	88	

*All rats were lightly anesthetized with ether prior to injection.

†RR = Righting Reflex

The criteria for complete recovery were a return of the righting reflex, normal motor co-ordination, non-ataxic movements and normal gross appearance.

caused deaths by respiratory paralysis in some animals, after about 20 min. These data demonstrate quite clearly that GBL exerts little observable depressant action while GHB is a potent depressant by the intracisternal route.

(3) *Effects elicited by intra-brain perfusion*

The most direct experiment to demonstrate the pharmacologically active form was the infusion of each compound into a discrete nuclear mass in the brain of an intact, unanesthetized animal. Since we had already demonstrated that neither brain nor cerebral spinal fluid contained any lactonase activity, and since we had obtained substantial evidence supporting the contention that GHB is the active form of the drug, it was believed likely that GBL delivered directly to the brain should be inactive because it could not be hydrolyzed to GHB until it diffused out of the brain. A suitable preparation in which to examine this hypothesis was the perfused monkey brain preparation of DELGADO and RUBENSTEIN (1964).

With a modified "chemitrode" assembly (see Methods) it was possible to infuse either compound directly into the thalamus of the *Macaca mulatta*, and record simultaneously from this region as well as from other brain regions. By means of this technique, a total injection of 100 μl. of GHB (sodium salt) into the thalamus, in a 4% solution delivered over a period of 10 to 30 min, caused a profound, long-lasting change in the EEG with a prominent increase in high amplitude, slow wave activity. This is illustrated in Fig. 3. This record shows typical EEG tracings before (control) and at 1, 15, and 60 min after GHB. Marked changes are seen in the EEG from the thalamic and caudate leads at these various time intervals after administration of the drug, notably a prominent increase in slow wave,

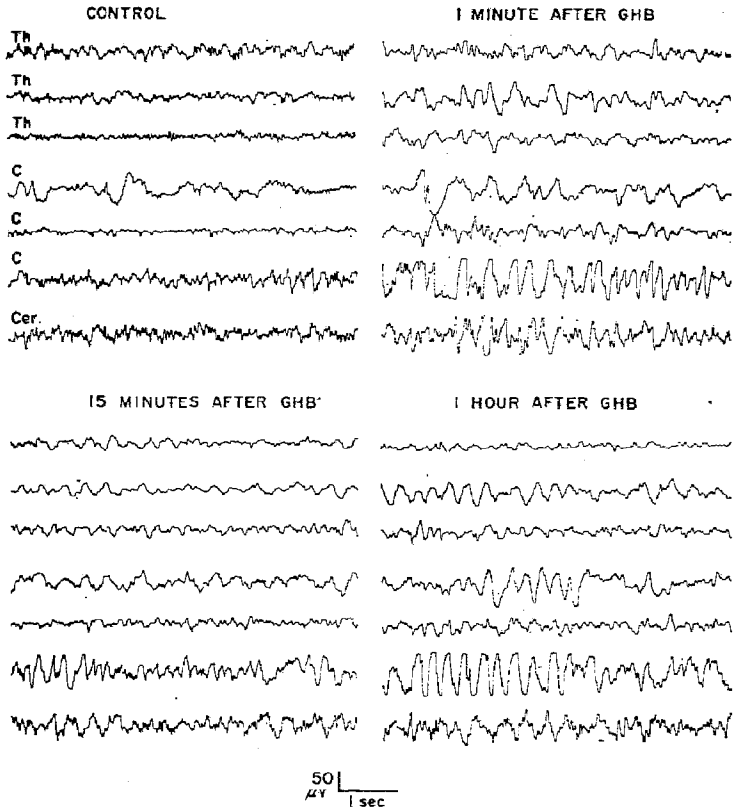

FIG. 3. Effects of intrathalamic administration of GHB (sodium salt) on the unanesthetized monkey. A total dose of 4 mg of GHB in a volume of 100 μl. was administered over a period of 10 min. EEG leads: Th = thalamus; C = caudate; Cer. = cerebellum.

high amplitude activity. The changes in EEG activity still persisted at 2½ hr, but returned to normal on the following day. On the other hand, the administration of an equimolar amount of the lactone (in isotonic saline) to the same monkeys four days later produced no significant changes in the EEG for periods up to 4 hr after GBL. Figure 4 shows typical EEG tracings before (control) and 1, 15, and 60 min after the lactone. Control injections of equal volumes (100 μl.) of isotonic saline solution and hypertonic saline solution produced no abnormal EEG effects. Similar experiments carried out in the hippocampus also clearly demonstrated that GHB was the only form that was active in producing EEG changes.

DISCUSSION

Evidence is presented in this work which directly implicates GHB as the active form of the GHB–GBL pair in producing depression of nerve activity, both in a peripheral nerve structure and in the brain. The most difficult finding to reconcile with this conclusion is the observation that GBL produces a longer lasting depression when equimolar doses by intravenous administration are compared. Our studies on the distribution of these two compounds into various tissues of the rat have clarified the apparent inconsistency (ROTH and GIARMAN, 1966). Since GBL, by virtue of its relatively high lipid solubility, can penetrate lipoidal anatomic barriers much more readily than the ionized acid (GHB),

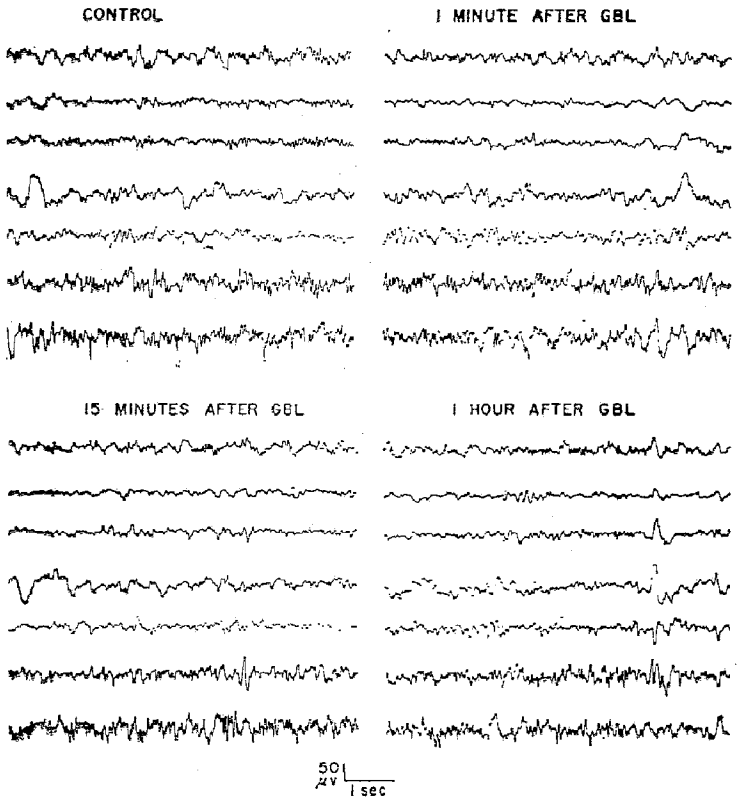

FIG. 4. Effects of intrathalamic administration of GBL on the EEG of the unanesthetized monkey. A total dose of 2·7 mg (equimolar to the dose of GHB in Fig. 3) in a volume of 100 μl. was administered over a period of 10 min. EEG leads reading from top down: first 3 are thalamic, next 3 are from the caudate and the last is cerebellar.

more richly perfused tissue, such as lean muscle, take up the lactone rapidly before it is hydrolysed to GHB. This effective removal of GBL from the circulation retards its rate of metabolism and serves to provide a slowly released pool of GBL which is converted to GHB and leads to a longer duration of action than that seen after the administration of GHB. The GHB is slow to traverse lipoidal barriers and is, therefore, not particularly sequestered by any organ, but is equally available to sites of pharmacologic action and of biotransformation.

It is interesting in this respect that WINTERS *et al.* (1965a) did not observe a significantly longer duration of action of GBL in rats. Their study, however, involved administration of the drugs by the intraperitoneal route which adds the unknown factor of the extent and rate of absorption of these drugs from the abdominal cavity. One would expect the absorption of GBL and GHB from this site to differ markedly, and perhaps this could explain why GHB has a more prolonged effect when given by the i.p. route. Since GHB is probably absorbed so much more slowly than GBL, this intra-abdominal pool of GHB would be protected from the metabolizing enzymes, just as is the larger pool of GBL in muscle after the intravenous administration of GBL.

When GBL is placed directly in the brain by intracisternal administration or by microinjection (via the chemitrode), no pharmacologic action ensues, because the brain cannot hydrolyze the lactone to GHB. A similar state of affairs is observed during the first 5–7 min

after the administration of an anesthetic dose of GBL into the peripheral circulation. Because of its high lipid solubility GBL reaches exceptionally high levels in the brain 1 min after its administration (ROTH and GIARMAN, 1965), but the animal shows no signs of depression until the brain GBL is re-distributed to the general circulation, hydrolyzed in blood and liver, and returned slowly to the brain as the active GHB. Thus the onset of action is rather protracted. There is a slow onset of action also after the administration of GHB into the peripheral circulation because of the relatively poor penetrability of GHB into brain. When GHB is deposited *directly* into the brain, however, there is an almost immediate onset of action.

It has been purely a matter of convenience for us to refer to the pharmacologic actions of GBL and GHB as "anesthetic" or "CNS-depressant", but from a strict electrophysiologic standpoint these compounds cannot be so classified. WINTERS and SPOONER (1965) have appropriately called attention to differences in properties of GHB and pentobarbital on the basis of gross behavior, EEG patterns and average evoked responses to clicks in cats. These investigators noted a similarity between GHB and "generalized non-convulsant epilepsy". In our studies with intra-thalamic administration of GHB in monkeys spike-and-wave patterns were seen in the cortical EEG interspersed within a generalized wave slowing. Similar and other patterns indicating some seizure activity after GHB have been observed by us in the EEG of cats with chronically implanted electrodes (ROTH, SUTIN and GIARMAN, unpublished data).

Acknowledgements—The authors gratefully acknowledge the cooperation of Dr. M. Gluckman of the Wyeth Laboratories in supplying us with γ-hydroxybutyric acid, sodium salt.

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EXHIBIT 19

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γ-BUTYROLACTONE AND γ-HYDROXYBUTYRIC ACID—I
DISTRIBUTION AND METABOLISM*

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Abstract—Some aspects of the distribution and metabolism of the central nervous system depressants, γ-butyrolactone and γ-hydroxybutyric acid, have been investigated. After the administration of a depressant dose of γ-hydroxybutyrate to the cat, there was a relatively higher concentration of γ-hydroxybutyrate in the cerebellum and in the lower temporal lobe of the cortex than in other areas of the brain examined. The γ-butyrolactone was found to concentrate more in lean muscle than γ-hydroxybutyrate, while there was no difference in the amount of each that appeared in the body fat. The latter finding is explained by the presence of a rapidly acting lactonase in blood and liver that catalyzes the hydrolysis of γ-butyrolactone to γ-hydroxybutyrate. ^{14}C-carboxyl-labeled γ-hydroxybutyrate and γ-butyrolactone were found to be metabolized very rapidly to $^{14}CO_2$ in the intact rat; both the brain and liver carry out this decarboxylation *in vitro*. The major pathway of metabolism does not appear to involve formation of succinic acid. These results are related to the nature of the pharmacologically active compound and its duration of action.

SOME current findings have focused attention upon the neuropharmacology and biochemistry of γ-butyrolactone (GBL) and its hydrolytic cleavage product, γ-hydroxybutyric acid (GHB). Early observations that depression of the central nervous system follows the administration of GBL[1, 2] and GHB[3, 4] to animals culminated in the demonstration that GHB is an effective anesthetic adjuvant in man.[5–7] The recent development of a senstive and specific gas chromatographic method for the differential estimation of GBL and GHB in tissues made possible the observation that when GBL is administered to the rat, it is rapidly hydrolyzed to GHB, which accounts for the subsequent depression of the central nervous system.[8] A preliminary report of the enzyme responsible for this conversion has also appeared.[9]

Within the context of investigating the distribution and metabolism of GHB and GBL, the purpose of this communication is twofold: (1) to offer some explanation for the finding that, although GHB is the active form of the drug, GBL has the longer duration of action; (2) to examine the distribution of GHB in specific regions of the brain.

* This work is derived from a dissertation presented to the Yale Graduate School by R. H. R. in partial fulfillment of the requirements for the Ph.D. degree. The study was aided in part by Grant 5-R01-NB-00940-10 from the National Institute for Neurological Diseases and Blindness. Part of this work was presented in a preliminary report in *Fedn. Proc.* **23**, 148 (1964).

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METHODS

1. *Assay for* GBL *and* GBH

The method used to identify and estimate amounts of GBL and GHB was essentially the same as that reported earlier,[8] with a few minor modifications as follows: the supernatant fraction was extracted twice with two volumes of benzene (fractionally distilled twice) instead of one volume; the benzene extract was passed over a dry-packed column of Dowex-2-chloride (2·5 × 1 cm) in order to remove small amounts of trichloracetic acid (TCA), collected, and evaporated as described, to a volume of 0·1–0·5 ml; about 3 μl of this extract was then placed on a gas chromatographic column packed with 12% ethylene glycol succinate on Anakrom ABS solid support. A flame ionization detector was employed to detect GBL under the following routine conditions: detector temperature = 220°; injector temperature = 230°; column temperature = 115°; nitrogen flow rate = 110 ml/min (inlet pressure = 32 lb); zero air flow rate = 450 ml/min (inlet pressure = 46 lbs); and zero hydrogen flow rate = 48 ml/min (inlet pressure = 21 lb). Recoveries with this method ranged from 80% to 95% depending upon the tissue under investigation. In all cases, the values reported below are corrected for recovery from the particular tissue studied.

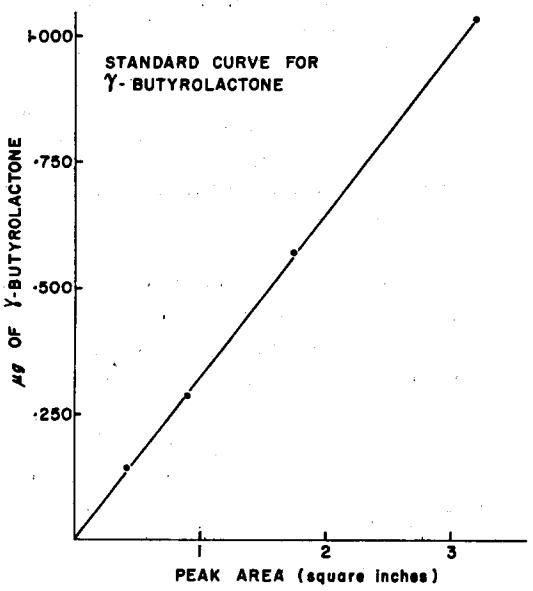

FIG. 1. Standard curve for the gas chromatographic assay of GBL with a flame ionization detector. Routine conditions as described in Methods were used. Peak areas were determined by means of a planimeter. Samples (1μl) containing the appropriate concentrations of GBL dissolved in benzene were used.

Authentic GBL was shown to have essentially the same retention time on the column by this technique as extracts of the brains of rats anesthetized with GBL.[8] Both the argon ionization and the flame ionization detectors were found to have a linear response to GBL over a wide range of concentrations. A standard curve for varying amounts of GBL obtained with a flame ionization detector is illustrated in Fig. 1.

2. *Regional brain distribution of* GHB

For this experimental series, mature cats of either sex, weighing at least 2 kg, were used. These animals were given sodium GHB in a dose of 350 mg/kg (expressed as free acid) via the right saphenous vein. The animals were sacrificed by decapitation 30 min after the drug. Each carotid artery was perfused for 10 sec with 15 ml of ice-cold isotonic sodium chloride solution to flush out residual blood in the cerebral vasculature. This procedure was found to remove very little GHB from brain. The brain was then isolated and sectioned into the desired areas, which were immediately frozen in liquid nitrogen at −196° and stored, if necessary, in dry ice subsequent to drying. Tissue sections prior to drying were broken into small pieces in a cold mortar containing powdered dry ice, and these pieces of brain were then dried at −40° for 3 days by means of a phosphorus pentoxide trap with a vacuum of about 0·001 to 0·005 mm Hg. The dried tissues were ground into a fine powder, and 100 mg homogenized in 5 ml of 10% TCA and rinsed into a centrifuge tube with distilled water. The suspension was centrifuged at 33,000 *g* for 7 min in a Sorvall refrigerated centrifuge at 0°; the supernatant fraction was decanted, heated to convert GHB to GBL, and extracted with benzene as described above. The amount of GBL in a 3-μl sample of the final extract was then determined by means of gas chromatography.

3. *Hydrolysis of* GBL

Samples of rat and guinea pig blood were obtained from adult male animals by decapitation and exsanguination. Cat blood was obtained by cardiac puncture of animals lightly anesthetized with ether; dog, rabbit, and human blood was obtained by aseptic venopuncture. In all studies with plasma, the blood was heparinized to prevent clotting, and plasma was obtained by centrifuging the blood at 27,000 *g* for 10 min at 2°. In studies of serum, no heparin was used. The clot was removed from the blood, kept in an ice bath, and the remaining fluid was centrifuged to remove residual erythrocytes.

All incubations were carried out at 37° in a Dubnoff metabolic incubator. The usual concentration of GBL employed in the studies *in vitro* was $1{\cdot}3 \times 10^{-2}$ M, although a wide range of concentrations was used with the technique that made use of a pH-stat. This high level was chosen to approximate the pharmacological levels present in rat blood *in vivo* after intravenous administration of anesthetic doses of GHB or GBL. Routinely, 2-ml aliquots were taken from the incubation vessel and carried through the standard gas chromatographic procedure for the separation and estimation of GHB or GBL. In one case the Angeli-Rimini reaction as used for the quantitative determination of esters by Hestrin[10] was adapted for estimation of the amount of GBL present. The optical density was read in a Klett photometer with a No. 54 filter. In this case only the disappearance of GBL was followed, whereas with the gas chromatographic method both the disappearance of the lactone and the formation of the acid were followed. Plasma was diluted 1:10 with isotonic sodium chloride–phosphate buffer (0·05 M) at pH 7·4.

After it was established that plasma could hydrolyze GBL to GHB very rapidly and that further metabolism by this tissue was negligible, a more rapid method was sought to follow the rate of hydrolysis. Titration of the acid formed in the reaction mixture was found to be very simple and reliable. All incubations in these studies were performed at 37°. The reactions were followed with a Radiometer Titrigraph type

SBR2/SBU1. Since no spontaneous hydrolysis of GBL was observed in sodium chloride–phosphate buffer or in saline at pH 7·4 within 60 min, and also since incubation of a 10% solution of serum in isotonic sodium chloride solution resulted in no acid production, this was considered a reliable method for estimation of the enzymic hydrolysis of the lactone.

In the analysis of "lactonase" activity, tissues were dissected as quickly as possible from male rats killed by decapitation, and a 10% homogenate was made with isotonic sodium chloride–phosphate buffer. Tissue suspensions were kept chilled until incubation. In one case a rat was anesthetized with pentobarbital (50 mg/kg), the abdomen opened, and the liver exposed. The artery to the left lateral lobe of the liver was carefully isolated, cannulated and flushed with saline to remove blood. When the liver became pale, it was quickly excised and a 10% homogenate prepared as described above.

4. *Radiorespirometric technique*

Some radiorespirometric studies were performed with a model 6000 Dynacon electrometer recording system with the DCF 250 ion chamber (ion chamber constant $= 4{\cdot}62 \times 10^{-12}$ A/μc $\pm$ 0·5%) in conjunction with a Delmar metabolism jar, equipped with a food chamber, water inlet, and ascarite trap, and adapted for separate feces and urine collection. The metabolism jar was swept with atmospheric air which was then passed through the ionization chamber of a Nuclear-Chicago Dynacon electrometer connected to a 1-mA Texas integrating linear recorder. All rats used in these experiments were 250-g male animals obtained from Charles River Co. Drugs were injected via the tail vein. In certain other radiorespirometric studies the technique was slightly modified. Rats were given labeled GHB by intravenous administration and placed in the metabolism jar for 40 min. In this case, the glass metabolism jar was swept with air at a rate of 300 ml/min, and the air was then bubbled through a Hyamine hydroxide trap (10 ml). At the end of the experimental period, 0·5 ml of the Hyamine hydroxide solution was pipetted into 15 ml of toluene PPO-POPOP and counted with a Packard Tri-Carb liquid scintillation spectrometer. Internal standards were run to avoid any erroneous effects due to quenching. The urine collection system was maintained acidic with 1 N HCl to release any $^{14}CO_2$ present in the urine. The efficiency of the method was estimated by means of $Na_2{}^{14}CO^3$ given intravenously to rats in a volume of 0·4 ml. Average recovery of respiratory $^{14}CO_2$ in 40 min was found to be about 60%.

5. *Carbon dioxide-^{14}C measurements*

Since it has been reported that, in a closed system, paper strips moistened with sodium hydroxide solution will quantitatively absorb carbon dioxide,[11] it seemed feasible to use this technique for measuring radioactive carbon dioxide evolved from respiring tissue slices. A simple incubation vial was constructed from a Packard polyethylene counting vial. From the cap a small piece of Whatman 3MM filter paper was hung in the center of the vial in a position such that it did not come into contact with the incubation mixture. This paper strip was moistened with 3·5 N NaOH prior to incubation and served to trap radioactive carbon dioxide produced by the tissue. When the incubation was complete, 1 ml of 20% TCA was added (by puncturing the vial cap with a 22-gauge needle) to stop the reaction as well as to release carbon

dioxide from solution. The vial was then incubated an additional 10 min at 37° to ensure complete carbon dioxide absorption by the filter paper. The vial cap with the paper strip still attached was carefully removed and screwed to the top of a new vial containing 10 ml ethanolic PPO–POPOP mixture (cf. succinic acid isolation method). The vial was stored in the cold (at − 20°) for 6 hr to ensure complete impregnation of the paper strip and then counted in a Packard Tri-Carb liquid scintillation spectrometer (window set at 35-1000, gain = 16).

The efficiency of this method to measure radioactive carbon dioxide was determined with sodium carbonate ^{14}C obtained from New England Nuclear Corp. A known amount of radioactive sodium carbonate was added to the incubation vial with the standard incubation mixture of Krebs Ringer phosphate buffer solution. The vial cover containing the sodium hydroxide-dampened filter paper was replaced, and 1 ml of 20% TCA added. The vials were allowed to equilibrate at 37° for 10 min; the filter paper was then removed and counted as described above. The average recovery of radioactive carbon dioxide was 72% ± 2·8%. This recovery value is not a reflection of lost ^{14}C-carbon dioxide but rather a decreased efficiency in the counting of radioactivity absorbed by filter paper.

6. *Separation and estimation of succinic acid*

Gas chromatography was used for separation and estimation of succinic acid. A column of 12% ethylene glycol succinate coated on Anakrom ABS solid support was employed to obtain an acceptable separation. The separation of dimethylsuccinate, dimethylmalonate, and GBL achieved on this column is shown in Fig. 2. Methylation of the organic acids was accomplished with a solution of diazomethane in diethyl ether, which was freshly generated from N-methyl-N-nitroso-*p*-toluene sulfonamide, available under the trade name of Diazald (Aldrich Chemical Co.). The diazomethane was added directly to the acids or to a methanolic solution of the acids until no more nitrogen was evolved and the solution remained yellow. The excess reagents and solvents were then evaporated to produce a convenient volume, and an aliquot was placed directly on the gas chromatographic column.

For the identification and estimation of succinic acid in tissue, some preliminary purification steps had to be taken. Proteins in the tissue or tissue suspension were precipitated with a volume of 95% ethanol which gave a final concentration of 80% ethanol. The precipitate was then centrifuged at 33,000 *g* for about 7 min and the supernatant fraction passed over a Dowex 1-formate column and washed through with 20 ml 80% ethanol, followed by 10 ml distilled water. The succinic acid was then eluted with 6 N formic acid. The first 15 ml of eluate was saved and passed through a Dowex-50 column to remove interfering cations. With ^{14}C-succinic acid as a marker it was found that 95% of the succinic acid was eluted from the Dowex 1-formate column between 3 and 9 ml. Retention of the first 15 ml therefore compensated for any variation in the column efficiency and also avoided the elution of any interfering anions. The column was then washed with 10 ml distilled water. The combined eluate was lyophilized and the residue reacted with an ethereal solution of freshly prepared diazomethane. The solution of dimethylsuccinate was then identified and assayed by gas chromatography. The routine conditions used were as follows: flash heater = 220°, cell bath = 190°, column = 115°, and argon flow rate = 80 ml/min. By means of an effluent splitter, about 95%–99% of the succinate peak could be trapped in a

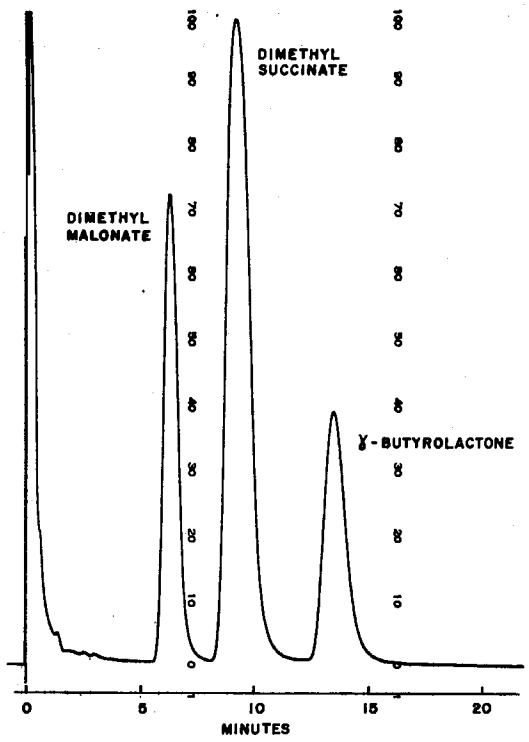

FIG. 2. Gas chromatographic analysis of a mixture of dimethylmalonate, dimethylsuccinate, and GBL. Conditions used: argon ionization detector; column of 12% ethylene glycol succinate coated on Anakrom ABS solid support, 70–80 mesh; cell temperature 190°; flash-heater temperature 220°; column temperature 115°; argon flow rate 80 ml/min; and gain of 10.

vial containing an ethanolic PPO-POPOP scintillation-counting mixture (Liquifluor) and counted with a Packard Tri-Carb liquid scintillation spectrophotometer.

7. Metabolic studies with tissue homogenates

Ten per cent homogenates (w/w) were routinely prepared by homogenizing 1 g tissue in 9 ml of suitable suspending medium, usually isotonic potassium chloride. The standard incubation mixture was prepared as follows:

		Final Molarity
3 ml of 10% homogenate in 0·15 M KCl		
0·6 ml	0·04 M DPN	0·004
0·6 ml	0·4 M nicotinamide	0·04
0·6 ml	0·2 M potassium malonate	0·02
0·3 ml	0·5 M phosphate buffer, pH 7·4	0·025
0·4 ml	0·1 M $MgCl_2$	0·0067
0·5 ml	^{14}C-GHB (sodium salt) spec. act. = 5·48 mc/m-mole, total conc. = 230 μg	

This mixture was incubated at 37° in a Dubnoff metabolic incubator, gassed with 100% oxygen. Incubation was carried out for 15 to 20 min; the homogenate was then

precipitated with 95% ethanol. This mixture was carried through the gas chromatographic technique for identification and estimation of succinic acid.

8. *Procedure for preparation and utilization of brain slices*

The rats used in these experiments were killed by decapitation and the brains quickly excised according to the procedure outlined by McIlwain and Rodnight.[12] The brains were transferred to a petri dish containing the incubation mixture, care being taken to remove all the dura. To avoid undue anoxia, the brains were then sliced as rapidly as possible by means of a Stadie blade. If cortical slices were to be made, the brain was placed upright on the moistened filter paper. If subcortical structures were to be studied, the whole brain was first halved by sagittal section along the longitudinal cerebral fissure. Half the brain was then returned to the incubation medium and the other half placed on moistened filter paper with its cut surface upright. Slices were made parallel to the cortical surface to obtain cortical slices (only two slices were taken from each brain). Brain slices were obtained sometimes by cutting parallel to the cut sagittal surface in order to obtain slices containing subcortical as well as cortical tissue. The slices were then washed into cold medium. Subsequently, the slices were hooked over a small wire rider, drained, weighed on a torsion balance, and transferred to the experimental vessel. Any slices that were too thick to be transparent were discarded.

The medium used for suspending brain slices during the incubation procedure was the standard Krebs-Ringer phosphate buffer described by Umbreit *et al.*[13] for tissue slices. This solution, after mixing was chilled and gassed with 100% oxygen. The precipitate of calcium phosphate that formed was suspended by shaking before use. The final concentration of glucose used in the incubation mixture was 5 mm. Routinely, an incubation volume of 3 ml, containing about 20 mg tissue/ml, was used.

RESULTS

1. *Distribution in blood, fat, and muscle*

When GBL or GHB (sodium salt) was administered to rats in equimolar doses, sufficient to induce anesthesia, it became apparent that initial total blood levels of GHB and GBL were about 50% lower after GBL than after GHB (Fig. 3). In addition, it was observed that the blood concentration fell more rapidly after GHB than after GBL.

In order to shed some light on these observations it appeared necessary to examine the distribution of total GHB and GBL in muscle and fat after the administration of these compounds intravenously in equivalent anesthetic doses. Figure 4 shows the results of such an experiment carried out in adult male rats. It is clear that during the entire time course studied, the levels in muscle after GBL were significantly higher than those after GHB. Since GBL is more lipid-soluble than GHB, however, it was unexpected to find that there were no differences in the levels in fat after administration of each of these compounds. This finding could be explained on the basis of our recent observation that rat blood and liver contain a rapidly acting lactonase which hydrolyzes GBL to GHB.[9] Apparently, GBL is hydrolyzed so rapidly by this enzyme that poorly perfused tissues like fat receive only limited quantities of GBL after its administration.

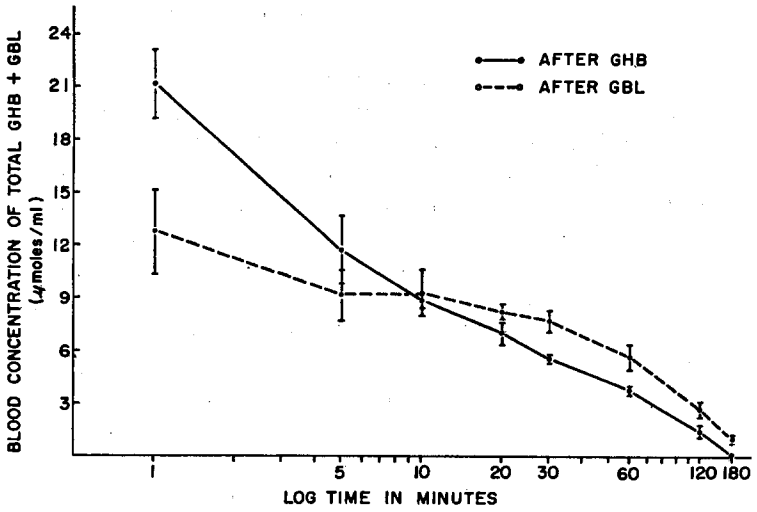

FIG. 3. Relationship of blood concentration of total GBL and GHB with time after the administration by the intravenous route of equimolar doses of GHB (sodium salt, 732 mg/kg) and GBL (500 mg/kg). Each point is the mean of at least 5 animals (male rats.) Vertical bars indicate the standard deviations of the means.

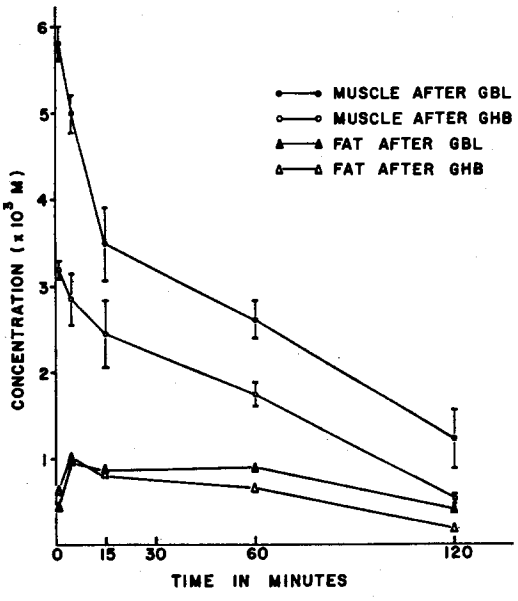

FIG. 4. Distribution of total GHB and GBL in lean muscle and fat after the intravenous administration of equimolar amounts of either GBL (500 mg/kg) or GHB (sodium salt, 732 mg/kg). Each point is the mean of at least 3 animals (male rats). Vertical bars span the standard deviations of the mean.

2. *Distribution in selected regions of cat brain*

Each of 6 cats was given GHB by the intravenous route (in a dose of 350 mg/kg) and sacrificed 30 min later, when all animals were found to be behaviorally asleep. Various regions of the brain were carefully dissected free, and determinations of GHB were carried out as described above. The results of these experiments are illustrated in Fig. 5.

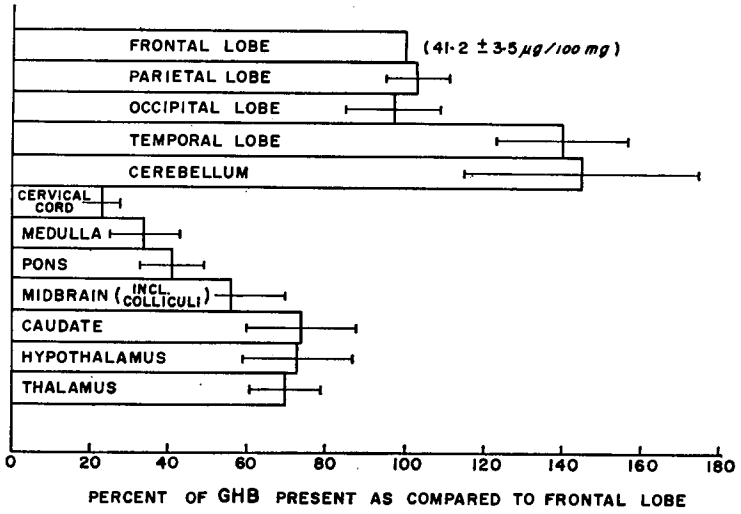

FIG. 5. Regional distribution of GHB in cat brain 30 min after the intravenous administration of GHB (sodium salt, 350 mg/kg). The results are expressed as the per cent of GHB compared to the amount found in the frontal lobe of the cortex. Each value represents the mean of at least 5 determinations, and the vertical bars represent standard deviations of the means.

It is clear that among the subcortical areas studied the concentration of GHB increases as the sections progress rostrally up the brain stem from the cervical cord until a constant level is reached in the thalamus, hypothalamus, and caudate nucleus. However, the highest levels were found in the cerebellum and the lower temporal lobe.

3. *Metabolism of* GBH *and* GBL

A. Radiorespirometric studies. Investigations with ^{14}-C-carboxyl-labeled GHB (sodium salt) indicated that this compound was metabolized very rapidly in the rat. After the intravenous administration of 2 μc 1-^{14}C-GHB, respiratory carbon dioxide-^{14}C was detected within about 4 min and a peak reached in about 15 min; about 60% of the total radioactivity administered was recovered within 2·5 hr in the respired air. Similar results were obtained with 1-^{14}C-GBL. However, in this case respiratory carbon dioxide-^{14}C was not evolved quite so rapidly, and a peak was reached in slightly less than 20 min. This can be seen quite clearly by the difference in the slopes of the carbon dioxide-^{14}C evolution curves illustrated in Fig. 6. This short delay was probably due to the time required for the GBL to be hydrolyzed to GHB by an enzyme in blood and liver before GHB could be metabolized. The broader peak and somewhat reduced

slope of the falling curve following GBL may be a reflection of the sequestering of the lactone in the lean muscle mass of the body, as shown in Fig. 4. This relatively slower velocity of metabolism is seen also in the slower rate of disappearance of drug from the blood after GBL (Fig. 1).

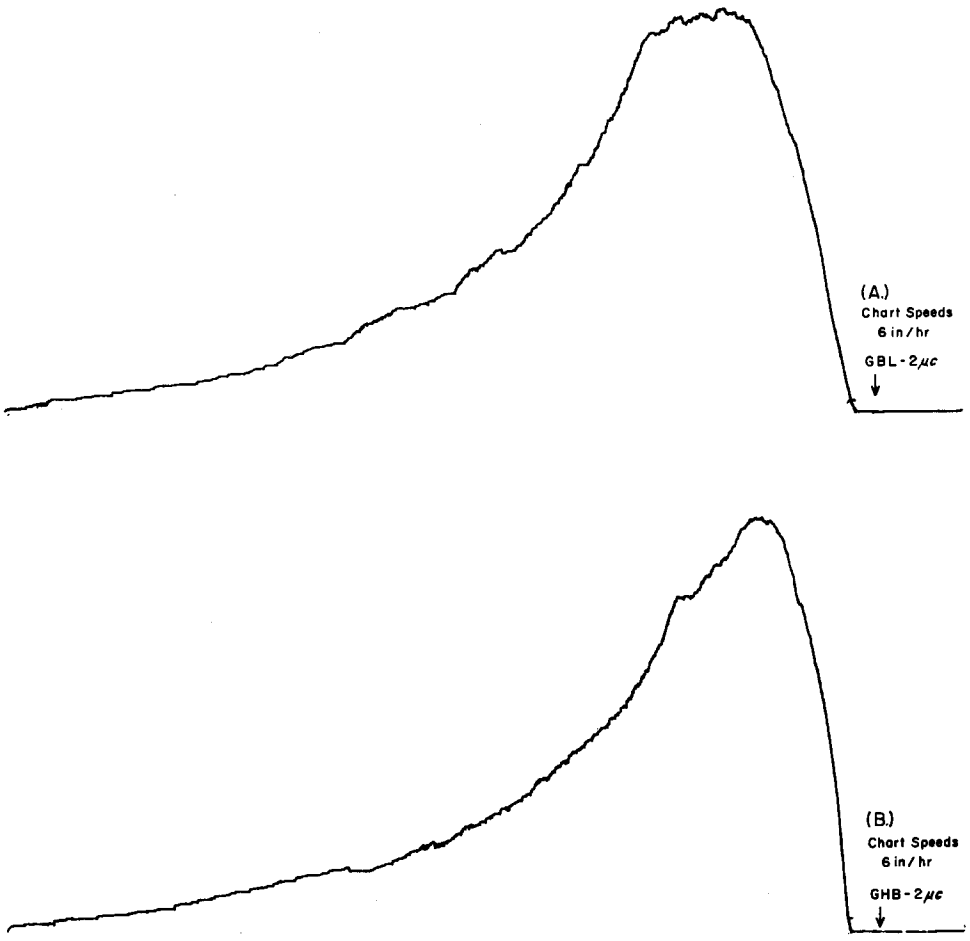

FIG. 6. Radiorespirometric curves obtained from rats after intravenous administration of 2 μc GBL-1-^{14}C (upper curve) and 2 μc GHB-1-^{14}C (lower curve). Specific activity of radioisotopic material was 5·478 mc/m-mole. Each chart division spans 10 min. Abscissa is time; ordinate is output of $^{14}CO_2$ in expired air.

B. Studies of the hydrolysis of GBL *by various tissues.* In our early investigation of the distribution of GHB and GBL it was apparent that when GBL was given by the intravenous route to the rat it was rapidly converted to GHB, which then entered the CNS and presumably caused the depression that ensued.[8] Roth and Giarman have presented evidence that an enzyme, with some cation requirement, catalyzes the hydrolysis of GBL.[9] When GBL and GHB were estimated by means of the gas chromatographic method previously described, whole rat blood was found to convert GBL

to GHB very rapidly; the half-time of conversion was less than 1 min. GBL was not hydrolyzed quite so fast by cat blood, as is illustrated in Fig. 7. Similar rates of hydrolysis were also obtained with the pH-stat method. This activity in blood was initially localized in rat plasma, hemolyzed erythrocytes being inactive.[9] Further studies showed that serum was substantially more active than plasma. Sera from rabbits, guinea pigs, cats, and humans were also active. Other tissues of the rat, such as

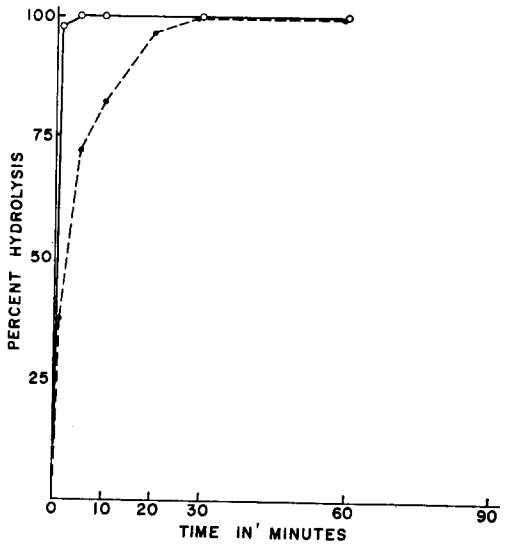

FIG. 7. Hydrolysis of GBL to GHB in the presence of blood from cat (dashed curve) and rat (solid curve) *in vitro* at 37°. Concentration of GBL used was $1{\cdot}3 \times 10^{-2}$ M.

brain, liver, kidney, heart, lung, skeletal muscle, and intestine, were examined for lactonase activity. Of these, only liver (blood removed by perfusion) was found to have any substantial activity. Human cerebrospinal fluid was also lacking in such activity.

The hydrolysis by rat and human sera was studied over a wide range of substrate concentrations, and the maximal initial rate was determined by means of the pH-stat method. With a crude enzyme concentration of 1 ml serum in 10 ml isotonic saline at pH 7·4 and a substrate concentration of $2{\cdot}6 \times 10^{-2}$ M, the maximal initial rate of hydrolysis was found to be about 40 m-equiv GBL/min/ml human serum, and the reaction rate was linear for about 2 min. A very high K_m value of $1\text{–}3 \times 10^{-2}$ M was found for both rat and human serum. The data of the study with the latter are plotted in Fig. 8.

C. Studies of metabolism in vitro. No direct experiments in intact tissue have been carried out to demonstrate that brain can metabolize GHB, although some studies with brain homogenates indicated this possibility.[14–16] It was of interest, therefore, to determine whether brain slices could metabolize GHB to carbon dioxide, a process

which has been shown to occur very rapidly in the whole animal.[17] Isotopically labeled compounds were used in this study to allow precise measurement of disappearance of minute quantities of substrate in the presence of large amounts of the substrate optimal for enzyme activity. With the measurement of carbon dioxide-^{14}C formation by brain slices from ^{14}C-carboxyl-labeled GHB, it was found that ^{14}C-GHB was

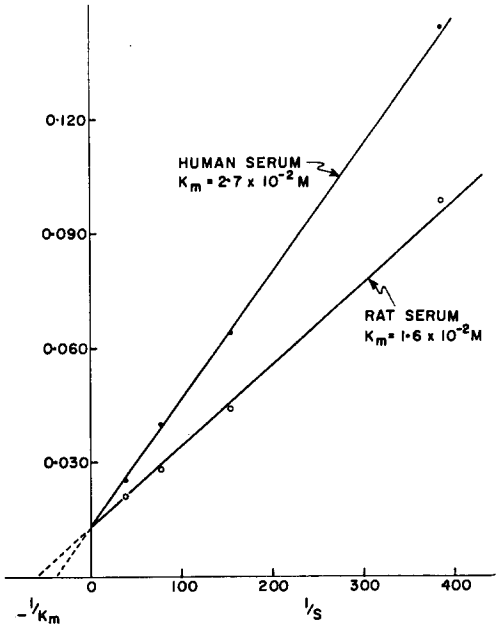

FIG. 8. Lactonase activity of human serum on GBL: reciprocal plot of velocity and substrate concentration.

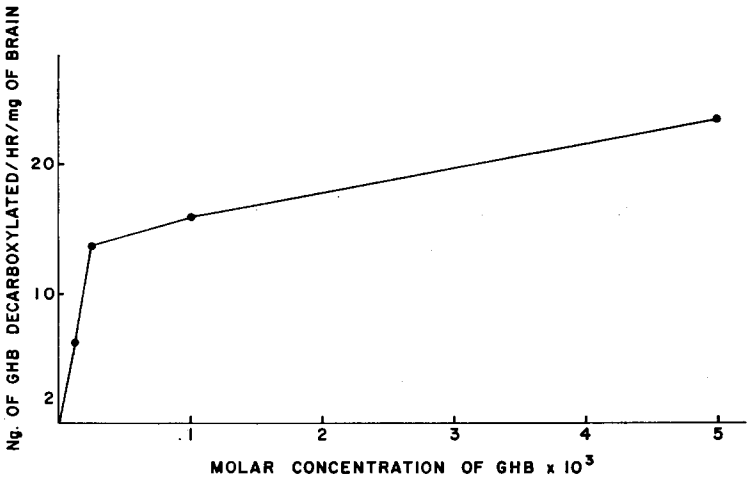

FIG. 9. Conversion of GHB-1-^{14}C to $^{14}CO_2$ by slices of rat brain cortex. Each point is the mean of at least 3 determinations.

metabolized quite rapidly. Figure 9 shows the extent of carbon dioxide-^{14}C formation by brain slices incubated in varying concentrations of labeled GHB. Liver slices were found to effect this conversion of GHB to an extent of about twice that of brain.

In view of the report by Fishbein and Bessman that GHB may enter the Krebs cycle,[15] we sought to isolate ^{14}C-labeled succinic acid after incubation of rat brain and liver homogenates and blood with GHB-^{14}C (sodium salt) in the presence of malonic acid (2×10^{-2} M), which was added to block the Krebs cycle at the succinate level. Succinic acid was isolated from possible interfering substances and analyzed by gas chromatography as described above. One to two per cent of the ^{14}C-isotope of the added GHB was found in the succinic acid from brain, and up to 6% was found in the succinate of liver; no isotope could be detected in the blood succinate. In view of the negative findings of Walkenstein *et al.*[16] with regard to labeling of succinate by GHB-^{14}C *in vivo*, the small percentage of isotope found in brain succinate in our experiments is probably an expression of a small amount of enzyme in the brain that under appropriate conditions can oxidize GHB. However, it could also be the result of random labeling of succinate due to carbon dioxide fixation. The higher percentage of the labeled succinate found in liver may be the result of alcohol dehydrogenase (ADH) activity, recently reported by Wollemann to oxidize GHB to succinic semialdehyde.[17]

The possibility of a block of metabolism in the Krebs cycle by GHB through the formation of glyoxalate by means of a mechanism suggested by Walkenstein *et al.*,[16] prompted us to seek a depression in the metabolism of uniformly ^{14}-C-labeled glucose by brain tissue (in view of the relatively inactive pentose phosphate shunt in brain). By means of uniformly labeled glucose, the evolution of carbon dioxide-^{14}C by brain slices (cortical and subcortical) was followed (cf. Methods), in the presence and absence of 10^{-3} M GHB. Only a slight depressant effect was observed on the metabolism of the labeled glucose to carbon dioxide; radioactive carbon dioxide formation was depressed about 10% in cortical and about 16% in subcortical slices. No greater depressant effect was observed when rats were pretreated with GBL (500 mg/kg) 30 min before sacrifice and preparation of brain slices.

Since the initial studies were carried out in an incubation medium of normal Krebs-Ringer phosphate buffer, the experiments were repeated with Krebs-Ringer phosphate buffer containing high potassium (100 mM) in order to stimulate neurons in the brain slices. This procedure was followed because it is known that the respiration of unstimulated brain cortical slices in the presence of glucose is only slightly affected by the presence of malonate, a potent inhibitor of the Krebs cycle.[18] On the other hand, potassium-stimulated brain respiration is highly sensitive to malonate.[19] In addition, stimulated respiration of isolated brain tissue approaches the magnitude of brain respiration *in vivo*, and possesses some of the characteristic features of brain *in vivo*, such as response to anesthetics and depressant drugs.[20] With potassium-stimulated brain cortical slices it was found that 10^{-3} M GHB inhibited the oxidation of pyruvate-2-^{14}C only about 20%. This relatively small inhibition of pyruvate oxidation was not impressive enough to warrant any conclusion concerning the mechanism of central depression for GHB.

D. Alteration of metabolism by β-hydroxybutyrate. Since β-hydroxybutyrate (βHB) is well tolerated by animals in high doses [21] and does not appear to produce marked sedation or loss of righting reflex in doses of 2 g/kg, the effect of this structurally similar

compound on the metabolism of GHB was examined. An interference with metabolism seemed likely, because Walkenstein *et al.* had postulated that GHB was metabolized in the rat via β-oxidation through the intermediate 3,4-dihydroxybutyric acid.[16] It was found unexpectedly that preadministration of βHB markedly *decreased* the sleep time of rats treated with either GHB or GBL (Table 1).

TABLE 1. REVERSAL WITH β-HYDROXYBUTYRIC ACID OF SLEEP INDUCED BY GBL AND GHB

Treatment (dose)	Duration of anesthesia (mean)		Mean brain level GHB* (μg/g ± S.D.)	Mean blood level GHB (μg/ml ± S.D.)	% ^{14}C-GHB metabolized to $^{14}CO_2$ ± S.D.
	Injection to RR† return	Duration RR lost			
GBL (350 mg/kg i.v.)	78	72	95 (4)‡ ± 7·6	254 (4) ± 36·2	
GHB (350 mg/kg i.v.)	54	46	68 (4) ± 12·4	155 (4) ± 13·1	11·2 (3) ± 0·7
β-OH-Butyric Acid (2 g/kg i.p.) followed by GBL*	46	37	45 (4) ± 14·8	139 (3) ± 29·7	
β-OH-Butyric Acid (2 g/kg i.p.) followed by GHB*	33	28	32 (4) ± 6·3	99 (4) ± 12·2	6·8 (3) ± 0·3

Animals sacrificed 50 min after GBL or 40 min after GHB treatment.
* Corrected for residual blood volume in cerebral vasculature and expressed as GBL equivalents.
† RR = righting reflex.
‡ Number of experiments shown in parentheses.
§ Interval between treatments, 20 min.

In addition, these studies showed that pretreatment with βHB caused significantly lower levels of GHB in both brain and blood to appear 50 min after the intravenous administration of GHB. Since both brain and blood levels were about halved, this suggested that βHB must be acting in some manner to stimulate the metabolism of GHB. However, experiments with liver slices in which carbon dioxide evolved from 1-^{14}C-GHB was measured showed that 10 mM βHB had a slight inhibitory effect rather than a stimulatory effect on GHB metabolism. This inhibitory effect of βHB on the metabolism of GHB was seen also with rat liver *in vitro*.

DISCUSSION

The observation of Benda and Perles[3] and of Jouvet *et al.*[22] that GBL has a longer duration of action in depressing animals than have equivalent amounts of GHB seems inconsistent with our finding[8] that GHB is the form of the drug associated with depression of the central nervous system. This greater duration of action of GBL, which we have confirmed,[8] has been used by others[23] to support the contention that GBL is the active form of the drug. In the present communication, two pieces of evidence are presented which bear upon this problem: (1) there is a lactonase in blood serum and liver of the rat that catalyzes the conversion of GBL to GHB at a high velocity; and (2) after the administration of GBL there is a higher concentration of total GBL and GBH in lean muscle than there is after the administration of GHB, but the levels in adipose tissue are the same after either compound. From these data it would appear

that richly perfused muscle can sequester a large part of an initial dose of GBL, thereby retarding its metabolism and prolonging its duration of action. On the other hand, the rate of hydrolysis of GBL by the liver and blood lactonase is so rapid relative to the poor rate of perfusion of fat that this tissue receives only a limited amount of the intact lipid-soluble GBL. The net result of these distribution phenomena is that blood levels of total GBL and GBH reach a lower peak and fall more slowly after the administration of GBL than after GBH.

The relatively higher concentrations of GHB found in the cerebellum and lower temporal lobe than in other parts of the brain that were studied provoke some interest. Low doses of GHB produce ataxia and incoordination, motor disorders which may arise in the cerebullum. The localization of GHB in the lower temporal lobe may be of significance in relation to the finding that GHB prolongs amygdaloid and hippocampal seizure activity.[24] Although such physiologic factors as blood supply undoubtedly exert an influence on drug distribution to certain areas of the brain, it seems reasonably clear from these data that other factors may also be important. Thus, the hypothalamus is one of the most richly vascular areas of the brain, yet this area showed no particular localization of GHB. This failure to be concentrated by the hypothalamus has been observed with phenothiazines[25] and mescaline.[26]

Our investigations of the metabolism of GBL and GBH established that these compounds are metabolized very rapidly in the whole animal to carbon dioxide, and that, for nonvolatile depressants of the CNS, they are relatively rapidly cleared from the body. In marked contrast to the barbiturates, which tend to accumulate in body fat and persist long after the end of a barbiturate-induced anesthesia, GHB is virtually absent from all body tissues by the time an animal recovers from a depressant dose. While it might have been expected that the liver would metabolize GHB to CO_2, it was of interest to find that brain carried out this conversion to a substantial extent —about half that of liver.

The possible enhancement by βHB of the clearance of GHB and the resulting reduction in the duration of central nervous system depression produced by GHB requires further study. Since it is known that βHB is metabolized very rapidly by the rat to acetyl CoA, and further that CoA transfers very well from acetyl CoA to butyrate,[27] it is conceivable that βHB antagonizes the effects of GHB by stimulating a transferase system that can remove GHB from the circulation by forming, e.g., GHB-CoA. Other possibilities for explaining the βHB interaction exist: (1) βHB may interfere with attachment of GHB at receptor sites in nervous tissue and thereby facilitate metabolism of GHB; (2) βHB may in some way promote a more rapid excretion of GHB from the body, the net result being a lower blood level of GHB and a shorter sleeptime.

Our data also indicate that GBL is rapidly hydrolyzed to GHB in blood and liver. The biological half-life of GBL is so short, in fact, that it is hardly likely that this molecular form of the pair would assume any importance in eliciting the pharmacological actions observed, especially in view of the relatively long delay in onset of action and the duration of action of 2 – 3 hr which have been reported. Data to the contrary[23–28] are best explained on a methodological basis; i.e. they are derived from a colorimetric assay technique based on the Hestrin reaction,[10] which is highly nonspecific and with which the following substances are likely to interfere: choline esters, noncholine esters, thioesters, anhydrides, lactides, sugar lactones, and even glucose.

In fact, Bessman and Skolnik reported that the color which developed in control extracts was due to the presence of glucose, but they discounted the significance of this on the basis that glucose does not vary in blood or tissues after the administration of either GHB or GBL.[23] This, however, is at variance with the finding of Fleming and LaCourt,[29] who have reported that GHB given in anesthetic doses to mice increases blood glucose about 35% and brain glucose about 250%.

Acknowledgements—The authors acknowledge with gratitude the help of the following individuals: Dr. S. J. Lipsky for advice in development of the gas chromatographic techniques; Dr. D. B. Ludlum for assistance in the use of the pH-stat for measurements of hydrolysis; and Dr. M. Gluckman of Wyeth Laboratories for a generous supply of the sodium salt of γ-hydroxybutyric acid.

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EXHIBIT 20

Developmental Brain Research, 1 (1981) 579–589
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ONTOGENY OF γ-HYDROXYBUTYRIC ACID. I. REGIONAL CONCENTRATION IN DEVELOPING RAT, MONKEY AND HUMAN BRAIN

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(Accepted December 19th, 1980)

Key words: gamma-hydroxybutyrate — ontogeny — development — epilepsy

SUMMARY

Steady state levels of γ-hydroxybutyrate (GHB) were measured in whole brain and discrete regions of brain in developing and adult rat, monkey, and human brain. Postmortem changes in concentration of GHB in rat and human brain were also assessed. There were no significant postmortem changes of GHB under the conditions which the ontogeny experiments were done. The concentration of GHB was uniformly higher in the immature brains of the 3 species studied. In the rat the highest concentration was in immature hypothalamus and cortex with a significant decrease occurring between postnatal day 12 and 14. In human, the highest concentration was in fetal cerebellum and adult hypothalamus.

Comparison of these data with published ontogeny data for γ-aminobutyric acid (GABA) suggest that there may be a source of GHB in brain other than GABA.

INTRODUCTION

Gamma-hydroxybutyric acid (GHB) is a naturally occurring substance[13,20] which has a number of potent neuropharmacological and neurophysiological properties[35]. The function of this compound in mammalian brain is not known, but its diverse properties suggest that it may have an independent role in neurotransmission or neuromodulation[26] rather than being simply an incidental metabolite of γ-aminobutyric acid (GABA)[21,28]. If GHB plays a role as a biologically significant neuroactive agent, this would infer the presence in brain of neuronal pathways in which this compound is synthesized, stored and released. The functional activity of such a pathway would depend on the interaction of a number of variables including the synthesis, storage, release, uptake and degradation of the neuroactive substance. Onto-

genetic studies of other neurotransmitter systems have indicated that these processes may develop independently of one another[9]. We have therefore measured the steady state concentration of GHB in developing brains of rats, non-human primates, and humans as a first step in describing the ontogeny of GHB. The object of this paper is to show when GHB makes its appearance in brain and to describe its development throughout brain maturation.

MATERIALS AND METHODS

Tissue procurement

Timed pregnant Sprague–Dawley rats (Charles River) were used to generate animals for the ontogeny studies. For the postnatal studies animals were sacrificed by decapitation at 1, 2, 4, 6, 7, 10, 12, 14, 19, 21, 28, 56 and 84 days after birth. The brains were removed and dissected on ice under a magnifying loupe by the method of Anderson et al.[2] into cerebellum, medulla, pons, striatum, hypothalamus, thalamus-midbrain, and cortex. Tissue was pooled from 4–6 animals and frozen at —76 °C until assayed for GHB. For the prenatal studies, the mothers were decapitated and the fetuses removed, decapitated, the brains removed and dissected on ice into cortex, subcortex, and cerebellum. Tissue was pooled from 8–11 animals and frozen at —76 °C until assayed. The prenatal time points were 15, 16, 18, 20 and 21 gestational days. Whole brain was assayed for GHB on the same pre- and postnatal time points. Rhesus monkeys (*Macaca mulatta*) were utilized for nonhuman primate studies and were sacrificed by an overdose of pentobarbital which would not be expected to have an effect on endogenous GHB levels[36]. These animals included neonatal monkeys within 24 h of birth, adolescent monkeys at 1 year of age and adult monkeys 5 years of age. The brains were obtained within 1 h of death and frozen at —76 °C until dissection and assay. The monkey brains were dissected into frontal and temporal cortex, caudate nucleus, pons, medulla, midbrain and cerebellum.

Postmortem human brain tissue was obtained from patients ranging in age from 13 min to 68 years, dying of non-neurological disease, who were autopsied within 12 h of death (mean = 5.85 h). All brains were dissected where possible into frontal, temporal, parietal, and occipital cortex and caudate, putamen, globus pallidus, hippocampus, thalamus, hypothalamus cerebellum and brain stem. Human fetal brain (4–24 weeks gestation) was obtained from fetuses within 1 h of legal abortion, dissected on ice, and frozen at —76 °C. The gestational age of each fetus was determined by crown–rump length[33].

Postmortem studies

The question of postmortem changes in GHB concentration in brain was examined in rat and human brain by varying the conditions of removal and storage of rat brain (Table I) and by altering conditions of refrigeration of multiple postmortem samples of human cortex from a single patient (Table II).

GHB assay

The assay procedure was a modification of an electron capture gas liquid

chromatographic technique previously described[14,36]. The only change from the published method was that the initial methylation reaction of gamma-butyrolactone with 14% boron trifluoride in methanol was carried out in sealed glass ampoules to eliminate the Teflon artifact that was an occasional problem when reaction vials were used. All data were analyzed by the Mann–Whitney U-test.

RESULTS

Postmortem experiments

The results of these experiments are summarized in Tables I and II. There was no significant change in concentration of GHB in rat brain frozen in situ vs those frozen immediately after removal, placed on ice for 40 min, freshly assayed or assayed after 2 months at —76 °C. The GHB concentration did increase significantly ($P < 0.01$) after 60 min at room temperature. The human brain postmortem experiments, (Table II) showed that GHB was stable at low temperature for up to 24 h, but then increased dramatically.

Ontogeny experiments

GHB was present in whole brain of immature rats at 400% of adult levels (Fig. 1, Table III), and was present at day 15 of gestation (Table IV). Regional studies showed an initial concentration in cerebellum which was higher than adult cerebellum but which reached adult levels by 12 days of age. With the exception of cortex and hypothalamus, adult patterns of distribution of GHB were established early in life with stable concentrations in subcortical structures throughout life, but markedly elevated concentrations in immature cortex and hypothalamus which declined significantly to adult levels in the third week of life.

In rhesus brain (Table V) GHB was higher in all areas of neonatal brain than adult brain. There was the least change in caudate with maturation and the most

TABLE I

Postmortem studies in rat brain

Each value represents the mean ± S.E.M. of 8 determinations.

Conditions of storage	*GHB (nmol/g)*
Brain frozen in situ	2.24 ± 0.19
Brain removed and frozen in liquid nitrogen	2.31 ± 0.14
Brain removed and kept on ice for 20 min	2.45 ± 0.21
Brain removed and kept on ice for 40 min	2.04 ± 0.18
Brain removed and kept at room temperature 30 min	2.52 ± 0.17
Brain removed and kept at room temperature 60 min	3.68 ± 0.29*
Brain removed, kept at room temperature for 180 min, chilled for 12 h at 4 °C and frozen	5.81 ± 0.46*
Brain removed and frozen —80 °C for 2 months	2.14 ± 0.18

* Significantly increased, $P < 0.01$.

TABLE II

Postmortem studies in human brain

These studies were done with frontal cortex obtained from a 13-year-old patient within 1 h of death. Each value represents the mean ± S.E.M. of 8 determinations.

Conditions	*GHB (nmol/g)*
Frozen immediately to —80 °C	13.27 ± 0.76 (n = 8)
Refrigerated at 4 °C for 24 h and then frozen to —80 °C	15.53 ± 1.14 (n = 8)
Refrigerated at 4 °C for 48 h and then frozen to —80 °C	83.4 ± 4.95 (n = 8)*

* Significantly increased, $P < 0.01$.

marked decline in the pons-medulla. Except for cortex and brain stem there was little difference in concentration between the adolescent and adult animals. There was a biphasic change noted in midbrain with high levels in the neonate, low levels in adolescence, and intermediate levels in adulthood. All these changes achieved significance ($P < 0.01$).

GHB was present in the youngest human fetuses examined at 4–6 weeks of gestation and was in highest concentration in fetal cerebellum at 12–19 weeks gestational age with a gradual decline to a concentration of 15 nmol/g around birth (Table VI). The concentration of GHB in human cerebellum remained constant throughout the first two decades of life and then declined to a concentration of 7 nmol/g (Fig. 2). The concentration of GHB was significantly ($P < 0.01$) higher in the hippocampus and all subcortical structures in brains of children compared to subcortical brain regions of adults (Table VII). The highest concentration in child's brain was in putamen, globus pallidus, hypothalamus and thalamus, with less marked differences between children and adults observed in caudate and brain stem, and no discernible difference in spinal cord where very small amounts of GHB were detected. There were no significant alterations of concentration in cerebral cortex throughout development. The levels of GHB in adult hypothalamus were twice those in hypothalamus from younger brain. This was the richest area in GHB in the adult brains having 3–8 times the concentration of GHB of any other brain area.

DISCUSSION

Our postmortem data showing no significant increase in GHB until 60 min at room temperature are in agreement with previously published studies[13,26] and validate our postmortem human experiments. Those results are in contradistinction to postmortem GABA studies which show a rapid postmortem increase in the concentration of GABA in rat brain[1,23]. This dichotomy between post-mortem changes in GABA and GHB would seem to indicate that GABA is not converted to GHB in postmortem brain.

The major regional change in GHB concentration in rat brain with development appears to be in cortex and hypothalamus with an initial GHB concentration in those

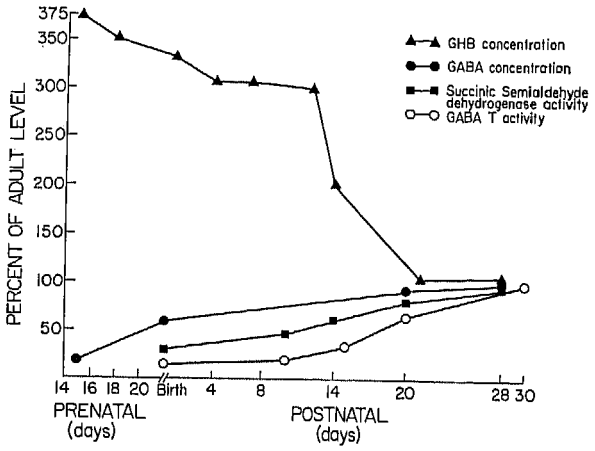

Fig. 1. Comparison of the ontogeny of whole brain GHB vs whole brain GABA[14], GABA-T activity[19], and succinic semialdehyde dehydrogenase activity[25] in the rat. The whole brain GHB data are original while the other data in the figure are taken from the literature[14,19,25].

immature brain areas much higher than adult. The GHB concentration in subcortical structures is fairly constant over development with an adult pattern of regional distribution established very early. The development of regionalization of GHB in monkey and human brain was different from rodent brain. There was higher concentration in all human subcortical structures except hypothalamus in younger brain with an early establishment of adult levels in cortex. The significance of the elevated GHB in hypothalamus and dramatic changes in that region with development is uncertain but noteworthy in view of the profound hypothermia produced by GHB in monkey[38].

The ontogenesis of GHB in developing brain should be considered in light of that of other neuroactive systems in brain with which GHB may either interact or be derived from[35], i.e. GABAergic, dopaminergic and cholinergic systems.

GABA, considered by some to be the main parent compound of GHB, is found in prenatal rat brain at 19 % of adult levels and is 60 % of adult brain concentration at birth[10] (Fig. 1), while GHB is 400 % of adult brain concentration early in life. A similar relationship between GHB and GABA with elevated GHB and depressed GABA has been demonstrated experimentally[3] and clinically[4] in Huntington's chorea and has been postulated to exist naturally in vivo[2]. The explanation put forth to explain the elevated brain GHB concentration in Huntington's chorea[3] is that in this disease there is a relative decrease in succinic semialdehyde dehydrogenase (succinate semialdehyde; NAD oxidoreductase) (EC 1.2.1.16) (SSDH), the major enzyme in the GHB degradation pathway[15], with a resultant increase in GHB. However, this explanation does not seem tenable in the developing animal, since in the rat at least, SSDH activity is 30 % (150 mmol/kg/h) of adult activity at birth reaching 67 % of adult level (536 mmol/kg/h) at 15 days[25]. This is a much higher initial activity and a more rapid increase than that of GABA-amino transferase (EC 2.6.1.19) (GABA-T) which catalyzes the first step in the formation of GHB from GABA[21]. GABA-T activity is only 14 mmol/kg/h at birth

TABLE III

Regional distribution of GHB in developing rat brain (nmol/g)

Each value represents the mean ± S.E.M. of 6 studies for the regional data and 10 studies for the whole brain data.

Age (days)	*Cerebellum*	*Medulla*	*Pons*	*Striatum*	*Hypothalamus*	*Thalamus*	*Cortex*	*Whole brain*
1	8.08 ± 0.56	4.94 ± 0.45	3.59 ± 0.21	3.82 ± 0.42	—	20.25 ± 2.51	4.98 ± 0.31	7.32 ± 0.91
4	8.93 ± 0.54	5.35 ± 0.52	5.60 ± 0.44	4.97 ± 0.60	119.16 ± 14.21	16.96 ± 2.30	6.59 ± 0.43	6.81 ± 0.22
7	8.06 ± 0.81	4.66 ± 0.47	5.10 ± 0.53	4.65 ± 0.47	116.76 ± 12.43	14.51 ± 1.67*	4.78 ± 0.33	7.38 ± 0.64
12	5.78 ± 0.42*	5.69 ± 0.56	4.95 ± 0.51	5.35 ± 0.6	127.19 ± 9.74	13.41 ± 1.31*	5.69 ± 0.44	6.61 ± 0.67
14	4.89 ± 0.34*	5.28 ± 0.55	5.25 ± 0.49	6.18 ± 0.71	—	—	5.69 ± 0.49	4.42 ± 0.43*
21	4.97 ± 0.61*	6.07 ± 0.72	4.48 ± 0.34	4.89 ± 0.61	28.06 ± 2.10*	15.20 ± 0.97*	2.26 ± 0.19*	2.51 ± 0.18*
28	4.34 ± 0.37*	4.34 ± 0.44	6.86 ± 0.59	4.1 ± 0.83	25.75 ± 2.34*	14.98 ± 1.10*	1.89 ± 0.12*	2.06 ± 0.10*
84	4.65 ± 0.36*	6.41 ± 0.57	4.66 ± 0.43	4.59 ± 0.52	26.31 ± 2.0*	15.53 ± 1.21*	1.57 ± 0.11*	2.12 ± 0.16*

* Significantly decreased from the concentration at 1 day of age, $P < 0.01$.

TABLE IV

GHB in prenatal rat brain (nmol/g)

Each value represents the mean ± S.E.M. of 6 determinations.

Gestational age (days)	*Whole brain*	*Cortex*	*Subcortex*	*Cerebellum*
15	9.49 ± 1.31	5.77 ± 0.54	9.84 ± 1.11	11.11 ± 1.15
16	10.89 ± 1.21	8.87 ± 0.98*	9.09 ± 0.98	12.32 ± 1.42
18	7.71 ± 0.83	6.82 ± 0.74	9.43 ± 0.97	6.47 ± 0.74*
19	6.34 ± 0.61*	7.41 ± 0.69	9.61 ± 0.99	5.25 ± 0.61*
20	7.50 ± 0.69*	6.87 ± 0.65	8.71 ± 0.85	9.13 ± 0.85*

* Significantly ($P < 0.01$) different from value at gestational age 15 days.

as opposed to adult levels of activity of 125 mmol/kg/h[33] (Fig. 1). Therefore, the activity of the degradative enzyme for GHB is higher than that of the initial enzyme responsible for its synthesis from GABA in immature brain. Another line of evidence against GABA being the main source of GHB is brain is that the other synthetic enzyme involved in human brain is the pathway from GABA to GHB, NADPH-dependent aldehdye reductase (alcohol NADP oxidoreductase) (EC 1.1.1.2) has a reducing capacity in human brain supernatants which is one-tenth of the oxidizing capacity of succinic semialdehyde dehydrogenase[7]. This indicates that if GABA were the sole source of GHB in brain, the activity of the synthetic reductase enzyme would have to be significantly higher than that of the degradative dehydrogenase in developing brain to account for the high steady state levels of GHB. Thus the evidence to date indicates that there may be a source for GHB other than GABA. Possible candidates for this source are the polyamines in brain which have been shown to have a metabolic interrelation with GABA[30,31]. One of the biosynthetic enzymes in this pathway, ornithine decarboxylase (EC 4.1.1.17) shows a transient increase of up to 400% of adult levels in immature rat brain[19]. However formation of GHB from

TABLE V

Regional distribution of GHB in developing rhesus brain (nmol/g)

Each value represents the mean ± S.E.M. of 7 values in the neonatal studies, 4 values in the adolescent studies, and 5 values in the adult studies. The mean ages of the animals were 16 h for the neonates, 13 months for the adolescents and 5.1 years for the adults.

Brain region	*Neonate*	*Adolescent*	*Adult*
Temporal cortex	9.2 ± 0.74	10.9 ± 1.1	5.75 ± 0.52*
Caudate	16 ± 1.28	12 ± 1.2*	11.4 ± 1.03*
Pons-medulla	19.38 ± 1.55	15.4 ± 1.49*	4.68 ± 0.42*
Midbrain	25 ± 2.3	8 ± 0.75*	15 ± 1.35*
Cerebellum	17 ± 1.36	10 ± 0.92*	8.48 ± 1.20*

* Significantly lower than neonatal concentrations ($P < 0.01$).

TABLE VI

Regional distribution of GHB in human fetal brain (nmol/g)

Each value represents the mean ± S.E.M. The number of separate experiments are indicated in parentheses.

Brain region	*Gestational age in weeks*			
	4–6	*9*	*12–19*	*20–24*
Whole brain	9 ± 1.3 (2)	16.8 ± 2.1 (2)	12 ± 0.8 (9)	
Cortex (forebrain)			21.3 ± 1.44 (9)	16.28 ± 1.11 (10)
Brain stem			24 ± 1.71 (9)	17.96 ± 1.21 (10)
Striatum			29 ± 0.89 (9)	16.83 ± 1.28 (10)
Cerebellum			90 ± 17.68 (9)	27 ± 1.81 (10)

polyamines would have to be via some route other than GABA[30,31] for the reasons outlined above.

GHB has profound effects on dopaminergic[29] and cholinergic[18,32] systems in brain. This activity has led to the hypothesis that GHB may play a role as a neuromodulator in brain particularly with respect to dopaminergic function[27]. Modulating mechanisms and feedback regulations of neuronal functions develop from 4 to 10 days postnatally in the rat with respect to dopaminergic and cholinergic systems[5,17,22], a time when GHB concentration is relatively high. Also in the rat, activation of tyrosine hydroxylase by GHB is present at 4 days postnatally, although axotomy does not activate the enzyme until 10 days postnatally[8].

Although the steady state levels of GHB in developing brain may not fully reflect the status of a system which might utilize this compound, our data showing increased concentration of this substance in immature brain is significant given the increased

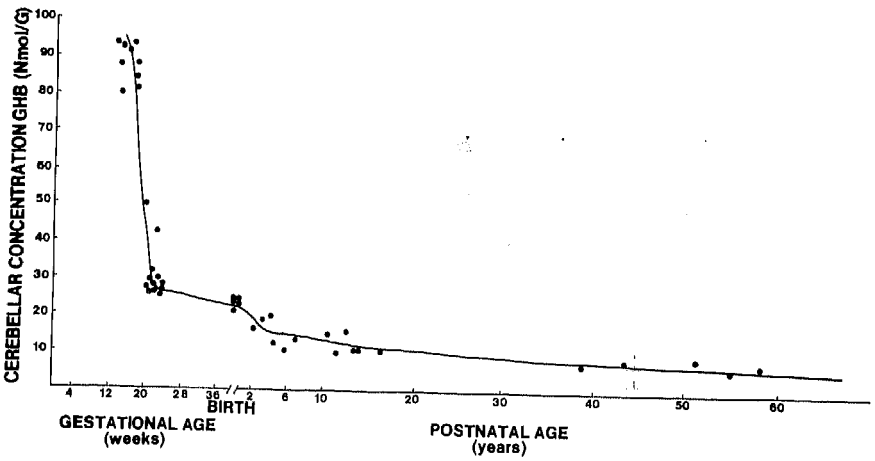

Fig. 2. Concentration of GHB in human postmortem cerebellum at various ages. Each point represents a single determination.

TABLE VII

Regional distribution of GHB in human brain (nmol/g)

Each value represents the mean ± S.E.M. The number of separate experiments is indicated in parentheses.

Brain region	*Age in years*	
	0–10	*14–68*
Cerebral cortex		
Frontal	15.34 ± 0.56 (10)	13.68 ± 1.10 (8)
Temporal	12.13 ± 1.36 (8)	13.63 ± 0.51 (12)
Parietal	16.3 ± 1.06 (6)	16.3 ± 1.06 (6)
Occipital	6.55 ± 0.84 (8)	5.80 ± 0.63 (6)
Hippocampus	12.14 ± 1.31 (5)	5.98 ± 0.86 (6)*
Cerebellum	15.91 ± 0.54 (6)	7.81 ± 1.29 (10)*
Caudate	13.16 ± 0.32 (8)	9.16 ± 1.3 (12)*
Putamen	25.26 ± 2.1 (4)	12.40 ± 2.11 (6)*
Globus pallidus	22.28 ± 1.87 (4)	11.36 ± 1.52 (5)*
Thalamus	16.43 ± 0.96 (4)	8.00 ± 0.56 (5)*
Hypothalamus	20.68 ± 0.94 (5)	42.43 ± 3.15 (5)**
Midbrain	11.56 ± 1.34 (4)	7.6 ± 0.84 (4)*
Pons-medulla	8.47 ± 0.87 (4)	4.9 ± 0.54 (5)*
Spinal cord (cervical)	0.84 ± 0.14 (3)	1.26 ± 0.34 (3)

* Significantly lower concentrations than in the first decade of life, $P < 0.01$.
** Significantly higher concentration than in the first decade of life, $P < 0.01$.

susceptibility of immature brain to the epileptogenic properties of GHB[37]. This compound has been shown to induce age-dependent seizure states when administered to animals which resemble human petit mal and myoclonic seizure disorders[16,20,36–40]. Thus, since GHB does profoundly alter the electrical activity of brain, rapidly changing concentrations of this substance in the immature nervous system at a time when the electrical rhythmicity of brain is developing[6,11,12,24] could conceivably influence that event. The marked elevation of GHB in immature subcortical structures such as the thalamus is particularly significant in this regard. Similarly the higher concentration of GHB in immature human brain could contribute to the increased susceptibility of immature brain to seizure under certain pathologic conditions[35].

Further studies of other aspects of GHB synthesis and degradation in the developing brain should, in conjunction with our data, provide more insight into the ontogeny and possible function of this substance.

ACKNOWLEDGEMENT

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EXHIBIT 21

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

OPENING EXPERT REPORT OF ROBERT S. LANGER

I. INTRODUCTION

1. My name is Dr. Robert S. Langer. I am currently an Institute Professor (one of twelve Institute Professors, the highest rank awarded to a faculty member) at the Massachusetts Institute of Technology (MIT). My appointments include those in the Department of Chemical Engineering at MIT, the Department of Biological Engineering, the Institute for Medical Engineering and Science, and the Harvard-MIT Division of Health Sciences and Technology.

2. I have been retained on behalf of Avadel CNS Pharmaceuticals, LLC ("Avadel") who I understand to be the defendant in the patent litigations identified in the caption of this report, to provide my opinions regarding the validity of certain claims of U.S. Patent Nos. 10,758,488 (the "'488 patent"); 10,813,885 (the "'885 patent"); 10,959,956 (the "'956 patent"); and 10,966,931 (the "'931 patent") (collectively, the "Sustained Release Patents").

3. My opinions are based on my review of relevant documents and information, my experience in the fields of pharmaceutical development and drug delivery, particularly as applied to pharmaceutical products, and my understanding of the relevant legal framework as explained to me by counsel for Avadel.

II. SCOPE OF THE REPORT

4. This report sets forth the opinions as to which, if asked, I will testify at trial with respect to the validity of the Sustained Release Patents.

5. Counsel informed me that Jazz has asserted the following claims from its Sustained Release Patents: claims 1-12 of the '488 patent; claims 1-15 of the '885 patent; claims 1-20 and 23-25 of the '956 patent; claims 1-15 of the '931 patent (collectively, the "Asserted Claims of the Sustained Release Patents"). Therefore, I have only provided my opinions as to the Asserted Claims of the Sustained Release, but I can provide opinions and analysis of the remaining claims of the Sustained Release if called upon to do so.

6. In addition, if asked, I may respond to the opinions and testimony of Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited's ("Jazz") witnesses regarding issues within my area of expertise. I reserve the right to supplement or amend my opinions in response to opinions expressed by Jazz's experts, or in light of any additional evidence, testimony, discovery or other information relating to the aforementioned issues that may be provided to me after the date of this report.

7. In addition, I expect that I may be asked to consider and testify about issues that may be raised by Jazz's experts at trial. To illustrate my opinions at trial, I may also rely on demonstratives, which have not yet been prepared.

III. QUALIFICATIONS AND EXPERIENCE

8. In addition to the brief summary provided below, I have attached my most recent curriculum vitae as Appendix A to this report, which summarizes my educational background, research and publications, honors and awards, and other credentials relevant to my qualifications as an expert in this case.

9. I have authored or co-authored over 1,500 articles and also have over 1,400 issued or pending patents worldwide, one of which was cited as the outstanding patent in Massachusetts in 1988 and one of 20 outstanding patents in the United States. My patents have been licensed or sublicensed to over 400 pharmaceutical, chemical, biotechnology and medical device companies. A number of these companies were launched on the basis of these patent licenses.

10. I served as a member of the United States Food and Drug Administration's (FDA) SCIENCE Board, the FDA's highest advisory board, from 1995 through 2002 and as its chairman from 1999 through 2002.

11. During my career, I have received over 190 major awards. For example, in 2022, I received the Balzan Prize for my contributions to biomaterials for nanomedicine and tissue

engineering. In 2021, I received the BBVA Foundation Frontiers in Knowledge Award, which recognizes world-class research and artistic creation, prizing contributions of singular impact for their originality and significance. In 2020, I was awarded the Maurice-Marie Janot Award Laureate for my contributions to the field of pharmaceutics, biopharmaceutics, and pharmaceutical technology. In 2019 I received the Dreyfus Award in Chemical Sciences, and in 2017 the Kabiller prize in Nanosciences and Nanomedicine. I received the 2015 Queen Elizabeth Prize for Engineering, the largest engineering prize in the world. In 2014, I received the Kyoto Prize for advanced Technology (Japan's highest award for global achievement) and the Breakthrough Prize in Life Sciences which recognizes excellence in research aimed at curing intractable diseases and extending human life (the largest science-based prize in the world). I received the 2013 Wolf Prize in Chemistry and the 2012 Priestley Medal, the highest award of the American Chemical Society. I am one of three living individuals to receive both the United States National Medal of Technology and Innovation (2011) and the United States National Medal of Science (2006), the two highest scientific honors bestowed in the United States. I received the 2002 Charles Stark Draper Prize, considered the equivalent of the Nobel Prize for engineers and the world's most prestigious engineering prize, from the National Academy of Engineering. I am also the first engineer to receive the Gairdner Foundation International Award; 96 recipients of this award have subsequently received a Nobel Prize. Among numerous other awards that I have received are the Dickson Prize for Science (2002), Heinz Award for Technology, Economy and Employment (2003), the Harvey Prize (2003), the John Fritz Award (2003) (given previously to inventors such as Thomas Edison and Orville Wright), the General Motors Kettering Prize for Cancer Research (2004), the Dan David Prize in Materials Science (2005), the Albany Medical Center Prize in Medicine and Biomedical Research (2005; the largest prize in the U.S. for medical research), the

Max Planck Research Award (2008), the Prince of Asturias Award for Technical and Scientific Research (2008), the 2008 Millennium Prize, the Warren Alpert Foundation Prize (2011) and the Terumo International Prize (2012). I was inducted into the National Inventors Hall of Fame in 2006. In 1998, I received the Lemelson-MIT prize, the world's largest prize for invention for being "one of history's most prolific inventors in medicine." I was elected in 1989 to the National Academy of Medicine and in 1992 to both the National Academy of Engineering and to the National Academy of Sciences. I am one of very few people ever elected to all three United States National Academies and the youngest in history (at age 43) to ever receive this distinction.

12. I have been named by Forbes Magazine (1999) and Bio World (1990) as one of the 25 most important individuals in biotechnology in the world. I was named by Discover Magazine (2002) as one of the 20 most important people in this area. I was selected by Forbes Magazine (2002) as one of the 15 innovators worldwide who will reinvent our future. Time Magazine and CNN (2001) named me as one of the 100 most important people in America and one of the 18 top people in science or medicine in America. I was selected by Parade Magazine (2004) as one of 6 "Heroes whose research may save your life." In both 2018 and 2019, I was named the Number 1 Translational Researcher in the world by Nature Biotechnology. I have served, at various times, on at least 15 boards of directors and 30 Scientific Advisory Boards of such companies as Wyeth, Alkermes, Moderna, Mitsubishi Pharmaceuticals, Warner-Lambert, and Momenta Pharmaceuticals.

13. I have received honorary doctorates from the ETH (Switzerland), the Technion (Israel), the Hebrew University of Jerusalem (Israel), the Universite Catholique de Louvain (Belgium), the University of Liverpool (England), the University of Nottingham (England), the University of Western Ontario (Canada), Université Laval (Canada), Hanyang University (South

Korea), National Institute of Astrophysics, Optics and Electronics (Mexico), Universidad de Santiago de Compostela (Spain), University of Limerick (Ireland), the University of New South Wales (Australia), Albany Medical College, Pennsylvania State University, Uppsala University (Sweden), Macau University of Science and Technology (Macau), Hong Kong University of Science and Technology (Hong Kong), Yale University, Harvard University, Columbia University, Rensselaer Polytechnic Institute, Northwestern University, the University of Maryland, Drexel University, Mount Sinai School of Medicine, Williamette University, Bates College, Boston University, Carnegie Mellon University, Ohio State University, University of Illinois, Gerstner Graduate School at Memorial Sloan Kettering Cancer Center, Ben Gurion University, Olin College of Engineering, Alfred University, Tel Aviv University and the University of California at San Francisco Medal. I received my Bachelor's Degree from Cornell University in 1970 and my Sc.D. from the Massachusetts Institute of Technology (MIT) in 1974, both in Chemical Engineering.

14. Additional details concerning the professional positions which I have held and other details of my professional qualifications, including publications that I have written either alone or in association with others, are set out in Appendix A.

15. The proceedings in which I have given expert deposition or trial testimony in the last five years are listed in Appendix B to this report.

IV. COMPENSATION

16. I am being paid my standard consulting fee of $2,000 per hour for my services and am being reimbursed for reasonable out-of-pocket expenses incurred as a result of my work on this case. My compensation is not in any way contingent upon the outcome of any litigation. I have no financial or personal interest in the outcome of this litigation.

dissolution apparatus 2 in deionized water at a temperature of 37 °C. and a paddle speed of 50 rpm." *See, e.g.*, '488 patent claim 11. However, as discussed below, that limitation would have been obvious.

IX. THE ASSERTED CLAIMS OF THE SUSTAINED RELEASE PATENTS ARE OBVIOUS

75. The Asserted Claims of the Sustained Release Patents would have been obvious over Liang 2006 in view of the general knowledge in the art.

76. Liang 2006 is relevant prior art because it is directed to the same field (*i.e.*, formulations of GHB) as the subject matter of the Sustained Release Patents and also is reasonably pertinent to the problem facing the inventors. The Sustained Release Patents describe the problem to be solved as addressing the "require[d] dosing of [sodium oxybate] twice during the night." '488 patent at col. 2 ll. 58-63. Liang 2006 is in the same field and directed to the same problem.

77. Specifically, Liang 2006 discloses gamma hydroxybutyric acid ("GHB") formulations made up of an immediate release portion and a delayed/controlled release portion. As in the Asserted Claims of the Sustained Release Patent, Liang 2006's delayed/controlled release formulations are made up of a functional coating deposited over a core, with the core comprising gamma-hydroxybutyric acid salts and the functional coating comprising a pH sensitive enteric release coat such as a methacrylic acid-methyl methacrylate co-polymer. I have attached Appendix D showing the disclosure of each limitation of the Asserted Claims of the Sustained Release Patents in Liang 2006.

78. In my opinion, a POSA would have arrived at the claimed amounts of GHB and the percentage of methacrylic acid-methyl methacrylate co-polymer in the coating through routine experimentation, with an expectation to succeed in achieving the claimed dissolution profile.

Thus, the claimed subject matter of the Sustained Release Patents would have been obvious to a POSA as of March 24, 2010.

A. The Asserted Claims of the Sustained Release Patents Would Have Been Obvious Based on the Prior Art

79. I have not opined on whether the Asserted Claims of the Sustained Release Patents are adequately described or enabled by the Sustained Release Patents. However, I have been instructed by counsel to assume for the sole purpose of the analysis below that the Asserted Claims of the Sustained Release Patents are adequately described and enabled by the Sustained Release Patents. I have no opinion with respect to the correctness of that instruction. In view of this instruction and my analysis below, the Asserted Claims of the Sustained Release Patents would have been obvious over Liang 2006.

1. A POSA Would Have Been Motivated to Arrive at the Claimed Percentage of Methacrylic Acid-Methyl Methacrylate in the Coating Through Routine Experimentation

80. As described below, it is my opinion that it would have been obvious to a POSA to arrive at a "functional coating compris[ing] one or more methacrylic acid-methyl methacrylate co-polymers that are from about 20% to about 50% by weight of the functional coating" (*see, e.g.*, '488 patent claim 1) in view of Liang 2006 and the general knowledge of the art through routine experimentation.

a. The Prior Art Taught the Use of Methacrylic Acid-Methyl Methacrylate Co-Polymer in the Functional Coating

81. A POSA would have understood that the use of methacrylic acid-methyl methacrylate co-polymer in a functional coating was a commonplace method for achieving a desired dissolution profile for controlled release formulations.

Dated: January 17, 2023

Dr. Robert S. Langer

EXHIBIT 22

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/025,487	07/02/2018	Clark ALLPHIN	JAZZ-043/02US 306882-2331	3698

128521 7590 05/02/2019

Cooley LLP / Jazz Pharmaceuticals
1299 Pennsylvania Ave., NW, Suite 700
Washington, DC 20004

EXAMINER	
GOTFREDSON, GAREN	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
05/02/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com

Office Action Summary	Application No. 16/025,487	Applicant(s) ALLPHIN et al.	
	Examiner GAREN GOTFREDSON	Art Unit 1619	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/27/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 109-116 and 118-119 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 109-116 and 118-119 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Claims 109-116 and 118-119 are pending in the application and under consideration on the merits.

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/27/2018 was filed prior to the mailing of a Final Office Action. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, it was considered by the Examiner.

Status of the Rejections

The 35 USC 112, 1st paragraph rejection is revised in view of the amendment.

The 35 USC 112, 2nd paragraph rejection is withdrawn in view of the amendment.

The 103 rejections are revised in view of the amendment.

The double patenting rejection is withdrawn in view of the abandonment of the copending application.

Claim Rejections - 35 USC §112

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which itis most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 109-116 and 118-119 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are very broadly drawn to encompass ANY dosage form for oral administration of GHB comprising GHB in ANY amount, and further comprising ANY immediate release portion and ANY controlled release portion so long as it has a methacrylic/methacrylate coating, wherein the formulation comprises ANY film former, and releases drug within the amounts and times recited by claims 109-112.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art,* (2) *partial structure,* (3) *physical and/or chemical properties,*

(4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function,* and the (5) *method of making the claimed invention.*

While all of the factors have been considered, only those required to establish a *prima facie* case are set forth below.

Knowledge in the Art

Anal ("Controlled-Release Dosage Forms," *Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing* (2010)) is a review of controlled release dosage forms, and discloses that there are numerous

> "disadvantages attached to the use of controlled-release dosage forms. These include higher cost of manufacturing, unpredictability, poor in vitro/in vivo correlation, reduced potential, and poor systemic availability in general and the effective release period is influenced and limited by the gastrointestinal (GI) residence time. The transit time of a dosage form through the GI tract is dependent on the physical characteristics of the formulation as well as on physiological factors such as stomach emptying time and effect of food on the absorption process" (paragraph bridging pages 2-3).

Anal goes on to disclose that there are a large number of variables that must be considered to design a controlled release product, including "drug properties including stability, solubility, partitioning characteristics, charge and protein binding behavior, routes of drug delivery, target sites, acute or chronic therapy, the disease, and the patient" (page 5, Section 4). Anal goes on to describe in detail how the foregoing

properties will affect the ability to formulate controlled release dosage forms at pages 5-11.

Consequently, the state of the art around the time of the instant invention was that successfully formulating a controlled release oral dosage form for a given drug and having desired release characteristics was not a foregone conclusion, and the design of such a formulation required extensive consideration of numerous variables that will affect the release properties of a drug from such a formulation.

Correlation between structure and function/method of making

The Examiner recognizes that a description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Consequently, the claimed invention may be adequately described if there is a (1) sufficient description of a representative number of species of oral controlled release dosage forms, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention.

The specification appears to disclose in Example 13 the in vivo administration of several GHB oral dosage forms comprising a compressed tablet controlled release core and the pharmacokinetic parameters resulting therefrom: Treatment B comprised administering the dosage form of Examples 1 -2 (comprising a core comprising 750 mg

GHB, Klucel EXF binder, and magnesium stearate lubricant, and a coating comprising ethylcellulose, hydroxypropyl cellulose and dibutyl sebacate); Treatment C differed in that it included poloxamer as a pore former as described in Example 4, and Treatments D and E differed in that they included an additional 250mg GHB as an immediate release overcoat.

The specification, however, does not appear to disclose any correlation between the structure of the materials that are used to form the compressed tablet dosage forms and the amounts of said materials, with the ability of the dosage forms to achieve the functional properties recited by the instant claims, including the release rates recited by claims 109-112.

As already discussed, the present claims encompass ANY dosage form (e.g., tablet, capsule, liquid) for oral administration of GHB comprising GHB in ANY amount, and further comprising ANY immediate release portion and ANY controlled release portion so long as the latter has a methacrylic/methacrylate coating in ANY amount, wherein the formulation comprises ANY film former, and releases drug within the amounts and times recited by claims 109-112. Therefore, the claims encompass an enormous number of species of dosage forms. Due to the exemplification of only a small handful of species of compressed dosage tablet forms, and the lack of disclosure of a correlation between the structures of the ingredients used to make up the dosage form and the ability of the dosage form to provide pharmacokinetic parameters within the claimed range that is sufficient for the skilled artisan to identify further species that would make up the claimed genus, the skilled artisan reading the instant disclosure could not have recognized the identity of a number of species of the claimed

dosage forms that are sufficient to be representative of the genus of dosage forms within the scope of the claims. Consequently, the skilled artisan would not have recognized that Applicant was in possession of the full scope of the claims at the time of the instant invention.

For the foregoing reasons, the written description requirement is prima facie not satisfied.

Response to Applicant's Arguments

Applicant notes that the claims have been amended to recite a specific range for the amount of the copolymer in the coating, the GHB in the immediate release portion and the total amount of GHB in the formulation, and argues that the disclosure adequately supports the amended claims. Applicant argues that the specification provides ample guidance to support the claims, because Examples 1-12 disclose various examples of the claimed solid dosage formulation and Example 13 provides a detailed method for testing and evaluating the performance features of these formulations, such that the skilled artisan would be able to identify the solid dosage formulation with the claimed functional limitations.

In response, the Office does not agree that Examples 1-12 disclose various examples of the claimed solid dosage formulation.

The present claims are directed to a formulation comprising a controlled release core comprising GHB in specified amounts and coated with a methacrylic acid-methacarylate copolymer in specified amounts, and an immediate release portion comprising GHB in specified amounts.

Example 1, however, discloses a controlled release core comprising sodium oxybate, HPC, and magnesium stearate. Example 2 discloses coating the core of Example 1 core with a coating comprising sodium oxybate, HPC, dibutyl sebacate, and ethylcellulose. Example 3 discloses coating the tablets of Example 2 with hypromellose and sodium oxybate. Examples 4-9 discloses that the release of drug is affected by the weight of the HPC or poloxamer in the coating (Examples 4-5), the amounts of poloxamer or HPC in the coating (Examples 6-7), and the molecular weight of the HPC (Example 8). Example 9 show that two different molecular weight ethylcelluloses both provided acceptable profiles when used in the coating. Example 10 discloses that the Example 9 tablets can be co-administered with ethanol without dose dumping occurring. Example 11 discloses that the tablet can be coated with ethylcellulose from an aqueous dispersion. Example 12 discloses the use of calcium oxybate as the active instead of sodium oxybate.

Therefore, NONE of the compositions disclosed by Examples 1-12 are even within the scope of the claims. For example, none of them comprise cores coated with methacrylic acid-methacarylate copolymer, instead making use of poloxamer, HPC, ethylceullose, or hypromellose coatings. There does not appear to be any disclosure of an embodiment whose structural configuration is actually within the scope of the claims, and that was found to possess the functional GHB release parameters recited by the claims. Additionally, the Examples provide evidence that the weight or molecular weight of the polymer in the coating affects drug release as discussed above, yet the present claims do not include any limitations to these parameters.

Consequently, while the amendments made to the claims succeed in pointing out with more particularity the structure of the claimed dosage forms, they do not in any way limit the claims to any embodiments disclosed by the specification as having drug release profiles within the ranges recited by the claims or to be fairly representative of the genus of solid release forms having the claimed release profiles. Applicant's claims recite functional properties of the claimed dosage form, but fail to recite structural features of the dosage form sufficient to describe a representative number of the species that would have said functional properties. Describing a compound by its functions will not substitute for written description of the structure of the compound. The invention should be explained in such a way as to describe what the invention is, not what the invention does.

While Applicant argues that Example 13 provides a detailed method for testing and evaluating the performance features of these formulations, such that the skilled artisan would be able to identify the solid dosage formulation with the claimed functional limitations, this is not the standard that must be met to establish written description. To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had **actual possession** of the claimed invention at the time of the invention. See, e.g., *Moba, B.V. v. Diamond Automation, Inc.,* 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d at 1563, 19 USPQ2d at 1116). Therefore, an assertion that the disclosure provides testing and evaluation methods that would allow the skilled artisan to perform additional research so as to discover what the invention is (in other words, which structural configurations

within the scope of the claims would possess the functional parameters recited by the claims) does not show **actual possession** of the invention at the time of the invention.

Therefore, the rejection is maintained.

Claim Rejections -35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 109-116 and 118-119 are rejected under 35 U.S.C. 103(a) as unpatentable over Liang et al. (US Pat. Pub. No. 2006/0210630; of record in IDS).

As to claims 109-116 and 118-119, Liang discloses a controlled release oral dosage form (claim 119) comprising gamma-hydroxybutyric acid ("gamma-

hydroxybutyrate") that may be in the form of its potassium or sodium salt (claims 114 and 115) and which also comprises an immediate release formulation comprising GHB (paragraphs 22, 26-29, 51, and 58). The GHB in the immediate release portion may be present in the amount of 20-100 wt% of the immediate release portion, which encompasses the about 75-98% range recited by claim 109 (paragraph 52). The controlled release portion may comprise a controlled release enteric coating comprising a methacrylic acid-methyl methacrylate copolymer such as EUDRAGIT S 100 (paragraphs 81-82). The immediate release portion may comprise an excipient such as hydroxypropyl cellulose or HPMC (a "film-former" of claim 109)(paragraphs 52-55 and 90). Liang also expressly teaches controlling the rate of release of the GHB by altering the thickness and/or composition of the coating compositions (paragraph 77). Figures 1-3 show the delayed dissolution rates of GHB that can be achieved using the controlled release portion of the Liang disclosure (e.g., with about 50% release occurring between about 2.5-3.5 hours), and Figures 4-6 show the high dissolution rates that can be achieved over a short period of time using the immediate release portion of the Liang composition (e.g., 80-90% release in less than an hour).

Regarding claim 113, Liang teaches that the controlled release portion may comprise an excipient such as hydrogenated vegetable oil (paragraph 61).

As to claims 109-116 and 118-119, Liang does not further expressly disclose that the dosage form releases drug in the amounts and times recited by claims 109-112. Additionally, while Liang teaches that the enteric methacrylic/methacrylate copolymer coating comprises 10-70% by weight of the coated controlled release portion

(paragraph 85), it does not expressly disclose the amount of the copolymer by weight of the coating itself as recited by claims 109 and 118 (paragraph 85). Finally, while Liang teaches the use of GHB in specific amounts in both the controlled release and immediate release components (paragraphs 48, 52, 58), it does not further specify the amount of GHB in the immediate release portion as a percentage of the drug in the overall composition as recited by claims 109 and 116 or the absolute mass of GHB in the total composition within the range recited by claim 109.

As to claims 109-116 and 118-119, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to modify the dosage form and method of administering thereof taught by Liang by formulating the dosage form such that it releases the drug in the amounts and time periods recited by the claims, since the Liang expressly suggests obtaining a desired release rate by altering the thickness and/or components of the coating composition and said amounts are result effective variables that will affect the plasma concentration of the drug as a function of time and therefore the magnitude of therapeutic effects and side effects, and additionally because the skilled artisan would have recognized that logic dictates that the amount of GHB released in the early period after administration necessarily can be increased as desired by increasing the percentage of the GHB in the formulation that is in the immediate release portion as opposed to the controlled release portion, such that apportioning the GHB between the immediate release and controlled release portions as desired and altering the thickness of the coating composition as desired can be used to obtain a desired release rate. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). It further would have been prima facie obvious to optimize the amount of the methacrylic/methacrylate copolymer drug in controlled release portion to be within the ranges recited by claims 109 and 118, since Liang expressly suggests obtaining a desired release rate by altering the thickness and/or components of the coating composition such that said amount is result effective variable that will affect the plasma concentration of the drug as a function of time and therefore the magnitude of therapeutic effects and side effects. It further would have been prima facie obvious to optimize the amount of the drug in the immediate release component and in the overall composition to be within the ranges recited by claims 109 and 116, since said amount is a result effective variable that will affect the amount of drug that is immediately released relative to the amount that is delayed released, resulting in alterations to the plasma concentration of the drug that will affect the therapeutic efficacy and side effect profiles of the composition.

Response to Applicant's Arguments

Applicant argues that Liang does not teach a core comprising a coating of methacrylic copolymers in the recited amount nor the amount of GHB in the immediate release portion. Applicant also argues that the claimed functional limitation regarding the amount of drug released within the recited times has not been shown to be present in the cited art. Applicant concludes that only through impermissible hindsight would the Office be able to allege that Liang teaches the recited release rates.

In response, the rejection recognizes that Liang does not expressly teach the amounts of GHB and methacrylic polymer coating nor the claimed functional limitations regarding release of the GHB, but this does not mean there is no prima facie case of obviousness, because the rejection establishes a motivation for the skilled artisan to modify the Liang composition to vary the amount of coating and GHB to arrive at the claimed functional parameters with a reasonable expectation of success. As discussed in the rejection, Liang expressly suggests obtaining a desired release rate by altering the thickness and/or components of the coating composition. Additionally, the skilled artisan would have recognized that the amount of GHB in the immediate release portion as opposed to the controlled release portion necessarily will result in a greater immediate release of the drug, such that apportioning the GHB between the immediate release and controlled release portions as desired and altering the thickness of the coating composition as desired can be used to obtain a desired release rate, such as the release rates recited by the claims. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAREN GOTFREDSON whose telephone number is (571)270-3468. The examiner can normally be reached on M-F 9AM-6PM.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Blanchard can be reached on 5712720827. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAREN GOTFREDSON/
Examiner, Art Unit 1619

/PATRICIA DUFFY/
Primary Examiner, Art Unit 1645

EXHIBIT 23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	ALLPHIN, CLARK, et al.	Confirmation No.:	3698
Serial No.:	16/025,487	Group Art Unit:	1619
Filed:	July 2, 2018	Examiner:	GOTFREDSON, GAREN

DECLARATION OF CLARK ALLPHIN UNDER 37 C.F.R. §1.132

1. I am a co-inventor of the above-identified application. I am currently employed by Jazz Pharmaceuticals, Inc. as the Executive Director of Process and Product Science, New Product and Technology Integration and have worked at Jazz Pharmaceuticals for 13 years in various capacities in the Technical Operations group. At Jazz I have been working on gamma-hydroxybutyrate (GHB) related projects for more than 10 years and have 10 GHB-related U.S. patents. I have over 20 years of development experience in the field of pharmaceutical formulations. I received a Bachelor of Science degree in Chemical Engineering from the University of California, Berkeley. I am familiar with the above-identified application and reviewed the Final Office Action dated May 2, 2019.

Background on GHB and controlled release formulations

2 GHB is a prescription medication used to treat two symptoms of narcolepsy: sudden muscle weakness and excessive daytime sleepiness. XYREM®, the only FDA-approved GHB formulation, is an immediate release formulation and requires dosing of the drug twice during the night, specifically, a first dose at bedtime and a second dose 2.5 to 4 hours later, due to the short half-life of GHB. As some patients do not want to awake in the middle of the night for the second dose, a once-nightly dosage form would eliminate this need.

3. A formulator, looking to develop a dosage form suitable to replace two or more separately administered immediate release dosage forms, would understand that an effective release profile would depend on the various pharmacokinetic properties of the particular drug. Significant work would go in to both determining the desired release profile for a particular drug

and developing a formulation that provides said profile. As discussed in more detail below, we used regional absorption studies and pharmacokinetic modeling to develop a formulation that contained a sustained release portion of GHB. This sustained release formulation provides for a gradual, but extended release of GHB over a period of time. This sustained release is not taught in the cited prior art and provides improved bioavailability over the formulations taught in the cited art.

Liang's Teachings

4. It is my understanding that the Examiner believes that the pending claims are obvious in view of Liang *et al.* (US 2006/0210630). As discussed herein, the present invention would not have been obvious based on Liang to someone with an understanding of pharmaceutical formulations.

5. I have been familiar with the work described in Liang for at least 10 years. To the best of my knowledge, this work on GHB dosage forms began at Orphan Medical in 2002. Orphan Medical was later bought by Jazz Pharmaceuticals, Inc. in 2005. These formulations, however, failed to provide sufficient bioavailability for a once-nightly, dose.

6. Liang discloses delayed release formulations of GHB. Delayed release formulations are formulations that, after a certain delay after ingestion, release the majority of the drug in a relatively short period of time (i.e, less than an hour). One way to do this is with coatings of enteric polymers. Enteric polymers are pH-sensitive polymers that are insoluble in the acidic pH of the stomach, but highly soluble at the relatively higher pH of the intestine. Liang's GHB prototypes were GHB cores with coatings comprising about 87 % by weight pH-sensitive enteric polymers. These pH sensitive coatings would release GHB relatively rapidly, i.e, in about an hour, upon exposure to intestinal pH (e.g. about pH 6 in the duodenum and above pH 7 in the colon), as shown in Example 6 and Figures 1-3 of Liang. Specifically, the coating on DR-1 was designed to release GHB in the colon, while DR-2 was designed to release GHB in the duodenum (paragraphs [0104], [0106], and [0114] of Liang). Based on the data provided in Liang from canine studies with DR-1 and DR-2, these formulations had bioavailability that was about a fourth to a half that of the immediate release form, with higher bioavailability in the

duodenum (DR-2) as compared to the colon (DR-1) as shown in paragraph [0115] and Table 3 of Liang.

Development of the presently claimed formulations through regional absorption studies and PK simulations

7. Jazz conducted a regional GHB absorption study in humans in response to the failure of the Liang formulations to achieve suitable bioavailability and in order to create an improved model of GHB delivery. Specifically, this study was designed to show where GHB was absorbed in the intestine so that we could know how to optimally target the *in vitro* release profile. This study measured the plasma bioavailability upon oral delivery of 900mg GHB to the jejunum (Regimen "A"), ileum (Regimen "B"), and ascending colon (Regimen "C") through Enterion™ capsule delivery, which allows for targeted delivery via a radiolabeled capsule that releases its contents at the target site when activated by an electromagnetic signal. Regimen "D" consisted of 900 mg of an oral dosage of immediate release GHB (e.g., Xyrem) without the Enterion™ capsule. The results are summarized in Table 1 of the Appendix. The human regional absorption data indicated that substantial absorption occurs in the ileum as well as the jejunum. Thus, our aim was to develop GHB formulations that primarily targeted the ileum ***and*** jejunum, i.e., proved sustained release throughout the ileum and jejunum, rather than Liang's delayed release, which more rapidly releases GHB in a single part of the intestinal tract, e.g., DR-1 was designed to release in the colon and DR-2 was designed to release in the duodenum.

8. While the human regional absorption data gave us a better understanding of what part of the intestine to target to maximize bioavailability of GHB, we still had to determine how long this sustained release should be and how soon after ingestion sustained release should start. Based on the human regional absorption data obtained above, my co-inventor on the present application, James Pfeiffer, performed plasma PK simulations. These simulations were intended to correlate an *in vitro* profile, a release rate that could be tested in a lab, with the plasma levels of the drug.

9. The results of these plasma PK simulations indicated that a sustained release formulation would provide improved bioavailability. Specifically, that sustained plasma levels can be reached with a formulation that has an *in vitro* release profile wherein a significant amount of

drug is released within 4-6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C and a paddle speed of 50 rpm. Additionally, we found that a 1 hour lag in release in yields a substantially flatter plasma PK profile as compared to a similar formulation without the lag time. Relatively flatter PK profiles are preferred, as the levels of drug in the blood vary less, thereby providing a more consistent therapeutic effect.

10. Based on these results, we targeted a sustained release formulation comprising an immediate release portion and a sustained release portion, wherein the sustained release portion releases less than 10% of its GHB within the first hour and at least about 40% of its GHB by 4 to 6 hours when it is tested at a neutral pH (i.e., in DI water) in order to target the ileum and jejunum, i.e., ***sustained release*** over a period of time.

11. In contrast, as discussed above, Liang proposed a different approach, with delayed release formulations. Liang's delayed release formulations provide rapid release of the drug in the duodenum or colon, as discussed above and shown in as shown in Example 6 and Figures 1-3 of Liang, and therefore would provide a significantly different *in vitro* release profile in DI water than is presently claimed, as well as a different, less preferred, PK profile.

12. Without additional information, one of skill in the art would not be motivated to modify a delayed release formulation to a sustained release formulation. If we had relied solely on Liang's teachings of delayed release formulations, we would not have arrived at the presently claimed sustained release formulations. Rather, it was only after conducting the regional absorption studies and the pharmacokinetic modeling that we were able to develop the claimed formulation and *in vitro* release profile.

13. Figure A of the Appendix shows that the dissolution profile of a sustained release portion of a GHB formulation meeting the limitations of the claims. The sustained release portion contains GHB (as sodium oxybate) coated with 28% (w/w) Eudragit L100 (methacrylic acid-methyl methacrylate copolymer), 55% (w/w) ethylcellulose, and 17% (w/w) poloxamer 188. Its dissolution profile was tested in a dissolution apparatus in deionized water at a temperature of 37° C, a dip rate of 30/min, and intervals of 30 minutes until 2 hours, then hourly thereafter. As shown in Figure A, the sustained release portion releases less than 10% of its GHB at 1 hour, about 45% of its GHB at 4 hours, and about 80% of its GHB at about 8 hours.

14. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Clark Allphin

5 March 2020

Date

APPENDIX

Table 1. Mean ± SD values of pharmacokinetic parameters for GHB.

Parameter	Regimen A n=10	Regimen B n=10	Regimen C n=9	Regimen D n=10
C_{max} (ng/mL)	30,100 ± 14,400	13,300 ± 4,440	4,930 ± 2,140	42,400 ± 10,100
t_{max} (hours)	0.50 (0.33 – 1.00)[a]	0.88 (0.50 – 1.50)[a]	1.50 (0.75 – 2.00)[a]	0.42 (0.33 – 0.75)[a]
t_{lag} (hours)	0 (0 – 0)[a]	0 (0 – 0)[a]	0 (0 – 0)[a]	0 (0 – 0)[a]
AUC_{0-t} (ng.h/mL)	27,900 ± 9,790	18,700 ± 5,490	11,100 ± 3,170	36,000 ± 10,100
$AUC_{ext-inf}/AUC_{0-inf}$ (ng.h/mL)	26,600 ± 9, 880 (n=8)	19,500 ± 5,490 (n=9)	10,900 ± 2,390 (n=8)	34,200 ± 8,010 (n=9)
$t_{1/2}$ (hours)	0.62 ± 0.18 (n=8)	0.63 ± 0.14 (n=9)	1.04 ± 0.50 (n=8)	0.62 ± 0.17 (n=9)
F_{rel} (%)	75.6 ± 21.3 (n=7)	57.8 ± 10.9 (n=8)	31.0 ± 8.2 (n=7)	-

[a] Median (range)

Regimen A Enterion™ capsule delivery of 900 mg sodium oxybate (freeze dried Xyrem®) to the jejunum.

Regimen B Enterion™ capsule delivery of 900 mg g sodium oxybate (freeze dried Xyrem®)to the ileum.

Regimen C Enterion™ capsule delivery of 900 mg g sodium oxybate (freeze dried Xyrem®) to the ascending colon.

Figure A. Dissolution profile of a sustained release portion of a GHB formulation

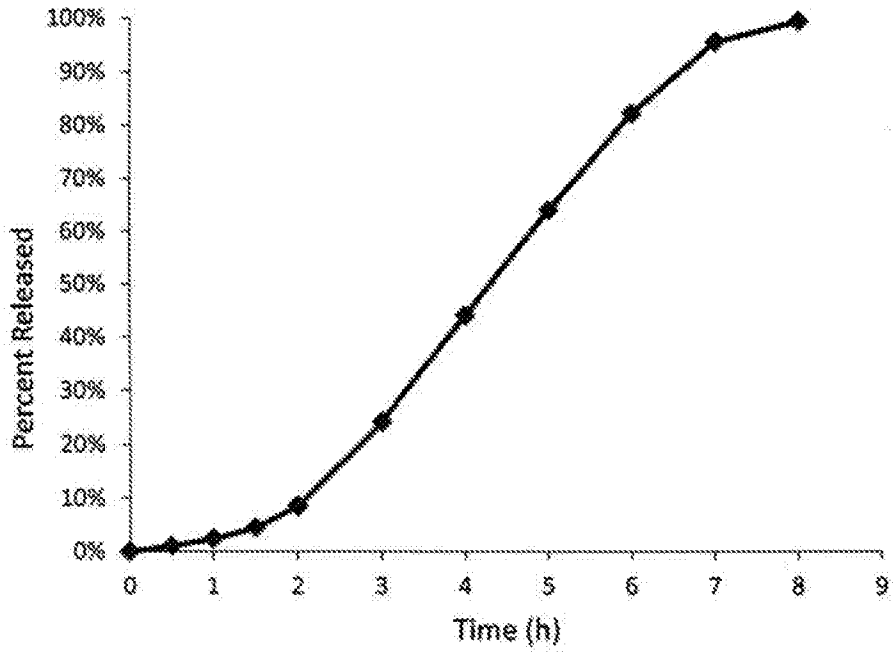

EXHIBIT 24

US011077079B1

(12) **United States Patent**
Allphin et al.

(10) **Patent No.: US 11,077,079 B1**
(45) **Date of Patent: Aug. 3, 2021**

(54) **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

(71) Applicant: **JAZZ PHARMACEUTICALS IRELAND LIMITED**, Dublin (IE)

(72) Inventors: **Clark Allphin**, Seattle, WA (US); **Scott Bura**, Gilroy, CA (US)

(73) Assignee: **Jazz Pharmaceuticals Ireland Limited**, Dublin (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/118,041**

(22) Filed: **Dec. 10, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/448,598, filed on Jun. 21, 2019, now abandoned, which is a continuation of application No. 15/047,586, filed on Feb. 18, 2016, now Pat. No. 10,398,662.

(60) Provisional application No. 62/117,889, filed on Feb. 18, 2015.

(51) **Int. Cl.**

A01N 25/04	(2006.01)
A61K 31/19	(2006.01)
A61K 31/785	(2006.01)
A61K 38/02	(2006.01)
A61K 9/50	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/19*** (2013.01); ***A61K 9/5031*** (2013.01); ***A61K 31/785*** (2013.01); ***A61K 38/02*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/19; A61K 31/785; A61K 9/5031; A61K 38/02
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See application file for complete search history.

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Primary Examiner — Yanzhi Zhang
(74) *Attorney, Agent, or Firm* — Cooley LLP

(57) **ABSTRACT**

The present application relates to GHB formulations and methods for manufacturing the same.

18 Claims, No Drawings

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GHB FORMULATION AND METHOD FOR ITS MANUFACTURE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 16/448,598, filed Jun. 21, 2019, which is a continuation of U.S. application Ser. No. 15/047,586, filed Feb. 18, 2016, now U.S. Pat. No. 10,398,662, which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed Feb. 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Gamma-hydroxybutyrate (GHB), also known as "oxybate," is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (See Snead and Morley, 1981, Brain Res. 227(4): 579-89). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e., daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency, reduces sleep apnea, and improves general anesthesia (see, e.g., U.S. Pat. Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; and 8,324,275; each of which is incorporated herein by reference in its entirety).

Sodium oxybate (Na.GHB), commercially sold as Xyrem®, is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It can be used for other sleep time disturbances. Na.GHB has also been reported to be effective for relieving pain and improving function in patients with fibromyalgia syndrome (See Scharf et al., 2003, J. Rheumatol. 30: 1070; Russell et al., 2009, Arthritis. Rheum. 60: 299), and in alleviating excessive daytime sleepiness and fatigue in patients with Parkinson's disease, improving myoclonus and essential tremor, and reducing tardive dyskinesia and bipolar disorder (See Ondo et al., 2008, Arch. Neural. 65: 1337; Frucht et al., 2005, Neurology 65: 1967; Berner, 2008, J. Clin. Psychiatry 69: 862).

SUMMARY OF THE INVENTION

GHB has a short in vivo half-life, so various embodiments of the invention include a formulation and a method for manufacturing a GHB formulation. One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Optionally, the formulation can contain supplemental anions separate from the coated or uncoated resin particles to facilitate exchange of the GHB when natural (e.g., physiologically produced) anions in the gut are depleted.

In another embodiment of the invention, a precursor to GHB, called gamma butyrolactone (GBL) is loaded onto a hydroxide form Type 1 strong base anion resin (or its equivalent) and the GBL is converted to GHB in the bead to form a GHB resinate product. One can achieve high loading efficiency of the GHB resinate product and a high reaction rate on the resin. Furthermore, organic non-anionic byproducts made in reaction or present in the GBL would not be captured on the resin.

In another embodiment of the invention, one can fully load GHB on the resin, then load a lipophilic agent on the resin with higher selectivity for the resin than GHB. The agent will slow the release of GHB.

In another embodiment, one can fully load an anionic hydrophobic agent, such as stearic acid, onto the resin with lower selectivity for the resin than GHB and then subsequently load GHB less completely, thereby retaining much of the hydrophobic agent and promoting a slower release of GHB.

In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the hydroxyl anions of the resin and form the GHB resinate in-situ. The coating will provide further controlled release characteristics. Examples of such coatings include films comprising polyvinyl acetate (PVAcetate), Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100, FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation.

Other embodiments include reducing the amount of water in the formulation. Oral administration may be achieved while reducing the amount of water by using agents that increase flow, such as slippants to reduce viscosity. Example slippants include polyethylene oxide (PEG) (and its equivalents) which is available in various grades of varying molecular weight and molecular weight distribution.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be in the form of a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Background information on GHB and its related compounds, use and methods for manufacture are listed below. Also, background information on ion exchange resins, their manufacture and uses can be found in the references listed below. The new formulations of the present invention described herein provide favourable sustained release profiles for GHB.

The following U.S. patents and applications relate to GHB and are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,461,197; 8,591,922; 8,731,963; 8,759,394; 8,771,735; 8,772,306; 8,778,301; 8,778,398; 8,901,173; and 2012/0076865. The following patents

are also incorporated by reference: U.S. Pat. Nos. 5,380,937; 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Information on ion exchange resins, their manufacture and uses can be found in the following references which are hereby incorporated by reference in their entireties for all purposes. Mahore J. G, Wadher K. J, Umekar M. J, Bhoyar P. K., Ion Exchange Resins: Pharmaceutical Applications And Recent Advancement, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March-April 2010; Article 002; Munot, Neha M., et al. "Ion exchange resins in pharmaceuticals: A review." Journal of Pharmacy Research 3.12 (2010). Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Srikanth, M. V., et al. "Ion-exchange resins as controlled drug delivery carriers." Journal of Scientific Research 2.3 (2010): 597; Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Ohta et al., Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content, European Journal of Pharmaceutical Sciences 26 (2005) 87-96; Akifuddin et al., Preparation, Characterization and In-vitro Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Ionotropic Gelation Technique, Journal of Applied Pharmaceutical Science Vol. 3 (04), pp. 035-042, April, 2013; Patil et al., A Review On Ionotropic Gelation Method: Novel Approach For Controlled Gastroretentive Gelispheres; International Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Suppl 4, 2012; Cabellero, et al., Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method, International Journal of Pharmaceutics 460 (2014) 181-188; J. M. C. Puguan, X. Yu, H. Kim, Diffusion characteristics of different molecular weight solutes in Ca-Alginate gel beads, Colloids and Surfaces A: Physicochemical and Engineering Aspects (2015), http://dx.doi.org/10.1016/j.colsurfa.2015.01.027; Takka and Gurel, Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and In Vitro Characterization, AAPS PharmSciTech, Vol. 11, No. 1, March 2010; Anand, et al., Ion-exchange resins: carrying drug delivery forward, DDT Vol. 6, No. 17 Sep. 2001. See also the Technical Information sheet for Dowex Ion Exchange Resins; the Product Data Sheet for Amberlite IRN78 Resin, both from Dow Chemicals. Also the Technical Sheet for Duolite AP143/1083 Pharmaceutical Grade Anion Exchange Resin (Cholestyramine Resin USP) from Rohm and Haas. The following U.S. Patents and applications are also incorporated by reference in their entireties for all purposes U.S. Pat. Nos. 4,221,778; 4,510,128; 6,322,819; 8,193,211, 8,202,537; 8,771,735; 8,778,398, 8,062,667, and 8,337,890; U.S. Patent Publication Nos. 2003/0180249; 2008/0003267; 2008/0118571; 2012/0076865; 2012/0148672; 2013/0273159; 2014/0004202; 2014/0093578; and 2014/0127306.

As used herein, the term gamma-hydroxybutyrate (GHB) or "oxybate" refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The manufacture, use, known dosage forms and dosing can be shown in the above patents. An effective dosage range of Xyrem is 6 g to 9 g, given at night in divided doses approximately 2-4 hours apart. GHB is typically given twice nightly due to a short in vivo half-life. It is subject to a controlled drug distribution system. See U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,591,922; and 8,772,306 which are incorporated above.

One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. As described above, a single dose is eliminated within a shorter period of time. One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours. Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities, such as work or driving a car. One embodiment of the invention is a controlled release formulation of GHB designed to maintain a level of GHB in the blood that satisfies the above criteria. In addition to the controlled or extended release properties of one embodiment, there can be an immediate release GHB formulation that is present in or accompanies the controlled release formulation. A sufficient amount of GHB must be present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration. It has been discovered that administration of food may extend the effects of GHB in some circumstances and care should be taken to consider this effect during administration. See U.S. Pat. Nos. 8,859,619; 8,778,398 and 8,591,922 as well as U.S. Pat. Publication 2012/0076865 among others.

The buffering capacity of GHB may affect gastric pH and compromise performance of enteric-coated dosage forms. Avoidance of the potential impact on gastric pH is another useful feature of the GHB resinate, since it has no effect on gastric pH.

In one embodiment, the present invention is directed to formulations of drugs that are carboxylic acids, as described herein, and are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dose or liquid dosage form.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a solid controlled release unit dosage form or liquid dosage form (e.g., combined with a controlled release GHB resinate component) or may be a separate immediate release composition. Therefore, an immediate release component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the immediate release component may also be formulated as part of a single dosage form that integrates both the above components. The immediate release component can furthermore be an oxybate salt such as sodium, potassium, calcium, or magnesium, the immediate release component can also comprise the GHB resinate particles without modification to retard release, or a combination of these GHB forms.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release component and immediate release component described

herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

Gamma butyrolactone (GBL) is a prodrug for GHB. It can be produced by the dehydrogenation of 1, 4 butanediol. GBL can be hydrolyzed under basic conditions (the use of a metal ion hydroxide) to produce GHB. See Arena, C, et al., "Absorption of Sodium γ-Hydroxybutyrate and its Prodrug γ-butyrolactone: relationship between n vitro transport and in vivo absorption", Journal of Pharmaceutical Sciences, 69(3), (March 1980), 356-358; and Lettieri, J, et al., "Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium Y-Hydroxybutyrate and Y-Butyrolactone", Research Communications in Chemical Pathology and Pharmacology, 22(1), (1978), 107-118.

The required dose of GHB, on a molar basis, is unusually high and quite different from most pharmaceutical agents normally considered for drug-resin complexes. A 9 g dose of sodium oxybate is 71 mMol of oxybate, a carboxylic acid. This stands in contrast to a typical moderately potent active pharmaceutical ingredient (API) having a molecular weight of about 400 daltons and a dose of 400 mg, which results in a molar dose of about 1 mMol. Thus, sodium oxybate dosing is about 70-fold higher (on a molar basis) than a more typical drug.

Much of the dose is required in immediate release form for initial therapeutic benefit. However, due to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6. This complicates formulation design, as rate-controlling polymers often have pH-dependent dependent solubility. In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating.

The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500 mg/mL concentration in water, or 42 wt %, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature of GHB at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies.

Furthermore, while extended release oxybate dosage forms are known, such extended release dosage forms are provided as solids, e.g. as tablets. Because the required dose of oxybate is high, such tablets can be quite large, and/or require the administration of multiple tablets. This can be problematic because some patient populations have difficulty swallowing solid dosage forms, or the need to swallow multiple tablets may reduce patient compliance. In addition, the sustained release matrix or coating compositions used to provide extended release are complex and expensive to produce. Accordingly, it would be desirable to provide oxybate (or analogous drugs which require administration in high doses) in an extended release, oral liquid dosage form (including suspensions of oxybate-containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

A drug-resin complex may address some of these limitations, as the drug is essentially insoluble as long as it remains bound to the resin. Instead, the drug release is regulated by exchange with other anions present in the gut, the most prevalent being chloride. Thus, the nature of the formulation challenge is to limit the diffusion of chloride anion into the dosage form rather than to limit the egress of the soluble drug, oxybate.

Drug-resin complexes including modified release drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable.

In one embodiment, a particularly convenient means of administering drug resinates is as a suspension of individual drug resinate beads. The beads may be a plurality of individual resin beads, each loaded with drug and optionally coated with a rate-controlling polymer and additives to influence its properties (such as permeability, flexibility, etc.). Coating formulations exist to address processing challenges, such as the swelling of beads and retention of film integrity. One such example is methylphenidate resinate beads as shown in U.S. Patent No. U.S. Pat. No. 8,202,537.

In one embodiment, the present invention provides a GHB formulation which delivers a controlled release profile, for example a controlled release profile suitable for once-a-day dosing as described herein. Due to the prolongation of the drug release, compositions of the present invention are useful because the once-a-day dose provides a more consistent supply (release) of GHB to patients who otherwise may have to take multiple doses a day. In one embodiment, the invention provides a multi-particulate composition, for example a suspension (e.g., homogeneous suspension), or solid compositions such as a tablet, capsule, powder, wafer, or strip system comprised of a plurality of such particles and optionally other excipients.

As used herein, the term "controlled release" refers to compositions, for example GHB resinate compositions as described herein, which are characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours, or about 4 to 6 hours, including about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours, inclusive of all ranges therebetween. The release profile may be assessed using in vitro dissolution assays known to those of skill in the art, e.g., USP apparatus 2 (paddle) or, more preferably, apparatus 4 (flow-through cell). Particularly when the molar dose of oxybate is large and approaches the amount of anion in the

dissolution media, a flow-through apparatus is desired so that the media composition and flow rate can better approximate the physiologic state. The release profile can be assessed for example (e.g., for bioavailability determinations), in pharmacokinetic studies using plasma concentrations to assess maximum concentration (C_{max}) and area under the curve (AUC). Such assays are well known to those of skill in the art.

In one embodiment, the present invention provides a drug-ion exchange resin composition for further use in a formulation with conventional pharmaceutically acceptable components to provide ingestible compositions. The finished dose compositions may take the form of liquid preparations, such as suspensions, or solid preparations such as tablets, capsules, liquigels, powders, wafers, strips, etc.

Ion-exchange matrices suitable for use in these preparations are water-insoluble and comprise in most embodiments a pharmacologically inert organic and/or inorganic matrix containing functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. In one embodiment, the ion-exchange matrix is anionic. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene, etc.), or partially synthetic (e.g. modified cellulose and dextrans). The inorganic matrix, in various embodiments, can comprise silica gel modified by the addition of ionic groups, or other similar inorganic materials functionalized with ionic groups. Covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid, phosphoric acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., primary amine), weakly basic (e.g. quaternary ammonium), or a combination of acidic and basic groups. In general, the types of ion exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are examples of materials suitable for use in the controlled release of drug preparations. Such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp: 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp: 344-361) in Chromatography. (E. Heftmann, editor), van Nostrand Reinhold Company, New York (1975). A high exchange capacity is desired to limit quantities of resin needed, and that typical values are about 4 mEQ/g

In one embodiment, the size of the ion-exchange particles is from about 5 microns to about 1,000 microns. In most embodiments the particle size is within the range of about 50 microns to about 750 microns (including about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, or about 740 microns, inclusive of all values and ranges therebetween) for liquid dosage forms, although particles up to about 1,000 micron (including the values and ranges herein, and in addition about 800, about 850, about 900, about 950, or about 1000 microns, inclusive of all values and ranges described herein) can be used for solid dosage forms, e.g., tablets and capsules. Particle sizes substantially below the lower limit are generally difficult to handle in all steps of the processing. Both uncoated and coated drug-ion exchange resin particles may be designed within this size range.

Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) which are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Dow XYS-40010.00 and Dow XYS-40013.00 (The Dow Chemical Company). Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. Irregularly shaped ion-exchange resins of this type are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Amberlite IRP-69 (Rohm and Haas). Two of the resins of some of the embodiments of this invention are Amberlite IRP-69 and Dow XYS-40010.00. Both are sulfonated polymers composed of polystyrene cross-linked with about 8% of divinylbenzene, with an ion-exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form). Their essential difference is in physical form. Amberlite IRP-69 consists of irregularly shaped particles with a size range of about 5 microns to about 149 microns produced by milling the parent large size spheres of Amberlite IRP-120. The Dow XYS-40010.00 product consists of spherical particles with a size range of 45 microns to 150 microns.

In one embodiment, suitable ion-exchange resins include anion exchange resins, such as have been described in the art and are commercially available. These resins are particularly well suited for use with acidic drugs including GHB, as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof, as well as other acidic drugs identified herein and/or known in the art such as salicylates, nicotinic acid, mefenamic acid, methotrexate, furosemide, phenolic drugs such as paracetamol, morphine, and levothyroxine, warfarin, phenylbutazone, indomethacin, barbiturates, phenytoin, sulphonamides, etc.

Any anion exchange suitable for pharmaceutical use can be employed in the compositions of the present invention, particularly strong anion exchange resins. An example of a suitable anion exchange resin is a cholestyramine resin, a strong base type 1 anion exchange resin powder with a polystyrene matrix and quaternary ammonium functional groups. The exchangeable anion is generally chloride which can be exchanged for, or replaced by, virtually any anionic species. Other examples include Type II resins, which contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide groups. Such Type I and Type II resins are available under the DOWEX® and Amberlite® trade names. A commercially available Cholestyramine resin is PUROLITE' A430MR resin. As described by its manufacturer, this resin has an average particle size range of less than 150 microns, a pH in the range of 4-6, and an exchange capacity of 1.8-2.2 eq/dry gm. Another pharmaceutical grade cholestyramine resin is available as DUOLITE' AP143/1094 (Rohm and Haas/Dow), described by the manufacturer as having a particle size in the range of 95%, less than 100 microns and 40%, less than 50 microns. The commercial literature from the suppliers of these and other resin is incorporated herein by reference (PUROLITE A-430 MR; DOW Cholestryramine USP, Form No. 177-01877-204, Dow Chemical Company; DUOLITE AP143/1083, Rohm and Haas Company, IE-566EDS—February 06). Other suitable anion exchange resins include POROS® XQ anion exchange resins available from ThermoFisher Scientific. Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for

example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. The regular and irregularly shaped particles can comprise any of the anion exchange resins disclosed herein.

For the oxybate resinate compositions of the present invention, the amount of oxybate present in the resinate should be high to minimize the amount of resin required. Furthermore, in most embodiments, the amount of GHB resinate administered, expressed as GHB mEq (i.e., mmoles) is about 20 to about 120 mEq, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, or about 120 mEq, inclusive of all values and ranges therebetween.

The selected ion-exchange resins may be further treated by the manufacturer or the user to maximize the safety for pharmaceutical use or for improved performance of the compositions. Impurities present in the ion-exchange resins may be removed or neutralized by the use of common chelating agents, anti-oxidants, preservatives such as disodium edetate, sodium bisulfate, and so on by incorporating them at any stage of preparation either before complexation or during complexation or thereafter. These impurities along with their chelating agent to which they have bound may be removed before further treatment of the ion exchange resin with a compound to slow drug release and coating with a diffusion barrier.

Various analogous binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are (a) resin (Cl^- form) plus drug (salt form); (b) resin (Cl^- form) plus drug (as free acid); (c) resin (OH^- form) plus drug (salt form); (d) resin (OH^- form) plus drug (as free acid); (e) resin (OH^- form) plus prodrug (γ-butyrolactone). All of these reactions except (d) and (e) have ionic by-products and the anions generated when the reactions occur compete with the anionic drug for binding sites on the resin with the result that reduced levels of drug are bound at equilibrium. For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reactions (d) and (e). The binding may be performed, for example as a batch or column process, as is known in the art.

Typically the drug-ion exchange resin complex thus formed is collected by filtration and washed with appropriate solvents to remove any unbound drug or by-products. The complexes can be air-dried in trays, in a fluid bed dryer, or other suitable dryer, at room temperature or at elevated temperatures which would not degrade the complex.

In one embodiment, the complexes of the present invention can be prepared by batch equilibration, in which a solution of the drug is contacted with finely divided ion-exchange resin powders. While ion exchange resins are typically provided in very fine particle sizes, which render conventional columnar ion-exchange processes inefficient, such methods can be used for ion exchange resins of suitable particle size. The total ion-exchange capacity represents the maximum achievable capacity for exchanging cations or anions measured under ideal laboratory conditions. The actual capacity which will be realized when loading a drug onto ion exchange resin will be influenced by such factors as the inherent selectivity of the ion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing ions also present in the loading solution. The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

In one embodiment, a batch or equilibrium process is used to load a drug onto an ion-exchange resin. It is usually desirable to load as much as possible of the drug, such as GHB or GBL, onto the ion exchange resin, as typical GHB doses required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy are quite high. Low loadings of GHB in the resinate would require quite large amounts of resin, resulting in unit dosages which would be too large to be conveniently administered and resin quantities that may give rise to more adverse effects such as gastrointestinal disturbance. Complete transfer of the drug from the loading solution into the ion-exchange resin is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the ion exchange resin. The use of two or more loading stages, separating the resin from the drug-containing liquid phase between stages, is a means of achieving maximum loading of the drug onto the ion exchange resin, although some loss of drug from the liquid phase of the final loading stage may occur.

The efficiency of loading the drug (e.g. GHB) onto the ion exchange resin can be influenced by the counter ion used in the ion exchange resin. Commercially supplied anionic resins for pharmaceutical use are almost exclusively in the chloride form. However, chloride ions have a much higher affinity for the exchange site in the resin relative to GHB. The affinity can be estimated based on the pK_a of GHB (4.44) relative to other short-chain fatty acids for which affinities are known. On that basis, GHB has approximately 18% affinity relative to chloride on the anion exchange resin. Bicarbonate, on the other hand, has an affinity of about 27% affinity relative to chloride. Therefore, when a bicarbonate-exchanged resin is contacted with GHB, a much higher efficiency of GHB incorporation may be achieved, because the affinity of GHB relative to bicarbonate is about 67% vs. about 18% relative to chloride. Other "intermediate" exchange anions can also be used, especially those with low affinity relative to chloride and much lower cost relative to oxybate. Thus in some embodiments, substantially all of the chloride counter ion of the e.g. commercially available pharmaceutical grade anion exchange resin is replaced with the intermediate anion (e.g. bicarbonate), in one or more batch equilibration steps as required. After rinsing with an appropriate solvent, the ion exchange resin exchanged with the lower affinity anion (relative to chloride) can then be then exchanged with oxybate.

Substantially complete incorporation (i.e., expressed as the percentage of theoretically available ion exchange sites) of oxybate in the anion exchange resin is desirable to minimize the amount of anion exchange resin required to provide a specified dose of drug (e.g. oxybate). In practice, 100% incorporation of the drug can be difficult and/or expensive to achieve, so somewhat less than substantially complete levels of incorporation of drug are also suitable. Typically, levels of incorporation of more than about 75% are acceptable, including about 75%, about 80%, about 85%, about 90%, about 92%, about 94%, about 96%, about 98%, about 99%, or about 100%, inclusive of all values and ranges therebetween.

When a multi-step batch equilibration is needed or desirable, the resinate slurry formed during equilibration can be decanted to remove the solution of oxybate. The decant can be collected for potential recovery of oxybate or waste disposal. The resinate is then rinsed with solvent, such as de-ionized water, and then charged to the batch equilibration tank where it is contacted with fresh or recovered oxybate to increase the level of incorporation of oxybate. Multiple

equilibration steps can be used with fresh or recycled oxybate solution until the desired level of incorporation, as described herein, is achieved.

Recovery of oxybate from a chloride-exchange process can be very challenging due to oxybate's high water solubility and relatively small size. If aqueous processing is used, all chloride salts are soluble. However, when an intermediate anion (e.g. bicarbonate) is used, the solubility can be manipulated with selection of the cationic form of oxybate. If full and complete exchange of oxybate is desired in one step, then the salt form of oxybate is selected such that the salt form of the exchanged anion is insoluble. For example, calcium salts of many exchangeable anions tend to have very low solubilities. Oxybate can be introduced as calcium oxybate, which is highly water-soluble and suitable for an aqueous exchange process. Precipitation drives the exchange process to near-completion, resulting in very high oxybate yield and incorporation. For example, bicarbonate would precipitate as calcium carbonate if the relatively insoluble calcium hydroxide is added in stoichiometric amount at the commencement of batch equilibration, as shown below. Other example intermediate examples include phosphate (precipitating as calcium phosphate), sulfate (precipitating as calcium sulfate), and hydroxide (precipitating as calcium hydroxide).

$$Ca^{++}(GHB^{-})_2+2R—HCO_3 \rightarrow Ca^{++}+2HCO_3^{-}+2R\text{-}GHB;\ R=resin$$

$$Ca^{++}+2HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+H_2O$$

Use of precipitation as a means to drive batch equilibration can result in some difficulties in recovering the resin, as the resinate and precipitate can both be small particles. In some embodiments, the exchange process is carried out under conditions such that all species remain soluble, and therefore the resinate and solution are easily separated. Next, the oxybate is recovered from the solution in a separate vessel by performing a displacement precipitation by addition of another salt or base. For instance, in the above example, the calcium hydroxide can be added in a separate step, thereby avoiding a difficult separation problem. Although this process may provide a somewhat less efficient equilibration per batch cycle, recovery of the un-exchanged oxybate can be nearly 100%, and multiple batch equilibrations can be performed economically. The technique can be more generally applied if sodium oxybate is used in the exchange process, because most sodium salts of the exchanged anion would remain soluble. In the recovery step, a calcium salt or base is added in near-stoichiometric amount to precipitate the exchanged oxybate and enable full recovery of the sodium oxybate. In one embodiment, calcium hydroxide is added to facilitate recovery. Because it has low solubility, calcium hydroxide can be used in excess without appreciably contaminating the recovered sodium oxybate with calcium.

$$Na^{+}GHB^{-}+R—HCO_3 \rightarrow Na^{+}+HCO_3^{-}+R\text{-}GHB;\ R=resin$$

$$2Na^{+}HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+2H_2O$$

In yet another embodiment of processes for forming the GHB resinate, the anion can be recovered by sub-stoichiometric addition of the soluble calcium oxybate to the sodium-exchanged intermediate anion in the recovery process. Most of the sodium oxybate can be recovered and recycled without causing precipitation during the batch equilibration.

In a particular embodiment, bicarbonate can be evolved as CO_2 gas and the sodium ions form sodium oxybate by adding GBL. This avoids a potentially difficult separation of precipitate during recovery. The sodium bicarbonate is first converted to sodium carbonate, and then the sodium carbonate is reacted with GBL to yield sodium oxybate and carbon dioxide as shown below.

$$NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$$

$$2GBL+Na_2CO_3+H_2O \rightarrow 2Na\text{-}GHB+CO_2(g)$$

In yet another embodiment, the bicarbonate form of an anion exchange resin (e.g., and type 1 strong base anion exchange resin), prepared, for example by ion exchange of the chloride form with sodium or potassium bicarbonate (or other soluble bicarbonate salts), is equilibrated with a solution of sodium or potassium oxybate. The resulting oxybate resinate can be separated from the oxybate equilibration solution by known methods (decanting, filtering, etc.). The oxybate equilibration solution can then be treated with sodium or potassium hydroxide to increase the pH, and then contacted with GBL. At the elevated pH, the GBL reacts with exchanged bicarbonate to form additional GHB (oxybate) and carbon dioxide, thereby regenerating the oxybate equilibration solution so that it can be reused, as the bicarbonate ions produced during the initial ion exchange/equilibration step is lost as carbon dioxide gas. The regenerated oxybate equilibration solution can then be re-equilibrated with the oxybate resinate formed in the initial equilibration step, so as to further increase the degree of exchange of oxybate in the resinate. The regenerated equilibration solution can be further regenerated, and further equilibrated with the oxybate resinate as many times as is needed or desired to obtain the desired degree of incorporation of oxybate in the oxybate resinate. A further advantage of this method is the minimization of oxybate waste due to the ability to regenerate and recycle the oxybate equilibration solution.

High loading capacity will be favored by high charge density in the drug. A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing ions, will also favor higher adsorption capacity.

Thus, in one aspect, the invention provides drug-ion exchange resin complexes comprising a drug loaded in an ion exchange resin as described herein. The drugs and ion exchange resins may be readily selected from amongst those drugs and resins described herein. In most embodiments, GHB and GBL are suitable drugs. The invention further provides drug-ion exchange resin matrixes defined as follows.

The drug-ion exchange resin complexes of the present invention can readily be formulated with pharmaceutically acceptable excipients according to methods well known to those of skill in the art, for example as described in Remington, The Science and Practice of Pharmacy, 22 Edition Philadelphia College of Pharmacy 2013 Pharmaceutical Press, herein incorporated by reference in its entirety for all purposes. In one embodiment, these formulations contain a substantially coated drug-ion exchange resin complex of the invention, optionally with a compound that will slow the release of the drug. In another embodiment, such formulations may also contain a selected amount of uncoated drug-ion exchange resin complex, optionally with a compound to slow the release as described herein. In certain formulations, mixtures of coated drug-ion exchange resin complexes and uncoated drug-ion exchange resin complexes

are present. These formulations may contain any suitable ratio of coated to uncoated product.

In one embodiment, the controlled release dosage form includes drug loaded onto beads (e.g., ion-exchange beads) in combination with one or more optional excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment of the compositions of the present invention that can be fashioned into a tablet or other solid form, beads containing GHB or GBL can include one or more binders that are known for use in tablet formulations. In one such embodiment, the solid form may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (crosslinked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the solid form included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight, including all ranges therebetween. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

One formulation of the present invention may include one or more lubricants to improve desired processing characteristics. One embodiment of the present invention may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added in a range of about 0.5% to 5% by weight. Particular embodiments may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight, inclusive of all ranges therebetween. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation. When "puffer" systems are used for tabletting, the compositions of the present invention can, but need not be, substantially free of lubricant (e.g., include only traces of lubricant deposited by contact with the lubricant coated tablet press).

In certain embodiments, where the compositions of the present invention are provided as liquid compositions, such as suspensions, the compositions of the present invention can further comprise colorants, flavoring agents (natural and artificial), stabilizing agents (EDTA salts, parabens, benzoates), thickeners (tragacanth, xanthan gum, bentonite, starch, acacia, cellulosics), humectants, sweeteners (sucralose, acesulfame K, saccharides, sorbitol, xylitol, mannitol, maltose), etc.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium titrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. In certain other embodiments, the pH adjusting agent may be a mixture of more than one acid and/or more than one base. In other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

The drug-ion exchange resin composition thus prepared may be stored for future use or promptly formulated with conventional pharmaceutically acceptable carriers to prepare finished ingestible compositions for delivery orally, or via other means. In one embodiment, a tablet of the invention is formulated as an orally disintegrating tablet. Such orally dissolving tablets may disintegrate in the mouth in less than about 60 seconds. See U.S. Patent Publication. 2012/0076865.

In one embodiment, the oral liquid compositions of the present invention may also comprise one or more surfactants in amounts of up to about 5.0% w/v or from about 0.02 to about 3.0% w/v of the total formulation. The surfactants useful in the preparation of the finished compositions of the present invention are generally organic materials which aid in the stabilization and dispersion of the ingredients in aqueous systems for a suitable homogenous composition. In particular embodiments, suitable surfactants are non-ionic surfactants such as poloxamers, polyoxyethylene ethers (BRIJ), alkoxylated fatty acids (MYRJ), polysorbates (TWEENs), macrogol mixtures (Gelucire, Labrasol), and sorbitan esters (SPANs). These are produced in a wide variety of structures and molecular weights.

When present, the surfactant component may comprise from about 0.01 to about 2.0% w/v of the total composition (for example 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0% w/v, inclusive of all ranges therebetween) and in particular embodiments will comprise about 0.1% w/v of the total of the composition.

One or more additional emulsifiers or surfactants can also be employed in one embodiment of the invention.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resinates and by selecting the degree of cross-linking and particle size of the resins without a coating process. Examples of ion exchange resins include simple resinates (i.e., uncoated drug-ion exchange resin complexes), microencapsulated or coated resinates (i.e., coated drug-ion exchange resin complexes), hollow fiber systems (i.e. hollow fibers with drug containing lumen), sigmoidal-release systems. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. See Mahore et al. Formulation of such drugs as resinates according to the present invention permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights.

Some embodiments of the present invention involve direct synthesis of oxybate resinate from one or more precursors. Using a hydroxide-form Type 1 strong base anion exchange resin, essentially 100% loading efficiency can be achieved with a simple aqueous reaction with GBL.

The ability to prepare an oxybate resinate, at high loading, in a one step process from GBL can be amenable to point-of-use synthesis (either in patient's hands or at clinical site), as it does not involve shipping or handling the regulated API (GHB). Such a direct synthesis can be carried out using a batch or equilibrium process as described herein, wherein a GBL loading solution is contacted with the particulate hydroxide-form strong base anion exchange resin. The GBL reacts in situ to form an ionic complex of oxybate with the ion-exchange resin, and releasing water as a by-product. It is possible to get 100% yield as well as 100% loading efficiency (i.e., oxybate ionically bound to 100% of the available binding sites) on the resin by such processes. For example, loading efficiencies higher than about 65% (e.g., 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, including ranges therebetween, can be achieved). Because GBL is uncharged and the reaction does not produce ionic byproducts, there are no anions to compete for reaction on the site. Such conditions can achieve 100% reaction on the resin, so the hydroxide-form resin can be used safely, whereas in other applications this may not be possible for patient safety reasons because any unexchanged hydroxide would leave the resin as sodium hydroxide, raising the pH at site of delivery and potentially causing gut wall irritation.

The one-step process is also advantageous because it simplifies purification of the GHB resinate. Because the reaction occurs on the resin and not in the bulk solution, any byproducts that would be made are rinsed off the product. These include any of the impurities in the GBL starting material, as well as unreacted GBL.

Because of the unusually large molar amount of GHB in the compositions of the present invention, relative to the molar quantity of anion present in the gut, the present inventors have found that the compositions of the present invention can provide sustained release without the use of diffusion controlling coatings on the resinate particles. The present inventors have recognized that because the volume and anion content of gastric juice in the fasted state is lower than the molar dose of GHB required for treating the conditions described herein, the rate of GHB release is strongly influenced by the rate of physiological production of anions, and therefore suitable GHB release profiles can be provided without the use of diffusion controlling coatings. For example, while the resinate beads are retained in the stomach, the release of GHB from the resinate beads provided by ion exchange with gastric ions (mainly Cl^-) can be limited by the rate of stomach acid secretion. Similarly, as the resinate beads transit the duodenum and small intestine, the remaining dose of bound GHB can exceed local anion capacity. Thus, the rate of GHB release can be limited by the rate of secretion or diffusion of anions into the gut.

The basal anion capacity of the GI tract is quite small. As summarized in McConnell (Int J Pharm 2008, 364: 213-226, Table 1), fasted state basal values of bile salts are so low that they may be ignored. The fasted state chloride balances are 4.6 mEq in the stomach and 13.1 mEq in the small intestine. Compared to an oxybate dose of about 100 mEq, there is almost an order of magnitude deficiency in resident anion capacity for exchange. Such a situation would not occur with the vast majority of drugs having doses in the <1 mMol range.

	Stomach	Small intestine
Volume, mL	45	105
Chloride, mM	102	125
Total mEq	4.6	13.1

Therefore, the present inventors have discovered that the release of the ion-exchange resin-bound oxybate can be limited by secretions of anions in the GI tract, of which chloride is dominant. In the stomach, basal acid output (as chloride) is about 3 mEq/h in the fasted state. Even in the event that fed-state behavior is induced upon dosing, the fed state maximum secretion is only about 25 mEq/h. Therefore, the stomach cannot support full exchange at rates required to impart a meaningful duration of effect.

Chloride is actively secreted in jejunum, at a rate of about 4 mEq/h/30 cm under conditions where 120 mM chloride is already present. (Davis G R, et al, Active chloride secretion in the normal human jejunum, J Clin Invest 66:1326-1333 (1980)) This translates to a basal rate of about 32 mEq/h in absence of a chloride gradient. In presence of a gradient, the present inventors have found that the contribution of passive diffusion can be sufficient, but may still provide a meaningful impediment to full and timely release of oxybate from the resin.

In the ileum, chloride secretions are substantially less, as characterized by Turnberg. (Turnberg L A et al, Interrelationships of chloride, bicarbonate, sodium, and hydrogen transport in human ileum, J. Clin Invest, 49: 557-567 (1970)). Most chloride secretion is associated with bicarbonate exchange when levels are high. One skilled in the art would appreciate that the perfusion studies by Turnberg indicate that chloride secretion in the ileum would almost certainly be insufficient to support the required exchange with GHB-resinate. For example, even in the extreme case where bicarbonate is almost 90 mM and chloride is only 40 mM, the chloride secretion—taking into account the whole length of ileum—would be expected to be at most 23 mEq/h. In the more typical case where bicarbonate is 40 mM, chloride is actually absorbed rather than secreted—even when chloride levels are set at 40 mM. Yet ileal fluid is maintained isotonic.

To further add to the limitations of biology, the reservoir of small intestinal fluid is small and not well distributed. Only about 10% of the physical volume of the small intestine is filled with fluid. The fluid is not continuously and evenly distributed, as reported by Schiller (Schiller C, et al, Intestinal fluid volumes and transit of dosage forms as

assessed by magnetic resonance imaging, Aliment Pharmacol Ther 2005; 22:971-979) but rather the majority of fluid exists in about 4 fluid pockets that access a relatively small amount of available surface area. This is not very limiting for non-resinate dosage forms, as long as drug dissolution can occur, as once the drug is dissolved, it can access most of the surface area of the small intestine for absorption. A resinate, on the other hand, requires exchange with dissolved anions in order to provide release of the drug. As exchange occurs, oxybate is released to, and chloride is depleted from, the surrounding fluid. Further exchange is limited until oxybate is absorbed and chloride is replenished in the surrounding fluid—both processes that require fluid contact with intestinal surface. Therefore, if only 10% of the intestinal surface is physically available at any given time, the rate of chloride replenishment must be 10-fold higher to reliably compensate. One skilled in the art considering these unusual aspects would conclude that, in the face of insufficient resident anion capacity in the small intestine, a resinate dosage form would not release its drug completely and, furthermore, what release occurs may not be well-regulated.

Given the above observations, permeability and amount of film may require adjustment to achieve the intended release profile.

Optionally, the release of GHB can be tailored by changing the bead size and/or degree of crosslinking of the beads to provide additional resistance to diffusion. For example, larger resinate beads have a lower surface area/volume ratio than smaller resinate beads, and therefore would release GHB more slowly than the smaller beads in the presence of a solution of the same ionic strength. Similarly, the degree of crosslinking of the beads relates to the degree of swelling of the beads, which in turn is related to the rate at which ion exchange, and this drug release can occur. Specifically, more highly crosslinked beads swell less, and thus have slower ion exchange kinetics, compared to less highly crosslinked beads, Thus, the kinetics of drug release can also be controlled by manipulating the degree of crosslinking of the beads. Effects of particle size, particularly 100 microns or greater, and crosslinking, particularly 4% or greater, that may be modest under normal circumstances may be more impactful in the absence of a rate-controlling coating and when gut anion concentrations are substantially diminished.

If no diffusion controlling coating is required, other processing schemes for making the resinate can be considered to improve manufacturing flexibility. For example, instead of using ~100 micron beads, the drug (e.g., GHB or GBL) can be loaded onto larger beads (e.g., 600 micron beads), and then ground to the desired particle size, particle size distribution, consistency, etc. to select or control the desired release characteristics. This could be carried out in an aqueous suspension, so that no isolation or drying of the resinate would be needed. Moreover, if there is no need to coat the particles (e.g., with a diffusion for coating), the irregular shape or dispersity in size distribution of ground particles, which is normally a complicating factor for coating processes, is not an issue.

In other embodiments, the compositions of the present invention can provide differential displacement of drug (e.g. oxybate) from the resinate. Core/shell release characteristics in the resinate beads can be provided by (a) loading oxybate onto an ion exchange resin such that complete loading is achieved, then (b) coating the beads with a portion of lipophilic agent (i.e. lipophilic anion) having much higher selectivity for the ion-exchange resin than GHB. The lipophilic agent will deposit in the outer shell, at the first sites it contacts, and will be relatively immobile resulting in reversible blockage of the bead pores. Suitable lipophilic agents would be, for example, sulfate salts of medium or long-chain fatty acids, such as sodium lauryl sulfate (SLS), or sulfonic esters, such as dioctyl sulfosuccinate (docusate). Other suitable agents may include alkylbenzene sulfonates, 2-naphthalene sulfonate, phenol, salicylic acid, or any other species that may bind more strongly to the resin than oxybate. In particular embodiments, the lipophilic agents are those which are bulky or present hydrophobic tails that may further hinder diffusion of chloride into the resin pore, or oxybate out of the pore after exchange. Although many effective agents may, in other contexts present toxicity concerns, because such agents are strongly bound to the resin, exposure of the agent to the patient is limited. In one embodiment, the lipophilic agent acts as a diffusion barrier both by blocking pores and by facilitating pore blockage by other hydrophobic agents, for example those added during manufacturing, or which may be present in the patient's digestive tract after administration. For example, if sufficient amounts of a surfactant such as SLS is employed, then a non-ionic hydrophobic agent may be more effectively introduced into the bead pore volume due to its compatibility with the hydrophobic "tail" of the SLS molecule. This provides retarded initial release of the drug (e.g., GHB). In other embodiments, further heat treating of the resinate beads can reduce the variability of release, or further retard release. In other embodiments the compositions of the present invention can comprise more than one population of beads, in which one or more of the bead populations is treated with a lipophilic agent, a combination of a lipophilic agent and a hydrophobic agent, or heat treated to as to provide the desired release characteristics. For example, untreated beads would provide more immediate or faster release, and treated beads would provide delayed or slower release.

If further control of release is needed, in a further embodiment the present invention provides a novel method for preparing GHB-containing resinate beads coated with a diffusion rate controlling coating. This embodiment takes advantage of the driving force supplied by reaction of GBL on the active (hydroxide-bearing) sites of hydroxide-form ion exchange resin beads, and the relatively high diffusion characteristics of the small and uncharged GBL molecule. Hydroxide-form ion-exchange resin beads (of any size) can be coated with a flexible film, such as PVAcetate, Eudragit RS, cellulose acetate 398, a mixture of Eudragit RS/RL or Eudragit NE, ethylcellulose, or an enteric such as Eudragit L100, L55 or FS100 with suitable plasticizer. The coated ion-exchange resin beads are then suspended in de-ionized water to equilibrate. GBL is introduced to the suspended beads, which then diffuses through the rate-controlling film, and reacts progressively with the OH-bearing sites within the resin. Sufficient batch equilibration time is provided to ensure complete reaction. The excess GBL is washed off, and the resulting wet resinate beads have a sustained release coating over GHB resinate, which were formed without starting with GHB resinate. This process may be useful for point-of-use preparation, or can improve the utilization of GBL in preparing the product: no GHB or GBL is lost due to processing during coating, as no GBL is present during the coating process.

In one embodiment of the present invention, the present formulation is administered to a patient once nightly. The patient is administered between 4 g and 10 g GHB/day, or 6 g and 9 g/day. Any of the compositions described herein can be used to provide retarded or delayed release of GHB. For example, the GHB resinate beads may be presented in

hydrated form as part of an aqueous suspension, or may be provided as dried beads for mixing with water immediately prior to ingestion or to be taken without water (e.g., as a powder, tablet, capsule etc.). As discussed herein, Type 1 strong base anion exchange resins swell in the presence of water, to an extent that depends on the degree of crosslinking and the nature of the anion bound to it. In the dried state, the sustained release resinate beads of the present invention can hydrate more slowly if release-retarding agents are used. As the beads hydrate, the diffusion of physiologically produced anions of the gastrointestinal tract (e.g. mainly chloride) into the beads can accelerate, thus producing a delayed or gradually increasing rate of release of oxybate.

In another embodiment, a water permeable but relatively insoluble coating is employed over the dry resinate beads such that, when the dry beads are suspended in water, water diffuses through the coating to hydrate and swell the resinate beads. The resulting expansion of the beads causes the coating to rupture, and allow release of the GHB. Suitable polymers for preparing such coatings include one or more of cellulosics such as ethyl cellulose, cellulose acetate, cellulose phthalate; polyvinyl acetate, acrylic polymers and copolymers such as those available under the Eudragit® trade name (e.g., Eudragit® NE30D, RL, and RS resins). Such coatings can be plasticized or unplasticized, and coated onto the beads using methods well-known in the art (pan coating, fluidized bed coating, etc.).

As discussed herein, the dose of GHB required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy is quite high, resulting in the administration not only of relatively large masses of GHB composition, but also water required for administration (particularly when the GHB composition is aqueous). However, since oxybate is administered at night, administering large quantities of water can cause bed-wetting. Accordingly, if administered as an aqueous suspension, the highest practical solids loading is desired. The factors which affect the solids loading (volume fraction) of the suspension include the medium used for dilution (water vs. alcohol) and its viscosity, the degree of swelling of the resinate, the sphericity and uniformity of the beads, and surface charge. See Seno and Yamabe, The Rheological Behavior of Suspensions of Ion—Exchange Resin Particles, Bulletin of the Chemical Society of Japan Vol 39, 776-778 (1966), herein incorporated by reference in its entirety for all purposes. In various embodiments, the compositions of the present invention can be administered as suspended resinate particles in a gel, suitable for ingestion by squeezing from a pouch. In other embodiments, the compositions of the present invention can be dosed in two stages: an initial loading dose followed by a chasing dose. Both the loading and chasing dose comprise suspended beads, but the chasing dose is less concentrated. In still other embodiments, the GHB resinate beads can be administered dry, e.g. by having the patient suck the dry beads through a tube or straw. In such embodiments, an added glidant, which is an excipient used in the art to facilitate powder flow by reducing interparticle friction and cohesion, can be used to facilitate administration. They are used in combination with lubricants as they have no ability to reduce die wall friction. Non-limiting examples include fumed silica, talc, and magnesium carbonate.

The oxybate resinate compositions of the present invention can include an immediate release and an extended release component of oxybate. Such compositions can include, for example, a combination of a population of uncoated resinate beads and a population of resinate beads with a diffusion rate controlling coating as described herein; a single resinate bead population that provides immediate release by ion exchange with physiological anions (e.g. chloride), followed by extended release of oxybate controlled by physiological production of e.g. chloride; combinations of populations of resinate beads having different particle sizes and/or crosslinking densities to control release; or any combination of immediate release and extended release resinate beads disclosed herein.

In one embodiment, the compositions of the present invention may be an immediate-release alternative to Xyrem®. Xyrem® has a steep dose-response curve, and inadvertently taking two doses at the same time would have an adverse effect on the patient. If sodium oxybate is instead provided in resinate form for immediate release, as described herein, the capacity of the stomach and small intestine to provide exchangeable anion would limit the consequences of an inadvertent overdose. A 4.5 g dose of Xyrem is 35.7 mEq oxybate. If the stomach has about 5 mEq chloride, then about 30 mEq of additional exchangeable anion must be provided with the resinate formulation of the present invention to ensure complete release of oxybate. This can be achieved by inclusion of exchangeable anion in the formulation, for example glycine or other amino acids, chloride, or in particular citrate. This embodiment would enable rapid release of the oxybate by providing supplementing exchangeable anions in the stomach.

In another embodiment, the supplemental anions are provided by digestion of proteins administered with or as part of the formulation. The resulting amino acids are then available for exchange with the resin and can provide a more convenient means of providing a large amount of supplemental anion.

In yet another embodiment, the supplemental anions are provided by digestion of a triglyceride administered with the formulation. When the triglyceride empties into the small intestine, lipolysis will generate anions available for exchange. In general, triglycerides of short-chain fatty acids (such as triacetin or tributyrin) can provide better oxybate release than medium- or long-chain triglycerides, because the binding affinity of the resulting anions are higher due to their pKa and size. Triglycerides with at least one short-chain fatty acid component are also suitable, particularly pharmaceutically acceptable short-chain triglycerides such as triacetin.

If the resinate particles are film-coated, then supplemental anions can be provided as separate coated particles, such that the supplemental anion is available when needed. The supplemental anion can be selected such that it is not absorbed rapidly yet has an affinity for the resinate that is much higher than that of oxybate. It can be particularly useful to target or enhance release of the supplemental anion in the ileum where chloride secretory deficit may be most pronounced, since absorption of organic acids might be considerably less in that location. Citric acid, glycine, and mesalazine (5-aminosalicylic acid) are examples of suitable supplemental anions. A non-limiting list of other suitable anions (or conjugate acids) includes pharmaceutically acceptable salts selected from the group consisting of chlorides, acetates, lactates, bicarbonates, sulfates, citrates, tartrates, malates, maleates, malonates, glutarates, succinates, fumarates, aspartates, glutamates, and combinations thereof.

These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after) of administering the drug resinate (e.g., oxybate resinate) compositions of the present invention, or simultaneously therewith. The amount of such supplemental anions can range from about

20 to about 200 mmoles, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mmoles, inclusive of all values and ranges therebetween. The supplemental anions can themselves be capable of anion exchange directly upon contact with the drug resinate (e.g., exchanging with the oxybate of the oxybate resinate), or can be "pro-anions"—that is, form anions upon biotransformation after administration to the patient. Non-limiting examples of such "pro-anions" are those described herein, such as triglycerides or proteins. The amount of such "pro-anions" suitable for use in treating patients according to the present invention are amounts that produce between about 20 and about 200 mmoles of anions, as described hereinabove.

If sustained release is desired, then extending gastric emptying can somewhat compensate for deficiencies in the jejunum and, particularly, the ileum. Reliably extending gastric emptying in the fasted state is very challenging. Although some investigators have found that administration of resinate particles can result in mucoadhesion, the unusually high molar doses of GHB of the resinate compositions of the present invention, approximately 100 mEq, will effectively cover the entire surface of the stomach many times over. Thus, observations made with conventional resinate formulations would not apply to GHB resinates. Therefore, a more effective means of promoting gastric retention would be administration of the compositions of the present invention with food or caloric liquid.

The oxybate compositions of the present invention, for example oxybate resinate compositions, provide therapeutically effective levels of oxybate over a period of at least about 3 to about 8 hours. In some embodiments, the composition can be considered to comprise a single population of resinate beads, wherein at least a portion of the resinate beads releases the oxybate quickly upon administration (essentially upon contacting physiologically produced anions such as chloride), and a remaining portion of the resinate beads releases oxybate more slowly, either controlled by the physiological rate of production of anions such as chloride, or by modification of the release characteristics of the resinate beads themselves (e.g., by providing a diffusion controlling coating, by control of bead diameter, or crosslinking density, or other method as described herein). If the compositions of the present invention comprise two or more distinct bead populations (distinguished by their oxybate release characteristics), the rapid (or immediate) release population provides therapeutically effective levels of oxybate for up to about 3 hours (including 1 or 2 hours) after administration, and the other population(s) provide therapeutically effective levels of oxybate for about 3 to about 8 hours (including 3, 4, 5, 6, 7, or 8 hours) after administration.

Xyrem for its approved indications is effective at between 6 g and 9 g administered twice nightly in equal amounts about 4 hours apart. A sustained release equivalent may require a matching AUC as compared to 9 g Xyrem. As disclosed in US2012076865, the overall relative bioavailability of an appropriately-timed sustained release would have at most about 75% relative to Xyrem. Therefore, about 12-13 grams of sodium oxybate would be required, or about 100 mMols.

Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L, maintained over a period of about 5-8 hours as described herein. For example suitable blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween.

The following examples are included to demonstrate particular embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute particularly suitable modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

All documents cited herein, including patents, patent publications, and non-patent publications are herein incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1

A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200 mesh was loaded with GHB as follows. Calcium oxybate was loaded onto resin in a batch equilibration by combining 10 mL of 4 M calcium oxybate solution (approximately 490 mg/mL), 31.7 mL of de-ionized water, and 20.27 g of Dowex 1X2 wet resin as chloride form with 2% crosslinking. After mixing for 2 hours, the resin was filtered under mild vacuum using a Buchner funnel. It was then washed with 700 mL of de-ionized water in approximately 100-150 mL aliquots to remove any free oxybate. The wet beads were then dried in a 60° C. oven for 3.5 hours, and finally sized through a 36-mesh screen. The resinate beads were assayed by suspending 1.5 g of resinate in 12.5 g of 1 M calcium chloride and allowing them to equilibrate overnight at room temperature. The solution was analyzed by HPLC, and the measured oxybate released from the beads was 1.09 mEq per gram of dry resinate. The calculated loading efficiency was 1.14 mEq/gram dry resin, or 33% of the theoretical exchange capacity of the resin.

Example 2

GHB resinate beads were prepared by contacting GBL with another Type 1 strong base anion exchange resin (Amberlite IRN78, Dow Chemical) having a median particle size of about 0.63 mm, as the hydroxide form with 8% crosslinking. Batch B1 was prepared with a 2:1 molar ratio of GBL to hydroxide-bearing sites by suspending 26.78 g of wet resin in 41.2 g of de-ionized water. While stirring, 8.28 g of GBL was added, and the reaction was monitored by HPLC analysis of unreacted GBL. The reaction was largely complete after 30 minutes. After 90 minutes, the resin was filtered under mild vacuum, rinsed with de-ionized water to remove unreacted GBL, and then placed in a 60° C. oven overnight to dry.

Batch B2 was prepared by reacting GBL in only 16% molar excess over hydroxide-bearing sites on the same resin. 2.6 g of GBL was added to 20 g of wet resin (as supplied) while stirring by hand with a spatula. About 5.3 g of

additional water was added to facilitate blending. After about 1 hour, the mass was placed in the 60° C. oven overnight to complete the reaction, if necessary. The beads were then rinsed with de-ionized water (70 mL), filtered under mild vacuum, and transferred to the 60° C. oven for drying over 3 days.

The two batches were analyzed for oxybate content by first suspending 1.0 g of resinate in 20 mL of 2 M NaCl for 2 hours with stirring. 10 mL of the resulting solution was then titrated with 1 N HCl and the results were compared with a blank of 10 mL of 2 N NaCl. The initial pH values of B1 and B2 were 7.0 and 8.3, respectively, thus indicating that very little, if any, unreacted hydroxide was present in the resinate product. The oxybate titration indicated that GHB loadings of 4.2 and 4.3 mEq/g dry resin for B1 and B2, respectively. The result further indicates that complete reaction occurred, as the theoretical capacity of the resin is approximately 4 mEq/g.

Example 3

A larger batch of GHB resinate beads are prepared by reacting GBL with Amberlite IRN78 under conditions represented by Batch B2. GBL (36.9 g) is slowly added to a slurry of wet resin (Amberlite IRN78, 279 g) and water (about 200 g). The reaction is allowed to proceed for at least 1 hour at room temperature, with stirring. The product is vacuum filtered, then rinsed with several volumes of de-ionized water. The wet product is then placed in a 40° C. oven to dry overnight. 2.1 g of dried GHB resinate beads are then administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage. Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content.

Example 4

Amberlite IRN78, a hydroxide form Type 1 anion exchange resin, is charged to a vessel and contacted with a 1M solution of sodium oxybate in a 2:1 stoichiometry to resin equivalents. After about 2 hours of equilibration, the mixture of sodium oxybate and sodium hydroxide is filtered from the resulting resinate. A sample of the solution is titrated to determine sodium hydroxide content, and then an equivalent amount of calcium oxybate is charged to the solution to precipitate calcium hydroxide. The calcium hydroxide is filtered from the solution of sodium oxybate, and the recovered sodium oxybate solution is returned to the equilibration tank and contacted with the wet resinate for 2 hours. The resinate is then filtered, and filtrate is recovered. The recovered filtrate is processed with calcium oxybate as in the first step, and set aside for future use. The resinate product is washed with several volumes of de-ionized water, and then dried.

Example 5

Cholestyramine (chloride form) is charged to a vessel and contacted with 1M sodium bicarbonate in a 2:1 stoichiometry (bicarbonate to resin). Five cycles of batch equilibration (2 h each) are conducted. The solutions in each cycle are not recycled, and resinate is rinsed with 2 volumes of de-ionized water between each cycle.

The wet, bicarbonate-exchanged resin is then contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Separately, the GHB-resinate is then washed with several volumes of de-ionized water. A sample of the first filtrate is titrated for bicarbonate content, and then a stoichiometric amount of calcium oxybate is added to the batch filtrate. The precipitated calcium carbonate is removed by filtration of the suspension, and the sodium oxybate solution is recovered and stored for future use.

Example 6

The above examples can involve difficult separation steps, as precipitated calcium carbonate is a thick slurry of fine particles at the concentrations used. In this example, filtration is avoided by use of a reaction in which the byproduct forms carbon dioxide rather than a precipitate.

The wet, bicarbonate-exchanged resin of Example 5 is contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Oxybate is recovered and bicarbonate is removed from the filtrate by addition of a stoichiometric amount of sodium hydroxide such that the bicarbonate is converted to carbonate by the reaction: $NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$. The pH drives this reaction to completion.

Next, GBL is added at a 1:1 stoichiometry. Sodium carbonate reacts with the GBL with the evolution of carbon dioxide gas, which drives the reaction to completion: $2\ GBL+Na_2CO_3+H_2O \rightarrow 2\ Na\text{-}GHB+CO_2(g)$. Optionally, a small excess of sodium hydroxide can be added to avoid conversion to bicarbonate during the reaction. This overall process avoids the filtration of carbonate, recovers all the sodium as unexchanged sodium oxybate, and replaces the exchanged sodium oxybate with new oxybate derived from GBL.

Example 7

Soy protein isolate is compressed into oblong or oval tablets of approximately 1000 mg, using compression aids such as fillers, microcrystalline cellulose, and lubricants as required. The tablets are enteric coated separately with two different polymers to achieve dissolution and release of the soy protein isolate in the jejunum and ileum. One batch is coated with Eudragit L30D-55 (jejunum-targeted), and the other is coated with Eudragit L100 (ileum-targeted). At least two of each kind of tablets are taken with one dose of GHB-resinate (35.7 mEq of resinate equivalent to 4.5 g oxybate) in a glass of water. This provides at least 36 mEq of amino acid content, as the protein is hydrolyzed. By releasing the protein in the small intestine rather than stomach, complete and rapid digestion is avoided. Instead, the protein is digested to amino acids more gradually as it transits the small intestine and as the tablet disintegrates. The amino acids are therefore available to facilitate exchange of the GHB-resinate taken concomitantly.

We claim:

1. A method of treating narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing a solid oxybate formulation,

mixing the formulation with water, and

orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

2. The method of claim 1, wherein the orally administering occurs at night.

3. The method of claim 1, wherein the oxybate formulation is mixed with water immediately prior to administration.

4. The method of claim 1, wherein the oxybate is administered with food.

5. The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours.

6. The method of claim 1, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

7. The method of claim 1, wherein the mixture is a suspension.

8. The method of claim 1, wherein the oxybate formulation further comprises an acid.

9. The method of claim 8, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:

administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing a solid oxybate formulation,

mixing the formulation with water, and

orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component.

11. The method of claim 10, wherein the orally administering occurs at night.

12. The method of claim 10, wherein the oxybate formulation is mixed with water immediately prior to administration.

13. The method of claim 10, wherein the oxybate is administered with food.

14. The method of claim 10, wherein the administering promotes the patient to sleep for 6 to 8 hours.

15. The method of claim 10, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate.

16. The method of claim 10, wherein the mixture is a suspension.

17. The method of claim 16, wherein the oxybate formulation further comprises an acid.

18. The method of claim 17, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

* * * * *

EXHIBIT 25

normally occurring metabolic products.

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Absorption of Sodium γ-Hydroxybutyrate and Its Prodrug γ-Butyrolactone: Relationship between *In Vitro* Transport and *In Vivo* Absorption

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Received August 20, 1979, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Amherst, NY 14260.* Accepted for publication October 11, 1979.

Abstract □ A qualitative relationship between *in vitro* transport and *in vivo* absorption of sodium γ-hydroxybutyrate and γ-butyrolactone was demonstrated. As with other short-chain acids, sodium γ-hydroxybutyrate showed capacity-limited transport *in vitro*, consistent with the previous observation that this drug exhibited slower *in vivo* absorption with increasing dose. The prodrug lactone, on the other hand, showed a higher intestinal flux than the acid in the everted gut, and *in vivo* absorption also was more rapid. Capacity-limited transport and absorption of the lactone appeared less evident. Thus, the increased oral hypnotic activity of the lactone over that of the acid most likely is a result of its more favorable intestinal transport characteristics.

Keyphrases □ Sodium γ-hydroxybutyrate—relationship between *in vitro* transport and *in vivo* absorption □ γ-Butyrolactone—prodrug for sodium γ-hydroxybutyrate, relationship between *in vitro* transport and *in vivo* absorption □ Hypnotic agents—sodium γ-hydroxybutyrate and γ-butyrolactone, relationship between *in vitro* transport and *in vivo* absorption

γ-Hydroxybutyrate (I), a metabolite of γ-aminobutyric acid, is found endogenously in the human brain (1). When introduced intravenously, I is a useful anesthetic (2) and is beneficial in Parkinson's disease (3). However, oral administration of this compound results in decreased and variable pharmacological activity (4–6). Recently, oral doses of I totaling 50 mg/kg were shown to be useful in the treatment of narcolepsy and cataplexy in patients, but the duration of sleep induction after each oral dose lasted only for ~2 hr (7).

BACKGROUND

In previous animal studies in these laboratories (8–10), orally administered I was shown to be subject to first-pass metabolism at low doses (≤200 mg/kg) in rats. At higher doses (400–1600 mg/kg), systemic availability approached 100%, presumably due to saturation of first-pass metabolism, but the relative absorption rate appeared to decrease with increasing dose. Thus, although the extent of drug absorption was almost complete, peak plasma I concentrations were relatively insensitive to increases in the oral dose and, in most animals, threshold hypnotic concentrations in plasma were not reached in spite of high oral doses.

The lactone analog of I, γ-butyrolactone (II), is hydrolyzed rapidly and exclusively *in vivo* to I (11, 12) and, therefore, can be classified as a prodrug. Compound II is rapidly and completely absorbed *in vivo* after oral administration over a wide dose range. In contrast to I, the peak drug concentration after oral dosing of II was proportional to the dose, and II was equally effective as a hypnotic whether given orally or intravenously (9).

The reason for the apparent difference in *in vivo* absorption characteristics between I and II has not been delineated. In this paper, *in vitro* experiments that compared the transport properties of these two compounds across the everted rat gut are described.

EXPERIMENTAL

Reagents—Compound I, obtained as the sodium salt[1], and II[1] were used without purification. The buffer and assay reagents[1–3] were all reagent or analytical grade.

Everted Rat Gut Preparation—Male Sprague–Dawley rats, 260–310 g, were sacrificed by decapitation. An intestinal segment, ~12 cm long, was taken from a region 20 cm from the pylorus sphincter; it was everted and mounted according to the technique originally devised by Wilson and Wiseman (13) and modified by Crane and Wilson (14).

Flux Experiment—The everted gut was placed inside a test tube with the mucosal side exposed to 90 ml of a 0.05 *M* physiological tromethamine buffer (pH 7.4) containing the appropriate drug concentration. All flux studies were carried out at 37°. At 5-min intervals up to 25 min, the serosal solution (~1 ml) was removed for the assay and replaced with an equal volume of fresh buffer. Three or four replicate flux experiments were conducted at each initial mucosal concentration.

Spectrophotometric Analysis—The Hestrin (15) assay for short-chain *O*-acyl derivatives as adopted for I and II by Guidotti and Ballotti (16) was employed. Conversion of I to II was effected by reaction with two parts of concentrated sulfuric acid[2] and subsequent neutralization with 10 parts of 6 *N* NaOH[2].

[1] Eastman Kodak Co., Rochester, NY 14650.
[2] Fisher Scientific Co., Fair Lawn, NJ 07410.
[3] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.

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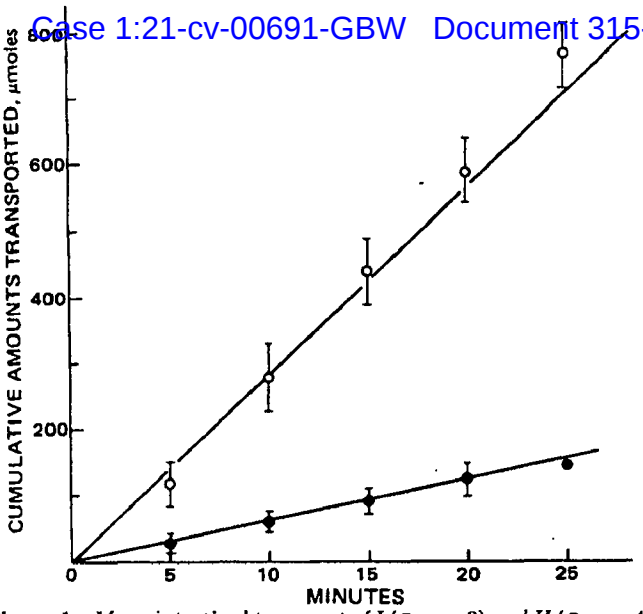

Figure 1—*Mean intestinal transport of I (●, n = 3) and II (○, n = 4) at 0.40 M. Bars indicate standard deviations. The point shown for I at 25 min represents the mean value of two measurements.*

RESULTS AND DISCUSSION

Transport of I and II through the everted rat gut was examined at various initial mucosal drug concentrations. Intestinal flux was determined for each animal preparation by linear regression of a plot of cumulative amount transported to the serosal side *versus* time. Representative plots showing intestinal transport of I and II at 0.40 *M* are given in Fig. 1. At low mucosal concentrations, linearity of flux was maintained throughout the experiment. However, at high I concentrations, positive deviations (increased flux) occurred at the later time points, suggesting possible tissue damage with prolonged drug exposure. In these instances, initial rates of transport restricted to the linear portion of the curve (usually 0–20 min) were used to calculate flux. In all experiments, the total amounts transported to the serosal side were small (<0.4% for I and <2.5% for II) compared to the total drug available from the mucosal pool. Thus, the initial mucosal concentration remained essentially unchanged throughout each experiment.

Figure 2 shows the relationships between intestinal flux of I and II and their respective mucosal concentrations. Over the concentration range studied, intestinal transport of II was considerably more rapid than that of I. At equimolar mucosal concentrations, the differences in flux between I and II were statistically significant at $p < 0.001$ using the Student t test. Compound II fluxes were ~5, 7, and 10 times higher than I fluxes at 0.40, 0.79, and 1.19 *M*, respectively. In addition, I transport leveled off at concentrations above 0.40 *M*. If nonspecific effects on intestinal permeability could be ruled out, this flux behavior suggested the presence of a capacity-limited transport system for I in the rat intestine. In comparison, concentration-dependent transport of II was less evident.

In these experiments, the ionic strength in the mucosal solution was not constant over the concentration range studied. Although the mucosal solution was prepared with buffer, high I concentrations also could affect the pH slightly because I, as its sodium salt, is mildly basic. The leveling in I flux could, in principle, have been partially contributed to by nonspecific ionic strength and/or pH effects created by increasing mucosal concentrations of the ionic drug. The possibility of this artifact was ruled out by the following experiment.

Flux studies were carried out at 0.08 *M* I under two sets of conditions. In one case, no pH or salt adjustments were made (Condition A: pH 7.4, $\mu = 0.23$ *M*); in the other case, sodium chloride and sodium hydroxide were added so that the pH and ionic conditions were equivalent to those present when flux was studied at 1.19 *M* I (Condition B: pH 8.1, $\mu = 1.34$ *M*). If ionic strength and pH affected flux significantly, then the observed fluxes under Conditions A and B would be different, with the flux of B similar to that observed at 1.19 *M* I. In fact, the flux of I was identical whether or not additional salt or alkalinizing agents were added.

In duplicate determinations, the fluxes obtained under Condition A were 2.2 and 2.3 μ*M*/min; those under Condition B both were 2.4 μ*M*/min. Thus, minor differences in pH and ionic strength contributed by changes

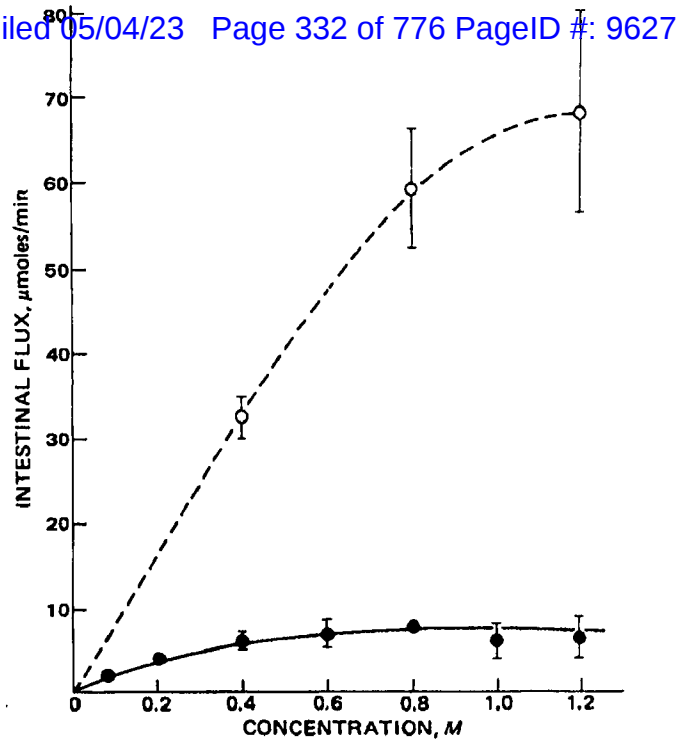

Figure 2—*Concentration effect on the intestinal fluxes of I (●) and II (○). Bars indicate standard deviations. When bars are absent, the standard deviations were too small to be shown.*

in the mucosal I concentration did not affect flux significantly. Since II is nonionic, ionic strength and pH effects produced by increasing II concentrations were presumed to be negligible. Bender *et al.* (17) found the second-order alkaline hydrolytic constant of II to be ~0.2 liter/mole-sec at 25°. At pH 7.4, the hydrolysis half-life would be about 1000 days. Thus, conversion of II to I in the buffered mucosal solution was insignificant during the experiment.

The *in vitro* transport characteristics of I and II are consistent with their *in vivo* absorption properties reported previously (8–10). Compound I, which showed capacity-limited transport *in vitro*, also exhibited relatively slower *in vivo* absorption rates with increasing oral dose (10). Other short-chain acids, such as acetic and butyric acids, also have been shown to be transported *via* an active system (18, 19). Therefore, a capacity-limited absorption mechanism might be a reason for the decreased and variable activity of I when given in high oral doses to humans (4–7). The prodrug lactone II, on the other hand, showed a much higher intestinal flux than I in the everted gut and was almost instantaneously absorbed when orally administered (9). Capacity-limited transport of II, if existent, appeared to occur at much higher drug concentrations.

The present study demonstrated a qualitative relationship between *in vitro* transport and *in vivo* absorption of the two compounds studied. Thus, the increased oral activity of the lactone over that of its open-chain hydroxy acid is most likely a result of its more favorable intestinal transport characteristics. The usefulness of II has not been investigated in humans.

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Temporal Variations in Trough Serum Theophylline Concentrations at Steady State

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Received June 21, 1979, from the **Drug Concentration Laboratory, University of Massachusetts Medical Center, Worcester, MA 01605*, and ‡*Fisons Corporation, Bedford, MA 01730.* Accepted for publication October 11, 1979.

Abstract □ Temporal variations in serum theophylline concentrations were observed in 14 healthy volunteers receiving multiple doses of theophylline. After repeated oral doses (6.9–18.2 mg/kg/day) of theophylline as either a nonalcoholic aminophylline solution or a controlled-release capsule, trough theophylline levels at steady state were significantly higher ($p < 0.05$) in the morning than in the afternoon or evening. With the solution, the mean ($\pm SE$) trough serum level at 7 am was 11.1 ± 0.9 μg/ml, and at 1 pm it was 9.6 ± 0.8 μg/ml. With the capsule, the mean ($\pm SE$) trough serum level at 8 am was 13.8 ± 0.9 μg/ml, and at 8 pm it was 10.7 ± 0.9 μg/ml. Temporal variations in serum theophylline concentrations have not been reported previously and may be important in therapeutic monitoring.

Keyphrases □ Theophylline—trough serum concentrations at steady state, temporal variations □ Bronchodilators—theophylline, trough serum concentrations at steady state, temporal variations □ Pharmacokinetics—theophylline, trough serum concentrations at steady state, temporal variations

Temporal variation in the absorption and disposition of drugs is an area of pharmacokinetics about which relatively little is known. In the few studies performed, the findings have not been consistent. For example, Shirley and Vesell (1) reported that temporal variations in the disposition of acetaminophen and phenacetin occur. However, Vesell *et al.* (2) observed no temporal variations in the pharmacokinetics of antipyrine (2), and Nakano and Hollister (3) reported no time-related changes in the disposition of nortriptyline. The causes of temporal variations in drug pharmacokinetics may be varied. Circadian rhythm apparently influences the distribution of potassium between body compartments (4), while changes in body posture alter the absorption of cephradine (5) and erythromycin (6) from the GI tract.

One mechanism suggested to account for the temporal variations in the disposition of phenacetin and acetaminophen was the occurrence of diurnal changes in the amount and activity of hepatic microsomal oxidases (1). Theophylline is a drug whose disposition also is determined by microsomal oxidases, so it seemed possible that temporal variations in theophylline disposition may occur. Since this aspect of theophylline kinetics had not been reported previously, one objective of this study was to determine if temporal variations exist.

EXPERIMENTAL

Subjects—The seven male and seven female volunteers were 21–40 years old, and their average weight was 67.5 kg. All volunteers were nonsmokers and were in good physical health with no history of alcoholism or cardiovascular disease.

Drug Administration and Blood Sampling—The volunteers randomly received either a nonalcoholic aminophylline solution or a controlled-release theophylline capsule. The oral theophylline dose was individualized for each volunteer, based on single-dose kinetics, to produce peak serum theophylline concentrations no larger than 18 μg/ml after repeated dosing. The daily doses ranged from 6.9 to 18.2 mg/kg. The solution was administered at 7 am, 1 pm, 7 pm, and 1 am, and the capsule was given at 8 am and 8 pm. Dosing was continued for 6 days prior to each study day. The study days were separated by 1 week during which the volunteers took the alternate formulation.

On each study day, 1 ml of serum was obtained immediately before the morning dose of each dosage form and 6 or 12 hr after administration of the solution or capsule, respectively.

Theophylline Assay—Serum theophylline determinations were made by high-pressure liquid chromatography using a method described previously (7).

Data Analysis—A paired t test was used to analyze within-subject differences between the am and pm trough theophylline concentrations observed for each dosage form.

RESULTS AND DISCUSSION

The am and pm trough serum theophylline concentrations determined for each dosage form are listed in Table I. The percentage changes in trough level are noted for each volunteer. The mean ($\pm SE$) serum theophylline concentration at 7 am for the solution was 11.1 ±0.9 μg/ml, while at 1 pm the serum theophylline concentration was 9.6 ± 0.8 μg/ml, representing a change of 13%. For the capsule, the mean ($\pm SE$) serum theophylline concentration at 8 am was 13.8 ± 0.9 μg/ml, and at 8 pm it was 10.7 ± 0.9 μg/ml, reflecting a decrease of 24%. The differences between the am and pm serum theophylline concentrations were significant ($p < 0.05$) for each dosage form.

Based on these results, there appear to be temporal variations in theophylline pharmacokinetics. Higher trough levels at 7 or 8 am compared to those at 1 or 8 pm may be related to a shorter plasma half-life at the latter times. Indeed, Shirley and Vesell (1) reported that plasma half-lives of phenacetin and acetaminophen were ~15% shorter at 2 pm than at 6 am. Another possible cause of higher am trough levels may be

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EXHIBIT 26

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IMPROVED PHARMACOLOGICAL ACTIVITY VIA PRO-DRUG MODIFICATION: COMPARATIVE PHARMACOKINETICS OF SODIUM γ-HYDROXYBUTYRATE AND γ-BUTYROLACTONE

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ABSTRACT

Although γ-butyrolactone (GBL) rapidly converts to γ-hydroxybutyrate (GHB) *in vivo*, the lactone gave significantly more prolonged hypnotic effects than GHB when equimolar doses were compared both parenterally and orally in rats. Plasma drug concentrations were higher after GBL administration through both routes, consistent with the observed differences in the pharmacological activity of these two compounds. Oral GBL was absorbed much faster than oral GHB, with the dual effects of decreasing potential first-pass metabolism and elevating plasma drug concentrations to the region where capacity-limited elimination is operative. Parenteral GBL produced a slower initial drug plasma clearance than parenteral GHB. In spite of the rapid metabolism of GBL to GHB, the apparent tissue distribution of these two compounds may be different.

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

INTRODUCTION

Sodium γ-hydroxybutyrate (GHB) has been found to be a very useful intravenous anesthetic in man, particularly in obstetric and pediatric procedures (Hunter et al., 1971). When used intravenously, GHB has also been shown to be beneficial in Parkinson's Disease (Boncinelli et al., 1971). Oral dosing of this drug, however, was shown to give decreased and variable activity (Jenney et al., 1962; Metcalf et al., 1966; Laborit, 1964). No improvement in Parkinsonian symptoms was observed even when oral doses of GHB were increased to 8 g/day in humans (Papavasiliou et al., 1973).

Lettieri and Fung (1976, 1978) showed that the oral absorption of GHB is quite extensive in rats. The lack of oral activity was attributed to the relatively slow absorption of this compound. Even at high doses, the plasma and/or brain GHB concentrations did not reach sufficient levels to elicit reproducible and sustained pharmacologic effects after oral administration.

γ-Butyrolactone (GBL), a pro-drug of GHB, appears to have greater oral activity. Following oral administration of GBL to rats, Guidotti and Ballotti (1970) observed much higher blood levels of drug than were attained with orally administered GHB. They also reported that rats given the lactone orally slept for 60-90 minutes, whereas those dosed with oral GHB did not sleep at all. Root (1965) also reported a more rapid onset of sleep with oral GBL in children than with GHB. Jenney (1962) reported that 1.5 g of GBL given orally produced sleep for about one hour.

Evidence has been presented that the blood of various species, including man, contains a lactonase enzyme which catalyzes the

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

hydrolysis of GBL to GHB. After intravenous dosing of GBL, Giarman and Roth (1964) attempted to isolate GHB and GBL simultaneously in blood but were unable to detect any significant levels of lactone. In vitro studies have indicated that the half-life of conversion in blood may be as rapid as one minute, but the lactonase activity in liver and brain was found to be less than that of blood (Roth and Giarman, 1966).

Interestingly, intravenously administered GBL also induced a more prolonged period of sleep in rats compared to an equimolar dose of GHB (Giarman and Roth, 1964; Guidotti and Ballotti, 1970; Bessman and Skolnik, 1964). This observation is somewhat surprising in view of the very rapid conversion of GBL to GHB in blood. Detailed comparisons of the pharmacokinetics of these drugs may be useful in understanding the differential pharmacological phenomena observed after GBL and GHB dosing. This study was aimed at characterizing the pharmacokinetics of GBL in relation to those of GHB, both as functions of dose and route of administration.

MATERIALS AND METHODS

Male Sprague-Dawley rats, 260-340 g, were used in all experiments. Prior to drug administration, the rats were fasted for approximately 15 hours. Two doses of GBL and GHB were given: 1.58 mmole/kg (equivalent to 136 mg/kg GBL and 200 mg/kg GHB) and 6.34 mmole/kg (equivalent to 546 mg/kg GBL and 800 mg/kg GHB). Oral doses were administered via gastric intubation to lightly anesthesized animals. Parenteral doses were given intracardially (1.58 mmole/kg) and intravenously (6.34 mmole/kg). Immediately after dosing, the animals were placed in

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

restraining cages and blood was collected at various time intervals from the tail vein. Orbital puncture or cardiac puncture was used as an alternate means of blood sampling when tail vein collection did not provide enough blood. The blood was immediately centrifuged and the separated plasma frozen until it was assayed for total GHB according to the procedure previously described (Lettieri and Fung, 1978a). Each dosing group consisted of at least four animals. No animal received more than a single dose.

In a single rat dosed with 6.34 mmole/kg of GBL, blood samples were taken between 0 and 3 hours and assayed differentially for GHB and GBL (Lettieri and Fung, 1978a).

The area under the plasma concentration-time curve (AUC) was determined from the time zero to time infinity for each animal studied. The trapezoidal rule was used for the time period in which data points were collected. For the remaining period, an estimate was obtained based on the observed terminal elimination half-life.

RESULTS AND DISCUSSION

Pharmacokinetic differences between GBL and GHB. The plasma-concentration time profiles obtained after intracardial and oral dosing of 1.58 mmole/kg GBL and GHB are shown in Fig. 1. The concentrations reported were those of total GHB and GBL, because the assay procedure used did not distinguish between GHB and GBL. Since GBL rapidly degrades in blood, it is likely that these concentrations were essentially those of GHB. This point will be addressed to later in this communication.

At the 1.58 mmole/kg level, there was rapid and extensive absorption or oral GBL. The oral/intracardial AUC ratio was 0.85 compared to 0.59

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

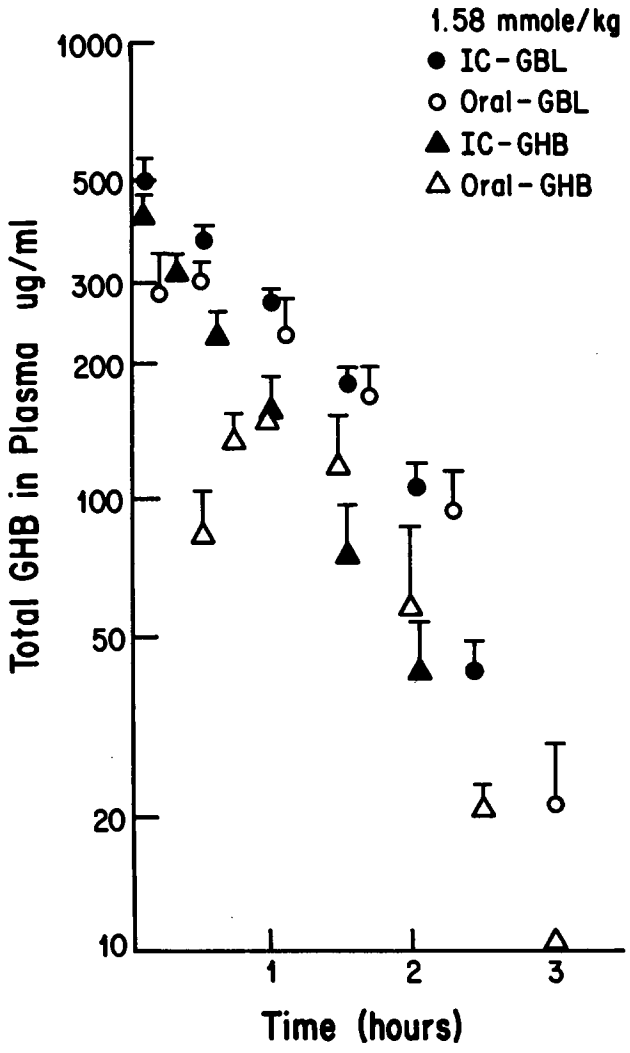

Fig. 1. Plasma concentrations of total GHB following oral and intracardial administration of 1.58 mmole/kg of GHB or GBL. Bars represent standard errors.

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

for a similar dose of GHB (Table I). The plasma-time curves obtained from two of the rats dosed with GBL actually resembled intravenous curves in that the initial sample had the highest concentration, indicating extremely rapid absorption. Peak levels after GBL were in the order of 350 µg/ml, whereas those following oral GHB at the same dose were never above 200 µg/ml. There was also considerably less variability in the total AUC after GBL than was observed after GHB dosing; the coefficient of variation of the areas was 10% following GBL compared to 33% found with GHB.

TABLE I

AUC ($0 \rightarrow \infty$) values after administration of GHB and GBL to rats

DOSE (mmole/kg)		AREA VALUES[a] (µg-hr/ml) x 10^{-2}	
		GHB	GBL
1.58	oral	2.2 ± 0.7	5.1 ± 0.5
	i.c.	3.7 ± 0.8	6.0 ± 0.2
6.34	oral	16.0 ± 3.2	61.8 ± 21.0
	i.v.	30.6 ± 2.6	59.1 ± 11.9

[a] Mean ± S.D.

The intracardial data also revealed a difference between the kinetics of GHB and GBL. Consistent with previous reports (Giarman and Roth, 1964), the lactone appeared to have a slower initial elimination. At later time points, the elimination half-life of GBL was approximately 0.3 hours, similar to that found with GHB. The AUC following intracardial

GBL dosing was significantly higher than that calculated for an equimolar dose of GHB ($P < 0.05$).

Similar results were seen at the higher dose level; viz., 6.34 mmole/kg (Fig. 2). Oral administration of GBL at this dose resulted in extremely rapid and virtually complete absorption. The oral AUC relative to the intravenous AUC at this dose of GBL was essentially unity. This compares to an area ratio of 0.52 found with an equivalent dose of GHB (Table I). The comparable levels obtained between the two routes of administration of GBL are quite evident. The dramatic increases in plasma levels achieved by oral administration of GBL compared to oral GHB are also apparent from Fig. 2. In principle, these results concur with those of Guidotti and Ballotti (1970) in that GBL acted as a much more bioavailable and active compound than GHB. However, the actual levels and effectiveness of both GHB and GBL were quite different between their study and ours. After oral or intravenous administration of a 5.8 mmole/kg dose, Guidotti and Ballotti reported peak concentrations in blood of 600-700 µg/ml and sleeping times of 1 to 1½ hours. However, the plasma levels obtained in the present investigation using a 6.3 mmole/kg dose, were greater than 1000 µg/ml for almost three hours following dosing. Also, the rats slept for approximately four hours.

As with GHB (Lettieri and Fung, 1978), the nonlinearity in GBL elimination was very pronounced (Figs. 1 and 2). Increasing the dose from 1.58 mmole/kg to 6.34 mmole/kg resulted in a 2.5-fold increase in the AUC/dose ratio.

Several factors may contribute to the elevated and prolonged plasma levels obtained with GBL. Following oral administration, the absorption rate is so rapid that concentrations are high enough to

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

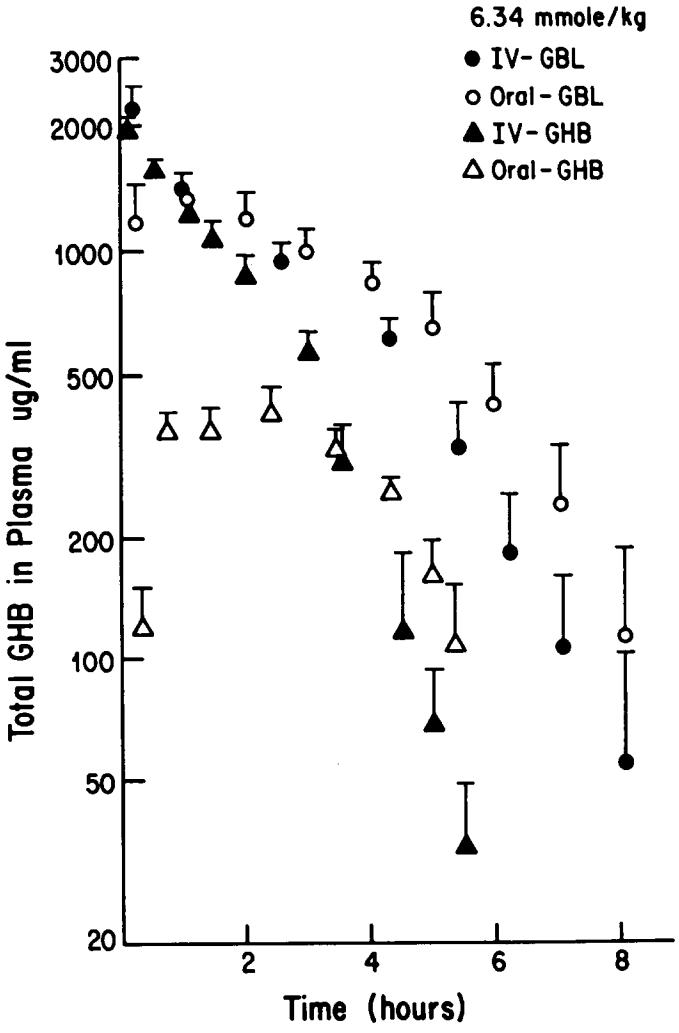

Fig. 2. Plasma concentrations of total GHB following oral and intravenous administration of 6.34 mmole/kg of GHB or GBL. Bars represent standard errors.

enter the nonlinear range, thereby delaying the apparent elimination. The apparent biological availability in nonlinear systems is also dependent on the absorption rate (Jusko et al., 1976). This could also contribute to the dramatic increases in AUC seen upon oral administration of GBL. The chemical modification from the hydroxy acid to the lactone also apparently offered some protection versus the first-pass metabolism observed for GHB (Lettieri and Fung, 1976). Because absorption of GBL was just as rapid for the high dose as in the low dose, GBL absorption is apparently not impaired by the possible capacity-limited process suggested for GHB absorption (Lettieri and Fung, 1978).

TABLE II

Mean sleeping time (hrs) after GHB and GBL dosing

DOSE (mmole/kg)		GHB		GBL	
1.58	oral	0	(0/4)	0.7	(1/5)
	i.c.	0.1	(3/4)	0.5	(6/6)
6.34	oral	0.5	(1/4)	4.6	(5/5)
	i.v.	2.4	(4/4)	4.7	(4/4)

( ) - indicates fraction of rats which slept in that group

Pharmacological differences between GBL and GHB. Table II compares the sleeping times observed after administration of either GHB or the lactone pro-drug. As might be expected from the plasma levels, the lactone resulted in much more prolonged hypnotic activity relative to GHB at equivalent doses. This is especially notable following oral

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

dosing. Even with the 1.58 mmole/kg dose of GBL, one of the animals slept for about 0.5 hours after oral dosing. Oral GHB was devoid of hypnotic activity at this dose. At the 6.34 mmole/kg dose level, all the rats given oral GBL slept for periods comparable to an intravenous dose of GBL. This contrasts with the results seen with GHB. In the case of the acid, 800 mg/kg orally (6.34 mmole/kg) was virtually ineffective as a hypnotic, and even a dose of 1600 mg/kg was only partially effective when given orally. Interestingly, GBL also exhibited enhanced activity relative to GHB even after intravenous dosing, indicating that increased absorption was not the only factor responsible for the pronounced activity of GBL.

In order to explore whether the prolonged activity of GBL might be due to the presence of intact lactone in the bloodstream, the blood from a rat dosed with GBL (6.34 mmole/kg) was assayed for GBL specifically. Most, if not all, of the lactone recovered could be accounted for by the artifactual conversion of GHB during the assay procedure (Lettieri and Fung, 1978a). Because of this uncertainty, it cannot be concluded that there were significant amounts of unchanged GBL in plasma, even at the earliest time points. These results are consistent with the reported rapid conversion of GBL to GHB in blood (Roth and Giarman, 1966).

It has been suggested that the increased activity of GBL might arise from its storage in a tissue depot from which release is relatively slow (Roth and Giarman, 1966). In spite of the rapid hydrolysis of the lactone in blood, the distributive pattern of GBL may be different from that of GHB. This suggestion is supported by several observations. For example, Giarman and Roth (1964) showed that brain levels of drug were about two times higher after GBL administration than after GHB.

VOL.22, NO.1
OCTOBER 1978

Research Communications in
Chemical Pathology and Pharmacology

Guidotti and Ballotti (1970) reported similar findings. Roth and Giarman (1964) also found a greater concentration of total drug (GHB + GBL) in muscle when the lactone form was given. Bessman and Skolnik (1964) obtained levels in various tissues following GHB and GBL and found that GBL produced higher concentrations of drug in brain, muscle, heart, blood and kidney, and slightly lower levels in liver.

CONCLUSION

The pronounced hypnotic activity of GBL over that of GHB is consistent with the pharmacokinetic behavior observed for these two drugs. In the rat, the behavioral responses and plasma drug concentrations seen with parenteral GHB can be realized with oral administration of comparable doses of GBL. On a molar basis, the hypnotic activity of GBL is superior to that of GHB regardless of route of administration. GBL appears to be an excellent pro-drug for GHB in that it not only increases the bioavailability but also confers a sustained release characteristic for the drug. It will be of interest to see whether lactone pro-drug of this kind can be equally successful for other hydroxy acids, e.g., prostaglandins.

ACKNOWLEDGMENTS

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EXHIBIT 27

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(12) **United States Patent**
Allphin et al.

(10) **Patent No.: US 11,147,782 B1**
(45) **Date of Patent: Oct. 19, 2021**

(54) **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/210,064**

(22) Filed: **Mar. 23, 2021**

Related U.S. Application Data

(63) Continuation of application No. 17/118,041, filed on Dec. 10, 2020, now Pat. No. 11,077,079, which is a continuation of application No. 16/448,598, filed on Jun. 21, 2019, now abandoned, which is a continuation of application No. 15/047,586, filed on Feb. 18, 2016, now Pat. No. 10,398,662.

(60) Provisional application No. 62/117,889, filed on Feb. 18, 2015.

(51) **Int. Cl.**

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A61K 9/50	(2006.01)
A61K 31/785	(2006.01)
A61K 38/02	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/19*** (2013.01); ***A61K 9/5031*** (2013.01); ***A61K 31/785*** (2013.01); ***A61K 38/02*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 31/19; A61K 31/785; A61K 38/02; A61K 9/5031
See application file for complete search history.

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(57) **ABSTRACT**

The present application relates to GHB formulations and methods for manufacturing the same.

24 Claims, No Drawings

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GHB FORMULATION AND METHOD FOR ITS MANUFACTURE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 17/118,041, filed Dec. 10, 2020, which is a continuation of U.S. application Ser. No. 16/448,598, filed Jun. 21, 2019, which is a continuation of U.S. application Ser. No. 15/047,586, filed Feb. 18, 2016 (now U.S. Pat. No. 10,398,662), which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed Feb. 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Gamma-hydroxybutyrate (GHB), also known as "oxybate," is an endogenous compound with hypnotic properties that is found in many human body tissues. GHB is present, for example, in the mammalian brain and other tissues. In the brain, the highest GHB concentration is found in the hypothalamus and basal ganglia and GHB is postulated to function as a neurotransmitter (See Snead and Morley, 1981, Brain Res. 227(4): 579-89). The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA-ketoglutarate transaminase and depression of glucose utilization but not oxygen consumption in the brain. GHB treatment substantially reduces the signs and symptoms of narcolepsy, i.e., daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations. In addition, GHB increases total sleep time and REM sleep, and it decreases REM latency, reduces sleep apnea, and improves general anesthesia (see, e.g., U.S. Pat. Nos. 6,472,431; 6,780,889; 7,262,219; 7,851,506; 8,263,650; and 8,324,275; each of which is incorporated herein by reference in its entirety).

Sodium oxybate (Na.GHB), commercially sold as Xyrem®, is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. It can be used for other sleep time disturbances. Na.GHB has also been reported to be effective for relieving pain and improving function in patients with fibromyalgia syndrome (See Scharf et al., 2003, J. Rheumatol. 30: 1070; Russell et al., 2009, Arthritis. Rheum. 60: 299), and in alleviating excessive daytime sleepiness and fatigue in patients with Parkinson's disease, improving myoclonus and essential tremor, and reducing tardive dyskinesia and bipolar disorder (See Ondo et al., 2008, Arch. Neural. 65: 1337; Frucht et al., 2005, Neurology 65: 1967; Berner, 2008, J. Clin. Psychiatry 69: 862).

SUMMARY OF THE INVENTION

GHB has a short in vivo half-life, so various embodiments of the invention include a formulation and a method for manufacturing a GHB formulation. One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Optionally, the formulation can contain supplemental anions separate from the coated or uncoated resin

particles to facilitate exchange of the GHB when natural (e.g., physiologically produced) anions in the gut are depleted.

In another embodiment of the invention, a precursor to GHB, called gamma butyrolactone (GBL) is loaded onto a hydroxide form Type 1 strong base anion resin (or its equivalent) and the GBL is converted to GHB in the bead to form a GHB resinate product. One can achieve high loading efficiency of the GHB resinate product and a high reaction rate on the resin. Furthermore, organic non-anionic byproducts made in reaction or present in the GBL would not be captured on the resin.

In another embodiment of the invention, one can fully load GHB on the resin, then load a lipophilic agent on the resin with higher selectivity for the resin than GHB. The agent will slow the release of GHB.

In another embodiment, one can fully load an anionic hydrophobic agent, such as stearic acid, onto the resin with lower selectivity for the resin than GHB and then subsequently load GHB less completely, thereby retaining much of the hydrophobic agent and promoting a slower release of GHB.

In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the hydroxyl anions of the resin and form the GHB resinate in-situ. The coating will provide further controlled release characteristics. Examples of such coatings include films comprising polyvinyl acetate (PVAcetate), Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100, FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation.

Other embodiments include reducing the amount of water in the formulation. Oral administration may be achieved while reducing the amount of water by using agents that increase flow, such as slippants to reduce viscosity. Example slippants include polyethylene oxide (PEG) (and its equivalents) which is available in various grades of varying molecular weight and molecular weight distribution.

DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the invention is a GHB formulation comprising polymeric beads and pharmaceuticals acceptable excipients. The formulation can be in the form of a solid or a liquid. Additional agents, such as surfactants, may be added to control the release of GHB from within the polymeric bead, such as sodium lauryl sulfate or stearic acid. The beads can be coated with a flexible film. Background information on GHB and its related compounds, use and methods for manufacture are listed below. Also, background information on ion exchange resins, their manufacture and uses can be found in the references listed below. The new formulations of the present invention described herein provide favourable sustained release profiles for GHB.

The following U.S. patents and applications relate to GHB and are hereby incorporated by reference in their entireties for all purposes: U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,

730; 7,765,106; 7,765,107; 8,461,197; 8,591,922; 8,731,963; 8,759,394; 8,771,735; 8,772,306; 8,778,301; 8,778,398; 8,901,173; and 2012/0076865. The following patents are also incorporated by reference: U.S. Pat. Nos. 5,380,937; 4,393,236 German Patent DD 237,309 A1; and British Pat. No. 922,029.

Information on ion exchange resins, their manufacture and uses can be found in the following references which are hereby incorporated by reference in their entireties for all purposes. Mahore J. G, Wadher K. J, Umekar M. J, Bhoyar P. K., Ion Exchange Resins: Pharmaceutical Applications And Recent Advancement, International Journal of Pharmaceutical Sciences Review and Research, Volume 1, Issue 2, March—April 2010; Article 002; Munot, Neha M., et al. "Ion exchange resins in pharmaceuticals: A review." Journal of Pharmacy Research 3.12 (2010). Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Srikanth, M. V., et al. "Ion-exchange resins as controlled drug delivery carriers." Journal of Scientific Research 2.3 (2010): 597; Singh, Inderbir, et al. "Ion exchange resins: drug delivery and therapeutic applications." FABAD J. Pharm. Sci 32 (2007): 91-100; Ohta et al., Development of a simple method for the preparation of a silica gel based controlled delivery system with a high drug content, European Journal of Pharmaceutical Sciences 26 (2005) 87-96; Akifuddin et al., Preparation, Characterization and In-vitro Evaluation of Microcapsules for Controlled Release of Diltiazem Hydrochloride by Ionotropic Gelation Technique, Journal of Applied Pharmaceutical Science Vol. 3 (04), pp. 035-042, April, 2013; Patil et al., A Review On Ionotropic Gelation Method: Novel Approach For Controlled Gastroretentive Gelispheres; International Journal of Pharmacy and Pharmaceutical Sciences, Vol 4, Suppl 4, 2012; Cabellero, et al., Characterization of alginate beads loaded with ibuprofen lysine salt and optimization of the preparation method, International Journal of Pharmaceutics 460 (2014) 181-188; J.M.C. Puguan, X. Yu, H. Kim, Diffusion characteristics of different molecular weight solutes in Ca-Alginate gel beads, Colloids and Surfaces A: Physicochemical and Engineering Aspects (2015), http://dx.doi.org/10.1016/j.colsurfa.2015.01.027; Takka and Gurel, Evaluation of Chitosan/Alginate Beads Using Experimental Design: Formulation and In Vitro Characterization, AAPS PharmSciTech, Vol. 11, No. 1, March 2010; Anand, et al., Ion-exchange resins: carrying drug delivery forward, DDT Vol. 6, No. 17 Sep. 2001. See also the Technical Information sheet for Dowex Ion Exchange Resins; the Product Data Sheet for Amberlite IRN78 Resin, both from Dow Chemicals. Also the Technical Sheet for Duolite AP143/1083 Pharmaceutical Grade Anion Exchange Resin (Cholestyramine Resin USP) from Rohm and Haas. The following U.S. Patents and applications are also incorporated by reference in their entireties for all purposes U.S. Pat. Nos. 4,221,778; 4,510,128; 6,322,819; 8,193,211, 8,202,537; 8,771,735; 8,778,398, 8,062,667, and 8,337,890; U.S. Patent Publication Nos. 2003/0180249; 2008/0003267; 2008/0118571; 2012/0076865; 2012/0148672; 2013/0273159; 2014/0004202; 2014/0093578; and 2014/0127306.

As used herein, the term gamma-hydroxybutyrate (GHB) or "oxybate" refers to the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid. The manufacture, use, known dosage forms and dosing can be shown in the above patents. An effective dosage range of Xyrem is 6 g to 9 g, given at night in divided doses approximately 2-4 hours apart. GHB is typically given twice nightly due to a short in vivo half-life. It is subject to a controlled drug distribution system. See U.S. Pat. Nos. 6,472,431, 8,263,650, 8,324,275; 8,859,619; 7,895,059; 7,797,171; 7,668,730; 7,765,106; 7,765,107; 8,591,922; and 8,772,306 which are incorporated above.

One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. As described above, a single dose is eliminated within a shorter period of time. One object of the invention is to maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours. Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities, such as work or driving a car. One embodiment of the invention is a controlled release formulation of GHB designed to maintain a level of GHB in the blood that satisfies the above criteria. In addition to the controlled or extended release properties of one embodiment, there can be an immediate release GHB formulation that is present in or accompanies the controlled release formulation. A sufficient amount of GHB must be present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration. It has been discovered that administration of food may extend the effects of GHB in some circumstances and care should be taken to consider this effect during administration. See U.S. Pat. Nos. 8,859,619; 8,778,398 and 8,591,922 as well as U.S. Pat. Publication 2012/0076865 among others.

The buffering capacity of GHB may affect gastric pH and compromise performance of enteric-coated dosage forms. Avoidance of the potential impact on gastric pH is another useful feature of the GHB resinate, since it has no effect on gastric pH.

In one embodiment, the present invention is directed to formulations of drugs that are carboxylic acids, as described herein, and are suited to the controlled release of high dose drugs that are highly water soluble. In addition, in certain embodiments, the formulations described herein provide controlled release of drugs that are highly hygroscopic, even where such drugs must be administered at relatively high doses. In particular embodiments, the controlled release formulations are provided as a unit dose or liquid dosage form.

The formulations and dosage forms of the present invention can also include an immediate release component. The immediate release component can form part of a solid controlled release unit dosage form or liquid dosage form (e.g., combined with a controlled release GHB resinate component) or may be a separate immediate release composition. Therefore, an immediate release component may be provided, for example, as a dry powder formulation, an immediate release tablet, an encapsulated formulation, or a liquid solution or suspension. However, the immediate release component may also be formulated as part of a single dosage form that integrates both the above components. The immediate release component can furthermore be an oxybate salt such as sodium, potassium, calcium, or magnesium, the immediate release component can also comprise the GHB resinate particles without modification to retard release, or a combination of these GHB forms.

In specific embodiments, controlled release and immediate release formulations can be dosed together to a subject to provide quick onset of action, followed by maintenance of therapeutic levels of the drug substance over a sustained period of time. However, because the controlled release

component and immediate release component described herein need not be present in a single dosage form, as it is used herein, the phrase "dosed together" refers to substantially simultaneous dosing of the controlled release and immediate release components, but not necessarily administration in the same dosage form. Dosing the controlled release and immediate release components together offers increased convenience, allowing patients to quickly achieve and maintain therapeutic levels of a drug over a sustained period of time, while reducing the frequency with which the drug must be dosed. Furthermore, dosing the controlled release and immediate release components together may avoid the disadvantages of dosing regimens and formulations that result in highly pulsatile plasma concentrations.

Gamma butyrolactone (GBL) is a prodrug for GHB. It can be produced by the dehydrogenation of 1, 4 butanediol. GBL can be hydrolyzed under basic conditions (the use of a metal ion hydroxide) to produce GHB. See Arena, C, et al., "Absorption of Sodium γ-Hydroxybutyrate and its Prodrug γ-butyrolactone: relationship between n vitro transport and in vivo absorption", Journal of Pharmaceutical Sciences, 69(3), (March 1980), 356-358; and Lettieri, J, et al., "Improved Pharmacological Activity via Pro-Drug Modification: Comparative Pharmacokinetics of Sodium Y-Hydroxybutyrate and Y-Butyrolactone", Research Communications in Chemical Pathology and Pharmacology, 22(1), (1978), 107-118.

The required dose of GHB, on a molar basis, is unusually high and quite different from most pharmaceutical agents normally considered for drug-resin complexes. A 9 g dose of sodium oxybate is 71 mMol of oxybate, a carboxylic acid. This stands in contrast to a typical moderately potent active pharmaceutical ingredient (API) having a molecular weight of about 400 daltons and a dose of 400 mg, which results in a molar dose of about 1 mMol. Thus, sodium oxybate dosing is about 70-fold higher (on a molar basis) than a more typical drug.

Much of the dose is required in immediate release form for initial therapeutic benefit. However, due to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6. This complicates formulation design, as rate-controlling polymers often have pH-dependent dependent solubility. In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating.

The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500 mg/mL concentration in water, or 42 wt %, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature of GHB at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies.

Furthermore, while extended release oxybate dosage forms are known, such extended release dosage forms are provided as solids, e.g. as tablets. Because the required dose of oxybate is high, such tablets can be quite large, and/or require the administration of multiple tablets. This can be problematic because some patient populations have difficulty swallowing solid dosage forms, or the need to swallow multiple tablets may reduce patient compliance. In addition, the sustained release matrix or coating compositions used to provide extended release are complex and expensive to produce. Accordingly, it would be desirable to provide oxybate (or analogous drugs which require administration in high doses) in an extended release, oral liquid dosage form (including suspensions of oxybate-containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

A drug-resin complex may address some of these limitations, as the drug is essentially insoluble as long as it remains bound to the resin. Instead, the drug release is regulated by exchange with other anions present in the gut, the most prevalent being chloride. Thus, the nature of the formulation challenge is to limit the diffusion of chloride anion into the dosage form rather than to limit the egress of the soluble drug, oxybate.

Drug-resin complexes including modified release drug-resin complexes are known. However, such complexes would typically be considered unsuitable for very high dose, low molecular weight drugs such as oxybate, because the molar amount of drug required is quite high, which would therefore necessitate correspondingly large amounts of ion exchange resin, particularly if the efficiency of binding is significantly less than 100%. Accordingly, for drugs such as oxybate that are dosed at much higher molar levels, e.g., approximately 100-fold higher compared to typical drug dosing, drug-resin complexes would not be considered acceptable.

In one embodiment, a particularly convenient means of administering drug resonates is as a suspension of individual drug resinate beads. The beads may be a plurality of individual resin beads, each loaded with drug and optionally coated with a rate-controlling polymer and additives to influence its properties (such as permeability, flexibility, etc.). Coating formulations exist to address processing challenges, such as the swelling of beads and retention of film integrity. One such example is methylphenidate resinate beads as shown in U.S. Pat. No. 8,202,537.

In one embodiment, the present invention provides a GHB formulation which delivers a controlled release profile, for example a controlled release profile suitable for once-a-day dosing as described herein. Due to the prolongation of the drug release, compositions of the present invention are useful because the once-a-day dose provides a more consistent supply (release) of GHB to patients who otherwise may have to take multiple doses a day. In one embodiment, the invention provides a multi-particulate composition, for example a suspension (e.g., homogeneous suspension), or solid compositions such as a tablet, capsule, powder, wafer, or strip system comprised of a plurality of such particles and optionally other excipients.

As used herein, the term "controlled release" refers to compositions, for example GHB resinate compositions as described herein, which are characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours, or about 4 to 6 hours, including about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 hours, inclusive of all ranges therebetween. The release profile may be assessed using in vitro dissolution assays known to those of skill in the art, e.g., USP apparatus 2 (paddle) or, more preferably, apparatus 4 (flow-through cell). Particularly when the molar dose of

oxybate is large and approaches the amount of anion in the dissolution media, a flow-through apparatus is desired so that the media composition and flow rate can better approximate the physiologic state. The release profile can be assessed for example (e.g., for bioavailability determinations), in pharmacokinetic studies using plasma concentrations to assess maximum concentration (C_{max}) and area under the curve (AUC). Such assays are well known to those of skill in the art.

In one embodiment, the present invention provides a drug-ion exchange resin composition for further use in a formulation with conventional pharmaceutically acceptable components to provide ingestible compositions. The finished dose compositions may take the form of liquid preparations, such as suspensions, or solid preparations such as tablets, capsules, liquigels, powders, wafers, strips, etc.

Ion-exchange matrices suitable for use in these preparations are water-insoluble and comprise in most embodiments a pharmacologically inert organic and/or inorganic matrix containing functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. In one embodiment, the ion-exchange matrix is anionic. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene, etc.), or partially synthetic (e.g. modified cellulose and dextrans). The inorganic matrix, in various embodiments, can comprise silica gel modified by the addition of ionic groups, or other similar inorganic materials functionalized with ionic groups. Covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid, phosphoric acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., primary amine), weakly basic (e.g. quaternary ammonium), or a combination of acidic and basic groups. In general, the types of ion exchangers suitable for use in ion-exchange chromatography and for such applications as deionization of water are examples of materials suitable for use in the controlled release of drug preparations. Such ion-exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp: 312-343) and "Techniques and Applications of Ion-Exchange Chromatography" (pp: 344-361) in Chromatography. (E. Heftmann, editor), van Nostrand Reinhold Company, New York (1975). A high exchange capacity is desired to limit quantities of resin needed, and that typical values are about 4 mEQ/g

In one embodiment, the size of the ion-exchange particles is from about 5 microns to about 1,000 microns. In most embodiments the particle size is within the range of about 50 microns to about 750 microns (including about 50, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, or about 740 microns, inclusive of all values and ranges therebetween) for liquid dosage forms, although particles up to about 1,000 micron (including the values and ranges herein, and in addition about 800, about 850, about 900, about 950, or about 1000 microns, inclusive of all values and ranges described herein) can be used for solid dosage forms, e.g., tablets and capsules. Particle sizes substantially below the lower limit are generally difficult to handle in all steps of the processing. Both uncoated and coated drug-ion exchange resin particles may be designed within this size range.

Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) which are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Dow XYS-40010.00 and Dow XYS-40013.00 (The Dow Chemical Company). Irregularly shaped particles are all particles not considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. Irregularly shaped ion-exchange resins of this type are exemplified by (but not limited to) any of the ion exchange resins disclosed herein, for example Amberlite IRP-69 (Rohm and Haas). Two of the resins of some of the embodiments of this invention are Amberlite IRP-69 and Dow XYS-40010.00. Both are sulfonated polymers composed of polystyrene cross-linked with about 8% of divinylbenzene, with an ion-exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form). Their essential difference is in physical form. Amberlite IRP-69 consists of irregularly shaped particles with a size range of about 5 microns to about 149 microns produced by milling the parent large size spheres of Amberlite IRP-120. The Dow XYS-40010.00 product consists of spherical particles with a size range of 45 microns to 150 microns.

In one embodiment, suitable ion-exchange resins include anion exchange resins, such as have been described in the art and are commercially available. These resins are particularly well suited for use with acidic drugs including GHB, as well as prodrugs such as GBL, salts, isomers, polymorphs, and solvates thereof, as well as other acidic drugs identified herein and/or known in the art such as salicylates, nicotinic acid, mefanimic acid, methotrexate, furosemide, phenolic drugs such as paracetamol, morphine, and levothyroxine, warfarin, phenylbutazone, indomethacin, barbiturates, phenytoin, sulphonamides, etc.

Any anion exchange suitable for pharmaceutical use can be employed in the compositions of the present invention, particularly strong anion exchange resins. An example of a suitable anion exchange resin is a cholestyramine resin, a strong base type 1 anion exchange resin powder with a polystyrene matrix and quaternary ammonium functional groups. The exchangeable anion is generally chloride which can be exchanged for, or replaced by, virtually any anionic species. Other examples include Type II resins, which contain dialkyl 2-hydroxyethyl ammonium chloride or hydroxide groups. Such Type I and Type II resins are available under the DOWEX® and Amberlite® trade names. A commercially available Cholestyramine resin is PUROLITE™ A430MR resin. As described by its manufacturer, this resin has an average particle size range of less than 150 microns, a pH in the range of 4-6, and an exchange capacity of 1.8-2.2 eq/dry gm. Another pharmaceutical grade cholestyramine resin is available as DUOLITE™ AP143/1094 (Rohm and Haas/Dow), described by the manufacturer as having a particle size in the range of 95%, less than 100 microns and 40%, less than 50 microns. The commercial literature from the suppliers of these and other resin is incorporated herein by reference (PUROLITE A-430 MR; DOW Cholestryramine USP, Form No. 177-01877-204, Dow Chemical Company; DUOLITE AP143/1083, Rohm and Haas Company, IE-566EDS—February 06). Other suitable anion exchange resins include POROS® XQ anion exchange resins available from ThermoFisher Scientific. Both regularly and irregularly shaped particles may be used as resins. Regularly shaped particles are those particles that substantially conform to geometric shapes such as spherical, elliptical, cylindrical and the like, (e.g., three dimensional shapes readily described by a three dimensional space group) Irregularly shaped particles are all particles not

considered to be regularly geometrically shaped (for example not readily described by a three dimensional space group), such as particles with amorphous shapes and particles with increased surface areas due to surface channels or distortions. The regular and irregularly shaped particles can comprise any of the anion exchange resins disclosed herein.

For the oxybate resinate compositions of the present invention, the amount of oxybate present in the resinate should be high to minimize the amount of resin required. Furthermore, in most embodiments, the amount of GHB resinate administered, expressed as GHB mEq (i.e., mmoles) is about 20 to about 120 mEq, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, or about 120 mEq, inclusive of all values and ranges therebetween.

The selected ion-exchange resins may be further treated by the manufacturer or the user to maximize the safety for pharmaceutical use or for improved performance of the compositions. Impurities present in the ion-exchange resins may be removed or neutralized by the use of common chelating agents, anti-oxidants, preservatives such as disodium edetate, sodium bisulfate, and so on by incorporating them at any stage of preparation either before complexation or during complexation or thereafter. These impurities along with their chelating agent to which they have bound may be removed before further treatment of the ion exchange resin with a compound to slow drug release and coating with a diffusion barrier.

Various analogous binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are (a) resin (Cl^- form) plus drug (salt form); (b) resin (Cl^- form) plus drug (as free acid); (c) resin (OH^- form) plus drug (salt form); (d) resin (OH^- form) plus drug (as free acid); (e) resin (OH^- form) plus prodrug (γ-butyrolactone). All of these reactions except (d) and (e) have ionic by-products and the anions generated when the reactions occur compete with the anionic drug for binding sites on the resin with the result that reduced levels of drug are bound at equilibrium. For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reactions (d) and (e). The binding may be performed, for example as a batch or column process, as is known in the art.

Typically the drug-ion exchange resin complex thus formed is collected by filtration and washed with appropriate solvents to remove any unbound drug or by-products. The complexes can be air-dried in trays, in a fluid bed dryer, or other suitable dryer, at room temperature or at elevated temperatures which would not degrade the complex.

In one embodiment, the complexes of the present invention can be prepared by batch equilibration, in which a solution of the drug is contacted with finely divided ion-exchange resin powders. While ion exchange resins are typically provided in very fine particle sizes, which render conventional columnar ion-exchange processes inefficient, such methods can be used for ion exchange resins of suitable particle size. The total ion-exchange capacity represents the maximum achievable capacity for exchanging cations or anions measured under ideal laboratory conditions. The actual capacity which will be realized when loading a drug onto ion exchange resin will be influenced by such factors as the inherent selectivity of the ion exchange resin for the drug, the drug's concentration in the loading solution and the concentration of competing ions also present in the loading solution. The rate of loading will be affected by the activity of the drug and its molecular dimensions as well as the extent to which the polymer phase is swollen during loading.

In one embodiment, a batch or equilibrium process is used to load a drug onto an ion-exchange resin. It is usually desirable to load as much as possible of the drug, such as GHB or GBL, onto the ion exchange resin, as typical GHB doses required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy are quite high. Low loadings of GHB in the resinate would require quite large amounts of resin, resulting in unit dosages which would be too large to be conveniently administered and resin quantities that may give rise to more adverse effects such as gastrointestinal disturbance. Complete transfer of the drug from the loading solution into the ion-exchange resin is not likely in a single equilibrium stage. Accordingly, more than one equilibration may be required in order to achieve the desired loading onto the ion exchange resin. The use of two or more loading stages, separating the resin from the drug-containing liquid phase between stages, is a means of achieving maximum loading of the drug onto the ion exchange resin, although some loss of drug from the liquid phase of the final loading stage may occur.

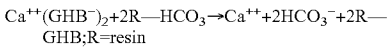
The efficiency of loading the drug (e.g. GHB) onto the ion exchange resin can be influenced by the counter ion used in the ion exchange resin. Commercially supplied anionic resins for pharmaceutical use are almost exclusively in the chloride form. However, chloride ions have a much higher affinity for the exchange site in the resin relative to GHB. The affinity can be estimated based on the pK_a of GHB (4.44) relative to other short-chain fatty acids for which affinities are known. On that basis, GHB has approximately 18% affinity relative to chloride on the anion exchange resin. Bicarbonate, on the other hand, has an affinity of about 27% affinity relative to chloride. Therefore, when a bicarbonate-exchanged resin is contacted with GHB, a much higher efficiency of GHB incorporation may be achieved, because the affinity of GHB relative to bicarbonate is about 67% vs. about 18% relative to chloride. Other "intermediate" exchange anions can also be used, especially those with low affinity relative to chloride and much lower cost relative to oxybate. Thus in some embodiments, substantially all of the chloride counter ion of the e.g. commercially available pharmaceutical grade anion exchange resin is replaced with the intermediate anion (e.g. bicarbonate), in one or more batch equilibration steps as required. After rinsing with an appropriate solvent, the ion exchange resin exchanged with the lower affinity anion (relative to chloride) can then be then exchanged with oxybate.

Substantially complete incorporation (i.e., expressed as the percentage of theoretically available ion exchange sites) of oxybate in the anion exchange resin is desirable to minimize the amount of anion exchange resin required to provide a specified dose of drug (e.g. oxybate). In practice, 100% incorporation of the drug can be difficult and/or expensive to achieve, so somewhat less than substantially complete levels of incorporation of drug are also suitable. Typically, levels of incorporation of more than about 75% are acceptable, including about 75%, about 80%, about 85%, about 90%, about 92%, about 94%, about 96%, about 98%, about 99%, or about 100%, inclusive of all values and ranges therebetween.

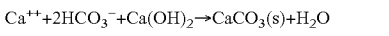
When a multi-step batch equilibration is needed or desirable, the resinate slurry formed during equilibration can be decanted to remove the solution of oxybate. The decant can be collected for potential recovery of oxybate or waste disposal. The resinate is then rinsed with solvent, such as de-ionized water, and then charged to the batch equilibration

tank where it is contacted with fresh or recovered oxybate to increase the level of incorporation of oxybate. Multiple equilibration steps can be used with fresh or recycled oxybate solution until the desired level of incorporation, as described herein, is achieved.

Recovery of oxybate from a chloride-exchange process can be very challenging due to oxybate's high water solubility and relatively small size. If aqueous processing is used, all chloride salts are soluble. However, when an intermediate anion (e.g. bicarbonate) is used, the solubility can be manipulated with selection of the cationic form of oxybate. If full and complete exchange of oxybate is desired in one step, then the salt form of oxybate is selected such that the salt form of the exchanged anion is insoluble. For example, calcium salts of many exchangeable anions tend to have very low solubilities. Oxybate can be introduced as calcium oxybate, which is highly water-soluble and suitable for an aqueous exchange process. Precipitation drives the exchange process to near-completion, resulting in very high oxybate yield and incorporation. For example, bicarbonate would precipitate as calcium carbonate if the relatively insoluble calcium hydroxide is added in stoichiometric amount at the commencement of batch equilibration, as shown below. Other example intermediate examples include phosphate (precipitating as calcium phosphate), sulfate (precipitating as calcium sulfate), and hydroxide (precipitating as calcium hydroxide).

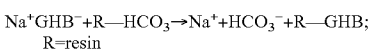


$Ca^{++}(GHB^{-})_2+2R—HCO_3 \rightarrow Ca^{++}+2HCO_3^{-}+2R—GHB;R=resin$

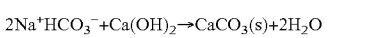


$Ca^{++}+2HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+H_2O$

Use of precipitation as a means to drive batch equilibration can result in some difficulties in recovering the resin, as the resinate and precipitate can both be small particles. In some embodiments, the exchange process is carried out under conditions such that all species remain soluble, and therefore the resinate and solution are easily separated. Next, the oxybate is recovered from the solution in a separate vessel by performing a displacement precipitation by addition of another salt or base. For instance, in the above example, the calcium hydroxide can be added in a separate step, thereby avoiding a difficult separation problem. Although this process may provide a somewhat less efficient equilibration per batch cycle, recovery of the un-exchanged oxybate can be nearly 100%, and multiple batch equilibrations can be performed economically. The technique can be more generally applied if sodium oxybate is used in the exchange process, because most sodium salts of the exchanged anion would remain soluble. In the recovery step, a calcium salt or base is added in near-stoichiometric amount to precipitate the exchanged oxybate and enable full recovery of the sodium oxybate. In one embodiment, calcium hydroxide is added to facilitate recovery. Because it has low solubility, calcium hydroxide can be used in excess without appreciably contaminating the recovered sodium oxybate with calcium.



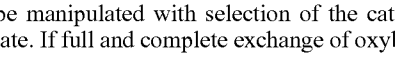
$Na^{+}GHB^{-}+R—HCO_3 \rightarrow Na^{+}+HCO_3^{-}+R—GHB;R=resin$



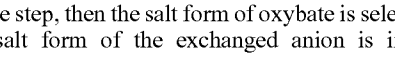
$2Na^{+}HCO_3^{-}+Ca(OH)_2 \rightarrow CaCO_3(s)+2H_2O$

In yet another embodiment of processes for forming the GHB resinate, the anion can be recovered by sub-stoichiometric addition of the soluble calcium oxybate to the sodium-exchanged intermediate anion in the recovery process. Most of the sodium oxybate can be recovered and recycled without causing precipitation during the batch equilibration.

In a particular embodiment, bicarbonate can be evolved as CO_2 gas and the sodium ions form sodium oxybate by adding GBL. This avoids a potentially difficult separation of precipitate during recovery. The sodium bicarbonate is first converted to sodium carbonate, and then the sodium carbonate is reacted with GBL to yield sodium oxybate and carbon dioxide as shown below.



$NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$



$2GBL+Na_2CO_3+H_2O \rightarrow 2Na—GHB+CO_2(g)$

In yet another embodiment, the bicarbonate form of an anion exchange resin (e.g., and type 1 strong base anion exchange resin), prepared, for example by ion exchange of the chloride form with sodium or potassium bicarbonate (or other soluble bicarbonate salts), is equilibrated with a solution of sodium or potassium oxybate. The resulting oxybate resinate can be separated from the oxybate equilibration solution by known methods (decanting, filtering, etc.). The oxybate equilibration solution can then be treated with sodium or potassium hydroxide to increase the pH, and then contacted with GBL. At the elevated pH, the GBL reacts with exchanged bicarbonate to form additional GHB (oxybate) and carbon dioxide, thereby regenerating the oxybate equilibration solution so that it can be reused, as the bicarbonate ions produced during the initial ion exchange/equilibration step is lost as carbon dioxide gas. The regenerated oxybate equilibration solution can then be re-equilibrated with the oxybate resinate formed in the initial equilibration step, so as to further increase the degree of exchange of oxybate in the resinate. The regenerated equilibration solution can be further regenerated, and further equilibrated with the oxybate resinate as many times as is needed or desired to obtain the desired degree of incorporation of oxybate in the oxybate resinate. A further advantage of this method is the minimization of oxybate waste due to the ability to regenerate and recycle the oxybate equilibration solution.

High loading capacity will be favored by high charge density in the drug. A high loading rate is favored by lower molecular weight. Higher drug concentrations in the loading solution, with a minimum of competing ions, will also favor higher adsorption capacity.

Thus, in one aspect, the invention provides drug-ion exchange resin complexes comprising a drug loaded in an ion exchange resin as described herein. The drugs and ion exchange resins may be readily selected from amongst those drugs and resins described herein. In most embodiments, GHB and GBL are suitable drugs. The invention further provides drug-ion exchange resin matrixes defined as follows.

The drug-ion exchange resin complexes of the present invention can readily be formulated with pharmaceutically acceptable excipients according to methods well known to those of skill in the art, for example as described in Remington, The Science and Practice of Pharmacy, 22 Edition Philadelphia College of Pharmacy 2013 Pharmaceutical Press, herein incorporated by reference in its entirety for all purposes. In one embodiment, these formulations contain a substantially coated drug-ion exchange resin complex of the invention, optionally with a compound that will slow the release of the drug. In another embodiment, such formulations may also contain a selected amount of uncoated drug-ion exchange resin complex, optionally with a compound to slow the release as described herein. In certain

formulations, mixtures of coated drug-ion exchange resin complexes and uncoated drug-ion exchange resin complexes are present. These formulations may contain any suitable ratio of coated to uncoated product.

In one embodiment, the controlled release dosage form includes drug loaded onto beads (e.g., ion-exchange beads) in combination with one or more optional excipients, such as binders, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, lubricants, glidants, or other suitable excipients. In one embodiment of the compositions of the present invention that can be fashioned into a tablet or other solid form, beads containing GHB or GBL can include one or more binders that are known for use in tablet formulations. In one such embodiment, the solid form may include at least one binder selected from hydroxypropyl cellulose (HPC), ethylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, povidone, copovidone, pregelatinized starch, dextrin, gelatin, maltodextrin, starch, zein, acacia, alginic acid, carbomers (cross-linked polyacrylates), polymethacrylates, carboxymethylcellulose sodium, guar gum, hydrogenated vegetable oil (type 1), methylcellulose, magnesium aluminum silicate, and sodium alginate. In specific embodiments, the solid form included in a controlled release dosage form as disclosed herein may comprise binder levels ranging from approximately 1% to 10% by weight. For example, the CR core may include a binder in an amount selected from about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, and 10% by weight, including all ranges therebetween. In certain such embodiments, the amount of binder included in the CR core may range from about 1 to 2%, 1 to 3%, 1 to 4%, 1 to 5%, 1 to 6%, 1 to 7%, 1 to 8%, 1 to 9% and 1 to 10% by weight.

One formulation of the present invention may include one or more lubricants to improve desired processing characteristics. One embodiment of the present invention may include one or more lubricants selected from at least one of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added in a range of about 0.5% to 5% by weight. Particular embodiments may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight, inclusive of all ranges therebetween. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation. When "puffer" systems are used for tabletting, the compositions of the present invention can, but need not be, substantially free of lubricant (e.g., include only traces of lubricant deposited by contact with the lubricant coated tablet press).

In certain embodiments, where the compositions of the present invention are provided as liquid compositions, such as suspensions, the compositions of the present invention can further comprise colorants, flavoring agents (natural and artificial), stabilizing agents (EDTA salts, parabens, benzoates), thickeners (tragacanth, xanthan gum, bentonite, starch, acacia, cellulosics), humectants, sweeteners (sucralose, acesulfame K, saccharides, sorbitol, xylitol, mannitol, maltose), etc.

In certain other embodiments of the present invention, the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids, bases, or combinations thereof. In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid. In certain other embodiments, the acid is selected from the group including, but not limited to, acetic, acetylsalicylic, barbital, barbituric, benzoic, benzyl penicillin, boric, caffeine, carbonic, citric, dichloroacetic, ethylenediaminetetra-acetic acid (EDTA), formic, glycerophosphoric, glycine, lactic, malic, mandelic, monochloroacetic, oxalic, phenobarbital, phenol, picric, propionic, saccharin, salicylic, sodium dihydrogen phosphate, succinic, sulfadiazine, sulfamerazine, sulfapyridine, sulfathiazole, tartaric, trichloroacetic, and the like, or inorganic acids such as hydrochloric, nitric, phosphoric or sulfuric, and the like. In a preferred embodiment, the acid is malic or hydrochloric acid. In certain other embodiments, the pH adjusting agent may be a base selected from the group including, but not limited to, acetanilide, ammonia, apomorphine, atropine, benzocaine, caffeine, calcium hydroxide, cocaine, codeine, ephedrine, morphine, papaverine, physostigmine, pilocarpine, potassium bicarbonate, potassium hydroxide, procaine, quinine, reserpine, sodium bicarbonate, sodium dihydrogen phosphate, sodium citrate, sodium taitrate, sodium carbonate, sodium hydroxide, theobromine, thiourea or urea. In certain other embodiments, the pH adjusting agent may be a mixture of more than one acid and/or more than one base. In other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH.

Additionally, any excipient, salt, acid, pH-mediating, adjusting or buffering compound or agent, flavoring, solution, solvent, dispersion, glycerol, glycol, oil, antibacterial and antifungal agents, antibiotics and antihistamines, binders, disintegrating agents, lubricants, sweetening agents, or any other additive or ingredient from those enumerated above or in the examples, or in any pharmaceutically acceptable composition or carrier described herein, or as would be known by one of skill in the art, is contemplated for use in aqueous mediums or solid forms of the GHB compositions of the invention. One or more of these compositions may be packaged with GHB or packaged separately from GHB prior to consumption. If packaged separately, useful compositions of GHB may be obtained by mixing GHB with the other components with an aqueous medium prior to consumption.

In certain embodiments, the pharmaceutical composition may also contain an antioxidant. An "antioxidant" is understood herein to mean certain embodiments which are substances that inhibits oxidation. Such antioxidants include, but are not limited to, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, potassium metabisulfite, sodium metabisulfite, anoxomer and maleic acid BP.

In some embodiments of the formulations of the present invention, the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

The drug-ion exchange resin composition thus prepared may be stored for future use or promptly formulated with conventional pharmaceutically acceptable carriers to prepare finished ingestible compositions for delivery orally, or via other means. In one embodiment, a tablet of the invention is formulated as an orally disintegrating tablet. Such

orally dissolving tablets may disintegrate in the mouth in less than about 60 seconds. See U.S. Patent Publication. 2012/0076865.

In one embodiment, the oral liquid compositions of the present invention may also comprise one or more surfactants in amounts of up to about 5.0% w/v or from about 0.02 to about 3.0% w/v of the total formulation. The surfactants useful in the preparation of the finished compositions of the present invention are generally organic materials which aid in the stabilization and dispersion of the ingredients in aqueous systems for a suitable homogenous composition. In particular embodiments, suitable surfactants are non-ionic surfactants such as poloxamers, polyoxyethylene ethers (BRIJ), alkoxylated fatty acids (MYRJ), polysorbates (TWEENs), macrogol mixtures (Gelucire, Labrasol), and sorbitan esters (SPANs). These are produced in a wide variety of structures and molecular weights.

When present, the surfactant component may comprise from about 0.01 to about 2.0% w/v of the total composition (for example 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.0% w/v, inclusive of all ranges therebetween) and in particular embodiments will comprise about 0.1% w/v of the total of the composition. One or more additional emulsifiers or surfactants can also be employed in one embodiment of the invention.

The sustained-release profiles of drug can be obtained by using a mix of uncoated and semipermeable coated resonates and by selecting the degree of cross-linking and particle size of the resins without a coating process. Examples of ion exchange resins include simple resonates (i.e., uncoated drug-ion exchange resin complexes), microencapsulated or coated resonates (i.e., coated drug-ion exchange resin complexes), hollow fiber systems (i.e. hollow fibers with drug containing lumen), sigmoidal-release systems. Examples of such drugs are frusemide, cyclosporin, allopurinol and ciprofloxacin. See Mahore et al. Formulation of such drugs as resonates according to the present invention permits particle sizes that make such release characteristics (e.g., sigmoidal) feasible at reasonable coating weights.

Some embodiments of the present invention involve direct synthesis of oxybate resinate from one or more precursors. Using a hydroxide-form Type 1 strong base anion exchange resin, essentially 100% loading efficiency can be achieved with a simple aqueous reaction with GBL.

The ability to prepare an oxybate resinate, at high loading, in a one step process from GBL can be amenable to point-of-use synthesis (either in patient's hands or at clinical site), as it does not involve shipping or handling the regulated API (GHB). Such a direct synthesis can be carried out using a batch or equilibrium process as described herein, wherein a GBL loading solution is contacted with the particulate hydroxide-form strong base anion exchange resin. The GBL reacts in situ to form an ionic complex of oxybate with the ion-exchange resin, and releasing water as a by-product. It is possible to get 100% yield as well as 100% loading efficiency (i.e., oxybate ionically bound to 100% of the available binding sites) on the resin by such processes. For example, loading efficiencies higher than about 65% (e.g., 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or about 100%, including ranges therebetween, can be achieved). Because GBL is uncharged and the reaction does not produce ionic byproducts, there are no anions to compete for reaction on the site. Such conditions can achieve 100% reaction on the resin, so the hydroxide-form resin can be used safely, whereas in other applications this may not be possible for patient safety reasons because any unexchanged hydroxide would leave the resin as sodium hydroxide, raising the pH at site of delivery and potentially causing gut wall irritation.

The one-step process is also advantageous because it simplifies purification of the GHB resinate. Because the reaction occurs on the resin and not in the bulk solution, any byproducts that would be made are rinsed off the product. These include any of the impurities in the GBL starting material, as well as unreacted GBL.

Because of the unusually large molar amount of GHB in the compositions of the present invention, relative to the molar quantity of anion present in the gut, the present inventors have found that the compositions of the present invention can provide sustained release without the use of diffusion controlling coatings on the resinate particles. The present inventors have recognized that because the volume and anion content of gastric juice in the fasted state is lower than the molar dose of GHB required for treating the conditions described herein, the rate of GHB release is strongly influenced by the rate of physiological production of anions, and therefore suitable GHB release profiles can be provided without the use of diffusion controlling coatings. For example, while the resinate beads are retained in the stomach, the release of GHB from the resinate beads provided by ion exchange with gastric ions (mainly Cl^-) can be limited by the rate of stomach acid secretion. Similarly, as the resinate beads transit the duodenum and small intestine, the remaining dose of bound GHB can exceed local anion capacity. Thus, the rate of GHB release can be limited by the rate of secretion or diffusion of anions into the gut.

The basal anion capacity of the GI tract is quite small. As summarized in McConnell (Int J Pharm 2008, 364: 213-226, Table 1), fasted state basal values of bile salts are so low that they may be ignored. The fasted state chloride balances are 4.6 mEq in the stomach and 13.1 mEq in the small intestine. Compared to an oxybate dose of about 100 mEq, there is almost an order of magnitude deficiency in resident anion capacity for exchange. Such a situation would not occur with the vast majority of drugs having doses in the <1 mMol range.

	Stomach	Small intestine
Volume, mL	45	105
Chloride, mM	102	125
Total mEq	4.6	13.1

Therefore, the present inventors have discovered that the release of the ion-exchange resin-bound oxybate can be limited by secretions of anions in the GI tract, of which chloride is dominant. In the stomach, basal acid output (as chloride) is about 3 mEq/h in the fasted state. Even in the event that fed-state behavior is induced upon dosing, the fed state maximum secretion is only about 25 mEq/h. Therefore, the stomach cannot support full exchange at rates required to impart a meaningful duration of effect.

Chloride is actively secreted in jejunum, at a rate of about 4 mEq/h/30 cm under conditions where 120 mM chloride is already present. (Davis GR, et al, Active chloride secretion in the normal human jejunum, J Clin Invest 66:1326-1333 (1980)) This translates to a basal rate of about 32 mEq/h in absence of a chloride gradient. In presence of a gradient, the present inventors have found that the contribution of passive

diffusion can be sufficient, but may still provide a meaningful impediment to full and timely release of oxybate from the resin.

In the ileum, chloride secretions are substantially less, as characterized by Turnberg. (Turnberg LA et al, Interrelationships of chloride, bicarbonate, sodium, and hydrogen transport in human ileum, J. Clin Invest, 49: 557-567 (1970)). Most chloride secretion is associated with bicarbonate exchange when levels are high. One skilled in the art would appreciate that the perfusion studies by Turnberg indicate that chloride secretion in the ileum would almost certainly be insufficient to support the required exchange with GHB-resinate. For example, even in the extreme case where bicarbonate is almost 90 mM and chloride is only 40 mM, the chloride secretion—taking into account the whole length of ileum—would be expected to be at most 23 mEq/h. In the more typical case where bicarbonate is 40 mM, chloride is actually absorbed rather than secreted—even when chloride levels are set at 40 mM. Yet ileal fluid is maintained isotonic.

To further add to the limitations of biology, the reservoir of small intestinal fluid is small and not well distributed. Only about 10% of the physical volume of the small intestine is filled with fluid. The fluid is not continuously and evenly distributed, as reported by Schiller (Schiller C, et al, Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging, Aliment Pharmacol Ther 2005; 22:971-979) but rather the majority of fluid exists in about 4 fluid pockets that access a relatively small amount of available surface area. This is not very limiting for non-resinate dosage forms, as long as drug dissolution can occur, as once the drug is dissolved, it can access most of the surface area of the small intestine for absorption. A resinate, on the other hand, requires exchange with dissolved anions in order to provide release of the drug. As exchange occurs, oxybate is released to, and chloride is depleted from, the surrounding fluid. Further exchange is limited until oxybate is absorbed and chloride is replenished in the surrounding fluid—both processes that require fluid contact with intestinal surface. Therefore, if only 10% of the intestinal surface is physically available at any given time, the rate of chloride replenishment must be 10-fold higher to reliably compensate. One skilled in the art considering these unusual aspects would conclude that, in the face of insufficient resident anion capacity in the small intestine, a resinate dosage form would not release its drug completely and, furthermore, what release occurs may not be well-regulated.

Given the above observations, permeability and amount of film may require adjustment to achieve the intended release profile.

Optionally, the release of GHB can be tailored by changing the bead size and/or degree of crosslinking of the beads to provide additional resistance to diffusion. For example, larger resinate beads have a lower surface area/volume ratio than smaller resinate beads, and therefore would release GHB more slowly than the smaller beads in the presence of a solution of the same ionic strength. Similarly, the degree of crosslinking of the beads relates to the degree of swelling of the beads, which in turn is related to the rate at which ion exchange, and this drug release can occur. Specifically, more highly crosslinked beads swell less, and thus have slower ion exchange kinetics, compared to less highly crosslinked beads, Thus, the kinetics of drug release can also be controlled by manipulating the degree of crosslinking of the beads. Effects of particle size, particularly 100 microns or greater, and crosslinking, particularly 4% or greater, that may be modest under normal circumstances may be more impactful in the absence of a rate-controlling coating and when gut anion concentrations are substantially diminished.

If no diffusion controlling coating is required, other processing schemes for making the resinate can be considered to improve manufacturing flexibility. For example, instead of using ~100 micron beads, the drug (e.g., GHB or GBL) can be loaded onto larger beads (e.g., 600 micron beads), and then ground to the desired particle size, particle size distribution, consistency, etc. to select or control the desired release characteristics. This could be carried out in an aqueous suspension, so that no isolation or drying of the resinate would be needed. Moreover, if there is no need to coat the particles (e.g., with a diffusion for coating), the irregular shape or dispersity in size distribution of ground particles, which is normally a complicating factor for coating processes, is not an issue.

In other embodiments, the compositions of the present invention can provide differential displacement of drug (e.g. oxybate) from the resinate. Core/shell release characteristics in the resinate beads can be provided by (a) loading oxybate onto an ion exchange resin such that complete loading is achieved, then (b) coating the beads with a portion of lipophilic agent (i.e. lipophilic anion) having much higher selectivity for the ion-exchange resin than GHB. The lipophilic agent will deposit in the outer shell, at the first sites it contacts, and will be relatively immobile resulting in reversible blockage of the bead pores. Suitable lipophilic agents would be, for example, sulfate salts of medium or long-chain fatty acids, such as sodium lauryl sulfate (SLS), or sulfonic esters, such as dioctyl sulfosuccinate (docusate). Other suitable agents may include alkylbenzene sulfonates, 2-naphthalene sulfonate, phenol, salicylic acid, or any other species that may bind more strongly to the resin than oxybate. In particular embodiments, the lipophilic agents are those which are bulky or present hydrophobic tails that may further hinder diffusion of chloride into the resin pore, or oxybate out of the pore after exchange. Although many effective agents may, in other contexts present toxicity concerns, because such agents are strongly bound to the resin, exposure of the agent to the patient is limited. In one embodiment, the lipophilic agent acts as a diffusion barrier both by blocking pores and by facilitating pore blockage by other hydrophobic agents, for example those added during manufacturing, or which may be present in the patient's digestive tract after administration. For example, if sufficient amounts of a surfactant such as SLS is employed, then a non-ionic hydrophobic agent may be more effectively introduced into the bead pore volume due to its compatibility with the hydrophobic "tail" of the SLS molecule. This provides retarded initial release of the drug (e.g., GHB). In other embodiments, further heat treating of the resinate beads can reduce the variability of release, or further retard release. In other embodiments the compositions of the present invention can comprise more than one population of beads, in which one or more of the bead populations is treated with a lipophilic agent, a combination of a lipophilic agent and a hydrophobic agent, or heat treated to as to provide the desired release characteristics. For example, untreated beads would provide more immediate or faster release, and treated beads would provide delayed or slower release.

If further control of release is needed, in a further embodiment the present invention provides a novel method for preparing GHB-containing resinate beads coated with a diffusion rate controlling coating. This embodiment takes advantage of the driving force supplied by reaction of GBL on the active (hydroxide-bearing) sites of hydroxide-form

ion exchange resin beads, and the relatively high diffusion characteristics of the small and uncharged GBL molecule. Hydroxide-form ion-exchange resin beads (of any size) can be coated with a flexible film, such as PVAcetate, Eudragit RS, cellulose acetate 398, a mixture of Eudragit RS/RL or Eudragit NE, ethylcellulose, or an enteric such as Eudragit L100, L55 or FS100 with suitable plasticizer. The coated ion-exchange resin beads are then suspended in de-ionized water to equilibrate. GBL is introduced to the suspended beads, which then diffuses through the rate-controlling film, and reacts progressively with the OH-bearing sites within the resin. Sufficient batch equilibration time is provided to ensure complete reaction. The excess GBL is washed off, and the resulting wet resinate beads have a sustained release coating over GHB resinate, which were formed without starting with GHB resinate. This process may be useful for point-of-use preparation, or can improve the utilization of GBL in preparing the product: no GHB or GBL is lost due to processing during coating, as no GBL is present during the coating process.

In one embodiment of the present invention, the present formulation is administered to a patient once nightly. The patient is administered between 4 g and 10 g GHB/day, or 6 g and 9 g/day. Any of the compositions described herein can be used to provide retarded or delayed release of GHB. For example, the GHB resinate beads may be presented in hydrated form as part of an aqueous suspension, or may be provided as dried beads for mixing with water immediately prior to ingestion or to be taken without water (e.g., as a powder, tablet, capsule etc.). As discussed herein, Type 1 strong base anion exchange resins swell in the presence of water, to an extent that depends on the degree of crosslinking and the nature of the anion bound to it. In the dried state, the sustained release resinate beads of the present invention can hydrate more slowly if release-retarding agents are used. As the beads hydrate, the diffusion of physiologically produced anions of the gastrointestinal tract (e.g. mainly chloride) into the beads can accelerate, thus producing a delayed or gradually increasing rate of release of oxybate.

In another embodiment, a water permeable but relatively insoluble coating is employed over the dry resinate beads such that, when the dry beads are suspended in water, water diffuses through the coating to hydrate and swell the resinate beads. The resulting expansion of the beads causes the coating to rupture, and allow release of the GHB. Suitable polymers for preparing such coatings include one or more of cellulosics such as ethyl cellulose, cellulose acetate, cellulose phthalate; polyvinyl acetate, acrylic polymers and copolymers such as those available under the Eudragit® trade name (e.g., Eudragit® NE30D, RL, and RS resins). Such coatings can be plasticized or unplasticized, and coated onto the beads using methods well-known in the art (pan coating, fluidized bed coating, etc.).

As discussed herein, the dose of GHB required for treating excessive daytime sleepiness and cataplexy in patients with narcolepsy is quite high, resulting in the administration not only of relatively large masses of GHB composition, but also water required for administration (particularly when the GHB composition is aqueous). However, since oxybate is administered at night, administering large quantities of water can cause bed-wetting. Accordingly, if administered as an aqueous suspension, the highest practical solids loading is desired. The factors which affect the solids loading (volume fraction) of the suspension include the medium used for dilution (water vs. alcohol) and its viscosity, the degree of swelling of the resinate, the sphericity and uniformity of the beads, and surface charge. See Seno and Yamabe, The Rheological Behavior of Suspensions of Ion-Exchange Resin Particles, Bulletin of the Chemical Society of Japan Vol 39, 776-778 (1966), herein incorporated by reference in its entirety for all purposes. In various embodiments, the compositions of the present invention can be administered as suspended resinate particles in a gel, suitable for ingestion by squeezing from a pouch. In other embodiments, the compositions of the present invention can be dosed in two stages: an initial loading dose followed by a chasing dose. Both the loading and chasing dose comprise suspended beads, but the chasing dose is less concentrated. In still other embodiments, the GHB resinate beads can be administered dry, e.g. by having the patient suck the dry beads through a tube or straw. In such embodiments, an added glidant, which is an excipient used in the art to facilitate powder flow by reducing interparticle friction and cohesion, can be used to facilitate administration. They are used in combination with lubricants as they have no ability to reduce die wall friction. Non-limiting examples include fumed silica, talc, and magnesium carbonate.

The oxybate resinate compositions of the present invention can include an immediate release and an extended release component of oxybate. Such compositions can include, for example, a combination of a population of uncoated resinate beads and a population of resinate beads with a diffusion rate controlling coating as described herein; a single resinate bead population that provides immediate release by ion exchange with physiological anions (e.g. chloride), followed by extended release of oxybate controlled by physiological production of e.g. chloride; combinations of populations of resinate beads having different particle sizes and/or crosslinking densities to control release; or any combination of immediate release and extended release resinate beads disclosed herein.

In one embodiment, the compositions of the present invention may be an immediate-release alternative to Xyrem®. Xyrem® has a steep dose-response curve, and inadvertently taking two doses at the same time would have an adverse effect on the patient. If sodium oxybate is instead provided in resinate form for immediate release, as described herein, the capacity of the stomach and small intestine to provide exchangeable anion would limit the consequences of an inadvertent overdose. A 4.5 g dose of Xyrem is 35.7 mEq oxybate. If the stomach has about 5 mEq chloride, then about 30 mEq of additional exchangeable anion must be provided with the resinate formulation of the present invention to ensure complete release of oxybate. This can be achieved by inclusion of exchangeable anion in the formulation, for example glycine or other amino acids, chloride, or in particular citrate. This embodiment would enable rapid release of the oxybate by providing supplementing exchangeable anions in the stomach.

In another embodiment, the supplemental anions are provided by digestion of proteins administered with or as part of the formulation. The resulting amino acids are then available for exchange with the resin and can provide a more convenient means of providing a large amount of supplemental anion.

In yet another embodiment, the supplemental anions are provided by digestion of a triglyceride administered with the formulation. When the triglyceride empties into the small intestine, lipolysis will generate anions available for exchange. In general, triglycerides of short-chain fatty acids (such as triacetin or tributyrin) can provide better oxybate release than medium- or long-chain triglycerides, because the binding affinity of the resulting anions are higher due to their pKa and size. Triglycerides with at least one short-

chain fatty acid component are also suitable, particularly pharmaceutically acceptable short-chain triglycerides such as triacetin.

If the resinate particles are film-coated, then supplemental anions can be provided as separate coated particles, such that the supplemental anion is available when needed. The supplemental anion can be selected such that it is not absorbed rapidly yet has an affinity for the resinate that is much higher than that of oxybate. It can be particularly useful to target or enhance release of the supplemental anion in the ileum where chloride secretory deficit may be most pronounced, since absorption of organic acids might be considerably less in that location. Citric acid, glycine, and mesalazine (5-aminosalicylic acid) are examples of suitable supplemental anions. A non-limiting list of other suitable anions (or conjugate acids) includes pharmaceutically acceptable salts selected from the group consisting of chlorides, acetates, lactates, bicarbonates, sulfates, citrates, tartrates, malates, maleates, malonates, glutarates, succinates, fumarates, aspartates, glutamates, and combinations thereof.

These supplemental anions can be coadministered with the oxybate compositions of the present invention, for example within about an hour (before or after) of administering the drug resinate (e.g., oxybate resinate) compositions of the present invention, or simultaneously therewith. The amount of such supplemental anions can range from about 20 to about 200 mmoles, including about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, about 110, about 115, about 120, about 125, about 130, about 135, about 140, about 145, about 150, about 155, about 160, about 165, about 170, about 175, about 180, about 185, about 190, about 195, or about 200 mmoles, inclusive of all values and ranges therebetween. The supplemental anions can themselves be capable of anion exchange directly upon contact with the drug resinate (e.g., exchanging with the oxybate of the oxybate resinate), or can be "pro-anions"—that is, form anions upon biotransformation after administration to the patient. Non-limiting examples of such "pro-anions" are those described herein, such as triglycerides or proteins. The amount of such "pro-anions" suitable for use in treating patients according to the present invention are amounts that produce between about 20 and about 200 mmoles of anions, as described hereinabove.

If sustained release is desired, then extending gastric emptying can somewhat compensate for deficiencies in the jejunum and, particularly, the ileum. Reliably extending gastric emptying in the fasted state is very challenging. Although some investigators have found that administration of resinate particles can result in mucoadhesion, the unusually high molar doses of GHB of the resinate compositions of the present invention, approximately 100 mEq, will effectively cover the entire surface of the stomach many times over. Thus, observations made with conventional resinate formulations would not apply to GHB resonates. Therefore, a more effective means of promoting gastric retention would be administration of the compositions of the present invention with food or caloric liquid.

The oxybate compositions of the present invention, for example oxybate resinate compositions, provide therapeutically effective levels of oxybate over a period of at least about 3 to about 8 hours. In some embodiments, the composition can be considered to comprise a single population of resinate beads, wherein at least a portion of the resinate beads releases the oxybate quickly upon administration (essentially upon contacting physiologically produced anions such as chloride), and a remaining portion of the resinate beads releases oxybate more slowly, either controlled by the physiological rate of production of anions such as chloride, or by modification of the release characteristics of the resinate beads themselves (e.g., by providing a diffusion controlling coating, by control of bead diameter, or crosslinking density, or other method as described herein). If the compositions of the present invention comprise two or more distinct bead populations (distinguished by their oxybate release characteristics), the rapid (or immediate) release population provides therapeutically effective levels of oxybate for up to about 3 hours (including 1 or 2 hours) after administration, and the other population(s) provide therapeutically effective levels of oxybate for about 3 to about 8 hours (including 3, 4, 5, 6, 7, or 8 hours) after administration.

Xyrem for its approved indications is effective at between 6 g and 9 g administered twice nightly in equal amounts about 4 hours apart. A sustained release equivalent may require a matching AUC as compared to 9 g Xyrem. As disclosed in US2012076865, the overall relative bioavailability of an appropriately-timed sustained release would have at most about 75% relative to Xyrem. Therefore, about 12-13 grams of sodium oxybate would be required, or about 100 mMols.

Suitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L, maintained over a period of about 5-8 hours as described herein. For example suitable blood levels of oxybate can be about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 mg/L, inclusive of all ranges therebetween.

The following examples are included to demonstrate particular embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute particularly suitable modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

All documents cited herein, including patents, patent publications, and non-patent publications are herein incorporated by reference in their entirety for all purposes.

EXAMPLES

Example 1

A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200 mesh was loaded with GHB as follows. Calcium oxybate was loaded onto resin in a batch equilibration by combining 10 mL of 4 M calcium oxybate solution (approximately 490 mg/mL), 31.7 mL of de-ionized water, and 20.27 g of Dowex 1X2 wet resin as chloride form with 2% crosslinking. After mixing for 2 hours, the resin was filtered under mild vacuum using a Buchner funnel. It was then washed with 700 mL of de-ionized water in approximately 100-150 mL aliquots to remove any free oxybate. The wet beads were then dried in a 60° C. oven for 3.5 hours, and finally sized through a 36-mesh screen. The resinate beads were assayed by suspending 1.5 g of resinate in 12.5 g of 1 M calcium chloride and allowing them to equilibrate overnight at room tem-

perature. The solution was analyzed by HPLC, and the measured oxybate released from the beads was 1.09 mEq per gram of dry resinate. The calculated loading efficiency was 1.14 mEq/gram dry resin, or 33% of the theoretical exchange capacity of the resin.

Example 2

GHB resinate beads were prepared by contacting GBL with another Type 1 strong base anion exchange resin (Amberlite IRN78, Dow Chemical) having a median particle size of about 0.63 mm, as the hydroxide form with 8% crosslinking. Batch B1 was prepared with a 2:1 molar ratio of GBL to hydroxide-bearing sites by suspending 26.78 g of wet resin in 41.2 g of de-ionized water. While stirring, 8.28 g of GBL was added, and the reaction was monitored by HPLC analysis of unreacted GBL. The reaction was largely complete after 30 minutes. After 90 minutes, the resin was filtered under mild vacuum, rinsed with de-ionized water to remove unreacted GBL, and then placed in a 60° C. oven overnight to dry.

Batch B2 was prepared by reacting GBL in only 16% molar excess over hydroxide-bearing sites on the same resin. 2.6 g of GBL was added to 20 g of wet resin (as supplied) while stirring by hand with a spatula. About 5.3 g of additional water was added to facilitate blending. After about 1 hour, the mass was placed in the 60° C. oven overnight to complete the reaction, if necessary. The beads were then rinsed with de-ionized water (70 mL), filtered under mild vacuum, and transferred to the 60° C. oven for drying over 3 days. The two batches were analyzed for oxybate content by first suspending 1.0 g of resinate in 20 mL of 2 M NaCl for 2 hours with stirring. 10 mL of the resulting solution was then titrated with 1 N HCl and the results were compared with a blank of 10 mL of 2 N NaCl. The initial pH values of B1 and B2 were 7.0 and 8.3, respectively, thus indicating that very little, if any, unreacted hydroxide was present in the resinate product. The oxybate titration indicated that GHB loadings of 4.2 and 4.3 mEq/g dry resin for B1 and B2, respectively. The result further indicates that complete reaction occurred, as the theoretical capacity of the resin is approximately 4 mEq/g.

Example 3

A larger batch of GHB resinate beads are prepared by reacting GBL with Amberlite IRN78 under conditions represented by Batch B2. GBL (36.9 g) is slowly added to a slurry of wet resin (Amberlite IRN78, 279 g) and water (about 200 g). The reaction is allowed to proceed for at least 1 hour at room temperature, with stirring. The product is vacuum filtered, then rinsed with several volumes of de-ionized water. The wet product is then placed in a 40° C. oven to dry overnight. 2.1 g of dried GHB resinate beads are then administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage. Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content.

Example 4

Amberlite IRN78, a hydroxide form Type 1 anion exchange resin, is charged to a vessel and contacted with a 1M solution of sodium oxybate in a 2:1 stoichiometry to resin equivalents. After about 2 hours of equilibration, the mixture of sodium oxybate and sodium hydroxide is filtered from the resulting resinate. A sample of the solution is titrated to determine sodium hydroxide content, and then an equivalent amount of calcium oxybate is charged to the solution to precipitate calcium hydroxide. The calcium hydroxide is filtered from the solution of sodium oxybate, and the recovered sodium oxybate solution is returned to the equilibration tank and contacted with the wet resinate for 2 hours. The resinate is then filtered, and filtrate is recovered. The recovered filtrate is processed with calcium oxybate as in the first step, and set aside for future use. The resinate product is washed with several volumes of de-ionized water, and then dried.

Example 5

Cholestyramine (chloride form) is charged to a vessel and contacted with 1M sodium bicarbonate in a 2:1 stoichiometry (bicarbonate to resin). Five cycles of batch equilibration (2 h each) are conducted. The solutions in each cycle are not recycled, and resinate is rinsed with 2 volumes of de-ionized water between each cycle.

The wet, bicarbonate-exchanged resin is then contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Separately, the GHB-resinate is then washed with several volumes of de-ionized water. A sample of the first filtrate is titrated for bicarbonate content, and then a stoichiometric amount of calcium oxybate is added to the batch filtrate. The precipitated calcium carbonate is removed by filtration of the suspension, and the sodium oxybate solution is recovered and stored for future use.

Example 6

The above examples can involve difficult separation steps, as precipitated calcium carbonate is a thick slurry of fine particles at the concentrations used. In this example, filtration is avoided by use of a reaction in which the byproduct forms carbon dioxide rather than a precipitate.

The wet, bicarbonate-exchanged resin of Example 5 is contacted with 1M sodium oxybate in a single equilibration step in a 2:1 molar ratio of oxybate to resin. After 2 h, the resinate is filtered, and filtrate collected. Oxybate is recovered and bicarbonate is removed from the filtrate by addition of a stoichiometric amount of sodium hydroxide such that the bicarbonate is converted to carbonate by the reaction: $NaOH+NaHCO_3 \rightarrow Na_2CO_3+H_2O$. The pH drives this reaction to completion.

Next, GBL is added at a 1:1 stoichiometry. Sodium carbonate reacts with the GBL with the evolution of carbon dioxide gas, which drives the reaction to completion: $2\ GBL+Na_2CO_3+H_2O \rightarrow 2\ Na\text{-}GHB+CO_2(g)$. Optionally, a small excess of sodium hydroxide can be added to avoid conversion to bicarbonate during the reaction. This overall process avoids the filtration of carbonate, recovers all the sodium as unexchanged sodium oxybate, and replaces the exchanged sodium oxybate with new oxybate derived from GBL.

Example 7

Soy protein isolate is compressed into oblong or oval tablets of approximately 1000 mg, using compression aids such as fillers, microcrystalline cellulose, and lubricants as required. The tablets are enteric coated separately with two different polymers to achieve dissolution and release of the soy protein isolate in the jejunum and ileum. One batch is

coated with Eudragit L30D-55 (jejunum-targeted), and the other is coated with Eudragit L100 (ileum-targeted). At least two of each kind of tablets are taken with one dose of GHB-resinate (35.7 mEq of resinate equivalent to 4.5 g oxybate) in a glass of water. This provides at least 36 mEq of amino acid content, as the protein is hydrolyzed. By releasing the protein in the small intestine rather than stomach, complete and rapid digestion is avoided. Instead, the protein is digested to amino acids more gradually as it transits the small intestine and as the tablet disintegrates. The amino acids are therefore available to facilitate exchange of the GHB-resinate taken concomitantly.

We claim:

1. A formulation of gamma-hydroxybutyrate comprising:

a plurality of immediate release particles comprising gamma-hydroxybutyrate;

a plurality of modified release particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

2. The formulation of claim **1**, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

3. The formulation of claim **1**, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

4. The formulation of claim **1**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

5. The formulation of claim **4**, wherein the lubricant is magnesium stearate.

6. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate.

7. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium gamma-hydroxybutyrate.

8. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate.

9. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate.

10. The formulation of claim **1**, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate.

11. The formulation of claim **1**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL.

12. The formulation of claim **1**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

13. The formulation of claim **1**, wherein the formulation is a multiparticulate composition.

14. A unit dose comprising a formulation of gamma-hydroxybutyrate,

wherein the formulation comprises:

a plurality of immediate release particles comprising gamma-hydroxybutyrate;

a plurality of modified release particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

15. The unit dose of claim **14**, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

16. The unit dose of claim **14**, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

17. The unit dose of claim **14**, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

18. The unit dose of claim **17**, wherein the lubricant is magnesium stearate.

19. The unit dose of claim **14**, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

20. The unit dose of claim **14**, wherein the unit dose comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate.

21. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate.

22. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate.

23. The unit dose of claim **14**, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate.

24. The unit dose of claim **14**, wherein the unit dose is a sachet.

* * * * *

EXHIBIT 28

UNITED STATES PATENT AND TRADEMARK OFFICE

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EXAMINER	
ZHANG, YANZHI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/24/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 17/118,041	Applicant(s) ALLPHIN et al.	
	Examiner YANZHI ZHANG	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 12/10/20.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-27 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-27 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

This action is a response to papers filed on December. 10, 2020. Claims 1-27 are pending in the application and under consideration on the merit.

Priority

Applicant states t(0001 of the specification) hat this application is a continuation of U.S. Application Ser. No. 16/448,598, filed June 21, 2019, which is a continuation of U.S. Application Ser. No. 15/047,586, filed February 18, 2016, now U.S. Patent No. 10,398,662, which claims priority to U.S. Provisional Application Ser. No. 62/117,889 (prov' 889), filed February 18, 2015, the disclosures of which are herein incorporated by reference in their entireties.

However, there is no support for the claimed subject matter in prov' 889. Key word "sachet" is not found. There are two paragraphs (shown below) related to "mixing".

(0053) … as dried beads for mixing with water immediately prior to ingestion or to be taken without water.

(0055) A gel-type Type 1 strong base anion exchange resin, Dowex 1X2 (Dow Chemical), 100-200mesh was loaded with GHB as follows.

Unfortunately, these two paragraphs have nothing to do with mixing the formulation with water as claimed.

Support for the limitation of "opening a sachet containing an oxybate formulation, mixing the formulation with water" implied in paragraph (0023), particularly, on top of page 9.

Part of the sentence on page 9 is reproduced below for clarity.

> particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user), using simply, readily controlled processing methods.

Therefore, the earliest priority for the claimed subject matter is the effective filing date of 02/18/2016.

Information Disclosure Statement

The Information Disclosure Statements filed 12/021/20 are in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements in English are fully considered by the examiner. The foreign language references, are only considered to the extent where an English translation available or examiner understands that language. A signed copy of form 1449 is enclosed herewith.

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 5-7, 10-12, 14-16, 19-21, and 23-25 are rejected under 35 U.S.C. 103 as obvious over Alshaikh et al ("Alshaikh", non-patent literature, Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012) in view of Oliver Luhn (non-patent literature, Pharmaceutical Technology Europe, Volume 23, Issue 1, published January 7, 2011) and online article written by unknown author; published by Neonatal and Paediatric Pharmacists Group ("NPPG", title: Oral rehydration salts published July 25, 2013).

Claims 1-27 embrace a method of treating a disease or condition or narcolepsy or cataplexy in a patient in need thereof the method comprising administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises: opening a sachet containing an oxybate formulation, mixing the formulation with water, and orally administering the mixture to the patient.

In addition, claims 1, 10, and 19 use the open-ended transitional phrase "comprising". Thus, they allow for the presence of additional unrecited steps or components.

Alshaikh is directed to **sodium oxybate** for n**arcolepsy with cataplexy**: systematic review and meta-analysis (title). Alshaikh indicates that the study objectives are to assess the efficacy and safety of sodium oxybate (SXB) in narcolepsy-cataplexy patients (abstract on page 451, read on the limitation of genus disease and condition in the instant claim 1 and the limitation of narcolepsy in the instant claim 10). Narcolepsy is a sleep disorder characterized by excessive daytime sleeping (EDS) associated with irresistible attacks of sleep, sudden loss of muscle tone (cataplexy), disrupted nocturnal sleep, hypnagogic/hypnopompic hallucinations, and sleep paralysis. Alshaikh teaches that SXB was recently approved by the FDA to treat patients diagnosed with narcolepsy and symptoms of cataplexy. Alshaikh also teaches that the trial arms uses sodium **oxybate dose** in various amounts, ranging from 3 grams to 9 grams or 5**0-60 mg/kg/night** (Table 1 on page 453, implying the limitation of the instant claims 2, 11, and 20). Alshaikh teaches that SXB in all trials resulted in significant reduction in cataplexy attacks and EDS (the 2nd para. of right-hand column under discussion on page 457) and the beneficial effect on cataplexy and daytime sleepiness persisted for four patients during the follow-up period (the 3rd para. of right-hand column under discussion on page 457). As to oral administration, there are at least three references in the references section titled f orally administered sodium oxybate, 23, 29, and 30, respectively. Thus, the limitation of orally administering in claim 1 and 10 are met.

While teaching sodium oxybate for narcolepsy, Alshaikh doesn't expressly teach the sachet dosage form and method of steps of using it. These deficiencies are cured by Luhn and NPPG, respectively.

Luhn is directed to using excipients in powder formulations (title). Luhn teaches that orally disintegration tablets (ODTs) have become very popular and are the starting point into a generation of drug products where patient friendliness is the decisive criteria to gain share in a saturated market environment; however, **sachets** can be faster and easier compared with ODTs (2nd para. on page 1/3 of the attached PDF, read on the limitation of sachet in the instant claims 1 and 10). Luhn also teaches that sachets may also beneficial when looking at compliance issues within geriatric patient groups. Direct oral applications mean you don't need water to dissolve the powder or swallow the tablet. Sachets also do not look like a pill —— it's important not to underestimate the psychological effects associated with a dosage form (bridging para. of pages 1-2/3 of the attached PDF).

NPPG teaches that an oral rehydration salts in the form of **powder** in a sachet Middle of page 2/6). NPPG also teaches that **open the sachet** and pour the contents into 200 mL of tap **water** (read on the limitation of the instant claim 7). Stir well until all the powder has gone and the mixture is clear (solution) or just slightly cloudy (a **suspension**). Make sure your child drinks the full dose needed (Under the heading: How should I give it on page 2/6, read on the limitation of the instant claims 3, 12, and 21) and the limitations of suspension in the instant claims 7, 16, and 25).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose sachet form of sodium oxybate as taught by Luhn as the particular dose form to be incorporated into the method of Alshaikh to take advantage of sachet being faster and easier. One of ordinary skill in the art, as of the effective filing date of the claimed invention, would choose the method of administering sachet form of sodium oxybate as taught by NPPG. One of ordinary skill in the art, as of the effective filing date of the claimed invention,

would choose the combination of sachet dose form and the method of administering the powder in a sachet as taught by NPPG because all of the particular options identified by Luhn and NPPG are predictable solutions to the problem of giving medication in sachet formulation, and the person of ordinary skill in the art would have a reasonable expectation to be of success in choosing any of those options. See MPEP 2143, part (I)(E).

Regarding the amount of oxybate in the instant claims 1, 6, 10, 15, 19, and 24, the principal of law is "[Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). This rule is limited to cases in which the optimized variable is a "result-effective variable." In re Antonie, 559 F.2d 618, 620 (CCPA 1977). In this case, Alshaikh have taught various amount depending on the formulations. Thus, finding the optimum or workable ranges by routine experimentation is *prima facie* obvious.

Regarding the administering promotes the patient to sleep for 6 to 8 hours in claims 5, 14, and 23, it is believed the duration of sleep depends on the dose given, the severity of the condition, age and gender. It would have been obvious to for a physician to adjust the dose accordingly to achieve the desired sleeping duration.

Claims 4, 13, and 22 are rejected under 35 U.S.C. 103 as obvious over Alshaikh et al ("Alshaikh", non-patent literature, Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012) in view of Oliver Luhn (non-patent literature, Pharmaceutical Technology Europe, Volume 23, Issue 1, published January 7, 2011) and online article written by unknown author; published by Neonatal and Paediatric Pharmacists Group ("NPPG", title: Oral rehydration salts published July 25, 2013) as applied to claims 1-3, 5-7, 10-12, 14-16, 19-21,

and 23-25 in further view of Borgen et al ("Borgen", Journal of Clinical Pharmacology, 2003; vol. 43, pp. 59-65).

The teachings of Alshaikh, Luhn and NPPG have been discussed as applied to claims 1-3, 5-7, 10-12, 14-16, 19-21, and 23-25. Alshaikh, Luhn and NPPG do not expressly teach the oral composition is administered with food. The deficiency is cured by Borgen.

Borgen is directed to The Influence of Gender and Food on the Pharmacokinetics of Sodium Oxybate Oral Solution in Healthy Subjects (title). Borgen teaches that food significantly altered the bioavailability of oxybate by decreasing mean peak plasma concentration, increasing median time-to-peak concentration, and decreasing the area under the plasma concentration-time curve. Food did not affect elimination and urinary excretion of unchanged drug (abstract, read on the limitation of the instant claims 4, 13, and 22). Borgen also teaches that mean AUC_0 values were likewise significantly higher in the fasted versus fed state ($p < 0.05$). The median t_{max} of 2.00 hours in the fed state is significantly later than the median tmax of 0.75 hours in the fasted state ($p = 0.0001$).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose administering sodium oxybate with food as taught by Borgen as the particular means to give patient the drug to take advantage of the delayed t_{max} to achieve night time sleep. The person of ordinary skill in the art would have a reasonable expectation to be of success in choosing any of those options with food or without food. See MPEP 2143, part (I) (E).

Claims 8-9, 17-18, and 26-27 are rejected under 35 U.S.C. 103 as obvious over Alshaikh et al ("Alshaikh", non-patent literature, Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012) in view of Oliver Luhn (non-patent literature, Pharmaceutical Technology

Europe, Volume 23, Issue 1, published January 7, 2011) and online article written by unknown author; published by Neonatal and Paediatric Pharmacists Group ("NPPG", title: Oral rehydration salts published July 25, 2013) as applied to claims 1-3, 5-7, 10-12, 14-16, 19-21, and 23-25 in further view of Allphin et al ("Allphin", US 8591922 B1, issued November 26, 2013).

The teachings of Alshaikh, Luhn and NPPG have been discussed as applied to claims 1-3, 5-7, 10-12, 14-16, 19-21, and 23-25. Alshaikh, Luhn and NPPG do not expressly teach the oral composition is administered with food nor the oral composition comprising an acid. These deficiencies are cured by Allphin.

Allphin is directed **gamma-hydroxybutyrate** (GHB) compositions and their use for the treatment of disorders (title). Allphin teaches that pharmaceutical compositions and formulations comprising mixed salts of GHB and **methods** of their use for the treatment of sleep disorders such as apnea, sleep time disturbances, narcolepsy, cataplexy, sleep paralysis, etc. (abstract, read on the claimed disease or conditions). Allphin also teaches that the chemical stability of GHB is affected by pH (col. 17, lines 10-11) and the pH adjusting or buffering agent is selected from the group consisting of malic acid, **citric acid**, acetic acid, boric acid, lactic acid, hydrochloric acid, phosphoric acid, sulfuric acid, sulfonic acid, and nitric acid. In certain embodiments, the pH adjusting or buffering agent is **malic acid** (col. 17, lines 45-50, read on the limitations of the instant claims 8-9, 17-18, and 26-27).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose using an acid (e.g. malic acid) as taught by Sun as the particular buffering agent to be incorporated into the method of Alshaikh. The person of ordinary skill in the art would be motivated to do so because Allphin recognizes the importance of pH to stabilize

GBH. Thus, one would have a reasonable expectation to be of success in choosing any of those acid taught by Allphin to resolve stability issue of GBH-containing formulations. See MPEP 2143, part (I)(A) or (E).

Relevant Art

Khediri, et al is provided, but not cited, to show the state of powder dosage formulation art at the time when the invention was filed.

Title: Efficacy of Diosmectite (Smecta) in the Treatment of Acute Watery Diarrhea in Adults: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study.

Hindawi Publishing Corporation; Gastroenterology Research and Practice Volume 2011, page 1-8.

CONCLUSION

No claim is allowed.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YANZHI ZHANG whose telephone number is (571)272-3117. The examiner can normally be reached on Monday-Friday 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is

encouraged to use the USPTO Automated Interview Request (AIR) at

http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 5712720646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YANZHI ZHANG/
Primary Examiner, Art Unit 1617

EXHIBIT 29

Applicant-Initiated Interview Summary	**Application No.** 17/118,041	**Applicant(s)** ALLPHIN et al.		
	Examiner YANZHI ZHANG	**Art Unit** 1617	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
YANZHI ZHANG	Primary Examiner	WebEx/Video Conference
Phil McGarrigle	Attorney of Record	
Clark Allphin	Inventor	
Jason Valentine	Attorney of Record	

Date of Interview: 26 April 2021

Issues Discussed:

35 U.S.C. 103

The discussion was focused on claim 1 after the slides (see attached) were presented. Applicant argued that one would not motivated to make a sachet dosage due to the hygroscopic nature of the drug, oxybate.

As set forth in the rejection of record, powder formulations including sachet was known to be powder formulations.

Claim language was discussed. But, no agreement was reached.

☑ Attachment

/YANZHI ZHANG/ Primary Examiner, Art Unit 1617	04/26/21

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Cooley

U.S. Patent Application No. 17/118,041

April 26, 2021

Privileged and Confidential

Agenda

- Introduction
- Oxybate background
- Presently claimed subject matter
- Obviousness Rejection/Applicant's Response

Portfolio

- Jazz patent portfolio goes back to 1999
- Relates to composition of matter, methods of use, drug distribution, DDI, formulations, etc.

Introduction

- Xyrem-Sodium GHB
- Xywav-mixed salt GHB
- Extended release GHB

Oxybate Background

- Physical form challenge: Oxybate salts are hygroscopic so it is challenging to formulate in solid dosage forms
- Formulation and unit dose challenge;
  - Existing formulations require dosing multiple times per day
  - Existing formulations are liquid and require patient to store unused portion for later administration. Liquid not amenable to simplified unit dosing.
  - Patients presently have (and use) the flexibility of adjusting the amount administered in each dosing.
- Present invention: Sachet containing a solid, once nightly unit dose product provides convenience, compliance and safety.

Claim 1

1. A method of treating a disease or condition treatable with oxybate in a patient in need thereof, the method comprising:

administering a **single daily dose** to the patient, the **single daily dose** comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:

opening a sachet containing an oxybate formulation,

mixing the formulation with water, and

orally administering the mixture to the patient.

Obviousness Rejection

- **Obviousness Rejection**:
  - Claims allegedly obvious over *Alshaikh* and *Luhn*
- **Examiner's position**:
  - From *Alshaikh*, POSITA would select claim-recited oxybate dose to treat narcolepsy
  - From *Luhn,* POSITA would understand that sachets have advantages compared to orally distintegrating tablets
  - POSITA would incorporate *Alshaikh*'s oxybate in *Luhn*'s sachet formulations because doing so is allegedly a predictable solution to the problem of administering a sachet formulation.

Explanation of Invention/ Applicant's Rebuttal

- Claimed Invention:
  - Administering a solid oral dosage form (sachet)
  - Administering a single daily dose
- No Motivation to Prepare Sachet Formulations:
  - Common oxybate salts known to be deliquescent solid
  - Existing dosage forms are oral solutions (not amenable to unit dosing)
  - Prior art does not identify ODTs as oxybate dosage form (*i.e.*, no analogy to *Luhn*'s teaching)
- All Claim Elements Not Addressed:
  - Single Daily Dose is not present or suggested by cited art, which uses multiple daily dosing
  - Examiner has not addressed this claim element

Thank you!

- Thank you for your time, Examiner Zhang.

EXHIBIT 30

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	CLARK ALLPHIN, et al.	Confirmation No.:	6759
Serial No.:	17/118,041	Group Art Unit:	1617
Filed:	December 10, 2020	Examiner:	ZHANG, YANZHI C

FOR: **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

DECLARATION OF CLARK ALLPHIN UNDER 37 C.F.R. §1.132

1. I am an inventor of the above-identified application, and I am currently employed by Jazz Pharmaceuticals, Inc. as the Executive Director of Process and Product Science, New Product and Technology Integration. I have twenty-five years of development experience in the field of pharmaceutical formulations.[1] I received a Bachelor of Science degree in Chemical Engineering from the University of California, Berkeley.

2. I am familiar with the above-identified application and reviewed the Office Action dated February 24, 2021, the references cited therein and the Applicant Initiated Interview Summary dated April 30, 2021.

3. It is my understanding that the Examiner believes the presently claimed methods are obvious over Alshaikh et al, Journal of Clinical Sleep Medicine, Vol. 8, No. 4, 2012 ("*Alshaikh*"); Luhn, O., Pharmaceutical Technology Europe, Volume 23, Issue 1, January 7, 2011 ("*Luhn*"); Oral rehydration salts, Neonatal and Pediatric Pharmacists Group, July 25, 2013 ("*NPPG*"); Borgen et al, Journal of Clinical Pharmacology, 2003; vol. 43, pp. 59-65 ("*Borgen*"); and U.S. Patent No. 8,591,922 B1 ("*Allphin*"). I respectfully disagree with the Examiner's conclusion.

[1] I have 35 years' experience as chemical engineer, 25 years in the pharmaceutical industry starting in oral product formulation for sustained release products.

4. As background to the claimed invention, oxybate's physical and pharmacokinetic characteristics present unique challenges when developing oxybate formulations and effective oxybate dosing regimens. Oxybate salts are known to be hygroscopic, *i.e.*, the monovalent salts readily and rapidly absorb moisture from the surrounding atmosphere, and in fact some of them deliquesce. Furthermore, oxybate is rapidly cleared from a patient's bloodstream after administration (i.e., oxybate has a short *in vivo* half-life) so multiple daily administrations are required to maintain therapeutically effective oxybate blood concentrations.[2]

5. In fact, when the present application was filed in 2015, the only FDA-approved oxybate-containing drug product was Xyrem®. Xyrem® was approved in 2002 to treat cataplexy and excessive daytime sleepiness in narcolepsy patients.[3] Xyrem® is a liquid, oral solution of sodium oxybate, and the product label instructions require twice-a-night administration for therapeutic effectiveness.

6. With this background, I do not think a skilled artisan would have considered the claimed methods to be obvious over the cited references. The presently-claimed inventions are directed to methods of treating oxybate-treatable conditions[4] by administering to a patient a single daily dose of a solid oxybate formulation that is dispensed from a sachet packaging and mixed with water prior to administration.

7. No cited reference describes or suggests administering a solid oxybate formulation in a sachet dosage form let alone according to a once-a-day administration schedule. *Alshaikh*, which I understand is the primary reference cited by the Examiner, merely summarizes clinical studies that were conducted using liquid oxybate formulations and where the oxybate was dosed twice-a-day. *Alshaikh* does not suggest using a sachet dosage form and, in fact, does not even describe the liquid formulations that were tested in the summarized clinical studies.

8. *Luhn* does not relate to oxybate at all. Instead, *Luhn* generally asserts that pharmaceutical sachets may be useful in certain circumstances, such as when existing dosage forms have poor

---

[2] Specification at paragraph (013)
[3] Specification at paragraph (003).
[4] Claim 10 is directed to the treatment of narcolepsy. Claim 19 is directed to the treatment of cataplexy or excessive daytime sleepiness associate with narcolepsy. Like claim 1, claims 10 and 19 require a solid dosage form (i.e., solid oxybate formulation packaged in a sachet) and effectively treat the conditions using a single daily oxybate dose.

patient compliance. Since the cited art does not teach any such issues with the existing liquid oxybate formulations, I do not consider *Luhn* to be particularly relevant to the specific challenges faced when developing an oxybate formulation. Furthermore, according to *Luhn*, sachets are common in the confectionary field but less so in pharmaceutical industry because of regulatory and manufacturing challenges. Regulatory and manufacturing challenges are often of primary concern when developing a pharmaceutical product. In my experience, pharmaceutical developers prefer to rely on known, proven technologies for product development. *Luhn* acknowledges that sachets are not a widely used pharmaceutical technology. Because *Luhn* only provides general guidance related to sachet formulations and acknowledges that sachets are not a generally-adopted pharmaceutical technology, it is my opinion that a skilled person would not be motivated by *Luhn* to prepare sachet oxybate formulations, especially provided the hygroscopic nature of oxybate salts (see above).

9. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 20 May 2021

Clark Allphin

EXHIBIT 31

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/210,064	03/23/2021	Clark ALLPHIN	JAZZ-025/04US 306882-2491	6700

128521 7590 06/18/2021

Cooley LLP / Jazz Pharmaceuticals
1299 Pennsylvania Ave., NW, Suite 700
Washington, DC 20004

EXAMINER	
ZHANG, YANZHI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
06/18/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

zIPPatentDocketingMailboxUS@cooley.com

Office Action Summary	Application No. 17/210,064	Applicant(s) ALLPHIN et al.	
	Examiner YANZHI ZHANG	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 03/23/21.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-24 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-24 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

This action is a response to papers filed on December. 10, 2020. Claims 1-24 are pending in the application and under consideration on the merit.

Priority

Applicant claims that this application is a continuation of U.S. Application Ser. No. 17/118,041, filed December 10, 2020, which is a continuation of U.S. Application Ser. No. 16/448,598, filed June 21, 2019, which is a continuation of U.S. Application Ser. No. 15/047,586, filed February 18, 2016 (now U.S. Patent No. 10,398,662), which claims priority to U.S. Provisional Application Ser. No. 62/117,889, filed February 18, 2015 ((001) of the specification as filed). However, there is no support for the claimed subject matter in prov' 889. The word "modified" is found 4 times, two of them are related to modified cellulose and silica gel ((0028) of the specification as filed). The other 2-paragraph are reproduced below for clarity.

(008) In still another embodiment of the invention, the hydroxide-bearing resin beads are coated with a flexible film, then loaded with GBL which, in turn, will diffuse through the film and react with the resin and form the GHB resinate in-situ. Coating will achieve further controlled release. Example films include PVAcetate, Eudragit RS, ethylcellulose, cellulose acetate or an enteric coating such as acrylic acid-based Eudragit L100,FS100 or L55, cellulose acetate phthalate, and shellac. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection. The coating may also be combined with suitable plasticizer and anti-tack agents to facilitate coating. Finely ground resin beads may also

be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation. It is understood that these films can be modified with pore formers to adjust permeability or degree of enteric protection (008) of the instant specification.

(0022) The solubility of sodium oxybate is unusually high. For example, a Xyrem solution is provided as 500mg/mL concentration in water, or 42 wt%, and its solubility limit is considerably higher. Furthermore, due to the small size and ionic nature at physiological pH, the drug is unusually mobile in solution. Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as core/shell or matrix formulations.

Support for the claimed subject matter of "a formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; a modified release portion comprising gamma-hydroxybutyrate" can be found in paragraph (0014) for controlled or extended release) and (0016-7), particularly, for immediate release component on top of page 6.

Therefore, the earliest priority for the claimed subject matter is 02/18/2016, the effective filing date of 15/047,586.

Information Disclosure Statement

The Information Disclosure Statements filed 03/30/21 (21-page), 04/27/21 (2-page), and 06/07/21 (3-page) are in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements in English are fully considered by the examiner. The foreign language references, are only considered to the extent where an English translation available or examiner understands that language. A signed copy of form 1449 is enclosed herewith.

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-23 are rejected under 35 U.S.C. 103 as obvious over Allphin et al ("Allphin", US 20120076865 A1, and published March 29, 2012).

Claims 1-23 embrace a formulation or a unit dose comprising a formulation of gamma-hydroxybutyrate comprising: an immediate release portion comprising gamma-hydroxybutyrate; a modified release portion comprising gamma-hydroxybutyrate; a viscosity enhancing agent; and an acid; wherein the viscosity enhancing agent and the acid are separate from the immediate release portion and the modified release portion.

In addition, claims 1 and 14 use the open-ended transitional phrase “comprising”. Thus, they allow for the presence of additional unrecited steps or components.

Claim interpretation: modified release portion. INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

As evidenced by Jha, titled modified release formulations to achieve the quality target product profile (QTPP) (see attached non-patent literature, published 01 August, 2012), “The United States Pharmacopoeia definition of an MR (modified-release) system is that: “the drug release characteristics of time, course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms...” This includes technologies that modify the site of drug delivery. The successful formulation of an MR device requires a comprehensive understanding of the mechanisms of drug release from the macroscopic effects of size, shape and structure through to chemistry and molecular interactions. The benefits offered by MR systems include reduced dosing frequency with improved patient compliance, better and more uniform clinical effects with lower incidence of side effects and possible enhanced bioavailability.

'Modified release' means that the escape of the drug from the tablet has been modified in some way. Usually this is to slow the release of the drug so that the medicine doesn't have to be taken too often and therefore improves compliance. The other benefit from modifying release is

that the drug release is controlled and there are smaller peaks and troughs in blood levels therefore reducing the chance of peak effects and increasing the likelihood of therapeutic effectiveness for longer periods of time. Thus, modified release portion is broadly interpreted as being modified in some way. Therefore, controlled release in the prior art reads on the limitation of modified release in the instant claims.

A unit dose is the amount of a medication administered to a patient in a single dose (quote from https://www.collinsdictionary.com/us/dictionary/english/unit-dose).

Allphin is directed to controlled release dosage forms for high dose, water soluble and hygroscopic drug substances (title). Allphin teaches that controlled release dosage forms for delivery of a drug selected from GHB (gamma-hydroxy butyrate) and pharmaceutically acceptable salts, and complexes of GHB. The controlled release dosage forms described herein may incorporate **both controlled release and immediate release** (IR) **formulations** in a **single unit dosage** form (abstract and [0065], read on the limitation of immediate release portion and modified release portion in the intent claims 1 and 14). Allphin also teaches that, in one embodiment, the controlled release dosage form comprises a CR core that includes drug substance in combination with **one or more excipients**, including **binders** selected from **hydroxypropyl cellulose**, ethylcellulose, hydroxypropyl methylcellulose, fillers, diluents, disintegrants, colorants, buffering agents, coatings, surfactants, wetting agents, **lubricants** selected from at least one of **magnesium stearate**, stearic acid, calcium stearate, hydrogenated castor oil; glidants, or other suitable excipients ([0044] and Table 1A on page 10 of the specification, read on the limitation of the instant claim 2, 4-5, 15, and 17-18). Allphin further teaches that the IR formulation is provided as an **immediate release component of a controlled release dosage form** as described herein. A unit dosage form that integrates both controlled

release and immediate release components can increase the convenience and accuracy with which a drug such as GHB is dosed to patients by providing a unit dosage form that not only provides quick onset of action, but also sustained delivery of GHB to the patient over a prolonged period of time ([0066], advantage of integrating both). Allphin indicates that sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH = 7.5 with **malic acid** ([0009], read on the limitations of acid in the instant claims 1, 3, 14, and 16). In man, the plasma half-life of **sodium oxybate** given orally is about 45 minutes and doses of **2.25 grams to 4.5 grams** induce about 2 to 3 hours of sleep and the controlled release dosage forms deliver therapeutically effective amounts of drug over a period selected from a range of about 4 to about 10 hours, about 5 to about 10 hours, about 5 to about 12 hours ([0009] and [0032]). Based on the nature of the drug, Allphin additionally teaches that, in order to maintain therapeutic efficacy, **4.5 g to 9 g** of drug must be administered to the patient in two separate doses within 2 to 5 hours. In certain embodiments, for a given dose of GHB, administration of GHB using controlled release dosage forms can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 μg/mL ([0035], read on the limitations of the amount in the instant claims 6-12 and 19-23). The total amount of drug contained within an integrated IR/CR dosage form according to the present description may be between about 500 mg and about 1,400 mg ([0075]). Furthermore, Allphin teaches that a granulation used to form CR cores and granulation parameters and **particle size** distribution are shown in Tables 1B and 1C, respectively ([0077], read on the limitation of multi-particulates in the instant claim 13).

Regarding wherein clause, the viscosity enhancing agent and the acid are separate from the immediate release portion and the modified release portion, in the instant claims 1 and 14, it is believed Allphin teaches or implies the limitation because the tablets from example 1 are coated with a solution containing ethylcellulose.

Regarding the amount of oxybate or oxybate equivalent of in the instant claims 6-10, and 20-23, the principal of law is "[Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). This rule is limited to cases in which the optimized variable is a "result-effective variable." In re Antonie, 559 F.2d 618, 620 (CCPA 1977). In this case, Alshaikh have taught various amount depending on the formulations. Thus, finding the optimum or workable ranges by routine experimentation is *prima facie* obvious.

Claim 24 is rejected under 35 U.S.C. 103 as obvious over Allphin et al ("Allphin", US 20120076865 A1, and published March 29, 2012) in view of Luhn (non-patent literature, Pharmaceutical Technology Europe, Volume 23, Issue 1, published January 7, 2011).

The teachings of Allphin have been discussed as applied to claims 1-23. Allphin does not expressly teach the formulation is a sachet. The deficiency is cured by Luhn.

Luhn is directed to using excipients in powder formulations (title). Luhn teaches that orally disintegration tablets (ODTs) have become very popular and are the starting point into a generation of drug products where patient friendliness is the decisive criteria to gain share in a saturated market environment; however, **sachets** can be faster and easier compared with ODTs (2nd para. on page 1/3 of the attached PDF, read on the limitation of sachet in the instant claim 24). Luhn also teaches that sachets may also beneficial when looking at compliance issues

within geriatric patient groups. Direct oral applications mean you don't need water to dissolve the powder or swallow the tablet. Sachets also do not look like a pill — it's important not to underestimate the psychological effects associated with a dosage form (bridging para. of pages 1-2/3 of the attached PDF).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose sachet form of sodium oxybate as taught by Luhn as the particular dose form to be incorporated into the method of Allphin o take advantage of sachet being faster and easier.

CONCLUSION

No claim is allowed.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YANZHI ZHANG whose telephone number is (571)272-3117. The examiner can normally be reached on Monday-Friday 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 5712720646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YANZHI ZHANG/
Primary Examiner, Art Unit 1617

EXHIBIT 32

Attorney Docket No. JAZZ-025/04US 306882-2491 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	ALLPHIN, Clark	Confirmation No.:	6700
Serial No.:	17/210,064	Group Art Unit:	1617
Filed:	March 23, 2021	Examiner:	Yanzhi ZHANG

FOR: **GHB FORMULATION AND METHOD FOR ITS MANUFACTURE**

Via EFS-Web
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE UNDER 37 C.F.R. § 1.111

This paper is in response to the non-final Office Action dated June 18, 2021 and the Examiner Interview Summary dated July 13, 2021. Thus, this response is timely filed by September 18, 2021.

Applicant requests reconsideration in view of the following amendments and remarks.

CLAIMS

1. (Currently amended) A formulation of gamma-hydroxybutyrate comprising:

   [[an]] a plurality of immediate release ~~portion~~ particles comprising gamma-hydroxybutyrate;

   a plurality of modified release ~~portion~~ particles comprising gamma-hydroxybutyrate;

   a viscosity enhancing agent; and

   an acid;

   wherein the viscosity enhancing agent and the acid are separate from the immediate release ~~portion~~ particles and the modified release ~~portion~~ particles.

2. (Original) The formulation of claim 1, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

3. (Original) The formulation of claim 1, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

4. (Original) The formulation of claim 1, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

5. (Original) The formulation of claim 4, wherein the lubricant is magnesium stearate.

6. (Original) The formulation of claim 1, wherein the formulation comprises an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate.

7. (Original) The formulation of claim 1, wherein the formulation comprises an amount of oxybate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium oxybate.

8. (Original) The formulation of claim 1, wherein the formulation comprises an amount of oxybate equivalent to about 6 g of sodium oxybate.

9. (Original) The formulation of claim 1, wherein the formulation comprises an amount of oxybate equivalent to about 7.5 g of sodium oxybate.

10. (Original) The formulation of claim 1, wherein the formulation comprises an amount of oxybate equivalent to about 9 g of sodium oxybate.

11. (Original) The formulation of claim 1, wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL.

12. (Original) The formulation of claim 1, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL.

13. (Original) The formulation of claim 1, wherein the formulation is a multiparticulate composition.

14. (Currently amended) A unit dose comprising a formulation of gamma-hydroxybutyrate, wherein the formulation comprises:

[[an]] a plurality of immediate release ~~portion~~ particles comprising gamma-hydroxybutyrate;

a plurality of modified release ~~portion~~ particles comprising gamma-hydroxybutyrate;

a viscosity enhancing agent; and

an acid;

wherein the viscosity enhancing agent and the acid are separate from the immediate release ~~portion~~ particles and the modified release ~~portion~~ particles.

15. (Original) The unit dose of claim 14, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof.

16. (Original) The unit dose of claim 14, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid.

17. (Original) The unit dose of claim 14, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate.

18. (Original) The unit dose of claim 14, wherein the lubricant is magnesium stearate.

19. (Original) The unit dose of claim 14, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL

20. (Original) The unit dose of claim 14, wherein the unit dose comprises an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate

21. (Original) The unit dose of claim 14, wherein unit dose contains an amount of oxybate equivalent to about 6 g of sodium oxybate.

22. (Original) The unit dose of claim 14, wherein unit dose contains an amount of oxybate equivalent to about 7.5 g of sodium oxybate.

23. (Original) The unit dose of claim 14, wherein unit dose contains an amount of oxybate equivalent to about 9 g of sodium oxybate.

24. (Original) The unit dose of claim 14, wherein the unit dose is a sachet.

REMARKS

I. Status of Claims

Claims 1 and 14 are amended. After entry of these amendments, claims 1-24 are pending.

Claims 1 and 14 are amended to more clearly define the present invention. The newly amended claims specify that the claimed formulations and unit doses contain a plurality of immediate release particles comprising GHB and a plurality of modified release particles comprising GHB and that these GHB-containing particles are separate from the viscosity enhancing agent and separate from the acid.

Support for these amendments is found throughout the originally-filed application.

No new matter is introduced by these amendments.

II. Examiner Interview Summary

Applicant thanks Examiner Zhang for the courtesies extended during the Interview conducted on July 8, 2021. Applicant generally discussed the issues raised by the present office action and its position on the obviousness rejection.

Applicant further thanks the Examiner for the courtesies extended during the subsequent phone interview conducted with Applicant's representative Jason Valentine on Tuesday, July 20, 2021. Applicant's representative discussed the Examiner's Applicant-Initiated Interview Summary dated July 13, 2021.

III. Claim Rejections under 35 U.S.C. § 103

Claims 1-23 are rejected under 35 U.S.C. §103 as allegedly obvious over U.S. Publication No. 2012/0076865 ("*Allphin*"). Claim 24 is rejected over *Allphin* in combination with Luhn, O., Pharmaceutical Technology Europe, Volume 23, Issue 1, January 7, 2011 ("*Luhn*"). The Applicants traverse.

a. Claimed subject matter

The presently claimed subject matter is directed to formulations and unit doses that comprise a plurality of immediate release GHB-containing particles and a plurality of modified

release GHB-containing particles, which are separate from the viscosity enhancing agent and separate from the acid.

b. The Newly Amended Claims Distinguish Over the Art

The Examiner cites *Allphin* for allegedly teaching formulations and unit doses that contain immediate release and modified release GHB-containing portions, a viscosity enhancing agent and an acid. [1] The Examiner specifically cites Examples 1 and 2 from *Allphin* to support this assertion. As clarified in the helpful Examiner Interview summary, it is the Examiner's position that the excipients present in the functional coating applied to the GHB-containing core from *Allphin*'s examples imply that the viscosity enhancing agent and the acid are on the same particle, but separate from the immediate release and modified release GHB portions.[2] Applicant traverses.

The Examiner has not articulated a legally sufficient motivation to separate the acid and viscosity enhancing agent from the immediate release and modified release particles to arrive at the presently claimed invention

Allphin and *Luhn* (for claim 24) alone or in combination, do not teach or suggest the claimed formulations and unit doses. As discussed below, a person of ordinary skill in the art ("POSA") would not be motivated by the cited references to arrive at the claimed invention containing all the recited elements.

The newly amended claims require a plurality of immediate release GHB-containing particles and a plurality of modified release GHB-containing particles, a viscosity enhancing agent and an acid and specify that the viscosity enhancing agent and an acid are separate from the GHB-containing particles.

Here, the Examiner asserts that the *Allphin*'s examples imply a formulation where the viscosity enhancing agent and an acid are separate from the GHB-containing portions on the same particle. Applicant asserts that the newly amended claims are now patentable in view of *Allphin* as they claim that the viscosifying agent and acid are separate from the GHB-containing particles. *Allphin*'s examples teach a GHB-containing formulation where the excipients are either directly mixed with GHB (in preparing the core from Example 1) or coated directly onto a GHB-containing

[1] Office Action at pages 3-10.
[2] Applicant-Initiated Interview Summary dated July 13, 2021 at page 1.

core (in applying the functional coating of Example 2). Thus, if anything, then, *Allphin* teaches against separating a viscosity enhancing agent and an acid from GHB-containing immediate release and modified release particles, as required by the present claims.

Regarding claim 24, *Luhn* does not cure *Allphin*'s deficiencies. *Luhn* does not relate to oxybate at all and is an unsupported opinion article that does not discuss providing a formulation containing an immediate release drug particle, a modified-release drug particle, a viscosity enhancing agent and an acid, where the viscosity enhancing agent and acid are separate from the drug-containing particle with respect to any particular drug, or class of drug, let alone GHB, as claimed.

Simply put, the Examiner has not provided a legally sufficient motivation why a POSA would go against the express teachings of *Allphin* and prepare a formulation where a viscosity enhancing agent and an acid are separate from the GHB-containing particles. As such, the claims are not obvious over the cited references.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that this application is in condition for allowance and request favorable action thereon. If it is deemed a telephone conference would expedite prosecution of this application, the Examiner is hereby invited to contact the undersigned by telephone.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

Dated: August 2, 2021

Respectfully submitted,
COOLEY LLP

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By: /Jason C. Valentine/
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EXHIBIT 33

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EDUCATION

Ph.D. **Chemical Engineering** Massachusetts Institute of Technology, May 2005
Minor: Biology
Dissertation: Poly(β-Amino Ester)s as pH Sensitive Biomaterials for Microparticulate Genetic Vaccine Delivery
Mentor: Robert Langer, Sc.D.

B.S. **Chemical Engineering** Youngstown State University, June 2000
Summa-Cum Laude
Minors: Chemistry & Mathematics

PROFESSIONAL EXPERIENCE

Distinguished Professor, University of Pittsburgh. Pittsburgh, PA. May 2021 – present.

John A. Swanson School of Engineering - Departments of Chemical and Petroleum Engineering and Bioengineering

School of Pharmacy – Department of Pharmaceutical Sciences

School of Medicine – Departments of Immunology, Ophthalmology and The McGowan Institute for Regenerative Medicine

Chair, Department of Chemical and Petroleum Engineering, University of Pittsburgh. Pittsburgh, PA. May 2012 – present.

William Kepler Whiteford Endowed Professor, University of Pittsburgh. Pittsburgh, PA. Sept 2015 – April 2021.

John A. Swanson School of Engineering - Departments of Chemical and Petroleum Engineering and Bioengineering

School of Pharmacy – Department of Pharmaceutical Sciences

School of Medicine – Departments of Immunology, Ophthalmology and The McGowan Institute for Regenerative Medicine

Associate Professor and CNG Faculty Fellow, University of Pittsburgh. Pittsburgh, PA. May 2012 – Aug 2015.

John A. Swanson School of Engineering - Departments of Chemical and Petroleum Engineering and Bioengineering

School of Medicine – Departments of Immunology, Ophthalmology and The McGowan Institute for Regenerative Medicine

Assistant Professor and Bicentennial Alumni Faculty Fellow, University of Pittsburgh. Pittsburgh, PA. Jan 2006 – April 2012.

John A. Swanson School of Engineering - Departments of Chemical and Petroleum Engineering and Bioengineering

School of Medicine – Department of Immunology, The McGowan Institute for Regenerative Medicine

NSF Graduate Research Fellow, Department of Chemical Engineering, Massachusetts Institute of Technology. Cambridge, MA. Sept 2000 - May 2005.

SURF Undergraduate Research Fellow, California Institute of Technology, Pasadena, CA. June 1999 – Aug 1999.

NSF REU Undergraduate Research Fellow, University of Pittsburgh. Pittsburgh, PA. June 1998 – Aug 1998.

SELECT FELLOWSHIPS AND AWARDS

Elected as a Fellow of the American Institute for the Advancement of Science (AAAS), 2022

Inducted into the National Academy of Inventors (NAI), 2022

- *For demonstrating a highly prolific spirit of innovation in creating and facilitating outstanding inventions that have made a tangible impact on the quality of life, economic development, and welfare of society.*

Appointed to the Special Faculty Rank of "Distinguished Professor" by the Chancellor of the University of Pittsburgh, 2021

- *Denotes extraordinary, internationally recognized scholarly attainment in the field*

Distinguished Service Award, Controlled Release Society, 2021

Reappointed as the William Kepler Whiteford Endowed Professor, 2020

Elected as a Fellow of the Controlled Release Society (CRS), 2020

- *For distinguished leadership in the field through impactful contributions in fundamental or applied research, technology, products and/or education.*

Chancellor's Distinguished Public Service Award of the University of Pittsburgh, 2019

- *The University of Pittsburgh's Highest Honor for Public Service*
- *The only individual in University History to Win all three Chancellor's Awards (Teaching in 2013 and Research in 2012).*

American Chemical Society "Pittsburgh Award", 2018

- *In recognition of outstanding leadership in chemical affairs in the local and larger professional community, increasing chemical knowledge, promoting the chemical industry, and benefitting humanity.*

Controlled Release Society Young Investigator Award, 2018

- *Given to one individual in the world each year under the age of 40*

Pittsburgh Business Times Innovation Award, 2017

- *Named one of 15 inaugural award winners in 2017 for founding Qrono Inc*

J Douglas Faires Memorial Colloquium Speaker Award of Youngstown State University, 2017

- *Named the 11th Distinguished Lecturer in Honor and Memory of One of YSU's Most Distinguished and Beloved Faculty Members, J Douglas Faires*

Elected as a Fellow of the American Institute for Medical and Biological Engineering (AIMBE), 2016

- *"Top 2% of the Most Accomplished Leaders in the Field of Medical and Biological Engineering"*

Elected as a Fellow of the Biomedical Engineering Society (BMES), 2015

- ***Citation:*** *"For exceptional contributions to the design and development of controlled release and biomimetic materials, Steven R. Little is recognized by being named a BMES Fellow"*

Named William Kepler Whiteford Endowed Professor of Chemical and Petroleum Engineering, 2015

Curtis W. McGraw Research Award of the American Society of Engineering Education (ASEE), 2015

- *Given to 1 individual in the United States each year representing all engineering disciplines*
- *The only individual in University of Pittsburgh history to receive this award.*

The Carnegie Science Award (Advanced Materials), 2015

Selected one of the Pittsburgh Business Times' Fast Trackers (University Leaders), 2015

Named as one of the Inaugural Fellows of the University Honors College, University of Pittsburgh, 2015

- *One of Only 3 Inaugural Fellows Selected in the School of Engineering including Prof George Stetton and Prof Harvey Borovetz*

Selected as one of Pittsburgh Magazine's "40 under 40", 2014

Phase II Coulter Translational Research Award, 2014

Named One of Five Pittsburgh "Disruptors" Who are "Shaking Up the Status Quo and Reshaping

Our World" by Pop City Pittsburgh, 2014

University of Pittsburgh Institute for Clinical Research Distinguished Alumni Award, 2014

Innovative Ophthalmic Research Award - Research to Prevent Blindness (RPB), 2014

Chancellor's Distinguished Teaching Award of the University of Pittsburgh, 2013

- *The University of Pittsburgh's Highest Honor for Teaching*
- *The only individual in University History to Win all three Chancellor's Awards (Research in 2012 and Public Service in 2019).*

The Carnegie Science Award (University Educator), 2013

Pitt Innovator Award, 2012

Best Mentor of an Underrepresented Student, 2012 Pitt EXCEL Summer Undergraduate Research Program

Named a "Camille Dreyfus Teacher-Scholar", 2012

- *One of only 4 engineers selected nationally in 2012*
- *Highlighted In: Angewandte Chemie International Edition (2012), 51(31): 7631*

Named CNG Faculty Fellow, School of Engineering, 2012

Invited Participant, National Academy of Engineering Frontiers of Engineering Symposium, 2012

Chancellor's Distinguished Research Award of the University of Pittsburgh, 2012

- *The University of Pittsburgh's Highest Honor for Research*
- *The only individual in University History to Win all three Chancellor's Awards (Teaching in 2013 and Public Service in 2019).*

Society for Biomaterials Young Investigator Award, 2012

- *One individual selected in the world each year*

Coulter Translational Research (Early Career) Award, 2011

Distinguished Alumni Award, Youngstown State University, 2010

Board of Visitors Award, Swanson School of Engineering, 2009

- *"Most Outstanding Faculty Member in the School of Engineering"*

Named Bicentennial Alumni Faculty Fellow, School of Engineering, 2009

Beckman Young Investigator Award, 2008

- *Traditionally, each University can only nominate one professor in the Sciences and Engineering.*

Institute for Clinical Research Education Award, for Most Outstanding Grant Proposal in Graduating Class, 2008

AHA Career Development Award, 2007

Distinguished Faculty Fellowship, School of Engineering, 2007

NIH K-Award, 2007

- *The NIH covers 75% of the salary of its K-Awardees for 4 years*

AAAS Excellence in Research Award, 2005

- *Awarded for outstanding PhD thesis nationally*

National Science Foundation Graduate Fellow, 2000 – 2003

Tau Beta Pi Graduate Fellow, 2000

Phi Kappa Phi Mavrigian-Grim Graduate Fellow, 2000

AIChE Professional Promise Award, 1999

- *Most outstanding senior*

Eugene D. Scudder Physical Chemistry Award, 1999

ACS Organic Chemistry Award, 1999

- Additional awards for founded companies included under section entitled "Entrepreneurship"

- Awards for mentored students included under section entitled "Mentee Awards"

ADDITIONAL RECOGNITION

Selected as a Member of the Awards Committee for the American Association of Pharmaceutical Scientists (AAPS) by the Board of Directors, 2022-2024

Selected as the Program Chair for the Controlled Release Society's (CRS) Annual Meeting in 2020, the Society's First Virtual Annual Meeting, by the CRS Board of Directors

Selected as an Editor - Drug Delivery and Translational Research, 2019

Elected to the Board of Directors (Director-At-Large) of the Controlled Release Society (CRS), 2018 – 2021

Selected as a member of the Scientific Advisory Board for the United Kingdom's Regenerative Medicine Platform Hub, 2015 – present

Selected by the Board of Directors of the Controlled Release Society (CRS) to Serve as Special Advisor on Leading an Effort to Create and Manage Divisional Entities within the Society, 2017

Named "Representative of the Board of Directors for Focus Groups" by the Board of Directors of

the Controlled Release Society (CRS), 2017 – 2018

Selected by the ASEE as one of the Department Chairs Nationwide to Advise them on a Pilot Program for a formal Department Chair Engineering Research Council (ERC) Conclave, 2015

Elected as the Chair of the American Institute of Chemical Engineers (AIChE) Chemical Engineering Department Chairs Division, 2015 – 2017

Elected to the Position of Representative for Special Interest Groups on the Board of Directors – Society for Biomaterials, 2013 – 2015

Associate Editor – Nanobiomedicine, 2014 – present

Elected to the Position of Chairman, Drug Delivery Special Interest Group – Society for Biomaterials, 2011 – 2013

Elected to the Position of Vice-Chairman, Drug Delivery Special Interest Group – Society for Biomaterials, 2009 – 2011

Science Advisory Board, Fox Center for Vision Restoration, 2009 – present

Research Website Awarded the Gold ADDY, American Advertising Federation. *"Most innovative flash website."* – **http://littlelab.pitt.edu**

Research Website Named "Best of Show", American Institute for Graphic Arts – http://littlelab.pitt.edu

Member, Board of Directors - EduNations – (March 2012 – January 2020) a charitable organization that establishes educational infrastructure by building schools, training teachers, and providing children with free education in Sierra Leone, Africa (consistently rated as the worst place to live on the planet). - www.edunations.org

PEER-REVIEWED PUBLICATIONS AND REVIEWS

118) Shehabeldin, M., Gao, J., Ki, Y., Chong, R., Tabib, T., Gaffen, S.L., Diaz. P.I., Lafyatis, **Little, S.R.**, Sfier, C.S. Local Delivery of CCL2 Reverses Murine Periodontitis and Accelerates Repair. (*Journal of Clinical Investigation*, submitted).

117) Acharya, A.P., Greene, A.C., Sezginel, K.B., Devanesan, H.P.G., Shanthi, P.M., Lawson, H.D., Liu, C., Rosi, N.L., Kumta, P.N., Tang, Y., Chan, S.Y., Wilmer C.E., Flynn, J.L., **Little, S.R.** In Silico Screening of Drug Delivery Materials: Discovery of a Metal-Organic Framework that Clears Mycobacterium Tuberculosis Infection. (*Journal of Controlled Release,* in press).

116) Sands, R., Binion, D., **Little, S.R.** Localized, Oral IBD Immunotherapy with TRI-MP to Enrich for Regulatory T-Cells and to Attenuate Colitis in a Murine Model of Inflammatory Bowel Disease. (*Journal of Crohn's and Colitis*, first review complete - responding to peer reviewers' comments).

115) Balmert, S.C., Carey, C.D., Fiorina, C.M., Erdos, G., Zhang, J., Larregina, A.T., Korkmaz, E., **Little, S.R.,** Falo, L.D. Engineering the Skin Microenvironment to Promote Antigen-Specific Immune Tolerance. (*Science Translational Medicine*, draft in hand).

114) Lorentz, K.L., Bruk, L.A., Gupta, P., Cunnane, E.M., Ramaswamy, A.K., Mandal, B.B, Fedorchak, M.V., **Little, S.R.,** Weinbaum, J.S., Vorp, D.A. Validation of Artificial MSCs for Use in Tissue

Engineered Vascular Grafts. (*Nature: Scientific Reports,* first review complete - responding to peer reviewers' comments).

113) Tanyeri, N.Y., Amer, M., Balmert, S.C., Korkmaz, E., Falo, L.D., **Little, S.R.** Microfluidic Systems for Manufacturing of Microparticle-Based Drug Delivery Systems: Design, Construction and Operation. (*ACS Biomaterials Science and Engineering,* 8(7):2864-2877).

112) Greene, A.C., Shehabeldin, M., Gao, J., Balmert, S.C., Ratay, M., Sfeir, C. (2022) Local Induction of Regulatory T Cells Prevents Inflammatory Bone Loss in Ligature-Induced Experimental Periodontitis in Mice. (*Nature: Scientific Reports,* 12:5032).

111) Shehabeldin, M., Gao, J., Ki, Y., Chong, R., Greene, A., **Little, S.R.,** Sfeir, C. Local Delivery of CCL2 Reverses Murine Periodontitis and Accelerates Repair. (*Journal of Dental Research,* in press).

- *Will be Featured on the Cover of the Journal Issue*

110) Schilling, A.L., Wang, E. W., Lee, S., **Little, S.R.** (2022) Advances in Controlled Drug Delivery to the Perinasal Sinuses. (*Biomaterials,* 282:121430).

109) Schilling, A.L., Cannon, E., Fullerton, S., Lee, S.E., Wang, E.W., **Little, S.R.** (2022) A Ready-to-use, Thermoresponsive and Extended-Release Delivery System for the Paranasal Sinuses. (*Drug Delivery and Translational Research*, 12:708-719).

108) Lorentz, K.L., Gupta, P., Shehabeldin, M.S., Lickert, E.M., Rodriguez, B.R., Cunnane, E.M., Ramaswamy, A.K., Fedorchak, M.V., **Little, S.R.,** Weinbaum, J.S., Sfier, C.S., Mandal, B.B., Vorp, D.A. (2021) CCL2 loaded microparticles promote acute patency in silk-based vascular grafts implanted in rat aortae. (*Acta Biomateriala,* 135:126-138).

107) Bentley, E., **Little, S.R.** (2021) Local Delivery Strategies for the Control of Immune Homeostasis (*Advanced Drug Delivery Reviews,* 178:113971).

106) Acharya, A.P., Tang, Y., Bertero, T., Tai, Y.Y., Woodcock, C., Sun, W., **Little, S.R.**, Chan, S.Y. (2021) Simultaneous Pharmacologic Inhibition of YAP1 and GLS1 via Inhaled Polymer Microparticles Improves Pulmonary Hypotension. (*Journal of the American Heart Association*, 2021;10:e019091).

105) Tanyeri, N.Y., Ahlmark, B.Z., **Little, S.R.** (2021) Advances in Multiplexed Paper-Based Analytical Devices for Cancer Diagnosis: A Review of Technological Developments., (*Advanced Materials Technologies*, early view (April 21, 2021) doi: 10.1002/admt.202001138).

- *Featured on the Frontispiece of the Journal Issue*

104) Borrelli, M., Turnquist, H.R., **Little, S.R.** (2021) Advances in Biologic Delivery for the Treatment of Cardiac Diseases. (*Advanced Drug Delivery Reviews,* 173: 181-215).

103) Bassin, E. Piganelli, J., **Little, S.R.** (2021) Auto-antigen and immunomodulatory agent based approaches for antigen-specific tolerance in NOD mice. (*Current Diabetes Reports*, 21(3):9).

102) Schilling, A.L., **Little, S.R.**, Wang, E.W., Lee, S.E. (2021) Reply: A preclinical model to tackle chronic rhinosinusitis. (*International Forum of Allergy and Rhinology,* (11)828-829).

101) Pacheco, C.M.F., Maltos, K.L.M., Thomas, L.L., Zhuang, Z., Yoshizawa, S., Garlet, G.P., **Little, S.R.**, Sfeir, C.S. (2021) Local sustained delivery of anti-IL-17A Antibodies Limits Inflammatory Bone Loss in Murine Experimental Periodontitis (*Journal of Immunology,* 206(10):2386-2392).

100) Patel, S.K., Greene, A.C., Desai, S.M., Rothstein, S.N., Basha, I. T., MacPherson, J.S., Wang, Y., Zou, Y., Shehabeldin, M., Sfier, C.S., **Little, S.R.**, Rohan, L.C. (2021) Biorelevant and Screening Dissolution Methods for Minocycline Hydrochloride Microspheres Intended for Periodontal Administration. (*International Journal of Pharmaceutics,* 596:120261).

99) Schilling, A.L, Moore, J., Kalahci, Y., **Little, S.R.**, Rigatti, L.H., Wang, E.W., Lee, S. (2021) Evaluating Inflammation in an Obstruction-Based Chronic Rhinosinusitis Model in Rabbits. (*International Forum of Allergy and Rhinology,* (4):807-809).

98) Bellotti, E., Schilling, A.L., **Little, S.R.**, Decuzzi, P. (2020) Injectable Thermoresponsive Hydrogels as Drug Delivery System for the Treatment of Central Nervous System Disorders: A Review. (*Journal of Controlled Release,* 329:16-35).

97) Bassin, E.J., Buckley, A.R., Piganelli, J.D., **Little, S.R.** (2020) TRI Microspheres Prevent Inflammatory Arthritis in a Collagen-Induced Arthritis Model. (*PLoS One,* 15(9): e0239396).

96) Schilling, A.L., Kulahci, Y., Moore, J., Wang, E.W., Lee, S.E., **Little, S.R.** (2020) A thermoresponsive hydrogel system for long-acting corticosteroid delivery into the paranasal sinuses. (*Journal of Controlled Release*, 330(889-897)).

95) Greene, A.C., Acharya, A.P., Lee, S.B., Gottardi, R., Peterson, S., Zaleski, E., Besingi, R., **Little, S.R.** (2020) Cranberry Extract-Based Formulations for Preventing Bacterial Biofilms. (*Drug Delivery and Translational Research,* e-pub ahead of print: DOI: 10.1007/s13346-020-00837-x).

94) Sarmento, B., Little, S.R. (2020) Fundamentals of Nanomedicines Toward Clinical Translation. (*Drug Delivery and Translational Research,* **10**: 571).

93) Ding, X., Gao, J., Acharya, A., **Little, S.R.,** Wang, Y. (2020) Azido-Functionalized Polyurethane Designed for Making Tunable Elastomers by Click Chemistry. (*ACS Biomaterials Science and Engineering,* **6**(2): 852-864).

92) Fisher, J.D., Zhang, W., Balmert, S.C., Schweizer, R., Aral, A.M., Unadkat, J.V., Komatsu, C., Dong, L., Erubas, V., Schnider, J., Zhaoxiang, Z., Turnquist, H.R., Solari, M.G., Gorantla, V.S., **Little, S.R.** (2020) Treg Inducing Microparticles Promote Donor-Specific Tolerance in Experimental Vascularized Composite Allotransplantation. (*Proceedings of the National Academy of Sciences,* **116**(51): 25784-25789).

91) Fisher, J.D., Zhang, W., Aral, A.M., Balmert, S.C., Kulahci, Y., Turnquist, H.R., Solari, M.G., Gorantla, V.S., **Little, S.R.** (2019) In situ recruitment of regulatory T cells promotes donor-specific tolerance in vascularized composite allotransplantation. (*Science Advances,* 13;6(11): eaax8429).

90) Azvedo, M.C., Garlet, T.P., Francisconi, C.F., Colavite, P.M., Tabanez, A.P., Melchiades, J.L., Trombone, A.P.F., Sfeir, C.S., **Little, S.R.**, Silva, R.M., Garlet, G.P. (2019) Vasoactive Intestinal Peptide (VIP) Immunoregulatory Role at the Periapex: Associative and Mechanistic Evidence from Human and Experimental Periapical Lesions. (*Journal of Endodontics,* **45**(10): 1228-1236).

89) Joseph, N., Lawson, H.D., Overhold, K.J., Domodaran, K., Gottardi, R., Acharya, A.P., **Little, S.R.** (2019) Synthesis and Characterization of Ca-Sr-Metal Organic Frameworks for Biodegradable Orthopedic Applications. (*Nature – Scientific Reports,* **9**: 13024).

88) Leong, H.S., Butler, K.S., Brinker, J., Azzawi, M., Conlan, S., Dufés, C., Owen, A., Rannard, S., Scott, C., Chen, C., Dobrovolskaia, M.A., […], Sarmento, B., das Neves, J., Santos, H.A., Mitragotri, S., **Little, S.R.,** Peer, D., Amiji, M.M., Alonso, M.J., […], Zheng, G., Pastore, C. (2019)

On the issue of transparency and reproducibility in nanomedicine. (*Nature Nanotechnology,* **14,** 629-635.)

87) **Little, S.R.** (2019) Perspective: The current status and future directions of CRS Focus Groups. (Invited Perspective Article, *Journal of Controlled Release,* **300**: 46-51).

86) Bellotti, E., Fedorchak, M.V., Velankar, S. S., **Little, S.R.** (2019) Tuning of Thermoresponsive pNIPAAm Hydrogels for the Topical Retention of Controlled Release Ocular Therapeutics. (*Journal of Materials Chemistry B,* **7**(8): 1276-1283).

85) Balazs, A.C., Whitesides, G.M., Brinker, C. J., Aronson, I., Chaikin, P., Dogic, A., Glotzer, S., Hammer, D., Irvine, D., **Little, S.R.**, de la Cruz, M. O., Parikh, A., Stupp, S., Szostak, J. (2018) Designing Biomimetic, Dissipative Material Systems. (*United States Department of Energy Office of Scientific and Technical Information, Invited Technical Report,* doi: 10.2172/1235400).

84) Zhuang, Z., Yoshizawa, S., Glowacki, A.J., Maltos, K., Pacheco, C., Mulkeen, M., Myers, N., Cong, R. Verdelis, K., Garlet, G.P., **Little, S.R.,** Sfeir, C.S. (2018) Induction of M2 Macrophages Prevents Bone Loss in Murine Periodontitis. (*Journal of Dental Research,* **98**(2): 200-208*).*

83) Ratay, M.L., Balmert, S.C., Bassin, E. J., **Little, S.R.** (2018) Controlled Release of an HDAC Inhibitor for Reduction of Inflammation in Dry Eye Disease. (*Acta Biomaterialia*, **71**: 261-270).

82) Fisher, J.D., Zhang, W., Aral, A.M., Balmert, S.C., Kulahci, Y., Turnquist, H.R., Solari, M.G., Gorantla, V.S., **Little, S.R.** (2018) Biomimetic Microparticles Promote Survival of Vascularized Composite Allografts. (*United States Department of Defense Report to the Executive Agent*, FY17: 217-218).

81) Francisconi, C.F., Vieira, A.E., Fonseca, A.C., d Avezdo, M., Trombone, A.P.F., Letra, A., Silva, R.M., Sfier, C.S., **Little, S.R.**, Garlet, G.P. (2018) RANKL Triggers Treg-mediated Immunoregulation in Inflammatory Osteolysis. (*Journal of Dental Research,* **97**(8): 917-927).

80) Nichols, D.A., Sondh, I.S., **Little, S.R.,** Zunino, P., Gottardi, R. (2018) Design and Validation of an Osteochondral Bioreactor for the Screening of Treatments for Osteoarthritis. (*Biomedical Microdevices*, **20**(1): 18).

79) Fuller, T.W., Acharya, A.P., Meyyappan, T., Yu, M., Bhaskar, G., **Little, S.R.**, Tarin, T.V. (2018) Comparison of Bladder Carcinogens in the Urine of E-cigarette Users Versus Non E-Cigarette Using Controls. (*Nature - Scientific Reports,* **8**: 507).

78) Hwang, M., Ding, Gao, J., Acharya, A.P., **Little, S.R.**, (2018) Wang, Y. A Biocompatible Betaine-functionalized Polycation for Coacervation. (*Soft Matter*, **14**(3): 387-395).

77) Ratay, M.L, Balmert, S.C., Acharya, A.P., Greene, A.G., Meyyappan, T., **Little, S.R.** (2017) TRI Microspheres Prevent Key Signs of Dry Eye Disease in an Experimental Inflammatory Model. (*Nature – Scientific Reports,* **7**:17527).

76) Ratay, M.L., Bellotti, E., Gottardo, R., **Little, S.R.** (2017) Modern Therapeutic Approaches for Noninfectious Ocular Diseases Involving Inflammation. (*Advanced Healthcare Materials,* **6**:1700733).

- *Featured on the Cover of the Journal*
- *Featured in Advanced Science News, December 24, 2017*

75) Washington, M.A., Balmert, S.C., Fedorchak, M.V., **Little, S.R.,** Watkins, S.C., Meyer, T.A. (2018)

Monomer Sequence in PLGA microparticles: Effects on Acidic Microclimates and *in vivo* Inflammatory Response. (*Acta Biomaterialia,* **65**: 259-271).

74) Acharya, A.P., Tarin, T., **Little, S.R.** (2017) An Inexpensive, Point-of-Care Urine Test for Bladder Cancer in Patients Undergoing Hematuria Evaluation. (*Advanced Healthcare Materials,* **6**:1700808).

73) Fedorchak, M.V., Conner, I.P., Cugini, A., Schuman, J.S., **Little, S.R.** (2017) Long Term Glaucoma Drug Delivery Using a Topically Retained Gel/Microsphere Eye Drop. (*Nature Scientific Reports,* **7**: 8639).

- *Technology described in this publication served the basis for founding OTERO, Inc.*

72) Balmert, S.C., Carey, C.D., Vu, J.R., Fedorchak, M.V., Falo, L.D., **Little, S.R.** (2017) In vivo Induction of Regulatory T Cells Promotes Allergen Tolerance and Suppresses Allergic Contact Dermatitis. (*Journal of Controlled Release*, **261**: 223-233).

71) Bayer, E., Jordan, J., Roy, A., Gottardi, R., Fedorchak, M.V., Kumta, P. N, **Little, S.R.** (2017) Programmed PDGF-BB and BMP-2 Delivery from a Hybrid Calcium Phosphate/Alginate Scaffold. (*Tissue Engineering Part A,* **23**(23/24): 1382-1393).

- *Featured on the Cover of the Journal*

70) Ratay, M.L., Glowacki, A.J., Balmert, S.C., Acharya, A.P., Polat, J., Andrews, L.P., Fedorchak, M.V., Schuman, J.S., Vignali, D.A.A., **Little, S.R.** (2017) Treg-Recruiting Microspheres Prevent Inflammation in a Murine Model of Dry Eye Disease. (*Journal of Controlled Release,* **258**: 208-217). PMID: 28501670

69) Acharya, A.P., Guaragno, M., Sinha, M., Balmert, S.C., Bandi, R., Kumta, P.N., Wang, Y., Vignali, D.A., **Little, S.R.** (2016) Localized Multi-Component Delivery Platform Generates Local and Systemic Anti-Tumor Immunity. (*Advanced Functional Materials,* **27**: 1604366).

68) Washington, M.A., Swiner, D.J., Bell, K.R., Fedorchak, M.V., **Little, S.R.**, Meyer, T.Y. (2016) The Impact of Monomer Sequence and Stereochemistry on the Swelling and Erosion of Biodegradable Poly(Lactic-co-Glycolic) Acid Matrices. (*Biomaterials,* **117**: 66-76).

67) Bayer, E., Fedorchak, M.V., **Little, S.R.** (2016) The Influence of Platelet-Derived Growth Factor and Bone Morphogenetic Protein Presentation on Tubule Organization by Human Umbelical Vascular Endothelial Cells and human Mesenchymal Stem Cells in Co-Culture. (*Tissue Engineering Part A,* 2016, **22**(21 & 22): 1296-1304).

- *Featured on the Cover of the Journal*

66) Roy, A., Jhunjhunwala, S., Bayer, E., Fedorchak, M.V., **Little, S.R.,** Kumt, P.N. (2016) Porous calcium phosphate-poly (lactic-co-glycolic) acid composite bone cement: A viable tunable drug delivery system. (*Materials Science and Engineering: C,* **59**: 92-101).

65) Francisconi, C.F., Vieira, A.E., Biguetti, C.C., Glowacki, A.J., Trombone, A.P.F., Letra, A., Silva, R.M., Sfeir, C.S., **Little, S.R.,** Garlet, G.P., (2016) Characterization of the Protective Role of Regulatory T Cells in Experimental Periapical Lesions Development and Its Chemoattraction Manipulation as a Therapeutic Tool. (*Endodontics,* **42**(1): 120-126*).*

- *Winner, Journal of Endodontics Award as selected by the Scientific Advisory Board*

64) Bayer, E., Fedorchak, M.V., Gottardi, R., **Little, S.R.** (2015) The Scope and Sequence of Growth

Factor Delivery for Vascularized Bone Tissue Regeneration. (*Journal of Controlled Release*, 2015, **219**: 129-140).

63) Lash, M.H., Fedorchak, M.V., McCarthy, J.J., **Little, S.R.,** (2015) Scaling Up Self-Assembly: Bottom-Up Approaches to Macroscopic Particle Organization. (*Soft Matter*, **11**: 5597-5609).

- *Featured on the Front Cover of the Journal*

62) Acharya, A. P., **Little, S.R.** (2015) Stapled Endosome Disrupting Alginate Particles for Cytosolic Delivery of Cations. (*Journal of Drug Targeting,* invited manuscript for special edition, **23** (7/8): 690-697).

61) Fisher, J. D., Acharya, A.P., **Little, S.R.**, (2015) Micro and Nanoparticle Drug Delivery Systems for Preventing Allotransplant Rejections. (*Clinical Immunology*, **160**: 24-35).

60) Guaragno, M., Gottardi, R., Fedorchak, M.V., Roy, A., Kumta, P.N., **Little, S.R. (**2015) One-Step Synthesis of Fluorescently Labeled Single-Walled Carbon Nanotubes. (*Chemical Communications,* **51**: 17233-17236).

59) Lash, M.H., Blevins, L., Jordan, J., Fedorchak, M.V., **Little, S.R.**, McCarthy, J.J. (2015) Non-Brownian Particle-based Materials with Microscale and Nanoscale Hierarchy. (*Angewandte Chemie*, **54**(20): 5854-5858).

- *Featured on the Inside Cover of the Journal*

58) Balmert, S.C., Zmolek, A.C., Glowacki, A.J., Knab, T.D., Rothstein, S.N., Wokpetah, J.M., Fedorchak, M.V., **Little, S.R.,** (2015) Positive Charge of "Sticky" Peptides and Proteins Impedes Release from Negatively Charged PLGA Matrices. *Journal of Materials Chemistry B*, **3**, 4723-4734).

57) Knab, T. D., **Little, S.R.,** Parker, R.S. (2015) A Systems Approach to Modeling Drug Release from Polymer Microspheres to Accelerate In Vitro to In Vivo Translation. (*Journal of Controlled Release*, **211**: 78-84).

56) Roy, A., Jhunjhunwala, S., Bayer, E., Fedorchak, M.V., **Little, S.R.**, Kumta, P.N. (2015) Porous Calcium Phosphate-Poly(lactic-co-glycolic) acid Composite Bone Cement: A Viable Tunable Drug Delivery System. (*Materials Science and Engineering C,* **1**(59): 92-101).

55) Araujo-Pires, A.C., Vieira, A.E., Francisconi, C.F., Biguetti, C.C., Glowacki, A., Yoshizawa, S., Campanelli, A.P., Trombone, A.P., Sfeir, C.S., **Little, S.R.**, Garlet G. P. (2015) IL-4/CCL22/CCR4 Axis Controls Regulatory T-Cell Migration That Suppresses Inflammatory Bone Loss in Murine Experimental Periodontitis. (*Journal of Bone and Mineral Research*, **30**(3):400-410).

54) Lash, M.H., Fedorchak, M.V., **Little, S.R.**, McCarthy, J.J. (2015) Fabrication and Characterization of Non-Brownian Particle-Based Crystals. (*Langmuir,* **31**(3):898-905).

- *Featured on the Inside Cover of the Journal*

53) Glowacki, A.J., Gottardi, R., Yoshizawa, S. A., Cavalla, F., Garlet, G.P., Sfeir, C.S., **Little, S.R.,** (2015) Strategies to Direct the Enrichment, Expansion, and Recruitment of Regulatory Cells for the Treatment of Disease. (*Annals of Biomedical Engineering,* **43**(3):593-602).

52) Rothstein, S.N., Donahue, C., Falo, L.D., **Little, S.R.** (2014) In Silico Programming of Degradable Microparticles to Hide and then Reveal Immunogenic Payloads *in vivo*. (*Journal of Materials Chemistry B,* **2**(37):6183-6187).

51) Fu, H., Hong, Y., **Little, S.R.**, Wagner, W.R. (2014) Collagenase-Labile Polyurethane Urea Synthesis and Processing into Hollow Fiber Membranes. (*Biomacromolecules*, **15**(8):2924-2932).

50) Garlet, G.P., Sfeir, C.S., **Little, S.R.** (2014) Restoring Host-Microbe Homeostasis via Selective Chemoattraction of Tregs. (*Journal of Dental Research*, invited review, **93**(9):834-839).

49) Fedorchak, M.V., Wingard, J., Medina, C., Albeiruti, E., Schuman, J., **Little, S.R.** (2014) 28-day Intraocular Pressure Reduction with a Single Dose of Brimonidine Tartrate-Loaded Microspheres (*Experimental Eye Research,* **125**:210-216).

- *Highlighted by the Wall Street Journal on Tuesday August 5th, 2014 in an Article Entitled "Eyes and the Needle: New Treatment"*
- *Technology described in this publication served the basis for founding OTERO, Inc.*

48) Rothstein, S.N., Huber, K.D., Sluis-Cremer, N., **Little, S.R.** (2014) *In Vitro* Characterization of a Sustained Release Formulation of Enfurvirtide. (*Antimicrobial Agents and Chemotherapy*, **58**(3):1797-9).

47) Mealy, J.E., Fedorchak, M.V., **Little, S.R.** (2014) *In Vitro* Characterization of a Controlled Release Ocular Insert for the Delivery of Brimonidine Tartrate. (*Acta Biomateriala,* **10**(1):87-93).

- *Technology described in this publication served the basis for founding OTERO, Inc.*

46) Glowacki, A.J., Yoshizawa, S.A., Jhunjhunwala, S., Vieira, A.E., Garlet, G.P., Sfeir, C.S., **Little S.R.** (2014) Prevention of Inflammation-Mediated Bone Loss in Murine and Canine Periodontal Disease via Recruitment of Regulatory Lymphocytes (*Proceedings of the National Academy of Science*, **110**(46):18525-30).

- *Highlighted in: Getting to the Root of Periodontal Disease, (2013) Nature, SciBX* ***6****(45) 6-7*
- *Highlighted on National Public Radio (WESA Pittsburgh) November 4, 2013*
- *Highlighted by the NIH on the NIDCR's "Science Spotlight"*

45) Fedorchak, M., Cugini, A., Schuman, J., **Little, S.R.** (2013) The Monthly Eye Drop: Development of a Long-Term, Noninvasive Glaucoma Treatment System. (*Investigative Ophthalmology & Visual Science,* **54**(15): 4294.).

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1) **Little, S.R.**, Lynn, D.M., Ge, Q., Anderson D.G., Puram S.V., Chen J., Eisen H.N., Langer, R. (2004) Novel Microparticles Enhance the Potency of Non-Viral Genetic Vaccines. (*Proceedings of the National Academy of Sciences*, **101**(26): 9534-39).

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PEER-REVIEWED CONFERENCE PROCEEDINGS

1) Bodnar, C.A., Beckman, E., McCarthy, J.M., **Little, S.R.** (2014) Work in Progress: A Vision for the First "Product Innovation Sequence" for Chemical Engineers. ASEE 2014 Annual Conference and Exposition, June 15-18, 2014. Indianapolis, Indiana.

PEER-REVIEWED BOOK CHAPTERS

3) **Little, S.R.** Foreword to *Engineering Polymer Systems for Enhanced Drug Delivery*, Wiley, New Jersey, Expected Publication Date: January 2014.

2) Balmert, S. C., **Little, S.R.** "Biomimetic, Anisotropic Drug Delivery Systems." in *Handbook of Biomimetics and Bioinspiration: Volume I,* World Scientific Publishing, Singapore, August 2013.

1) **Little, S.R**., Anderson, D. G., Langer, R. "Non-Viral Genetic Vaccines for Cancer." in *Gene Therapy for Cancer*, Humana Press, New Jersey, December 2006.

INVITED TALKS

85) **PLENARY: American Society for Reconstructive Transplantation Annual Meeting (Host: Gerald Brandacher)** Can Re-Establishing Immunological Homeostasis Promote Regeneration? Chicago, IL (*November 2022).*

84) **West Virginia University (Host: Srinivas Palanki)** Engineering Mimetic Solutions to Re-Establish Immunological Homeostasis. Morgantown, WV (*October 2022).*

83) **Carnegie Mellon University Innovation Workshop (Host: Melanie Simko)** Challenges in Translating a Complex Technology from a University Environment (*July 2022*).

82) **Materials Research Society Annual Meeting – (Host: Ritchie Chen)** Mimicking Tumors as a S.M.A.R.T.E.R. Way to Treat Transplant Rejection (*May 2022).*

81) **Science and Entrepreneurship Series from CRS Italia – (Host: Paulo Decuzzi)** Challenges in Translating a Complex Technology from a University Environment (*April 2022).*

80) **Regulatory T cell-Enriching Microparticles for Promoting Vascularized Composite Allotransplantation – (Host: Eddie Almeida)** US Department of Defense Congressionally Directed Medical Research Program Meeting (*March 2022).*

79). **Teraski Institute – (Host: Ali Khademhosseini)** Engineering Mimetic Solutions to Reestablish Immunological Homeostasis. Virtual Seminar (*May 2021).*

78) **AWARD TALK**: **Controlled Release Society International Annual Meeting – (Host:**

Conference Chairs, Mark Prausnitz and Bruno Sarmento) Mimicking Tumors as a S.M.A.R.T.E.R. Way to Treat Transplant Rejection. Virtual Annual Meeting (*July 25-29th, 2021).*

77) **KEYNOTE: Polymers for Advanced Technologies International Conference – (Host: Joseph Kost)** Medicine that Imitates Life Through Biomimetic Drug Delivery. Jerusalem, Israel, (*October 3-7, 2021*).

76) **Vanderbilt University (Host: David Pine)** (Department of Chemical and Biomolecular Engineering Seminar Series) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Nashville, TN, (*Date TBD – Rescheduled due to COVID19*).

75) **PLENARY: SIPCD (Biannual) Symposium on Innovative Polymers for Controlled Delivery – (Host: Kinam Park)** Medicine that Imitates Life Through Biomimetic Drug Delivery. Suzhou, China. (*Date TBD – Rescheduled due to COVID19*).

74) **University of South Carolina (Host: Michael Gower)** (Department of Chemical Engineering Seminar Series) – Controlling "Controlled Release" to Make Medicine that Imitates Life. Columbia, SC, Fall Semester (*Virtual Seminar*), October 8, 2020.

73) **New York University (Host: David Pine)** (Department of Chemical and Biomolecular Engineering Seminar Series) – Controlling "Controlled Release" to Make Medicine that Imitates Life. New York, NY, March 6th, 2020.

72) **PLENARY: Annual Meeting of the Spanish/Portuguese Local Chapter of the Controlled Release Society – (Host: Maria José Alonso)** University of Santiago de Compostela. Controlling Controlled Release to Make Medicine that Imitates Life. Santiago de Compostela, Spain, January 24th, 2020.

- *Covered by the by La Voz de Galacia in the article entitled: Avanzamos en fármaco con menos efectos adversos y más personalizados (Advancement of drugs with fewer adverse effects in a more personalized way):* https://www.lavozdegalicia.es/noticia/santiago/2020/01/25/especialista-universidad-pittsburghavanzamos-farmacos-efectos-adversos-personalizados/0003_202001S25C2992.htm

71) **University of Porto (Host: Bruno Sarmento)** (Instituto Universitário de Ciências da Saúde) – Immunoengineering the Local Immunological Microenvironment for Recruitment and Differentiation of Endogenous Regulatory T Cells. Porto, Portugal, January 21st, 2020.

70) **Ohio State University Department of Chemical and Biomolecular Engineering (Host: Katelyn Reilly) -** Controlling Controlled Release to Make Medicine that Imitates Life. September 26th, 2019. Columbus, OH.

69) **University of Florida Department of Chemical Engineering (Host: Carlos Rinaldi) -** Controlling Controlled Release to Make Medicine that Imitates Life. October 7th, 2019. Gainesville, FL.

68) **KEYNOTE: Chinese Biomaterials Congress (Host: Art Coury) -** Controlling Controlled Release to Make Medicine that Imitates Life. August 22-25, 2019. Dalian, China.

67) **Technion – Israel Institute of Technology, Department of Chemical Engineering (Host: Avi Schroeder)** - Controlling Controlled Release to Make Medicine that Imitates Life. Scheduled for May 2019. Haifa, Israel.

66) **Tel Aviv University, Center for Nanoscience and Technology (Host: Dan Peer) -** Controlling

Controlled Release to Make Medicine that Imitates Life. Scheduled for May 2019. Tel Aviv, Israel.

65) **Johns Hopkins University, Wilmer Eye Institute and Center for Nanomedicine (Hosts: Ian Pitha and Justin Hanes) –** Next Generation Delivery Systems for Treatment of Ocular Diseases. May 2019. Baltimore, MD.

64) **Colorado School of Mines, Department of Chemical and Biological Engineering (Host: Kevin Cash)** - Controlling Controlled Release to Make Medicine that Imitates Life. April 19, 2019. Golden, CO.

63) **ANNUAL ENGINEERING WEEK SPEAKER: Northeastern University, Department of Chemical Engineering (Hosts: Hicham Fenniri and Tom Webster) –** Controlling Controlled Release to Make Medicine that Imitates Life. February 22nd, 2019. Boston, MA.

62) **AIChE Annual Meeting: Young Faculty Forum (Host: Anju Gupta) –** The Most Important Things to the Success of Junior Faculty. October 31st, 2018. Pittsburgh, PA.

61) **Materials Science and Technology 2018 Annual Meeting (Host: Roger Narayan) -** Controlling Controlled Release to Make Medicine that Imitates Life. Scheduled for October 14th -18th, 2018. Columbus, OH.

60) **KEYNOTE: Texas Regional Biomaterials Conference (Host: Society for Biomaterials Student Chapter Organizing Committee) -** Controlling Controlled Release to Make Medicine that Imitates Life. June 1st, 2018. College Station, TX.

59) **AIChE Annual Meeting, Materials Engineering and Science Division (MESD) Division 8 Plenary Session (Host: John Ekerdt (UT Austin) and Michael Kilby (U Tennessee)) –** Controlled Release Systems for Recruitment and Differentiation of Endogenous Regulatory T Cells. 2018 Annual Meeting.

58) **Materials Research Society (MRS) Annual Meeting, Session: Immune Modulatory Materials – From Design to Translational Applications (Host: Evan Scott, (Northwestern University)) –** Immunoengineering Biomaterials for Recruitment and Differentiation of Endogenous Regulatory T Cells. April 2nd – 6th, 2018. Phoenix, AZ.

57) **University of Washington, Department of Chemical Engineering (Host: Francois Baneyx)** - Controlling Controlled Release to Make Medicine that Imitates Life. November 6th, 2017. Seattle, WA.

56) **DISTINGUISHED LECTURE:** Youngstown State University, the J. Douglas Faires Distinguished Lecture (Host: Angela Spalsbury) - Controlling Controlled Release to Make Medicine that Imitates Life. September 20th, 2017. Youngstown, OH.

55) **Northwestern University, Department of Chemical and Biological Engineering (Host: Joshua Leonard) –** Controlling Controlled Release to Make Medicine that Imitates Life. May 18th, 2017. Evanston, IL.

54) **Northwestern University, Department of Chemical and Biological Engineering (Host: William Miller) –** Controlling Controlled Release. May 17th, 2017. Evanston, IL.

53) **Johnson and Johnson, Consumer and Personal Products Division (Host: Sherket Peterson) –** Controlled Release for Delivery of Agents to Control Bacterial Biofilms. April 6th, 2017. Skillman, NJ.

52) **GRADUATE STUDENT CHOICE SEMINAR: University of Maryland, Fischell Department of Bioengineering (Host: Silvina Matysiak) –** Controlling Controlled Release to Make Medicine that Imitates Life. February 3rd, 2017. College Park, MD.

51) **KEYNOTE: University of Florida / Society for Biomaterials Annual Biomaterials Day (Host: Alex Collins, President of UF Chapter of the Society for Biomaterials) -** Medicine That Imitates Life Through Biomimetic Controlled Release. March 11th, 2016. Gainesville, FL.

50) **University of Kentucky, Department of Chemical and Materials Engineering (Host: Douglas Kalika) –** Controlling Controlled Release to Make Medicine that Imitates Life. March 2nd, 2016. Lexington, KY.

49) **PANELIST: Chemical Heritage Foundation (Host: Director, Jody Roberts) –** Medicine That Imitates Life Through Biomimetic Controlled Release. October 6th, 2015. Philadelphia, PA.

48) **PLENARY: Arnold and Mabel Beckman Foundation Young Investigator Award Symposium (Host: Executive Director Jacqueline Dorrance) -** Medicine That Imitates Life Through Biomimetic Controlled Release. August 8th, 2015. National Academies, Irvine, CA.

47) **KEYNOTE: Department of Pharmaceutical Sciences Annual Retreat (Host: Barry Gold) -** Medicine That Imitates Life Through Biomimetic Controlled Release. June 1st, 2015. Ogelbay Resort, Wheeling, WV.

46) **Council for Chemical Research Annual Meeting (Host: Mario Eden and Mark McCready)** - Invited Panelist for: "Methods for Incentivizing Faculty In Today's Chemical Engineering Department". May 4th, 2015. Alexandria, VA.

45) **Penn Periodontal Conference (Host: Diana Graves) –** Recruitment of Regulatory Lymphocytes for Periodontitis. University of Pennsylvania, Philadelphia, PA, July 1, 2015.

44) **NIH K12 Panel (Host: Wishwa Kappoor) –** Advice from Successful Past K-Award Winners. Pittsburgh, PA, February 25, 2015.

43) **7th Ocular Diseases Drug Discovery Conference (Host: Stephanie Chow) –** Advanced Controlled Release Systems for Next Generation Opthalmic Drug Delivery. San Diego, CA, March 19-20, 2014.

43) **University of Pittsburgh Department of Pharmacology (Host: Bruce Freeman) -** Controlling Controlled Release to Make Medicine That Imitates Life. Pittsburgh, PA, March 17, 2015.

42) **Merck Pharmaceuticals (Host: Michael Kress) –** Controlling Controlled Release. West Point, PA, November 3, 2014.

41) **Materials, Science, & Technology Annual Meeting (Host: Roger Narayan) –** Biomaterials for Recruitment and Differentiation of Endogenous Cells. In "Next Generation Biomaterials". Pittsburgh, PA, October 13, 2014.

40) **University of Oklahoma – Department of Chemical, Biological & Materials Engineering (Host: Friederike Jentoft) –** Controlling Controlled Release to Make Medicine That Imitates Life. Norman, OK, October 2, 2014.

39) **GRADUATE STUDENT CHOICE SEMINAR: University of California, San Diego – Center for Excellence in Nanomedicine and Engineering (Host: Adah Almutairi) -** Controlling Controlled Release to Make Medicine That Imitates Life. San Diego, CA, May 28, 2014.

38) **PPG Innovations in Materials Chemistry Symposium (Host: Nat Rosi) –** Controlling Controlled Release from Biodegradable Systems. Pittsburgh, PA, May 2, 2014.

37) **SESSION KEYNOTE: American Institute of Chemical Engineering Annual Meeting (Host: Christopher Jewell) –** Next Generation Controlled Release Systems for Immunoregulation. Biomaterials for Immunological Applications. San Francisco, CA, November 3 – 8, 2013.

36) **University of Buffalo (Host: Stelios Andreadis)** (Department of Chemical and Biological Engineering) – Medicine that Imitates Life Through Biomimetic Controlled Release. Buffalo, NY, October 23, 2013.

35) **Syracuse University and SUNY (Hosts: Chris Nomura and Rebecca Bader)** (Departments of Chemistry and Biomedical and Chemical Engineering Seminar Series) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Syracuse, NY, March 2012.

34) **PLENARY: University of Minnesota, iPRIME (Industrial Partners for Research in Interfacial and Materials Engineering) (Host: Ron Siegel) –** Controlling Controlled Release from Biodegradable Systems. Minneapolis, MN, January 15, 2013.

33) **PLENARY: American Society for Reconstructive Transplantation Annual Meeting (Host: Gerald Brandacher) –** Nanomedical Approaches to Drug Delivery. In Reconstructive Transplantation: What's on the Horizon? Chicago, IL, November 17, 2012.

32) **Vanderbilt University (Host: Paul Laibinis)** (Department of Chemical and Biomolecular Engineering Seminar Series) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Nashville, TN, November 12, 2012.

31) **University of Texas, Austin (Host: Nicholas Peppas)** (Department of Bioengineering Seminar Series) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Austin, TX, September 6, 2012.

30) **Materials, Science, & Technology Annual Meeting (Host: Roger Narayan) –** Can Restoring Immunological Homeostasis in the Periodontium Lead to Regeneration? Pittsburgh, PA, October 26, 2012.

29) **KEYNOTE: Society of Analytical Chemists of Pittsburgh Regional Meeting (Host: Geoffrey White) –** Medicine that Imitates Life Through Biomimetic Drug Delivery. Duquesne University, Pittsburgh, PA, October 1, 2012.

28) **American Chemical Society Fall Meeting (Host: Klok Harm-anton) –** Rationally Designed Controlled Release Systems for Periodontal Disease that Promote Immunological Homeostasis. Symposium on Polymers at the Interface of Biology, Philadelphia, PA, August 19, 2012.
   - ***Selected for an ACS Press Release and press interview in Philadelphia***
   - ***Disseminated to thousands of print and online press outlets around the globe***

27) **PLENARY: Induction Conference for 2012 Beckman Young Investigators (Host: Jacqueline Dorrance) –** Medicine that Imitates Life Through Biomimetic Drug Delivery. Center for the National Academy of Science and Engineering. Irvine, CA, August 3 – 5, 2012.

26) **Fox Center Conference on Vision Restoration: Regenerative Medicine in Ophthalmology (Host: Joel Schuman) –** Advanced Controlled Release Systems for Next Generation Ophthalmic Therapy. Pittsburgh, PA, May 11, 2012.

25) **Gordon Research Conference on Biology and Pathobiology of the Cornea (Host: Suzanne**

Fleiszig) – Advanced Controlled Release Systems for Next Generation Ophthalmic Therapy. Ventura, CA, March 29, 2012.

24) **Senior Vice-Chancellor's Distinguished Lecture (Host: Arthur Levine)** – Medicine that Imitates Life Through Biomimetic Drug Delivery. Pittsburgh, PA, March 2, 2012.

23) **18th Annual Hilton Head Workshop (Short Course on Controlled Release Strategies for Regeneration and Immune Modulation) (Host: Julia Babensee)** – Can Restoring Immunological Homeostasis in the Periodontium Lead to Regeneration? Hilton Head, SC, March 14, 2012.

22) **International Association of Dental Research Annual Meeting and Exhibition (Host: Elia Beniash)** – Treatments for Periodontal Disease that Recruit Regulatory T-cells. Tampa, FL, March 21 – 24, 2012.

21) **Materials Research Society Fall Meeting (Host: Darrell Irvine)** (Micro- and Nanoscale Processing of Biomedical Materials Symposium) – Anisotropic, Patchy Microspheres with Soft Protein Islets. Boston, MA, November 2011.

20) **University of Florida (Host: Benjamin Keselowsky)** (Department of Biomedical Engineering Seminar Series) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Gainesville, FL, October 2011.

19) **KEYNOTE: Youngstown State University QUEST Regional Symposium (Host: Jeff Coldren)** – Engineering the Next Generation of Cell Interactive Medicine. Youngstown, OH, April 5, 2011.

18) **Materials Research Society Spring Meeting (Host: Samir Mitragotri and Joerg Lahann)** (Symposium on Biomimetic Engineering of Particles) – Anisotropic, Patchy Microspheres with Soft Protein Islets. San Francisco, CA, April 2011.

17) **Case Western University (Host: Erin Lavik)** (Department of Bioengineering) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Cleveland, OH, March 31, 2011.

16) **McGowan Institute for Regenerative Medicine (Host: Alan Russell)** (Annual Retreat) – Biomimetic Controlled Release Formulations that Prolong Survival of Whole Limb Transplants. Farmington, PA, March 6 – 9, 2011.

15) **Carnegie Mellon University (Host: Chris Bettinger)** (Department of Chemical Engineering and Bioengineering Seminar Series) – Medicine that Imitates Life Through Biomimetic Drug Delivery. Pittsburgh, PA, January 24, 2011.

14) **American Chemical Society National Meeting (Host: Darrell Irvine)** – Rationally Designed Biomimetic Delivery System for Immunosuppression. Boston, MA, August 23, 2010.

13) **Particles 2010 (Host: Roger Narayan)** (Medical/Biochemical Diagnostic, Pharmaceutical, and Drug Delivery Applications of Particle Technology) – Polymeric Particles as a Platform for Biomimetic Drug Delivery. Lake Buena Vista, FL, May 23 – 25, 2010.

12) **Duquesne University (Host: Wilson Meng)** (School of Pharmacy) – Polymeric Microcapsulates as a Platform Technology for Biomimetic Drug Delivery. Pittsburgh, PA, May 19, 2010.

11) **University of Pittsburgh (Host: Harvey Borovetz)** (Department of Bioengineering) – Controlling Controlled Release from Biodegradable Systems. Pittsburgh, PA, December 3, 2009.

10) **Materials, Science, & Technology Annual Meeting 2009 (Host: Roger Narayan)** – Polymeric Microcapsulates as a Platform Technology for Biomimetic Drug Delivery. Pittsburgh, PA,

October 26, 2009.

9) **Auburn University (Host: Mark Byrne)** (Department of Chemical Engineering) – Polymeric Microcapsulates as a Platform Technology for Biomimetic Drug Delivery. Auburn, AL, October 21, 2009.

8) **American Chemical Society National Symposium (Host: Anna Balazs)** – Polymeric Microcapsules: Theory, Experiment and Applications. Philadelphia, PA, March 22 – 26, 2009.

7) **Youngstown State University (Host: Douglas Price)** (Cross-listed in Departments of Chemistry and Chemical Engineering) – Overcoming Challenges in the Non-Viral Delivery of Genetic Vaccines. Youngstown, OH, November 2006.

6) **Thomas E. Starzl Transplantation Institute (Host: Fadi Lakkis)** (Cross-listed with the Department of Immunology) – Functional, Non-Viral Genetic Vaccine Vectors. Pittsburgh, PA, June 2006.

5) **Society for Biomaterials National Meeting (Host: Joel Collier)** – Overcoming Challenges in the Non-Viral Delivery of Genetic Vaccines. Pittsburgh, PA, April 2006.

4) **Biomaterials Group, University of Pittsburgh (Host: Kacey Marra)** – Functional, Non-Viral Genetic Vaccine Vectors. Pittsburgh, PA, April 2006.

3) **US-Japan Symposium on Drug Delivery Systems (Selected for invited talk after being awarded "best poster")** – High Throughput Fabrication of Polymeric Microparticles. Maui, HI, December 2005.

2) **Zycos (MGI Pharmaceuticals) (Host: Mary Lynne Hedley)** – Enhancing Microparticulate Genetic Vaccine Delivery using Poly-Beta Amino Esters. Lexington, MA, October 2004.

1) **MIT Cancer Research Center (Host: Douglas Lauffenberger)** – Functional, Non-Viral Genetic Vaccine Vectors. Boston, MA, September 2003.

INTELLECTUAL PROPERTY

20) "pH Triggerable Polymeric Microparticles" (US7943179B2) - **Inventors: Little, S.R.,** Lynn, D.M., Anderson, D.G., Langer, S.R.

- *Licensed by Zycos Inc. (prior to being acquired by MGI Pharma)*

19) "pH Triggerable Polymeric Particles or Films Containing a Poly (Beta-Amino Ester)" (WO2005055979A2) - **Inventors: Little, S.R.**, Lynn, D.M., Anderson, D.G., Langer, S.R.

- *Licensed by Zycos Inc. (prior to being acquired by MGI Pharma)*

18) "High-Throughput Fabrication of Microparticles"(WO2007078765A3) - **Inventors:** Little, S.R., Lynn, D.M., Anderson, D.G., Langer, S.R.

17) "Hierarchically Self-Assembling Linear-Dendritic Hybrid Polymers for Delivery of Biologically Active Agents" (WO2007002663A2) - **Inventors:** Hammond, P., Cunningham, K.G., Langer, R., Little, S.R.

16) "Artificial Cell Constructs for Cellular Manipulation" (US8846098B2 and US10449151B2) - **Inventor: Little, S.R.**

15) "Vasoactive Intestinal Peptide Release from Micoparticles" pending (US20140142039A1) – **Inventors: Little, S.R.,** Glowacki, A.J.

14) "Engineered Microparticles for Macromolecule Delivery" pending (US20170290917A1) - **Inventors: Little, S.R.,** Rothstein, S.N.

- *Licensed by Qrono Inc.*

13) "Methods to Prepare Patchy Particles" (US9211519B2) - **Inventors: Little, S.R.,** Kamalasanan, K.

12) "Controlled Release Formulations for the Induction and Proliferation of Blood Cells" - (US10765634B2). **Inventors: Little, S.R.,** Raimondi, G., Thomson, A.W., Jhunjhunwala, S.

11) "Recruitment of Mesenchymal Stem Cells Using Controlled Release Systems"(US10195252B2). **Inventors: Little, S.R.,** Gottardi, R., Hwang, M.P., DeSantis, D.

10) "Osteoarthritis Treatment with Chemokine-Loaded Alginate Microparticles" pending (US20190209651A1). **Inventors: Little, S.R.,** Gottardi, R., Hwang, M.P., DeSantis, D.

9) "Thermoresponsive Hydrogel Containing Polymer Microparticles for Noninvasive Ocular Delivery" pending (US20150374633A1). **Inventors:** Fedorchak, M.V., **Little, S.R.,** Schuman, J.S.

- *Optioned by the Cystinosis Foundation*

8) "Treating Soft Tissue via Controlled Drug Release" (US10179111B2) **- Inventors: Little, S.R.,** Gottardi, R., Hwang, M.P., DeSantis, D.

7) "Assay for Detection of Bladder or Prostate Cancer" pending (US20190120843A1) – **Inventors:** Acharya, A., **Little, S.R.,** Tarin,T.V.

6) "Biomimetic Drug Delivery of an Immunomodulatory Agent for the Treatment of Ocular Conditions" pending (US20170367981A1) – **Inventors: Little, S.R.,** Guaragno, M.L., Glowacki, A.G., Fedorchak, M.V., Balmert, S.C.

5) "Thermoresponsive Hydrogel Containing Polymer Microparticles for Controlled Drug Delivery to the Ear" (WO2019118330A1) – **Inventors: Little, S.R.,** Fedorchak, M.V., Schuman, J.S.

- *OTERO Inc. intends to license this technology from the University of Pittsburgh*

4) "Artificial Cells and Delivery Devices for Use in Tissue Engineering and Related Methods" (US20190336444A1) – **Inventors:** Fedorchak, M.V., Krawiec, J., **Little, S.R.,** Lorentz, K., Vorp, D.A., Weinbaum, J.

3) "Treatment of Ocular Conditions Utilizing a Histone/Protein Deacetylase Inhibitor" (US20200261366A1) – **Inventors: Little, S.R.,** Ratay, M.L.

2) "Compositions and Methods for Administering a YAP1/WWRT1 Inhibiting Composition and a GLS1 Inhibiting Composition" – **Inventors:** Acharya, A.P, Chan, S.Y., **Little, S.R.**

- *This IP is the basis for founding of a new spin-off company from the University of Pittsburgh called Synhale Tx, Inc.*

1) "Probiotics and Probiotic Compositions for Regulating Body Weight" (WO2019168990A1) – **Inventors:** Acharya, A.P, **Little, S.R.**

ENTREPRENEURSHIP

1) Founded **Qrono Inc.**, the first custom-design controlled release service company in 2011 in Pittsburgh, PA., with Co-Founder, CEO and former graduate student: Sam Rothstein, PhD.

- **Raised $3.8M over the course of positioning for IND enabling studies**

Awards for Qrono Inc.

- 2017 – Pittsburgh Business Times Innovation Award Winner (Inaugural Winner)
- 2017 – NIH Commercial Accelerator Program Award
- 2015 – US Department of Defense Phase I STTR Award
- 2014 – National Institutes of Health Phase I STTR Award (NCI)
- 2014 – US Department of Defense Phase II STTR (September 2014 – August 2016)
- 2013 – Pittsburgh Technology Council Tech 50 Award Winner in the category of "Innovator of the Year"
- 2013 – US Department of Defense Phase I STTR Award
- 2012 – CNBC's "15 Promising New Startups"
- 2012 – National Institutes of Health Phase I STTR Award (NIGMS)
- 2011 – One of the Kauffman Foundation's "Most Promising Ventures from Around the World"
- 2010 – 1st Place, University of Pittsburgh's "Big Idea" Competition for New Product Ideas

2) Founded **OTERO Therapeutics Inc.** to develop the first semi-permanent eye drop for treatment of glaucoma in 2018 with Co-Founder and former post doc, Morgan Fedorchak, PhD and with Co-Founder and collaborator, Joel Schuman, MD.

- **Technology licensed by the Cystinosis Foundation**

3) Founded **Oraxsys Therapeutics Inc.** to develop the first formulations that are designed to recruit the body's own cells to treat diseases of dysregulated immune function.

4) Currently founding a startup (currently proposed name: **Synhale Inc.**) to translate patented

technology for treatment of pulmonary hypertension with Co-Founder and collaborator, Stephen Chan, MD.

FUNDING (COMPETITIVE, PEER-REVIEWED EXTERNALLY)

37) NIH NHLBI (1 R01 HL157017-01A1) - Preclinical Assessment of a Compliance Matched Biopolymer Vascular Graft. $3,468,332.00. September 2021 – August 2026.
Role: Co-PI
The aim of this work is to engineer a pre- and post-implantation compliance controlled fully biodegradable tissue engineered vascular graft.

36) NSF ECO-CBET (2133423) – Sustainability from the Bottom Up: A Wholistic Solution to Balancing the N-Cycle. $1,699,999. September 2021 – August 2025.
Role: Co-Investigator
The aim of this work is to engineer nitrogen delivery systems for efficient nutrient delivery for agricultural products.

35) United States Department of Defense (#RT200049) – Sustained-release, Microparticle-based, Anti-Rejection through Enhancement of Regulatory T-cells (S.M.A.R.T.E.R) Platform for VCA Immunomodulation. $1,200,000. October 1, 2021 –September 30, 2024.
Role: PI
The aim of this work is to test engineered systems designed to orchestrate a patient's own regulatory T cells in a non-human primate model of VCA graft survival.

34) United States Department of Defense (#RT200012P2) – Reparative Treg and Microparticle Therapy for the Prevention of VCA Acute and Chronic Rejection. $1,200,000. October 1, 2021 – September 30, 2024.
Role: Co-PI
The aim of this work is to explore enrichment of a patient's own reparative regulatory T cells through microparticle (MP)–based systems that are engineered to release key cytokines, immunosuppressive agents, and chemokines to promote long-term VCA graft survival.

33) NIH NIDCR R01 Research Project Grant (1R01DE029034-01) – Treatment of Periodontitis by Homing M2 Macrophages. $1,886,728. July 2020 – June 2025.
Role: Co-PI
The goals of this proposed project are to test mimetic controlled release systems that cause the homing of endogenous M2 macrophages to regulate local inflammation of the periodontium.

32) DARPA, The Regents of the University of California - Berkeley – Next-Generation CRISPR and anti-CRISPR Tools and Delivery Systems for Safely Engineering the Genome and Epigenome. $183,339. May 1, 2019 – October 30, 2021.
Role: Co-Investigator
This work aims to facilitate the development of methods to induce immune tolerance to Cas9 protein. Specifically, Micro- and Nano-Particles and MicroNeedle Arrays production, quality control testing and strategy development for maximum efficacy delivery system.

31) NIH, NIDCR Michigan-Pitt-Weiss Resource Center - Controlled Release System for Immunoregulation and Treatment of Periodontal Disease. $100,000. March 2019 – February 2021.

Role: PI
The goal of the proposal is to take the next steps in developing non-antibiotic, controlled release system that mimics the body's natural immune regulation mechanisms and harnesses natural, endogenous cells as agents of periodontal disease treatment.

30) DoE, GAANN – An Integrated Education in the Engineering of Functional Materials. $597,000. Sept 2019 – August 2022.
Role: Co-Investigator
The aim of this grant is to fund graduate students in national areas of need in the area of functional materials.

29) NIH, NIAMS R01 – Engineering the Skin Microenvironment to Produce Allergen Tolerance. (1R01 AR074285-01). $2,300,000. August 2018 – June 2023.
Role: PI
The aim of this project is to develop an antigen specific strategy to prevent and treat contact dermatitis through local control over presentation of regulatory cell inducing factors in the skin microenvironment.

28) NIH, NIDCR Michigan-Pitt-Weiss Resource Center - Controlled Release System for Immunoregulation and Treatment of Periodontal Disease. (C1-0616). $146,202. March 2018 – February 2019.
Role: PI
The goal of the proposal is to develop non-antibiotic, controlled release system that mimics the body's natural immune regulation mechanisms and harnesses natural, endogenous cells as agents of periodontal disease treatment.

27) NIH, NIDCR Michigan-Pitt-Weiss Resource Center. September 2017 – August 2022.
Role: Member of Technical Readiness Assessment Team (5% Effort Annually, $9,600)
The aim of this consortium is to support research projects of interest to the NIDCR that are translational in nature as movement toward first in human studies. The goal of the Technical Readiness Assessment Team is to evaluate the technical readiness for Interdisciplinary Technology Projects (ITP) and provide guidance related to the scientific, engineering (including in vitro/in vivo components) and manufacturability of dental, oral and craniofacial technologies.

26) NIH NIAID R01 – Parameters that Underlie Treg Insufficiency in Autoimmune Diabetes (2R01DK089125-05A1). $200,155. September 2016 – August 2021.
Role: Co-Investigator
The aim of this project is to develop drug delivery systems for maintenance of Treg in models of autoimmune diabetes.

25) NIH NIDCR R21 - Treatment of Periodontitis by Homing of M2 Macrophages (1R21DE025735-01A1). $37,010. September 2016 – August 2018.
Role: Co-Investigator
The aim of this project is to develop sustained release systems for M2 macrophage chemokines for treatment of periodontal disease.

24) NIH NHLBI R01 – Artificial Stem Cells for Vascular Tissue Engineering. $1,925,000. July 1, 2016 – June 30, 2021.

Role: Co-Investigator
The goal of the proposed work is to explore cell-sized degradable microspheres that release secreted factors from mesenchymal stem cells in order to provide a cell-free vascular tissue engineering solution.

23) Johnson and Johnson – Controlled Release Carriers that Target Oral Biofilms. $211,118. October 1, 2016 – September 30, 2018.
Role: PI
The aim of this project is to develop controlled release systems for proprietary molecules used by Johnson and Johnson to eliminate bacterial plaques.

22) US Food and Drug Administration – A Biorelevant Dissolution Method for Particulate Dosage Forms in the Periodontal Pocket. $30,000. September 1, 2015 – August 31, 2017.
Role: Co-PI
The aim of this project is to create a new dissolution method for pharmaceutical formulations designed for administration to the periodontal pocket.

21) Wallace H. Coulter Foundation – SoliDrop – Long-term, Noninvasive Glaucoma Drug Delivery System. $100,000. September 1, 2015 – August 31, 2016.
Role: Co-Investigator
The goal of this project is to explore the safety and translatability of thermo-gelling eye drop formulations for sustained treatment of glaucoma.

20) United States Department of Defense (#MR141093) – Regulatory T-Cell Enriching Microparticles for Promoting Vascularized Composite Allotransplant Survival. $1,133,302. September 15, 2015 – September 14, 2021.
Role: PI
The aim of this work for the DoD is to test the hypothesis that both expansion and recruitment of suppressive lymphocytes called regulatory T cells (Tregs) using biomimetic microparticle (MP)–based systems that release key cytokines, immunosuppressive agents, and chemokines can be orchestrated to promote long-term graft survival in preclinical rat and swine composite tissue allotransplantation (CTA) models.

19) NSF – I-Corps Sites: University of Pittsburgh - Advancing Innovation, Entrepreneurship and Opportunity Commercialization. $300,000. March 15, 2015 – February 28, 2015.
Role: PI
The goal of the NSF I-Corps Site is to prepare our engineers to extend their focus beyond the University laboratory and accelerate the economic and societal benefits of NSF-funded, basic-research projects that are ready to move toward commercialization.

18) NIH NEI R01 Research Project Grant (1R01EY024039 – 01A1) – Combined Hydrogel/Microparticle Eye Drops for Sustained Delivery of Glaucoma Medication. $1,562,397. December 1, 2014 – November 30, 2020.
Role: PI
The goals of this NIH Research Project Grant is to develop a new, easy-to-administer, and noninvasive treatment capable of long-term release of glaucoma medication to the surface of the eye.

17) Phase II Wallace H. Coulter Foundation Translational Research Award – Treatment of Periodontitis via Recruitment of Regulatory Lymphocytes. $410,000. September 2014 – August 2016.
Role: PI
The aim of this work is to develop first-of-their kind treatments for periodontal disease that recruit a patient's own regulatory cells to resolve inflammation.

16) Research to Prevent Blindness (RPB) Innovation in Ophthalmic Research Award. $100,000. January 2014 – December 2016.
Role: PI
The aim of this work is to develop the first, long-acting eye drop formulation for treatment of glaucoma.

15) NIH Small Business Technology Transfer Grant (STTR) Phase I (1R41GM106342-01A1) - A New *In Silico* Design Platform for Building Custom Controlled Release Systems. $139,207. September 2012 – December 2014.
Role: PI
The goals of the proposed research are to rapidly build and validate three, very different controlled release formulations using a model-aided design process that precisely meets a set of representative "needs" in the field.

14) Camille Dreyfus Teacher-Scholar Award – Mimicking Biological Structure and Behavior Using Polymeric Release Systems and Carbon Nanotubes. $75,000. September 2013 – August 2017.
Role: PI
This award has no project goals and is given to the awardee based on merit with no restrictions.

13) Wallace H. Coulter Foundation Translational Research Partnership (TPII) Award - Treatments for Periodontitis that Restore Immunological Homeostasis. $100,000. September 2013 – August 2016.
Role: PI
The goal of this work is to move toward a successful FDA IND application for Treg-recruiting formulations as a treatment for human periodontitis.

12) NRRC/NIH Equipment Grant (S10 RR026349) - Request for whole animal fluorescence tomographic imaging device, VisEn FMT2500 (Perkin Elmer). April 2011 – March 2012.
Role: Co-PI
The goal of this proposal was to obtain the resources necessary to purchase and maintain a high resolution, live animal imaging device at the University of Pittsburgh Cancer Research Center.

11) NIH NIDCR R01 Research Project Grant (1R01DE021058-01 A1) – Treatment of Periodontitis via Recruitment of Regulatory Lymphocytes. $1,780,000. September 2011 – August 2015.
Role: PI
The goals of this proposed project are to design mimetic controlled release systems to explore a new treatment for periodontitis – one that employs the body's own sophisticated methods for regulation of inflammation.

10) NIH NIDCR High Priority, Short Term Award (1R56DE021058 – 01; Tied to R01 Above) – Treatment of Periodontitis via Recruitment of Regulatory Lymphocytes. September 2010 – September 2011.
Role: PI
The goals of this proposed project are to precisely design mimetic, controlled release systems and

apply them as a new type of treatment in a mouse model of periodontitis.

9) Phase I Wallace H. Coulter Foundation Translational Research Award – Treatments for Periodontitis that Restore Immunological Homeostasis. $180,000. September 2011 – August 2013.
Role: PI
Our goals are to obtain preclinical data (in a canine model) supporting new therapies that restore immunological homeostasis in the periodontium (as opposed to current therapies that only aim to temporarily remove recurring pathogens).

8) Department of Defense Advance Regenerative Medicine Grant (ARMIV) – Rational Synthesis of Triggerably-Dissolvable Materials for Minimally Invasive Removal of WoundCAP Delivery Devices. $151,200. July 2010 – June 2012.
Role: Co-PI
PI: William Wagner
The major goal of this program is to develop a robust, hollow fiber-based system (WoundCAP) to deliver regenerative growth factors to a wound site while including the means for minimally invasive removal/dissolution of the delivery system.

7) NSF Cyber-Enabled Discovery and Innovation (CDI) Type I (#0941260) - Computational Models to Enable the Experimental Self-Assembly of Modified Carbon Nanotubes into Biomimetic Synthetic Cellular Vesicles $850,000. Sept 2009 – August 2012.
Role: PI
Our goal is to develop and experimentally verify computational models for the self-assembly and function of biomimetic, cylindrical channel-like building blocks to create a synthetic cellular membrane. By integrating computational and experimental efforts, we aim to achieve control over architecture, rate of transport, onset of secretion, and even selectivity of transport.

6) Department of Defense Advanced Regenerative Medicine Grant (ARMIII) - Temporal Delivery of Angiogenic Factors $91,000. February 2009 - June 2010.
Role: PI
The major goals of this project are to utilize externally regulated delivery systems in order to explore the effects of changing the sequences of angiogenic growth factor delivery.

5) Beckman Foundation Young Investigator Award - Synthetic Dendritic Cells $300,000. September 2008 - August 2011.
Role: PI
The major goals of this project are to explore modifications of surface presentation in order to improve the ability of synthetic dendritic cells to better mimic their biological counterpart.

4) United States Army Institute for Regenerative Medicine (AFIRM) Multicenter Grant - Synthetic Bone $80,000,000. April 2008 - March 2011.
Role: Co-PI
The aims of this multicenter, collaborative project are to mimic the physiologic milieu of bone by providing temporal and special delivery of bone growth factors in tandem with natural materials including calcium phosphate ceramics.

3) NIH NIAID R01 Research Project Grant (AI076060) - Immunization Strategies for Autologous HIV I Immunotherapy $1,250,000. April 2008 - March 2013.
Role: Co-Investigator
PI: Lou Falo
The aims of this grant as it pertains to my role involve utilizing new biomaterials to deliver

genetic vaccines for HIV immunotherapy to dendritic cells.

2) NIH K-Award, K12 - Grant # 5KL2 RR024154 02 - Synthetic, Biomimetic Delivery Constructs for Immunosupression, $637,827. September 2007 - August 2011.
Role: PI
The major goals of this project are to develop the PI into an independent investigator that works between the fields of engineering and transplant immunology.

1) American Heart Association (National), Artificial Antigen Presenting Cells for *In Vivo* Manipulation of Regularity T Cells, $65,000. January 2007 – December 2008.
Role: PI
The goals of this proposal were to explore synthetic, cell-sized particles as a means to mimic tolerogenic dendritic cells and their therapeutic effects in a model of heterotopic heart transplantation.

FUNDING (COMPETITIVE, REVIEWED INTERNALLY)

20) Commonwealth of Pennsylvania Manufacturing Innovation Program – Scalable Manufacturing of Monodisperse Biodegradable Microspheres Using Microfluidics. $68,242. September 2021 – August 2022.
Role: PI
The goal of this work is to explore microfluidic technologies for production of formulations with monodisperse particle sizes.

19) Commonwealth of Pennsylvania Research Development – Therapies for COVID-related Disease and Technology Development. $126,000. September 2021 – August 2023.
Role: Co-PI
The goal of this project is to explore novel formulations for treatment of COVID-related disease.

18) Central Research Development Program, University of Pittsburgh - A conforming thermogel retained in the sinuses for long-acting treatment of chronic rhinosinusitis. $17,000. July 2019 – June 2021.
Role: PI
The goal of this work is to explore a new, thermoresponsive hydrogel for delivery of factors to inflamed sinus tissue and measure outcomes.

17) Center for Medical Innovation, University of Pittsburgh – Local induction of tolerogenic T cells to ameliorate inflammation in inflammatory bowel disease. $15,000. July 2018 – June 2019.
Role: co-PI
The goal of this work is to explore induction of endogenous regulatory T-cells as a way to treat inflammatory bowel disease.

16) Center for Medical Innovation, University of Pittsburgh – At home diagnostics: Early detection and monitoring of prostate cancer. $15,000. January 2014 – December 2015.
Role: co-PI
The goal of this work is to develop a facile, at-home test to detect prostate cancer in urine of patients.

15) Innovation Works TCC Grant – Translation of Cell Recruiting Formulations for Treatment of

Inflammatory Disorders. $25,000. January 2015 – December 2016.
Role: PI
This TCC grant provides Commonwealth of Pennsylvania support for translational milestones.

14) Commonwealth of Pennsylvania Research Development – Tuning of thermogels to be used as sustainable eye drops. $44,000. January 2015 – June 2015.
Role: Co-PI
The goal of this project is to use the seed funding to explore formulation and physical properties of reverse thermogels as a retention unit for delivery to the eye

13) Center for Medical Innovation, University of Pittsburgh – PerioMag GBR Barrier Membrane. $12,000. July 2014 – June 2015.
Role: co-PI
The goal of this work is to develop a "PerioMag GBR system" that includes a mechanically reinforced, yet fully degradable, barrier membrane comprised of a metallic magnesium (Mg) mesh embedded in an FDA approved polymer (PLGA).

12) Commonwealth of Pennsylvania Research Development – Establishing Dominant Tolerance in Vascularized Composite Allotransplantation via Biomimetic Recruitment and Expansion of Regulatory T Cells. $40,000. January 2014 – June 2014.
Role: PI
This project will investigate the potential of using biomimetic drug delivery systems to promote long-term VCA survival in the absence of systemic immunosuppression via the in situ recruitment and expansion of a patient's own suppressive regulatory T cells.

11) Commonwealth of Pennsylvania Research Development – A Novel, "Micro-CaP" Scaffold System for the Recruitment and Differentiation of Endothelial Cells and Osteoblast Precursors. $40,000. September 2012 – June 2013.
Role: PI
Our goals are to design and assess a novel scaffolding construct, called a "MicroCaP" scaffold, to address the need for a tissue engineered material that recruits appropriate cell types to support bone formation at the appropriate time.

10) Commonwealth of Pennsylvania Research Development – A New *In Silico* Design Platform for Building Custom Controlled Release Systems. $50,000. September 2011 – June 2012.
Role: PI
Our goals are to design and build formulations that deliver: 1) ranibizumab for six months, 2) quetiapine for one-month (injectable), and 3) NO2-OA for four weeks.

9) Ocular Tissue Engineering and Regenerative Ophthalmology Research (OTERO) Program - Combating Blindness with Convenient and Comfortable Glaucoma Treatments. $70,000. February 2011 – January 2012.
Role: PI
The major goals of this project are to develop a controlled-release formulation for a common glaucoma medication using polymer microparticles that can improve patient compliance and treatment efficacy.

8) Commonwealth of Pennsylvania Research Development – Preclinical Evaluation of New Periodontal Therapies Based Upon Recruitment of Regulatory T-cells. $50,000. September 2010 – June 2011.
Role: PI

The major goals of this proposal are to utilize a widely accepted pre-clinical canine model of periodontitis to evaluate therapeutic and prophylactic administration of new treatments based upon the recruitment of regulatory T-cells.

7) Vertex Pharmaceuticals Pilot Grant. Manipulation of Dendritic Cells Towards Targeted Therapeutics. $10,000. May 2010 – September 2010.
Role: PI
The major goal of this proposal is to identify a combination of drugs that can effectively manipulate dendritic cell function to achieve a desired clinical outcome.

6) Commonwealth of Pennsylvania Research Development – 3D-Spheroidal Co-Culture Model for Modulation of Osteo-Angiogenesis. $10,000. March 2010 – June 2010.
Role: PI
The major goals of this proposal are to use a new 3D spheroid co-culture model that mimics *in vivo* osteo-angiogenic processes in order to evaluate various growth factors (and schedules thereof) on dual tissue formation.

5) Central Research Development Program, University of Pittsburgh - Dissolvable, Synthetic Vasculature for Delivery of Growth Factors. $16,000. July 2007 – July 2009.
Role: PI
The major goals of this work are to explore hollow fibers composed of cellulose as externally regulated release devices that can be triggerably dissolved upon application of enzyme.

4) Commonwealth of Pennsylvania Research Development - Regenerating Periodontal Structures by Restoring Immunological Regulation. $78,000. August 2008 - July 2009.
Role: PI
The major goals of this work are to explore therapies that recruit regulatory lymphocytes to the periodontium and, in turn, regulate harmful and destructive inflammation.

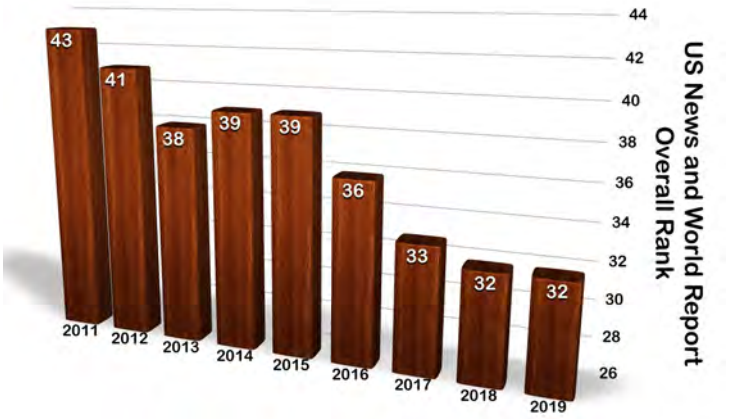
3) Commonwealth of Pennsylvania Research Development - Murine Matrigel Plug Assay for Evaluating Release from Cellulose Hollow Fibers. $100,000. August 2007 - July 2008. Role: PI
The major goals of this proposal are to establish a new ECM-like assay for release, detection, and measurement of biological activity for growth factors that are released from embedded porous hollow fibers.

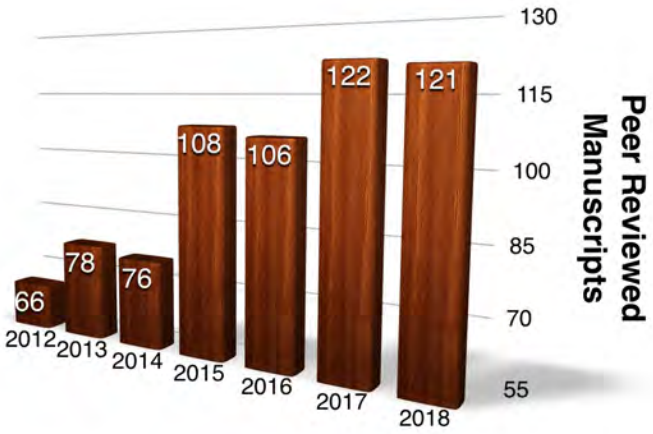
2) MIT Biology Processing and Engineering Center (BPEC), Grant # EEC- 95443790 - Gene Delivery/Microparticle Protein Stability. $150,000. January 2002 - January 2005.
Role: Co-PI
The goal of this work is to explore the biological activity of plasmid DNA after encapsulation and incubation in degradable, polyester microparticles.

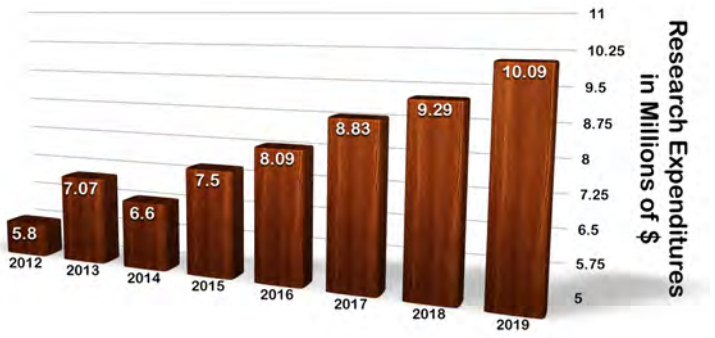
1) MIT Center for Minimally Invasive Therapies (CIMIT), Grant # DAMD17-02-2-006 - Gene Delivery Using Micro and Nanoparticles $450,000. January 2002 - January 2005.
Role: Co-PI
The goal of this work is to explore the stability of plasmid DNA in degradable particles containing a mixture of degradable polyester and degradable poly(beta-amino) esters.

CONTRIBUTIONS AS DEPARTMENT CHAIR (2012 – PRESENT)

- Department ranking broke into the **Top 20 in Public Rankings (#19) for first time in the Department's history in 2018. Entered into the top 20 for AAU Universities in 2016, with the current rank being #17 in 2018. Overall US News and World Report Ranking was #32 in 2019, which represents a >10-point increase over 7 years and the highest rank in Department history.**
- Number of publications from **66** peer-reviewed manuscripts (core faculty) and **83** overall peer-reviewed manuscripts (including associated faculty) **in 2012** to **121** peer-reviewed manuscripts (core faculty) and **221** peer-reviewed manuscripts overall (including associated faculty) **in 2018.**
- **Number of proposals submitted by our core faculty through the Swanson School of Engineering and the School of Medicine increased** from an average of 4 proposals per faculty member in 2012/2013 to an average of 8 proposals per faculty member in 2016/2017.
- **Research expenditures increased from $7M in 2012/2013 to $8.8M in 2016/2017.**
- **Undergraduate enrollment produced $9.29M in 2018 – up from $5.8M in 2012.**



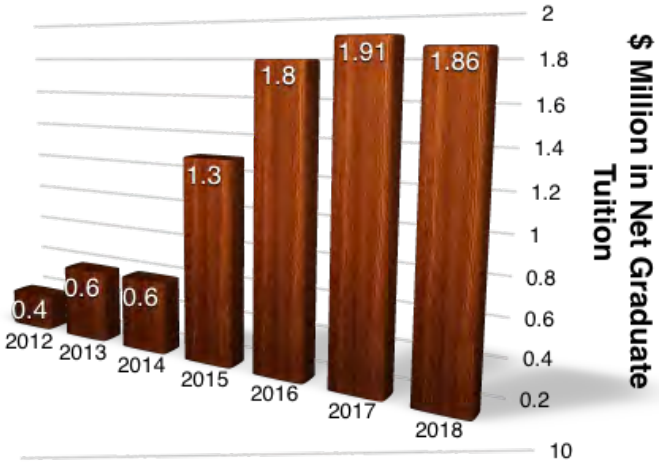


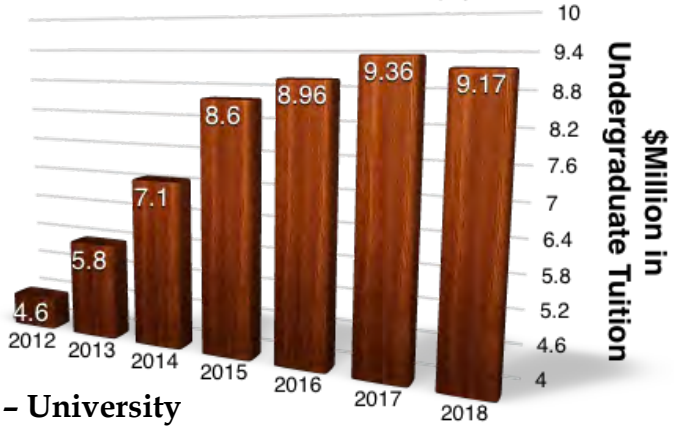


- Rebuilt a 750 sq. ft. Graduate Lounge on the 9th floor of Benedum Hall. Re-established graduate student council.
- **Established MS program in ChemE that (along with PhD program) produces $1.86M in revenue generation annually (2018)** – up from $0.4M in net graduate tuition in 2012.
- **Established the James Pommershiem Award for Excellence in Teaching ($2,000 award)** for

faculty deemed most productive in teaching annually through a partnership with James Pommershiem.

- Department was **#1 in overall teaching effectiveness (OTE) in the School (in competition with all Departments) every year from 2012-2019**.
- Established a **$1.2M Strategic Alliance with the Lubrizol Corporation**, the first of its kind in the Swanson School of Engineering. This Alliance led to an additional $1M in grants to the Office of Research and now projects in the Departments of Mechanical Engineering and Materials Science.
- After 3 years of effort, the **Lubrizol Strategic Alliance was renewed for another 3 years**, with Lubrizol executives citing significant value provided through the multi-million dollar relationship.
- As a result of the Strategic Alliance, our faculty and the Lubrizol Corporation (led by Professor Götz Veser) competed for, and received a large, multi-year grant from the national, DOE RAPID Initiative, bringing the **total value of the Lubrizol – University of Pittsburgh Alliance to >$11M.**





- Member of a team that established a **first-of-its-kind Chemical Engineering Product Design Sequence for undergraduates** culminating in a prototyping experience in the Senior Year.
    - Original Idea Submitted to ASEE and was Awarded Best Poster at the ASEE Annual Meeting in 2015.
    - Led to the founding of Aeronics Inc, a spinoff from the University of Pittsburgh by our undergraduate students, now a startup based in Manhattan, NYC.
    - Students have won numerous awards for their ideas including placing in the money in national innovation competitions in Washington, DC, multiple national Innocentive competitions, and the University of Pittsburgh's Big Idea Competitions multiple years in a row as well, netting our students thousands of dollars in prize money.
- Established the **Department History Wall and the Department Chairs Wall** that highlights the rich history and legacy of leadership from the Department of Chemical and Petroleum Engineering at the University of Pittsburgh dating back to 1911.
- **Department faculty were awarded** two (2) DoE GAANNs and two (2) NSF REUs from 2012-2015, led by Professors Robert Parker and Joe McCarthy.
- **Negotiated the hire of thirteen (13) faculty over a period of 7 years** including: 1) John Keith (TS), 2) Giannis Mpourmpakis (TS), 3) Andrew Bunger (TS) 4) Chris Wilmer (TS), 5) Jason Shoemaker (TS), 6) Susan Fullerton (TS), 7) Michael Matuszewski (NTS), 8) Taryn Bayles (NTS), 9) James McKone (TS), 10) Tagbo Niepa (TS) 11) Hseen Baled (NTS), 12) Joaquin Rodriguez (NTS), 13) Mohammad Masnadi.
- **Five (5) of the Assistant Professors recruited by Dr. Little have received the NSF CAREER Award including three (3) awards all in the same year (2017), the first time to our knowledge,**

in NSF History that 3 Awards will go to the same Department in the same year: 1) John Keith (2017), 2) Giannis Mpourmpakis (2017), 3) Chris Wilmer (2017), 4) Susan Fullerton (2018) and 5) Jason Shoemaker (2020).

- **Hired seven (7) staff members** including: 1) Michael McMahon (Undergrad Labs), 2) Matthew Detzel (Undergraduate Labs), 3) Angela Dillon (Executive Assistant), 4) Julia Roberts (Executive Assistant and Department Reception), 5) Alice Liang (Executive Assistant and Post-Award Administrator), 6) Kristen Harper (Event Coordinator), 7) Emily Kerr (Undergraduate Coordinator).
- Established leadership delegation structure in the Department including Vice Chair for Undergraduate Education, Vice Chair for Graduate Education, Vice Chair for Research, Director of Administration (Chief of Staff), Director of External Relationships, and Director of Entrepreneurship positions.
- Established a new, **goal-oriented, transparent evaluation process** for faculty in 2012 that contributed to the increase in productivity outlined above.

- Selected in 2018 as the Department Chair to speak at the AIChE Annual Meeting in the Young Faculty Forum on the most important things to the success of junior faculty.
- Progress Toward a More Diverse and Inclusive Department
  - **Implemented a modification of the Rooney Rule in faculty hiring.**
  - Hired the **only, current African American, Tenure-Stream Assistant Professor in the Swanson School of Engineering.**
  - Department was the **2015 winner of the Swanson School of Engineering Diversity Award.**
  - Through targeted recruitment efforts, our **percentage of Latino-American engineers (16.7%) is now approximately 3 times the national average for Ph.D. engineering degrees awarded (5.3%), and women engineers now comprise 33% of our entering Ph.D. class, which compares very favorably to the national average for graduating women engineers (32.7%).**
  - Financially supported the **re-establishment of the Graduate Women Engineering Network (GWEN) in the SSOE** entirely through leadership of Chemical Engineering Faculty (Bodnar, Fedorchak, Yang).
  - Retention rate for graduate students in both masters (three year) and PhD (six year) in the Department are now **100% for both women and underrepresented minorities.**
  - Our five-year undergraduate graduation rate for women (sophomore to senior) is **96%, and for underrepresented minorities, it is 100%.**

- **Successful nominations for Awards:**
  - Götz Veser – Chancellors Distinguished Teaching Award, 2022
  - In 2021, 3 out of 3 nominations from Chemical and Petroleum Engineering for Endowed Professorships/Faculty Fellowships were awarded
    - Giannis Mpourmpakis – BiCenntennial Alumni Faculty Fellow, 2021
    - John Keith – R.K. Mellon Faculty Fellow, 2021
    - Judy Yang – William Kepler Whiteford Endowed Professor, 2021
  - Joseph McCarthy – William Kepler Whiteford Endowed Professor, 2020
  - James McKone – Arnold and Mabel Beckman Young Investigator Award, 2020
  - In 2019, 3 out of 3 nominations from Chemical and Petroleum Engineering for Endowed Professorships/Faculty Fellowships were awarded

        - Susan Fullerton – BiCenntennial Alumni Faculty Fellow, 2019
        - Chris Wilmer – William Kepler Whiteford Faculty Fellow, 2019
        - Karl Johnson – William Kepler Whiteford Endowed Professor, 2019
    - Giannis Mpourmpakis – Bodossaki Foundation Distinguished Young Scientist, 2019.
    - Ipsita Banerjee – Swanson School of Engineering Diversity Award, 2019
    - Susan Fullerton – AAAS Marion Milligan Mason Award, 2018
    - Bob Parker - Swanson School of Engineering Board of Visitors Award, 2017
    - In 2017, 5 out of 5 nominations from Chemical and Petroleum Engineering for Endowed Professorships/Faculty Fellowships were awarded
        - Giannis Mpourmpakis – BiCenntennial Alumni Faculty Fellow, 2017
        - John Keith – R.K. Mellon Faculty Fellow, 2017
        - Götz Veser – Nickolas Dececco Endowed Professor, 2017
        - Robert Enick – Bayer Endowed Professor, 2017
        - Robert Parker - Robert van der Luft Endowed Professor, 2017
    - Anna Balazs – John Swanson Endowed Chair in Engineering, 2017
    - Chris Wilmer – CoMSEF Young Investigator Award (Co-Nomination with Karl Johnson), 2017
    - Robert Parker – Swanson School of Engineering Outstanding Educator Award, 2017
    - Susan Fullerton – Ralph E. Powe Junior Faculty Enhancement Award, 2016
    - Judy Yang – Nickolas DeCecco Endowed Professor, 2016
    - Gerald Holder – Distinguished Service Professor (Co-Nomination with Harvey Borovetz), 2016
    - Eric Beckman – Distinguished Service Professor, 2015
    - Joseph McCarthy – Chancellors Distinguished Teaching Award, 2015
    - Yadong Wang – Carnegie Science Award (Life Sciences), 2015
    - Prashant Kumta – Carnegie Science Award (Advanced Materials), 2015
    - Anna Balazs – MRS Polymer Physics Prize (**first woman ever to win this prize**), 2015
    - Joseph McCarthy – William Kepler Whiteford Endowed Professor, 2015
    - Judy Yang – Drexel ELATE, 2015
    - Götz Veser – SSOE Outstanding Educator Award, 2014
    - Karl Johnson – William Kepler Whiteford Endowed Professor, 2014
    - Anna Balazs – Robert van der Luft Endowed Professor, 2014
    - Anna Balazs – MRS Fellow, 2014
    - Anna Balazs – WCC Award for Excellence in the Chemical Sciences, 2014
    - Jay Jikich – SSOE Adjunct Faculty Award, 2014
    - Anna Balazs – ACS Langmuir Lecturer, 2014
    - Robert Enick – Swanson School of Engineering Board of Visitors Award, 2014
    - Anna Balazs – SF Boys A Rahman Award from the Royal Society of Chemistry, 2014
    - Anna Balazs – Colorado School of Mines, Mines Medal, 2013
    - Di Gao – Whiteford Faculty Fellowship, 2013
    - Robert Parker – BP America Faculty Fellowship, 2013
    - Götz Veser – Nickolas Dececco Endowed Professor, 2012
    - Robert Enick – Bayer Endowed Professor, 2012
- **Leadership and Service on School and University Committees:**
    - Member, University of Pittsburgh Steering Committee for the Plan for Pitt 2025 (University Strategic Plan), 2019 – present.
    - Member, Chancellor's Hiring Committee for Senior Vice Chancellor for Institutional Advancement, 2017
    - Member, Chancellor's Hiring Committee for Senior Vice Chancellor for Research, 2016-2017
    - Chair of the Committee to determine the Future Vision for the Swanson School of Engineering,

2016- present
- Chair of the Committee to honor Dean Gerald Holder's 20 years of service as Dean of the Swanson School of Engineering, 2016
- Selected to serve on the Swanson School's Committee for incentivization of innovation and entrepreneurship, 2016
- Selected to serve on the University's Innovation and Entrepreneurship committee for promotion of the University's Innovation Institute, 2016
- SSOE Planning and Budget Committee, 2015 – 2017
- Selected to serve on the University's Research Vision and Planning Committee, 2015- present
- Mechanical Engineering Department Chair Selection Committee – Selected Brian Gleeson to lead the Department in 2014
- SSOE Leadership Development Committee, 2014
- Selected to Serve on the University's Committee for Excellence in Education, 2014 – 2017
- Swanson School of Engineering Leadership Team, 2012 – present

TEACHING EXPERIENCE

Lecturer - Department of Chemical Engineering and Bioengineering, University of Pittsburgh. 2006 – present.

Guest Lecturer - Department of Bioengineering, Carnegie Mellon University. 2011.

Guest Lecturer - School of Dental Medicine, University of Pittsburgh. 2009 – present.

Lecturer/Teaching Assistant - Department of Chemical Engineering, Massachusetts Institute of Technology. Spring, 2003.

Research Project Demonstrator/Lecturer - Professional Education Program, Massachusetts Institute of Technology. Summer 2001 – 2005.

Courses Taught (Average Overall Weighted Teaching Effectiveness = 4.8 / 5.0):

Controlled Drug Delivery (ChemE / BioE 1533/2533/3533) – Spring 2006. Primary Instructor.
Enrollment: **12**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: **4.3 / 5.0**

Biomaterials and Biocompatibility (BioE 1810) – Fall 2006. Invited Lecturer.
Enrollment: **35**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: NA

Controlled Drug Delivery (ChemE 3533) – Spring 2009. Primary Instructor.
Enrollment: **12**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: **4.63 / 5.0**

Introduction to Transport Processes (ChemE 0300) – Fall 2010. Primary Instructor.
Enrollment: **78**
Contact Hours Per Week: **6**

Overall Teaching Effectiveness Score: **4.97 / 5.0**

Current Topics in Oral Health Research (DENT 5340) – Spring 2011. Invited Lecturer.
Enrollment: **15**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: NA

Introduction to Biomaterials (CMU 42-511) – Spring 2011. Invited Lecturer.
Enrollment: **25**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: NA

Introduction to Transport Processes (ChemE 0300) – Fall 2011. Primary Instructor.
Enrollment: **101**
Contact Hours Per Week: **6**
Overall Teaching Effectiveness Score: **4.88 / 5.0**

Controlled Drug Delivery (ChemE / BioE 1533/2533/3533) – Spring 2013. Primary Instructor.
Enrollment: **28**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: **4.77 / 5.0**

Controlled Drug Delivery (ChemE / BioE 1533/2533/3533) – Spring 2014. Primary Instructor.
Enrollment: **26**
Contact Hours Per Week: **3**
Overall Teaching Effectiveness Score: **3.63 / 5.0**

Educational Honors:

- Chosen as a Member of the Advisory Board for the National Science Foundation sponsored TUES (Transforming Undergraduate Education in Science) research project entitled: "Design for Impact: Effective Activities that Faculty will use"
- Recipient of the 2013 Carnegie Science Award for University Educators
- Recipient of the 2013 Chancellors Distinguished Teaching Award of the University of Pittsburgh

Research Mentor for:

Postdoctoral Research Associates:

Furkan Ertem Immunoengineering Treatments for the Colon. 2021-Present. Support Source. Department of Gastroenterology.

Roger (Warren) Sands Immunoengineering Treatments for Colitis. 2018-Present. Support Source. NIH T32 Awarded to Applicant.

Stephen Balmert Engineering the Immunological Microenvironment of the Skin for Type IV Hypersensitivity, 2018 – present. Support Source: NIH R01.

Nihan Yonet-Tanyeri Engineering the Skin Microenvironment to Promote Allergen Tolerance.

2018 – Present. Support Source: NIH R01 AR074285.

Yalcin Kulahci Vascularized Composite Tissue Allotransplantation. 2017 – 2019. Support Source: DoD (#MR141093). *– Now Microsurgical Fellow at Wake Forest Institute for Regenerative Medicine*

Sang Beom Lee (Visiting Research Assistant Professor) Biomimetic Polymer Engineering, 2016 – 2017.

Elena Bellotti Engineering a One-Month Ocular Delivery System for Glaucoma, 2016-2018. Support Source: NIH R01 *– Now Marie Curie Postdoctoral Fellow at the Italian Institute of Technology.*

Andrew Glowacki Delivery of Regulatory Cell Recruitment Factors for Periodontal Disease, 2015 – 2016. Support Source: Wallace H. Coulter Foundation. *– Now Senior Scientist at Johnson and Johnson.*

Abhi Acharya Recruitment and Reprogramming of Endogenous Tolerogenic Dendritic Cells for the Treatment of Cancer. 2014 – 2018. Support Source: NIH R01. *– Now Tenure Stream Assistant Professor at Arizona State University.*

Riccardo Gottardi "Zero Dimensional" Single Walled Carbon Nanotubes, 2011 – 2018. Support Source: Ri.MED Postdoctoral Fellows Program, University of Pittsburgh School of Medicine. *– Now Research Assistant Professor in the Department of Orthopedics at the University of Pittsburgh.*

Sayuri Yoshizawa Pre-Clinical Evaluation of Treatments for Periodontal Disease that Restore Immunological Homeostasis, 2011 – 2017. Support Source: NIH R56 and NIH R01 Grants. *– Now Research Assistant Professor at the University of Pittsburgh School of Dental Medicine.*

Huili Fu New Materials for Porous, Dissolvable Hollow Fibers, 2011 – 2014. Support Source: Department of Defense ARM IV Grant. *– Now Postdoctoral Associate at the UPMC Cardiovascular Institute.*

Morgan Fedorchak (Currently Tenure Stream Assistant Professor of Ophthalmology at the University of Pittsburgh) Engineering a One-Month Ocular Delivery System for Glaucoma, Spring 2011 – 2014. Support Source: Ocular Tissue Engineering and Regenerative Ophthalmology Research (OTERO) Grant. *– Now Tenure Stream Assistant Professor (NIH K Award Winner) in Ophthalmology at the University of Pittsburgh.*

Zuwei Ma New Materials for Porous, Dissolvable Hollow Fibers, 2009 – 2014. Support Source: Department of Defense ARM IV Grant. *– Now Senior Scientist at Neograft Technologies.*

Kaladhar Kamalasanan Synthetic Immunological Synapses, 2009 - 2012. Support Source: NSF CDI Type I Grant. *– Now Tenure Stream Assistant Professor at Amrita University.*

PhD Students:

Felicity Orndoff (Department of Chemical Engineering, University of Pittsburgh) Immunoengineering of Formulations for Transplantation Tolerance. Winter 2022 – Present. Source: US Department of Defense.

Julie Kobyra (Department of Bioengineering, University of Pittsburgh) Translation of Treg Recruitment Formulations for Treatment of Periodontitis and Exploration of the Interaction of MSCs and Treg in Regulation of Periodontitis. Fall 2020 – Present. Source: NIDCR MPWRM Consortium

Elizabeth Bentley (Department of Bioengineering, University of Pittsburgh) Immunoengineering the ATP-Adenosine Axis to Mediate Transplant Rejection, Fall 2019-present. Source: NIH T32.

Matthew Borrelli (Department of Chemical Engineering, University of Pittsburgh) Sustained Release Microspheres for Engineering the Infarct Microenvironment, Summer 2018 – present. Source: NIH R01/T32.

Andrea Schilling (Department of Chemical Engineering, University of Pittsburgh) A Conforming Thermogel Retained in the Sinus Cavities for Long-Acting Treatment of Chronic Sinusitis, Fall 2016 – Fall 2021. Source: NIH R01/T90/CRDF/EEF Gift. *– Now Scientist at Moderna*

Ashlee Greene (Department of Chemical Engineering, University of Pittsburgh) Development of a New Standardized In Vitro Dissolution Assay for Controlled Release Systems in the Periodontal Pocket, Fall 2015 – Fall 2021. Support Source: US Food and Drug Administration Grant. *– Now Scientist at Vivani Medical*

Ethan Bassin (Department of Immunology, University of Pittsburgh) Encapsulation and Controlled Release of Conditioned Media from Regulatory T Cells, Summer 2016 – December 2020. Support Source: NIH R01. *– Now Life Science Specialist at L.E.K. Consulting*

Thiagarajan (Thiagu) Meyyappan (Physician Scientist Training Program, University of Pittsburgh) Training Lymphocytes Ex-Vivo Using Microfluidic Environments for Antigen-Specific Tolerance, Summer 2014 – Summer 2018. Support Source: University of Pittsburgh MSTP Program. *– Now Resident at University of Pittsburgh Medical Center.*

Michelle Ratay (Department of BioEngineering, University of Pittsburgh) "Zero Dimensional" Single Walled Carbon Nanotubes, Summer 2013 – December 2017. Support Source: Coulter Translational Research Award, NIH T32. *– Now Medical Science Liaison at Allergan.*

Timothy Knab (Department of Chemical Engineering, University of Pittsburgh) Systems Based Modeling of Controlled Release *In Vivo*, 2011 – 2017. Support Source: Department of Education GAANN. *– Senior Scientist at Metrum Research.*

Emily Bayer (Department of BioEngineering, University of Pittsburgh) Temporal Delivery of Factors for Bone Tissue Regeneration, 2011 – 2016. Support Source: CATER T32 Grant. *– Now Director of Development at Carmell Therapeutics.*

Stephen Balmert (Department of BioEngineering, University of Pittsburgh) Engineering Smart Immunotherapeutics for Rapid IgM Responses, 2010 – present. Support Source: NSF Graduate Research Fellowship, NIH R01. *– Defended His Thesis in November 2017. Currently Postdoctoral Associate in Falo and Little Labs.*

James Fisher (MD/PhD Program, Department of BioEngineering, University of Pittsburgh) Engineering Smart Immunotherapeutics for Autoimmunity, 2010 – present. Support Source: DoD Funded Grant, NIH T32 Training Grant. *– Now Resident at University of Pittsburgh Medical Center.*

Melissa Lash (Graduated, Currently Scientist at Johnson and Johnson; Previously, Department of Chemical Engineering, University of Pittsburgh) Particle Based Scaffolds with Anisotropic Patches that Disassemble and then Reassemble via Chemical Cue, 2011 – 2016. Support Source: Department of Education GAANN, Provost's Fellowship. *– Now Head of Biologics Technical Operations at Detect.*

Andrew Glowacki (Graduated, Currently Postdoctoral Associate in LittleLab; Previously, Department of Chemical Engineering, University of Pittsburgh) Delivery of Regulatory Cell

Recruitment Factors for Periodontal Disease, 2008 – 2016. Support Source: NIH F31 Fellowship. – *Now Principal Scientist at Johnson and Johnson Consumer Health.*

Christopher Mahoney (Transferred to Marra Lab at Pitt; Department of BioEngineering, University of Pittsburgh) "Sustained Release of Antivirals for the Treatment and Prevention of HIV", Fall 2013 – Spring 2014. Support Source: Engineering Office of Diversity Fellowship.

Xiaoran (Zel) Zhang (Left Group for Personal Reasons; Previously, MD/PhD Program, Department of Immunology, University of Pittsburgh) Controlled Release Vaccine, Summer 2012 – Fall 2013. Support Source: University of Pittsburgh Medical Scientist Training Program. *(Left research group for personal reasons).* – *Now PGY-2 Medical Resident at University of Pittsburgh School of Medicine.*

Mintai (Peter) Hwang (Left research group for military service requirement; Previously, Department of BioEngineering, University of Pittsburgh) Biomimetic Delivery of Multiple Stimuli to Osteoblasts and Osteoclasts, 2008 – 2011. Support Source: NSF CDI Type I Grant. *(Left research group for military service requirement. Returned to receive his PhD under Yadong Wang).* – *Now Postdoctoral Associate at Cornell University.*

Daniel Hachim (Transferred to Brown Lab; Department of BioEnginering, University of Pittsburgh) Recruitment and Manipulation of Mesenchymal Stems Cells Using Biomimetic Drug Delivery, 2012 – 2013. Support Source: Fulbright Foundation Scholarship. (*One year and a half with no project deliverables from student. Transferred to a new project in Brian Brown's Laboratories in 2013).*

Heidi Hofer (Transerred to Tuan Lab; Department of BioEngineering, University of Pittsburgh) Prediction of Novel Biomaterials for Delivery of Osteoconducive Genes from Biodegradable Scaffolds, 2007 – 2010. Support Source: McGowan Institute CATER T32 Training Grant. (*Training Grant Expired with No Project Deliverables From Student. Transferred to a new project in Rocky Tuan's Laboratories in 2010).* – *Now Manufacturing Associate at Gradalis, Inc.*

Sam Rothstein (Department of Chemical Engineering, University of Pittsburgh) Prediction of Controlled Release from Biodegradable Polymer Matrices, 2006 – 2012. Support Sources: Commonwealth of PA Research Development Grant and NIH K-Award. - *Now CEO of Qrono, Inc.*

Siddharth Jhunjhunwala (Department of BioEngineering, University of Pittsburgh) Biomimetic Delivery of Multiple Stimuli to T Cells, 2006 – 2011. Support Source: Arnold and Mable Beckman Foundation Young Investigator Award. – *Now Tenure Stream Faculty Member at the Indian Institute of Science, Postdoctoral Fellow in Bioengineering at MIT.*

Jillian Tengood (Department of BioEngineering, University of Pittsburgh) Synthetic, Elastic Hollow Fibers as Artificial Capillaries for Wound Healing, 2006 – 2011. Support Source: University of Pittsburgh Cardiovascular BioEngineering T32 Training Grant. – *Now Senior Manager at ECRI Institute, Previously NIH Postdoctoral Fellow at University of Pennsylvania Children's Hospital.*

Masters Students:

Doug Francioni (Department of Chemical Engineering, University of Pittsburgh) Immunoengineering of Formulations for Transplantation Tolerance. Winter 2022 – Present. Source: US Department of Defense.

Lilian Ngobi (Department of Chemical Engineering, University of Pittsburgh) Predicting Plasma Concentration as a Result of Local Controlled Release Using a New, Broadly Applicable Mathematical Model, Spring 2011 – 2012. Support Source: Self-supported. - *Now Scientist at L'Oreal.*

Tianzhou (Vera) Wu (Department of Chemical Engineering) A Process Control Approach to Controlled Release Through Successive Matrices, Spring 2011 – 2012. Support Source: Self-supported. *– Now Senior Scientist at CDC/NIOSH.*

Daniel DeSantis (Department of Chemical Engineering, University of Pittsburgh) Examination of the Effect of Sequence of Osteoconductive and Osteogenic Factors on 3D *In Vitro* Culture of Mesenchymal Stem Cell and Endothelial Mixtures, Spring 2011 – 2013. Support Source: Self-supported. *– Now Project Engineer at Strategic Analysis Associates.*

Anu Karunanidhi Temporal Delivery of Growth Factors for Osteogenesis, 2009 – 2010. Support Source: United States Army Institute for Regenerate Medicine (AFIRM). *– Now Lecturer at Sri Ramachandra Medical College.*

Undergraduate Students (58 to date):

Reetwan Bandyopadhyay (**Department of Bioengineering, University of Pittsburgh**). Spring 2020 – Present.

Benjamin Ahlmark (**Department of Chemical Engineering, University of Pittsburgh**) Landscape Analysis of Lateral Flow Assays and Cancer Diagnostics. Spring 2020 – Present.

James O'Sullivan (**Research Experience for Undergraduates Fellow, The Ohio State University**) Bladder Cancer Diagnosis REU Fellowship. Summer 2018.

Matthew Rytel (**McGowan Institute for Regenerative Medicine, University of Pittsburgh**) Direct Evolution of Probiotics for Intra-intestinal Metabolism of Lipids and Carbohydrates. Spring 2018 - present.

Adam Carcella (**Department of Chemical Engineering, University of Pittsburgh**) Small molecule release from controlled release systems for ciliary regeneration in chronic rhinosinusitis. Spring 2018 - 2019. *– Now Field Engineer at Biogen.*

Erin Cannon (**Department of Chemical Engineering, University of Pittsburgh**) The effect of pH on drug release from a microparticle-thermogel system for treatment of chronic rhinosinusitis. Spring 2018 - present.

Kayla LeMaster (**Department of Chemical Engineering, University of Pittsburgh**) Induction of Regulatory T Cells for Treatment of Periodontitis. Spring 2016 – Spring 2018. *– Now Field Engineer at Schlumberger.*

Inderbir Sondh (**Department of Bioengineering, University of Pittsburgh**) Development of A Bioreactor Aimed at Designing Spatial and Temporal Drug Delivery Profiles for Bone Regeneration Protocols. Spring 2016 – Spring 2018. *– Now PhD Candidate at University of Minnesota.*

Harrison Lawson (Department of Chemical Engineering, University of Pittsburgh) Development of Mucoadhesive, Bacteria Killing Micro and Nonparticles for Oral Hygiene. Summer 2016 – Spring 2018. *– Now PhD Candidate at Michigan State University*

Sydney Anderson (Department of Chemical Engineering, University of Pittsburgh) REU Fellow. Summer 2017.

Sandra Walton (Department of Chemical Engineering, University of Arkansas) Summer Research Fellow**.** Summer 2017 – *Now Chemical Engineer & Maintenance Supervisor at Cargill.*

Naomi Joseph ((Department of Chemical Engineering, University of Pittsburgh) Drug Delivery Approaches for Induction of Bone using Metal Organic Frameworks (MOFs). 2017 – Spring 2018. – *Now PhD Candidate at Case Western Reserve University*

Gillian Schriever (Department of Chemical Engineering, University of Pittsburgh) Treg-Inducing Microspheres for the Prevention of Dry Eye Disease. Summer 2016 – Fall 2018. – *Now Business Technology Analyst at Deloitte*

Nicholas Yuhas (Department of Chemical Engineering, University of Pittsburgh) Generating and Testing a Panel of Arestin® Comparators: Minocycline-Loaded PLGA Microspheres. Spring 2016 – Spring 2018. - *Now enrolled at WVU School of Medicine (M.D.)*

Jahnelle Jordan (Department of Bioengineering, University of Pittsburgh) Development of Controlled Growth Factor Delivery Scaffolding for Bone Tissue Engineering. Summer 2013 – 2016. – *Now PhD Candidate in Biological Sciences at Columbia University.*

Patrick Bianconi (Department of Bioengineering, University of Pittsburgh) Controlled Release of Dorsomorphin to Prevent the Terminal Differentiation of Mesenchymal Stem Cells: A Potential Method for Articular Cartilage Regeneration. Fall 2012 – 2015. – *Now Quality Engineer at Baxter International.*

Sevahn Voperian (Department of Chemical Engineering, Carnegie Mellon University). Interferon Gamma Releasing Particles as a Treatment for Acute Myeloid Leukemia. Fall 2015 – 2016. – *Now Medical Student at Columbia University Medical Center.*

Felix Nguyen (Department of Immunology, University of Pittsburgh) Exploration of Conditioned Mesenchymal Stem Cell Media as an Alternative to *Ex Vivo* Mesenchymal Stem Cell-Based Treatments for Ocular Regeneration. Fall 2012 – present. – *Now Medical Student at the University of Pittsburgh School of Medicine.*

Anthony Cugini (Department of Bioengineering, University of Pittsburgh) Development of a Hydrogel Matrix for Drop-Like Delivery of Drug-Loaded Microparticles to the Inferior Fornix of the Eye. Spring 2012 – 2016. – *Now PhD Candidate in Bioengineering at the University of Pittsburgh.*

Meghana Patil (Department of Bioengineering, University of Pittsburgh) Controlled-Released Kartogenin: A Treatment for Cartilage Regeneration in Osteoarthritis. Spring 2012 – 2015. – *Now MD Student at Temple University.*

Erin Sarosi (Department of Bioengineering, University of Pittsburgh) Investigation of Particle Porosity and Burst Release Behavior for Improved Pulmonary Drug Delivery. Summer 2013. – *Now Mechanical Engineering Machine Technician, University of Pittsburgh.*

Skylar Wilkox (Department of Chemical Engineering, University of Pittsburgh) Regulation of Cell Migration and Differentiation by Microparticle-based Controlled Delivery. Fall 2012 – Spring 2013. – *Now Propylene Contact Engineer, ExxonMobil.*

Dhruv Srinivasachar (Department of Bioengineering, University of Pittsburgh) Design of Formulations for the *In Vivo* Induction of Regulatory T-cells in a Composite Tissue Allograft (CTA) Model. Fall 2012 – Spring 2014. – *Now MD/PhD Candidate at the Virginia Commonwealth University School of Medicine.*

Bon Ikwuagwu (Department of Chemical Engineering, University of Pittsburgh) Inverse, Hierarchical Colloidal Crystal-Based Scaffolds. Fall 2013 – Spring 2014. *– Now PhD Candidate in Chemical and Biological Engineering at Northwestern University.*

Stephen Kita (Department of Chemical Engineering, University of Pittsburgh) Artificial Thermalization and Self Assembly of Non-Brownian Particulate Systems. Fall 2012 – January 2013. *– Now R&D Engineer at ZSX Medical, LLC.*

Matthew Simson (Department of Chemical Engineering, University of Pittsburgh) The Effect of Controlled Delivery of PDGF-BB on the Chemotaxis and Proliferation of Mesenchymal Stem Cells. Spring 2012 – January 2013. *– Now Process Engineer at Praxair.*

Laura C. Blevins (Visiting Undergraduate Student, University of Maryland, Baltimore County) Creating Large-scale Colloidal Crystals through Artificial Thermalization, Summer 2012. *– Just received her PhD in Neuroscience at American University, Washington DC.*

Joseph Lownik (Visiting Undergraduate Student, Beloit College) Controlled Release of Serum and Conditioned Media as a Potential Regenerative Therapeutic in Ocular Pathology. Summer 2012. *– Now MD/PhD Candidate at the Virginia Commonwealth University School of Medicine.*

Danelys Estades Quiros (Visiting Undergraduate Student, University of Puerto Rico-Mayaguez Campus) Regulation of Cell Migration and Differentiation by Microparticle-based Controlled Delivery. Summer 2012. *– Now PhD Candidate in Chemical Engineering at University of Puerto Rico.*

Emmeline Blanchard (Department of Chemical Engineering, University of Pittsburgh) Examination of the Effect of Sequence of Osteoconductive and Osteogenic Factors on 3D *In Vitro* Culture of Mesenchymal Stem Cell and Endothelial Mixtures. Fall 2011 – Fall 2013. *-Now PhD Candidate in Bioengineering at Georgia Tech.*

Andrew Zmolek (Department of Chemical Engineering, University of Pittsburgh) Polymer-drug Interactions Govern Release of Molecules from Poly (lactic-co-glycolic) Acid Microspheres. Fall 2011 – Spring 2013. *– Just successfully defended his PhD in Chemical Engineering at MIT.*

Sydney Cope (Visiting Undergraduate Student, Northwestern University) Use of Poly (lactic-co-glycolic) Acid Microspheres as a Delivery Vehicle for Glaucoma Medication. Summer 2011. *– Now Principal Engineer at Baxter International.*

Joseph Wokpetah (Visiting Undergraduate Student, City College of New York) Polymer-Drug Interactions Govern Release of Molecules from Poly (lactic-co-glycolic) Acid Microspheres, Summer 2011. *– Now Scientist at Merck Pharmaceuticals.*

Elaine Yu (Visiting Undergraduate Student, Rutgers University) Synthesizing Particles that Present Surface-Bound Molecules While Simultaneously Releasing Other Signals from its Interior. Summer 2011. *– Now Systems Engineer at Magnetic Insight Inc. after receiving her PhD in Bioengineering from the University of California, Berkeley.*

Joshua Mealy (Department of Bioengineering, University of Pittsburgh) Rational Design of a Controlled Release System for Brominidine Tartrate. Spring 2011 – Spring 2013. *Now NSF Graduate Fellow and PhD Candidate in Bioengineering at the University of Pennsylvania.*

Ross Brodsky (Department of Chemical Engineering, University of Pittsburgh) Sequential Delivery of VEGF and S1p Using a Fully Injectable and Degradable Release System. Fall 2010 – Fall 2011. *– Now Instructor at Phillips Exeter Academy.*

Dan Maskarinec (Department of Bioengineering, University of Pittsburgh) Mathematical Model Validation for Sequential Delivery of Growth Factors Using Porous Hollow Fibers. Fall 2010 – Fall 2011. *– Now Engineer at Epic Technical Services.*

Joseph Miccio (Department of Chemical Engineering, University of Pittsburgh) Development of Synthetic Synapses on the Surface of Cell-sized Particles. Fall 2010 – Fall 2011. *– Now PGY-2 Resident Physician at Yale - New Haven Hospital.*

Jacob Sacks (Department of Bioengineering, University of Pittsburgh) Quantitative PCR Analysis of Tissue Samples Treated with Treg Recruiting Formulations. Fall 2010 – Fall 2011. *– Now PhD Candidate in Electrical and Computer Engineering at Georgia Tech.*

Alexandra Swanson (Department of Bioengineering, University of Pittsburgh) Application of "Synthetic Cells" to Stimulation of Biological Cells in Culture. Fall 2010 – Fall 2012. *– Now Medical Student at Jefferson Medical College.*

Ryan Ridenour (Visiting Summer Student, Allegheny College) Hollow Fiber Characterization and Release, Gradient Separation of SWNTs and Characterization. Summer 2010.

Adam Dobson (Department of Chemical Engineering, University of Pittsburgh) Troubleshooting Controlled Release of Highly Electropositive Proteins. Summer 2010 – Summer 2011. *– Now Senior Research Assistant in the Division of Biomaterials and Biomechanics at the Oregon Health and Science University.*

Drew Bundschuh (Visiting Undergraduate Student, Bucknell University) Strategies to Improve the Release of PGDF and Other Charged Proteins. Summer 2010. *– Now Associate Scientist at Glaxo Smith and Kline.*

Julie Fatula (Department of Chemical Engineering, University of Pittsburgh) Controlled Release of Vasoactive Intestinal Peptide. 2009 – 2011. *– Now Project Manager at Covestro, Houston Texas.*

Nathan Luke Clohecy (Department of Chemical Engineering, University of Pittsburgh) DNA Release from PBAE-PLA Scaffolds. Fall 2008 – 2009.

Ruchi Desai (Department of Chemical Engineering, Carnegie Mellon University) Single Injection Vaccine Project. Fall 2008 – 2009. *– Now Internal Medicine Resident at Hershey Medical Center, Penn State University.*

Erin Nichols (Department of Immunology, University of Pittsburgh) Dendritic Cell Specific Delivery of HDAC Inhibitors. Fall 2008 – 2010. *– Now Ophthalmology Resident at Wills Eye Hospital, Vanderbilt University School of Medicine.*

Sherri Hall (Department of Bioengineering, University of Pittsburgh) Recruitment of Regulatory T Cells Using Chemokine Encapsulated Microparticles. Fall 2008 – 2010. *– Now Senior Regulatory and Quality Engineer at R&Q Solutions, previously Research Intern at Cohera Medical.*

Jennifer Kay (Department of Chemical Engineering, University of Pittsburgh) Production of PLGA Microspheres Capable of Delivery Peptides or Proteins at a Constant Rate over One Month. Fall 2008 – 2010. *– Successfully defended her PhD in Bioengineering at MIT.*

Nakul Agarwal (Department of Chemical Engineering, Carnegie Mellon University) Production of PLGA Microspheres that Deliver a Protein Antigen at an Approved Vaccine Dosing Schedule. Summer 2008. *– Now Instructor at NSIT Indian Institute of Technology, Delhi.*

Kyle Kovach (Department of Bioengineering, University of Pittsburgh) *In Vitro* and *In Vivo*

Testing of Cellulose Hollow Fibers. 2008 – 2009. *– Now DARPA Biomedical Quality Engineer at Case Western Reserve University.*

Patrick Vescovi (Department of Chemical Engineering, University of Pittsburgh) Murine Matrigel Plug Assay for Hollow Fiber Testing. 2008 – 2010. *– Now Project Manager at Venture Engineering, Pittsburgh, PA.*

Brian Freeman (Department of Chemical Engineering, Carnegie Mellon University) Cellulose Hollow Fiber Characterization and Release Properties. 2008 – 2009. *– Now Scientist at StemCell Technologies, Vancouver, Canada.*

Rachael Scalese (Department of Chemical Engineering, University of Pittsburgh) New Methods for Fabrication of Porous Microparticulates using Osmolality. 2007 – 2008. *- Now Senior Engineer at Bechtel Marine Propulsion Corp. Naval Defense and Nuclear Security.*

Naomi Choodnovskiy (Summer Visiting Student, MIT) Controlled Release of Osteogenic Growth Factors from Microparticle Delivery Systems. 2005. *– Now Science Instructor at United Nations International School.*

Priya Shah (Department of Chemical Engineering, MIT) 3rd Generation PBAE Microparticle Delivery Systems. 2004 – 2005. *– Now Tenure-Stream Assistant Professor at UC Davis Department of Chemical Engineering.*

Sidharth Puram (Department of Bioengineering, MIT) Formulation and Characterization of PBAE Microparticle Delivery Systems. 2001 – 2005. *– Now M.D., Ph.D., Otolaryngologist at Mass. Eye and Ear.*

Mentee Awards:

- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2022 – **Aiden Bell**
- NIH T32 CATER Fellowship, 2023/2024 – **Julie Kobyra**
- NIH T32 Oral Craniofacial Fellowship, 2022/2023 – **Julie Kobyra**
- Department of Chemical Engineering, Best Paper Award, 2022 – **Matthew Borrelli**
- Drug Delivery and Translational Research, Best Paper Award, 2022 – **Andrea Schilling**
- University Honors College Research Fellowship, 2021 – **Reetwan Bandyopadhyay**
- Provost's Graduate Fellowship, 2020 – **Ashlee Greene**
- Chancellors Undergraduate Research Fellowship, 2020 – **Reetwan Bandyopadhyay**
- CRS Immuno Delivery Focus Group Trainee Award, 2020 – **Stephen Balmert**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2020 – **Benjamin Ahlmark**
- Plastics Pioneers Association Scholarship, 2019 – **Gillian Schriever**
- Marie Curie Postdoctoral Fellowship, 2018 **– Elena Bellotti**

- NIH K-Award (75% salary coverage for 5 years for Young Faculty), 2018 – **Morgan Fedorchak**
- CRS Foundation's Robert Langer Student Travel Grant Award, 2017 – **Jim Fisher**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2017 – **Harrison Lawson**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2016 – **Gillian Schriever**
- First Prize Poster Presentation, Immunology Department Retreat, 2016 – **Ethan Bassin**
- Howard Hughes Medical Institute Medical Research Fellow, 2016 – **Thiagu Meyyappan**
- ASEE Chemical Engineering Division Best Poster Award, 2015 – **Team: Bodnar, McCarthy, Beckman, Little**
- NIH T32 Fellowship, 2015 **– Michelle Ratay**
- University of Pittsburgh's Big Idea Competition, 1st Prize, 2015 – **Andrew Glowacki**
- NIH STTR Award to Qrono Inc., 2014 **– Sam Rothstein**
- NSF Graduate Research Fellowship, 2014 – **Joshua Mealy**
- James Coull Award, Department of Chemical Engineering, 2014 – **Andrew Glowacki**
- Chancellor's Distinguished Teaching Fellowship, 2014 – **Meghana Patil**
- University Honors College Health Sciences Fellowship, 2014 – **Felix Nguyen**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2014 – **Patrick Bianconi**
- DOD STTR Award to Qrono Inc. **– Sam Rothstein**
- AHA Postdoctoral Fellowship, 2013 – **Jillian Tengood**
- ARCS Foundation National Award, 2013 – **Michelle Ratay**
- American Heart Association PRISE Fellowship, 2013 - **Felix Nguyen**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2013 – **Meghana Patil**
- Chancellor's Undergraduate Research Fellowship, 2012 – **Dhruv Srinivasachar**
- 1st Place in National AIChE Poster Competition, 2012 Annual Meeting – **Joshua Mealy**
- 3rd Place in National AIChE Poster Competition, 2012 Annual Meeting – **Laura Blevins**
- Georgia Berner Research Fellowship, 2012 – **Andrew Zmolek**
- Foerderer Award for Excellence in Research, 2012 – **Jillian Tengood**
- American Institute of Chemical Engineering Professional Promise Award, 2012 – **Andrew Zmolek**

- Society for Biomaterials STAR Award Honorable Mention, 2012 – **Jim Fisher**
- Society for Biomaterials STAR Award Honorable Mention, 2012 – **Stephen Balmert**
- "Best Research" of all Pitt Excel Undergraduate Research Fellows, 2012 – **Amy Howell**
- NIH STTR Award to Qrono Inc, 2012 – Company PI: **Sam Rothstein**
- Research Named "Emerging Trends and Hot Topics" by ARVO, 2012 – **Morgan Fedorchak**
- Chancellors Undergraduate Research Fellowship, 2012 – **Andrew Zmolek**
- First Place – AIChE Regional Poster Competition, 2012 – **Andrew Zmolek**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2012 – **Emmaline Blanchard**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2012 – **Andrew Zmolek**
- 2nd place – Carnegie Science Awards, 2012 **– Sam Rothstein**
- NIH National Eye Institute Travel Award – ARVO Annual Meeting, 2012 – **Morgan Fedorchak**
- Chancellors Undergraduate Teaching Fellowship, 2012 – **Andrew Zmolek**
- University of Pittsburgh Big Idea Competition, 1st Prize, 2012 **– Jim Fisher**
- Edward B. Stewart and Geraldine J. Stewart Memorial Scholarship, 2011 – **Andrew Zmolek**
- John W. Tierney Scholarship, 2011 – **Julie Fatula**
- NIH T32 Fellowship, 2011 – **Jim Fisher**
- RiMED Postdoctoral Fellowship, 2011 – **Riccardo Gottardi**
- OTERO Postdoctoral Fellowship, 2011 – **Morgan Fedorchak**
- Idea Foundry Life Science Start Up Award, 2011 – **Sam Rothstein**
- Society for Biomaterials STAR Award, 2011 – **Siddharth Jhunjhunwala**
- Teaching Assistant of the Year Award, 2011 – **Andrew Glowacki**
- First Place – Poster Competition, MIRM Annual Retreat, 2011 – **Stephen Balmert**
- Finalist, Stifung Charite's International Enterprise Competition, 2011 – **Sam Rothstein**
- Shio-ming Chang Scholarship, 2011 – **Julie Fatula**
- National Math and Science Young Leader, 2011 – **Julie Fatula**
- NSF Graduate Research Fellowship, 2011 – **Stephen Balmert**
- Bevier Graduate Fellow, 2011 – **Stephen Balmert**

- University of Pittsburgh's Big Idea Competition, 1st Prize, 2010 – **Sam Rothstein**
- Barry Goldwater Scholarship (honorable mention), 2010 **– Patrick Vescovi**
- Lubrizol Foundation Scholarship, 2010 – **Jenny Kay**
- George Washington Prize, 2010 – **Jenny Kay**
- John W. Tierney Scholarship, 2010 – **Patrick Vescovi**
- First Place - Office of Enterprise Development's Elevator Pitch Competition, 2010 – **Sam Rothstein**
- First Place - Pittsburgh Enterprise Forum's Elevator Pitch Competition, 2010 – **Sam Rothstein**
- Department of Chemical Engineering's Research Assistant of the Year, 2010 – **Sam Rothstein**
- Sunoco Chemicals Award Recipient, 2010 – **Sam Rothstein**
- George Washington Prize, 2010 – **Patrick Vescovi**
- American Heart Association Undergraduate Research Fellowship, 2010 – **Ross Brodsky**
- NIH Ruth Kirschstein F31 Graduate Fellowship, NIDCR, 2010 – **Andrew Glowacki**
- Teaching Assistant of the Year Award, 2010 – **Andrew Glowacki**
- First Place – Poster Competition, MIRM Annual Retreat, 2009 – **Sam Rothstein**
- Teaching Assistant of the Year Award, 2009 – **Andrew Glowacki**
- Teplitz Memorial Scholarship, 2009 – **Patrick Vescovi**
- National Institutes of Health T32 Fellowship, 2009 – **Jillian Tengood**
- National Football Foundation Scholar-Athlete Award, 2009 – **Brian Freeman**
- First Place – Poster Competition, MIRM Annual Retreat, 2008 – **Siddharth Jhunjhunwala**
- First Place – Poster Competition, MIRM Annual Retreat, 2008 – **Andrew Glowacki**
- Hugh Henry Brackenridge Undergraduate Research Fellowship, 2008 – **Erin Nichols**
- Mohammad Dubois Graduate Fellowship, 2008 – **Andrew Glowacki**
- Fisher Scientific Biomedical Engineering Research Award, 2008 – **Sam Rothstein**
- Society for Biomaterials STAR Award, 2007 – **Sam Rothstein**
- American Institute of Chemical Engineering Professional Promise Award, 2007 – **Patrick Vescovi**
- CED Student of the Year, 2007 – **Patrick Vescovi**
- National Institutes of Health T32 Fellowship, 2006 – **Sam Rothstein**

PRESENTATIONS

182) Balmert, S.C., Carey, C.D., Erdos, G., Korkmaz, E., **Little, S.R.**, Falo, L.D. Microneedle Arrays Engineer the Skin Microenvironment to Promote Antigen-Specific Immune Tolerance. The 6th International Conference on Microneedles (Virtual). November 10 - 11, 2021.

181) Balmert, S.C., Carey, C.D., Erdos, G., Korkmaz, E., **Little, S.R.**, Falo, L.D. Microneedle Arrays Engineer the Skin Microenvironment to Promote Antigen-Specific Immune Tolerance. Controlled Release Society Annual Meeting (Virtual). June 29 - July 2, 2021.

180) Balmert, S.C., Carey, C.D., Erdos, G., Korkmaz, E., **Little, S.R.**, Falo, L.D. Engineering the Skin with Microneedle Arrays to Induce Immune Tolerance. Society for Investigative Dermatology Annual Meeting (Virtual). May 13 - 16, 2021.
***This abstract was also published: *Journal of Investigative Dermatology* 140(7):S11.

179) Schilling, A.L., Carcella, A.R., Wang, E.W, Lee, S., **Little, S.R.** "Promoting Sinonasal Cilia Regeneration with Sustained Retinoid Delivery." Controlled Release Society Annual Meeting (Virtual). July 25 – 29, 2021.

178) Balmert, S.C., Carey, C.D., Erdos, G., Korkmaz, E., **Little, S.R.**, Falo, L.D. Microneedle Arrays Engineer the Skin Microenvironment to Promote Antigen-Specific Immune Tolerance. Microneedles 2020 Online Conference. November 10 - 11, 2020.

177) Yonet-Tanyeri, N., Falo, L.D., **Little, S.R.** A Comparative Study on Fabrication Methods for Microparticle-Based Drug Delivery Systems. American Association of Pharmaceutical Scientists PHARMSCI 360 Annual Meeting (Virtual). October 26-Novemver 5, 2020.

176) Greene, A., Shehabeldin, M., Ratay, M., Sfeir, C., **Little, S.R.** Extended Release (Regulatory T Cell Inducing) Microsphere Formulation for the Treatment of Periodontal Disease. American Association of Pharmaceutical Scientists PHARMSCI 360 Annual Meeting (Virtual). October 26 - November 5, 2020.

175) Schilling, A.L., Wang, E.W., Lee, S. Little, S.R. Local Corticosteroid Delivery to the Paranasal Sinuses via a Thermoresponsive and Extended Release System. American Association of Pharmaceutical Scientists PHARMSCI 360 Annual Meeting (Virtual). October 26 - November 5, 2020.

174) Schilling, A.L., Moore, J., Kulahci, Y. **Little, S.R.**, Wang, E.W., Lee, S. Evaluating Inflammation in an Obstruction-based Chronic Rhinosinusitis Model in Rabbits. 66th Annual Meeting of the American Rhinologic Society, Virtual, Sept. 10, 2020

173) Greene, A., Shehabeldin, M., Ratay, M., Sfeir, C., **Little, S.R.** Treatment of Periodontal Disease through an Immunomodulatory (Regulatory T Cell Inducing) Microsphere Formulation. Controlled Release Society Annual Meeting. Las Vegas, NV (Virtual Meeting due to COVID19). June 30, 2020.

172) Bassin, E.J., Buckley, A.R., Piganelli, J.D., **Little S.R.** TRI-MP treatment for the prevention of

collagen-induced arthritis. On-demand talk presented at: Controlled Release Society Annual Meeting. Las Vegas, NV (Virtual Meeting due to COVID19). June 30, 2020.

171) Yonet-Tanyeri, N., Falo, L.D., **Little, S.R.**, Microfluidic systems affect bioactivity of therapeutic agents. Controlled Release Society Annual Meeting. Las Vegas, NV (Virtual Meeting due to COVID19). June 30, 2020.

170) Schilling, A.L., Kulahci, Y., Moore, J., Wang, E.W, Lee, S. **Little, S.R.** Local, Sustained Steroid Delivery for Treatment of Chronic Rhinosinusitis. Controlled Release Society Annual Meeting. Las Vegas, NV (Virtual Meeting due to COVID19). June 29, 2020.

169) Balmert, S.C., Carey, C.D., Erdos, G., Korkmaz, E., **Little, S.R.**, Falo, L.D. Microneedle Arrays Engineer the Skin Microenvironment to Promote Antigen-Specific Immune Tolerance. Controlled Release Society Annual Meeting. Las Vegas, NV (Virtual Meeting due to COVID19). June 30, 2020.

168) Balmert, S.C., Carey, C.D., Erdos, G., Korkmaz, E., **Little, S.R.**, Falo, L.D. Engineering the Skin with Microneedle Arrays to Induce Immune Tolerance. Society for Investigative Dermatology Annual Meeting. Scottsdale, AZ (Virtual Meeting due to COVID19). May 2020.

167) Rodriguez, B., Lorentz, K., Gupta, P., Cunnane, E., Shehabeldin, M., Fedorchak, M., Weinbaum, J., **Little, S.R.**, Sfeir, C., Mandal, B., Vorp, D.A. In Vivo Response to Cytokine Encapsulated Microparticles in Vascular Grafts. Biomedical Engineering Society Conference. Philadelphia, PA, USA, October 19, 2019.

166) Balmert, S.C., Carey, C.D., Erdos, G., **Little, S.R.**, Falo, L.D. Microneedle Arrays Engineer the Skin Microenvironment to Promote Allergen Tolerance. Society for Investigative Dermatology Annual Meeting. Chicago, IL, May 2019.

165) Lorentz, K.L., Gupta, P., Cunnane, E.M., Shehabeldin, M., Fedorchak, M.V., Weinbaum, J.S., Sfeir, C.S., Mandal, B., **Little, S.R.**, Vorp, D.A. Cytokine mimicking microspheres-loaded silk scaffolds for vascular tissue engineering: In-vitro and in-vivo assessment (Poster Presentation), 18th Annual McGowan Institute Scientific Retreat. Pittsburgh, PA, March 11 – 12, 2019.

164) Lorentz, K.L., Gupta, P., Cunnane, E.M., Shehabeldin, M., Fedorchak, M.V., Weinbaum, J.S., Sfeir, C.S., Mandal, B., **Little, S.R.**, Vorp, D.A. Cytokine mimicking microspheres for use in porous scaffolds. (Oral Presentation), 18th Annual McGowan Institute Scientific Retreat. Pittsburgh, PA, March 11 – 12, 2019.

163) Acharya, A.P., Grene, A., **Little, S.R.**, Sezginel, K.B., Wilmer, C.E. Ultrahigh and Multiple Anti-Tuberculosis Drugs Loaded BioMOFs Clear Mycobacterim Tuberculosis Infection in Macrophages. Annual Meeting of the American Institution of Chemical Engineers. Pittsburgh, PA, October 2018.

162) Acharya, A.P., Sinha, M., Ratay, M.L., Ding, X., Balmert, S.C., Workman, C.J., Wang, Y., Vignali D.A.A., **Little, S.R.** Localized Multi-component Delivery Platform Generates Local and Systemic Anti-tumor Immunity. Next Generation Biomaterials — Biomaterials VI, Materials Science and Technology, Columbus, OH, October 2018.

161) Greene, A., Shehabeldin, M., Ratay, M., Sfeir, C., **Little, S.R.** Local Induction of Endogenous Regulatory T Cells for the Treatment of Periodontal Disease. Annual Meeting of the American Institution of Chemical Engineers. Pittsburgh, PA, October 2018.

160) Desai, S., Patel, S.K., Greene, A.C., MacPherson, J.S., Basha, I.T., Zou, Y., Rothstein, S.N., Sfeir, C.S., **Little, S.R.**, Rohan, L.C. Development of Quality Control and Biorelevant Dissolution Methods for PLGA Microparticles Used in Periodontitis. American Association of Pharmaceutical Scientists (AAPS) 10th Annual Pharmaceutical Sciences Research Symposium, West Virginia University, Morgantown, WV, July 27, 2018.

159) Patel, S., Greene, A., MacPherson, J., Basha, I., Desai, S., Zou, Y., Sfeir, C.S., Rothstein, S.N., **Little, S.R.**, Rohan, L.C. Design, Fabrication, and Evaluation of a Small Volume Biorelevant Dissolution Apparatus for Extended Release Periodontal Microparticles. Controlled Release Society Annual Meeting. New York, NY. July 22, 2018.

158) Balmert S.C., Carey C.D., Erdos G., **Little S.R**., Falo L.D. Engineering the Skin Microenvironment to Promote Antigen Specific Tolerance. Tumor, Transplant, and Tolerance Retreat. Pittsburgh, PA. May 30, 2018.

157) Greene, A., Yoshizawa, S., Ratay, M., Sfeir, C., **Little, S.R.** Multi-Factor Microparticle Formulation for Local Induction of Regulatory Lymphocytes and Treatment of Periodontal Disease, Annual Meeting of the American Institution of Chemical Engineers. Minneapolis, MN, October 2017.

156) Bellotti, E., Fedorchak, M.V., **Little, S.R.** Development of an Engineered Thermoresponsive pNIPAAM Hydrogel for the Topical Retention of Controlled Release Ocular Therapeutics, Annual Meeting of the Controlled Release Society. Boston, MA, July 2017.

155) Ratay, M., Balmert, S., Acharaya, A., Greene, A., Meyyappan, T., **Little, S.R.** TRI Microspheres prevent key signs associated with Dry Eye Disease in an experimental inflammatory model, Controlled Release Society, 44th Annual Meeting & Exposition of the Controlled Release Society. Boston, MA, July 2017.

154) Fisher, J.D., Zhang, W., Schweizer, R., Dong, L., Aral, A., Zhang, Z., Komatsu, C., Erubas, V., Unadkat, J., Diaz-Perez, J., Solari, M., Gorantla, V.S., **Little, S.R.** Regulatory T Cell Enriching Microparticles for Promoting Vascularized Composite Allotransplant Survival, Controlled Release Society 2017 Annual Meeting. Boston, MA, July 2017.

153) Fuller, T., Acharya, A.P., Bhaskar, G., Yu, M., **Little, S.R.,** Tarin, T. Evaluation of E-cigarettes Users Urine for Known Bladder Carcinogens, Annual Meeting of the American Urological Association. Boston, MA, May 2017.

152) Ratay, M., Balmert, S., Acharaya.A, Greene, A., Meyyappan, T., **Little, S.R.** TRI Microspheres prevent key signs associated with Dry Eye Disease in an experimental inflammatory model, Bioengineering Day. University of Pittsburgh, Pittsburgh, PA, April 2017.

151) Patel, S.K., Greene, A.C., Rothstein, S., Zou, Y., Choi, S., Glowacki, A., Gottardi, R., Sfeir, C.S.,

Little, S.R., Rohan, L.C. Application of USP 4 Dissolution Apparatus to Assess Dissolution of Microparticles for Periodontal Disease, American Associate of Pharmaceutical Scientists (AAPS) Annual Meeting. Denver, CO, November 2016.

150) Sondh, I.S., Nichols, D.A., Bayer, E.A., Gottardi, R., **Little S.R.** Development of a bioreactor aimed at designing spatial and temporal drug delivery profiles for bone regeneration protocols, Biomedical Engineering Society Annual Meeting. Minneapolis. MN, October 2016.

149) Sondh, I.S., Nichols, D.A., Bayer, E.A., Gottardi, R., **Little S.R.** Development of a bioreactor aimed at designing spatial and temporal drug delivery profiles for bone regeneration protocols, 2016 Summer Research Symposium. Duquesne University, Pittsburgh PA, August 2016.

148) Guaragno, M., Glowacki, A., Acharya, A., Polat, J., Fedorchak, M., **Little, S.R.** Biomimetic Drug Delivery of a Chemokine to recruit endogenous Regulatory T cells(Tregs) to abrogate Dry Eye Disease, Bioengineering Day. University of Pittsburgh, Pittsburgh, PA, April 2016.

147) Fisher, J.D., Schweizer, R., Unadkat, J.V., Fries, A., Komatsu, C., Oksuz, S., Solari, M.G., Davis, M., Gorantla, V.S., **Little, S.R.** Biomimetic Microparticles can Establish Dominant Tolerance in Vascularized Composite Allotransplantation via Endogenous Regulatory T Cell Enrichment, (Oral and Poster Presentation), 15th Annual McGowan Institute Retreat. Nemacolin Woodlands, PA, March 2016.

146) Balmert, S.C., Carey, C.D., Falo, L.D., **Little, S.R.** Sustained Delivery of Treg-Inducing Factors to Skin Draining Lymph Nodes Suppresses Allergic Contact Dermatitis, US-Japan Symposium on Drug Delivery Systems. Lahaina, HI, December 2015.

145) Guaragno, M., Glowacki, A., Fedorchack, M., Polat, J., Acharaya, A., **Little, S.R.** Drug Delivery of a Chemokine to Recruit Endogenous Regulatory T-Cells (Tregs) in a Model of Dry Eye Disease. US-Japan Symposium on Drug Delivery Systems, Lahaina, HI, December 2015.

144) Pezzone, D., Krawiec, M., Josowitz, A., Fedorchak, M.V., D'Amore, A., Weinbaum, J., Wagner, W., **Little, S.R.,** Vorp, D. Seeding of Microspheres into A Porous Tubular Scaffold as A Tissue Engineered Vascular Graft. Biomedical Engineering Society (BMES) Annual Meeting, Tampa, FL, October, 2015.

143) Josowitz, J., Krawiec, M., Fedorchak, M.V., D'Amore, A., Weinbaum, J., Rubin, J., Wagner, W., **Little, S.R.** Vorp, D. Characterizing The Seeding Distribution of Microspheres in Tissue Engineered Vascular Grafts'. Biomedical Engineering Society (BMES) Annual Meeting, Tampa, FL, October, 2015.

142**)** Gottardi, R., Bianconi, P.A., Manner, P.G. Alexander, R.S. Tuan, R.S., **Little, S.R**. Prevention of Articular Cartilage Calcification by Controlled Release of Dorsomorphin. Penn Orthopaedics 2015 Cartilage Repair Symposium, Philadelphia, PA, May 2015.

141) Guaragno, M., Gottardi, R., Fedorchak, M., Tan, S., Di Maio, R., Conway, J., Kuksenok, O., Balazs, AC., **Little, S.R.** Zero Dimensional Single-Walled Nanotubes as Synthetic Ion Channel. Bioengineering Day, University of Pittsburgh, Pa, April 2015.

140) Gottardi, R., Bianconi, P.A., Manner, P.A., Alexander, P.G., Tuan, R.S., **Little, S.R**. Prevention of

Articular Cartilage Calcification by Controlled Release of Dorsomorphin. Penn Orthopedics 2015 Cartilage Repair Symposium, Philadelphia, PA, April 2015.

139) Fedorchak, M.V., Conner, I.P., Schuman, J.S., **Little, S.R**. Preclinical testing of a novel drug delivery system for glaucoma. Society for Biomaterials (SFB) Annual Meeting, Charlotte, NC, April 2015.

138) Lash, M.H., Jordan, J.J., McCarthy J.J., **Little, S.R.,** Particle-based Scaffolds with Macro- and Micro-Scale Hierarchy, McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Nemecolin, PA, March 2015.

137) Fisher, J.D., Schweizer, R., Unadkat, V., Komatsu, C., Oksuz, S., Thomson A.W., Solari, M., Gorantla, V.S., **Little, S.R.** Regulatory T Cell Enriching Microspheres Can Establish Dominant Tolerance in Vascularized Composite Tissue Allotransplants. McGowan Institute for Regenerative Medicine Annual Retreat, Nemacolin Woodlands PA, March 2015.

136) Bayer, E., Fedorchak, M.V., Roy, A., Kumta, P., **Little, S. R**. Sequential Growth Factor Delivery for Bone Tissue Regeneration, McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Nemacolin, PA, March 2015.

135) Guaragno, M., Gottardi, R., Fedorchack, M., Tan, S., Balazs, A.C., **Little, S.R.** Zero-dimensional Single-Walled Nanotubes as Synthetic Ion Channels. McGowan Institute for Regenerative Medicine Scientific Retreat, Farmington, PA, March 2015.

134) Fedorchak, M.V., Conner, I.P., Schuman, J.S., **Little, S.R**. Update on the Monthly Eye Drop for glaucoma. McGowan Institute for Regenerative Medicine (MIRM) Annual Retreat, March 2015, Farmington, PA.

133) Garlet, G.P., **Little, S.R.**, MyD88 mediates inflammatory and healing/regenerative responses to classic biomaterials (Ti): evidences for DAMPs as host response triggers. Hilton Head Regenerative Medicine Workshop, Hilton Head SC, March 13-16, 2015.

132) Fedorchak, M.V., Conner, I.P., Schuman, J.S., **Little, S.R**. The Monthly Eye Drop: Development of a novel controlled release system for glaucoma. Association for Ocular Pharmacology and Therapeutics (AOPT) Biennial Meeting, Charleston, SC, February 2015.

131) Lash, M.H., Jordan, J.J., Fedorchak, M.V., **Little, S.R.,** McCarthy J.J., Fabrication of (Non-) Colloidal Crystals with Customizable Hierarchy, AIChE Annual Meeting, Atlanta, GA, November 2014.

130) Lash, M.H., Fedorchak, M.V., McCarthy, J.J., **Little, S.R.,** Fabrication of (Non-)Colloidal Crystals for Hierarchically-Ordered Materials Development, Presented at AIChE Annual Meeting, Atlanta, GA, November 2014.

129) Fisher, J.D., Schweizer, R., Unadkat, V., Komatsu, C., Oksuz, S., Thomson A.W., Solari, M., Gorantla, V.S., **Little, S.R.** Biomimetic Micropartcles can Establish Dominant Tolerance in Vascularized Composite Allotransplant via Endogenous Regulatory T Cell Enrichment. 4th Biennial Meeting of the American Society of Reconstructive Transplantation, Chicago IL, November 21-22, 2014.

128) Lash, M.H., Fedorchak, M.V., McCarthy, J.J., **Little, S. R.,** Fabrication and Characterization of (Non-)Colloidal Crystals with Customizable Hierarchy (poster), AIChE Annual Meeting, Atlanta GA, October 2014.

127) Glowacki, A.G., Yoshizawa, S., Khanwilkar, P., Green, C., Sfeir, C., **Little, S.R.**, Treating the root cause of gum disease. Pennsylvania Bio, Philadelphia, PA, October 13-14th 2014.

126) Lash, M.H., Fedorchak, M.V., McCarthy, J.J, **Little, S. R**., Fabrication of (Non-)Colloidal Crystals for Hierarchically-ordered Materials Development, AIChE Annual Meeting, Atlanta GA, October 2014.

125) Patil, M.A., Gottardi, R., Ulici, V., **Little, S.R.**, Tuan, R.S. Three-Dimensional Cell Culture Effects on Chondrogenesis of Kartogenin-Treated hMSCs. BMES Annual Meeting, San Antonio, TX, October 2014.

124) Bianconi, P.A., Gottardi, R., Ulici, V., Tuan, R.S., **Little, S.R**. Preventing Articular Cartilage Calcification by the Controlled Release of Dorsomorphin. Biomedical Engineering Society Annual Meeting, San Antonio, TX, October 2014.

123) Fisher, J.D., Schweizer, R., Unadkat, V., Komatsu, C., Oksuz, S., Solari, M., Gorantla, V.S.**, Little, S.R.** Enrichment of Suppressive Lymphocytes via Biomimetic Constructs Promotes Immune Tolerance in Vascularized Composite Allotransplantation. 31st Annual Meeting of The Northeastern Society of Plastic Surgeons. Providence RI, September 12-14, 2014.

122) Bodnar, C.A., Beckman, E.J., McCarthy, J.J., **Little, S.R**. Work in Progress: A Vision for the First "Product Innovation Sequence" for Chemical Engineers. ASEE Annual Meeting, Indianapolis, IN, June 2014.

121) Fisher, J.D., Schweizer, R., Unadkat, V., Komatsu, C., Oksuz, S., Solari, M., Gorantla, V.S., **Little, S.R**. Tumor Inspired Microparticle Formulations for Preventing Vascularized Composite Allotransplant Rejection. University of Pittsburgh Department of Plastic Surgery Resident Research Day, Pittsburgh PA, June 27th, 2014.

120) Fisher, J.D., Unadkat J.V., Schweizer, R., Komatsu, C., Oksuz, S., Solari, M., Gorantla V.S.**, Little, S.R.** Emulating Nature's Genius: Engineered Biomimetic Formulations for Suppressing Rejection in Vascularized Composite Allotransplantation. Ohio Valley Society of Plastic Surgeons 57th Annual Meeting, Greenbrer WV, June 5-7, 2014.

119) Bayer, E., Blanchard, E., Fedorchak, M., Roy, A., Kumta, P., **Little, S.R.** Choeographing Regeneration with BoneSCRIPT. University of Pittsburgh Department of Pathology Research Day. Pittsburgh, PA, May 2014.

118) Fisher, J.D., Schweizer, R., Unadkat J.V., Fries, A., Komatsu, C., Oksuz, S., Solari, M.G., Davis, M., Gorantla, V.S., **Little, S.R**. Establishing Dominant Tolerance in Vascularized Composite Allotransplantation via Biomimetic Lymphocyte Enriching Microparticles. 60h Annual Scientific Meeting of the Robert H. Ivy Society of Plastic Surgeons, Bedford PA, May 17th, 2014.

117) Guaragno, M., Gottardi, R., Fedorchak., M., Roy., A., Kumta., P., **Little, S.R**. Fluorescently Labeled Single-Walled Carbon Nanotubes for Synthetic Ion Channels. Department of Bioengineering Day, University of Pittsburgh, Pa, April 2014

116) Lash, M.H., Jordan, J.C., McCarthy, J.J., Fedorchak, M.V., **Little, S. R**., Self-Assembly of Binary Colloidal Crystals for the Production of Inverted Crystalline Scaffolds (poster), McGowan Institute for Regenerative Medicine Annual Retreat, Farmington, PA, March 2014.

115) Gottardi, R., Bianconi, P., Manner, P., Alexander, P., Tuan, R.S., **Little, S.R**., Prevention of Articular Cartilage Hypertrophy by Controlled Release of Dorsomorphin, McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Nemacolin, PA, March 2014.

114) Mahoney, C., Fedorchak, M. V., Rothstein, S., **Little, S. R**. Engineering Antigen Delivery Kinetics in Microparticle-based Vaccines for the Development of Protective Immunity, McGowan Institute of Regenerative Medicine Annual Scientific Retreat, Nemacolin, PA, March 2014.

112) Bayer, E., Blanchard, E., Fedorchak, M., Roy, A., Kumta, P., **Little, S.R.** Choeographing Regeneration with BoneSCRIPT. McGowan Institute for Regenerative Medicine annual meeting. Farmington, PA, March 2014.

113) Glowacki, A. J., Yoshizawa, S., Jhunjhunwala, S., Vieira, A. E., Garlet, G. P., Sfeir, C., **Little, S. R.** Treating periodontal disease by targeting immune dysfunction. McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Nemacolin, PA, March 2014.

112) Guaragno, M., Gottardi, R., Fedorchack, M., Tan, S., Balazs, A., **Little. S.R.** Fluorescent Single-Walled Nanotubes for Synthetic Ion Channels, McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Nemacolin, PA, March 2014.

111) Lash, M.H., **Little, S. R.**, McCarthy J. J. Artificial Thermalization of Non-Brownian Microparticles for the Fabrication of Close-Packed Colloidal Crystals, AIChE Annual Meeting, San Francisco, CA, November 2013.

110) Patil, M., Gottardi, R., Velankar, S.S., **Little, S.R.** Carbon Nanotube Thin Film via Interfacial Film Climbing: A Potential Platform for Cell Growth. BMES Annual Meeting, Seattle, WA, September 2013.

109) Gottardi, R., Hwang, M.P., Simson, M., Manner, P.A., Tan, J., Alexander, P.G., **Little, S.R.**, Tuan, R.S. Autologous Stem Cell Recruitment for Articular Cartilage Regeneration. TERMIS-AM: Annual Conference, Las Vegas, NV, July 2013.

108) Bayer E, DeSantis D, Blanchard E, Fedorchak M, Roy A, Kumta P, **Little S.R.** Composite Micro-CaP Scaffold for Bone Regeneration. University of Pittsburgh Department of Pathology Research Day. Pittsburgh, PA, May 2013.

107) Gottardi, R., Simson, M., Manner, P., Tan, J., Alexander, P., Tuan, R.S., **Little S.R.** Autologous Stem Cell Recruitment for Articular Cartilage Regeneration, McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Nemacolin, PA, April 2013.

106) Lash, M.H., McCarthy J. J**., Little, S.R.,** Fabrication of Highly Ordered and Close Packed Colloidal Crystals from Large Microparticles for Biomedical Applications (poster), McGowan Institute for Regenerative Medicine Annual Retreat, Farmington, PA, March 2013.

105) Bayer E, DeSantis D, Blanchard E, Fedorchak M, Roy A, Kumta P, **Little S.R.** Composite Micro-CaP Scaffold for Bone Regeneration. McGowan Institute for Regenerative Medicine annual meeting. Farmington, PA, March 2013.

104) Balmert S.C., Vu JR, Jhunjhunwala S., Raimondi G., Thomson A.W., Falo L.D., **Little S.R**. Suppression of Local Inflammation with Engineered Treg-Inducing Microparticle Systems. McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Farmington, PA, March 2013.

103) Glowacki, A. J., Yoshizawa, S., Jhunjhunwala, S., Vieira, A. E., Garlet, G. P., Sfeir, C., **Little, S. R.** Preclinical evaluation of regulatory lymphocyte recruiting microparticles for the prevention of periodontitis. McGowan Institute for Regenerative Medicine Annual Scientific Retreat, Farmington, PA, March 2013.

102) Hong, Y., Fu, H., **Little, S.R.,** Wagner, W.R. Developing an Enzymatically-Triggered, Rapidly Degradable Polyurethane Hollow Fiber Membrane. BMES Annual Meeting, Atlanta, GA, October 2012.

101) Patil, M., Gottardi, R., Velankar, S.S., **Little, S.R.** Interfacial Interactions of Zero-Dimensional Carbon Nanotubes and Their Application as Thin Films: A Potential Platform for Cell Growth. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

100) Zmolek, A., Balmert, S.C., Glowacki, A.J., Rothstein, S., Wokpetah, J., **Little, S.R.** Analyzing the Release Kinetics of 'Sticky' Peptides from PLGA (Poly(lactic-co-glycolic) acid) Microspheres. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

99) Mealy, J.E., Fedorchak, M.V., **Little, S.R.** Development of a Controlled Release Ocular Insert for Brimonidine Tartrate. AIChE Undergraduate Student Poster Session, Pittsburgh, PA, October 2012.

98) Li, S., Lash, M.H., **Little, S.R.**, McCarthy, J.J. Dissipative Particle Dynamics Simulation of Sonication-Mediated Particle Interactions. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

97) Cugini, A., Fedorchak, M.V., **Little, S.R.** Developing a Hydrogel Based Ocular Insert for the Treatment of Glaucoma. Science 2012, Pittsburgh, PA, October 2012.

96) Patil, M., Gottardi, R., Velankar, S.S., **Little, S.R.** Interfacial Interactions of Zero-Dimensional Carbon Nanotubes and Their Application as Thin Films: A Potential Platform for Cell Growth. Science 2012, Pittsburgh, PA, October 2012.

95) Howell, A., Balmert, S.C., Lash, M.H., Glowacki, A.J., **Little, S.R.** Patchy Particles: Inducing Surface Anisotropy for a Biomimetic Immune Synapse. Science 2012, Pittsburgh, PA, October 2012.

94) Gottardi, R., Stolz, M., Raiteri, R., Dueggelin, M., Lozito, T., Alexander, P., **Little, S.R.** Tuan, R.S. Cartilage Degeneration and Repair – Seeing and Operating at the Nanoscale. Science 2012, Pittsburgh, PA, October 2012.

93) Zmolek, A., Balmert, S.C., Glowacki, A.J., Rothstein, S., Wokpetah, J., **Little, S.R.** Analyzing the Release Kinetics of 'Sticky' Peptides from PLGA (Poly(lactic-co-glycolic) acid) Microspheres. Science 2012, Pittsburgh, PA, October 2012.

92) Blanchard, E., DeSantis, D., Gottardi, R., and **Little, S.R.** Developing a Controlled, Sequential Delivery System of Alginate Microparticles for the Release of Positively Charged Growth Factors. Science 2012, Pittsburgh, PA, October 2012.

91) Glowacki, A.J., Yoshizawa, S., Sfeir, C.S., Zack, J., **Little, S.R.** Translation of Periodontal Treatments that Restore Immunological Homeostasis. University of Pittsburgh First Look Technology Showcase, Pittsburgh, PA, October 2012.

90) Glowacki, A.J., Yoshizawa, S., Jhunjhunwala, S., Garlet, G.P., Sfeir, C.S., **Little, S.R.** Preclinical Evaluation of Treg Recruiting Microparticles for the Treatment of Periodontitis. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

89) Knab, T.D., Rothstein, S.N., **Little, S.R.,** Parker, R.S. System Identification and Frequency Response Techniques for the Design of Controlled Release Drug Delivery Systems. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

88) Lash, M.H., Kamalssanan, K., Li, S., McCarthy J.J., **Little, S.R.** Fabrication of Highly Ordered and Close Packed Colloidal Crystals from Large Microparticles. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

87) Fedorchak, M.V., Wingard, J.B., Medina, C.A., Albeiruti, E., Schuman, J.S., **Little, S.R.** 28-Day Ocular Delivery of Brimonidine Tartrate from Rationally Designed, Degradable Microparticles in a Rabbit Model. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

86) Rothstein, S.N., **Little, S.R.** Critical Quality Attributes (CQAs) of Biodegradable Polymer Matrices and Particles: Impact of a Recent Mathematical Model. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

85) Wu, T., Ngobi, L.M., Rothstein, S.N., Yutzy, S., Wiener, E., Parker, R.S., **Little, S.R.** Magnetic Resonance Imaging as a Powerful Tool for Visualizing Controlled Release from Biodegradable Microparticles. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

84) Fisher, J.D., Jhunjhunwala, S., Thomson, A.T., Unadkat, J.V., **Little, S.R.** Biomimetic Sustained Release Formulations for Suppressing Composite Tissue Transplant Rejection. Society for Biomaterials Annual Conference, New Orleans LA, October 2012.

83) Fisher, J.D., Jhunjhunwala, S., Thomson, A.T., Unadkat, J.V., **Little, S.R.** Biomimetic Sustained Release Systems for Regulating Inflammation in Composite Tissue Transplant Rejection. AIChE Annual Conference, Pittsburgh, PA, October 2012.

82) Kamalasan, K., Gottardi, R., Tan, S., Chen, Y., Godugu, B., Rothstein, S.N., Balazs, A.C., Star, A., **Little, S.R.** "Zero Dimensional" Single Walled Carbon Nanotubes. AIChE Annual Meeting, Pittsburgh, PA, October 2012.

81) Balmert, S.C., Jhunjhunwala, S., Raimondi, G., Vu, J.R., Thomson, A.W., Falo, L.D., **Little, S.R.** Controlled Release Systems to Increase Local Numbers of Regulatory T Cells and Suppress Contact Hypersensitivity. Society for Biomaterials 2012 Fall Symposium, New Orleans, LA, October 2012.

80) Balmert, S.C., Jhunjhunwala, S., Raimondi, G., Vu, J., Falo, L., Thomson, A.W., **Little, S.R.** Sustained Release Systems to Locally Expand Regulatory T Cell Populations and Suppress Inflammation, AIChE Annual Meeting, Pittsburgh, PA, October 2012.

79) Hong, Y., **Little, S.R.,** Wagner, W.R. Developing an Enzymatically-Trigged, Rapidly Degradable Polyurethane Hollow Fiber Membrane. Biomedical Engineering Society Annual Fall Meeting, Atlanta, GA, October 2012.

78) Raimondi, G., Jhunjhunwala, S., Nichols, E.E., Thomson, A.W., **Little, S.R.** All-trans Retinoic Acid and Rapamycin Synergize with Transforming Growth Factor-β1 to Induce Regulatory T Cells but Confer Distinct *In Vivo* Migratory Capacities. Joint Annual Meeting of the International Cytokines Society and International Society for Interferon and Cytokine Research, Geneva, Switzerland, September 2012.

77) Yoshizawa, S., Glowacki, A.J., **Little, S.R.,** Sfeir, C.S. Preclinical Evaluation of Treatments for Periodontitis that Recruit Regulatory T-cells. International Association for Dental Research, Iguaçu Falls, Brazil, June 2012.

76) Fedorchak, M.V., Wingard, J.B., Medina, C.A., Albeiruti, E., Schuman, J.S., **Little, S.R.** 28-day Ocular Delivery of Brimonidine Tartrate from Rationally Designed Degradable Microparticles in a Rabbit Model. Association for Research in Vision and Ophthalmology Annual Meeting, Ft.

Lauderdale, FL, May 2012.

- ***Selected as an ARVO "Emerging Trends and Hot Topics"***

75) Zmolek, A., Balmert, S.C., Glowacki, A.J., Rothstein, S., Wokpetah, J., **Little, S.R.** Defining the Role of Peptide Charge on Release Kinetics from PLGA (Poly(lactic-co-glycolic) acid) Microspheres. AIChE Regional Conferences 2012, Hoboken, NJ, April 2012.

74) Zmolek, A., Balmert, S.C., Glowacki, A.J., Rothstein, S.N., Wokpetah, J., **Little, S.R.** Defining the Role of Peptide Charge on Release Kinetics from PLGA (Poly(lactic-co-glycolic) acid) Microspheres. URC-PA: Undergraduate Research at the Capitol, Harrisburg, PA, March 2012.

73) Fedorchak, M.V., Wingard, J.B., Medina, C.A., Albeiruti, E., Schuman, J.S., **Little, S.R.** Combating Blindness with Convenient and Comfortable Glaucoma Treatments. McGowan Institute for Regenerative Medicine Scientific Retreat, Farmington, PA, March 2012.

72) Lash M.H., Kamalasanan K., McCarthy J.J., **Little S.R**. Engineering Particles to Rationally Assemble Using Surface Anisotropy-Based Information. McGowan Institute for Regenerative Medicine Scientific Retreat, Farmington, PA, March 2012.

71) Fisher, J.D., Jhunjhunwala, S., Thomson A.T., **Little, S.R.** Biomimetic Sustained Release Formulations for Suppressing Composite Tissue Transplant Rejection Via Naïve, Regulatory T Cells. McGowan Institute for Regenerative Medicine Scientific Retreat, Farmington, PA, March 2012.

70) Balmert S.C., Jhunjhunwala S., Raimondi G., Dons E., Nichols E.E., Thomson A.W., **Little S.R.** Biomimetic Microparticle Systems to Promote Local Immune Tolerance, McGowan Institute for Regenerative Medicine Scientific Retreat. Farmington, PA, March 2012.

69) Raimondi, G., Jhunjhunwala, S., Brandisher, G., Thomson, A.W., **Little, S.R.** Biomimetic Controlled Release of CCL22 for *In Vivo* Recruitment of Regulatory T Cells and Prolongation of Allograft Survival. American Transplant Congress, Philadelphia, PA, May 2011.

68) Kamalasanan, K., Jhunjhunwala, S., Swanson, A., Wu, J., Gao, D., **Little, S.R.** Synthetic Cells with Ordered Protein Patches. PINCE Research Fair, Pittsburgh, PA, May 2011.

67) Jhunjhunwala, S., Raimondi, G., Nichols, E., Thorne, S., Thomson, A.W., **Little, S.R.** Biomimetic Sustained Release Formulation for Modeling Local Immune Responses. Materials Research Society, San Francisco, CA, April 2011.

66) Kamalasanan, K., **Little, S.R.** Synthetic Cells with Ordered Protein Patches. Society for Biomaterials Annual Meeting, Orlando, FL, April 2011.

65) Jhunjhunwala, S., Raimondi, G., Nichols, E., Thorne, S.H., Thomson, A.W., **Little, S.R.** Controlled Release Formulations for Increasing Local Numbers of Regulatory T Cells. Society for Biomaterials Annual Meeting, Orlando, FL, April 2011.

64) Glowacki, A.J., Jhunjhunwala, S., Garlet, G., Sfeir, C.S., **Little, S.R**. Recruiting Regulatory T-cells to Treat Periodontitis and Promote Regeneration. AADR Annual Meeting, San Diego, CA, March 2011.

63) Glowacki, A.J., Jhunjhunwala, S., Garlet, G., Sfeir, C.S., **Little, S.R.** Recruiting Regulatory T-cells to Treat Periodontitis and Promote Regeneration. McGowan Institute for Regenerative Medicine, Farmington, PA, March 2011.

62) Tengood, J., Federspiel, W.J., **Little, S.R.** Release of Angiogenic Growth Factors from Porous

Hollow Fiber Membranes. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2011.

61) Wu, T., Ngobi, L., Rothstein, S.N., Parker, R., **Little, S.R**. A Compartmental Model of Controlled Release that Accounts for Multiple Barriers to Micro-Needle-Based Transdermal Drug Delivery. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2011.

60) Ngobi, L., Rothstein, S.N., **Little, S.R.**, Parker, R. Exploring New Techniques for "Fingerprinting" the Barriers to Controlled Release *In Vivo*. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2011.

59) Balmert S.C., Jhunjhunwala S., **Little S.R.** Biomimetic Microparticle-Based System to Induce Local Immune Tolerance *In Vivo*. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2011.

58) Hwang, M.P., **Little, S.R.** Controlled Delivery of CCL5 Induces MC3T3-Osteoblastic Chemotaxis and Survival. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2011.

57) Ma, Z., Hong, Y., Nelson, D.M., Tengood, J., **Little, S.R.,** Wagner, W.R. Biodegradable Poly(urethane urea) (PUU) Elastomers with Diverse Properties for Biomedical Applications. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2011.

56) Rothstein, S., **Little, S.R.** Augmenting Biologics with Cost-Effective Controlled Release Formulations. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

55) Glowacki, A.J., Jhunjhunwala, S., Garlet, G., Sfeir, C.S., **Little, S.R.** Treating Periodontal Disease through the Recruitment of Regulatory Lymphocytes. AIChE, Salt Lake City, UT, November 2010.

54) Dutt, M., Nayhouse, M., Kuksenok, O., **Little, S.R.** Design of Synthetic Vehicles through Self-Assembly of End-Functionalized Nanotubes and Lipids. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

53) Dutt, M., Kuksenok, O., **Little, S.R.**, Balazs, A.C. Forming Trans-Membrane Channels Using End-Functionalized Nanotubes. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

52) Glowacki, A.J., Jhunjhunwala, S., Gustavo, G., Sfeir, C.S., **Little, S.R.** Treating Periodontal Disease through Recruitment of Regulatory Lymphocytes. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

51) Rothstein, S.N., **Little, S.R.** Rationally Designed Controlled Release Therapeutics. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

50) Kamalasanan, K., **Little, S.R.** Self-Assembly of Quantum Single Walled Carbon Nanotubes. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

49) Kamalasanan, K., **Little, S.R.** Anisotropic Protein Patterned Microspheres. AIChE Annual Meeting, Salt Lake City, UT, November 2010.

48) Jhunjhunwala, S., Raimondi, G., Hall, S., Thorne, S.H., Thomson, A.W., **Little, S.R.** Bio-inspired Controlled Release for Regulatory T Cell Recruitment *In Vivo*. The American Association of Immunologist, Immunology 2010, Baltimore, MD, May 2010.

47) Fierro, J.A., Ramirez, V., Silvia, C., Ruiz, P., Gleisner, A., Morales, J., Jhunjhunwala, S., **Little,**

S.R., Bono, M.R., Rosemblatt, M. Transference of Phagosomes in an Allogeneic Immunization Protocol Down Regulates the Production of anti-MHC Antibodies and T Cell Mediated Alloreactivity. American Transplant Congress, San Diego, CA, May 2010.

46) Tengood, J., Russell, A.J., **Little, S.R.** Sequential Delivery of VEGF and S1P for Angiogenesis. Society for Biomaterials Annual Meeting, Seattle, WA, April 21st – 24th, 2010.

45) **Little, S.R.** Regenerating Periodontal Structures Through Recruitment of Regulatory Lymphocytes. ICRE Annual Meeting, Washington DC, April 2010.

44) Balazs, A.C., Dutt, M., Kuksenok, O., **Little, S.R.** Modeling the Interactions Between Amphiphilic Nanotubes and Lipid Bilayers. Materials Research Society Spring Meeting, San Francisco, CA, April 2010.

43) **Little S.R.** Biomimetic Drug Delivery. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

42) Hwang, M.P., **Little, S.R.** Controlled Delivery of Platelet-Derived Growth Factor Induces MC3T3-E1-Osteoblastic Cell Proliferation and Chemotaxis. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

41) Hofer, H., Sfeir, C.S., **Little, S.R.** Biomaterial-Associated Osteogenesis *In Vitro*. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

40) Glowacki, A.J., Jhunjhunwala, S., Gustavo, G.P., Sfeir, C.S., **Little, S.R.**, Treating Periodontitis Through Recruitment of Regulatory Lymphocytes. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

39) Tengood, J., Russell, A.J., **Little, S.R.** Sequential Delivery of Angiogenic Growth Factors. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

38) Jhunjhunwala, S., Raimondi, G., Hall, S., Thorne, S., Thomson, A.W., **Little, S.R.** Bio-inspired controlled release for the recruitment of regulatory T cells. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

37) Rothstein, S. N., **Little SR.** Customizing Timed Release Formulations: a Visual Whitepaper for ChroKnow Solutions. McGowan Institute for Regenerative Medicine Retreat, Farmington, PA, March 2010.

36) **Little, S.R.** Controlling Controlled Release from Biodegradable Systems, US-Japan Symposium on Drug Delivery Systems. Lahaina, HI, December 2009.

35) Rothstein, S.N., **Little S.R.** Engineering Sustained Release in Therapeutics. Biotech 2009, Mid-Atlantic Region Biosciences Annual Meeting, Philadelphia, PA, November 2009.

34) Rothstein, S.N., **Little, S.R**. *In Vivo* Evaluation of Rationally Designed Single Injection Vaccine. Disease Therapies, AIChE Annual Meeting, Nashville, TN, November 2009.

33) Rothstein, S.N., **Little, S.R**. Engineering Efficacious Controlled Release Therapeutics, Meet the Faculty Candidate. AIChE Annual Meeting, Nashville, TN, November 2009.

32) Kamalasanan, K., **Little, S.R**. Modeling the Interactions of Amphiphilic Nanotubes and Lipid Bilayers. Self-Assembled Biomaterials, AIChE Annual Meeting, Nashville, TN, November 2009.

31) Rothstein, S. N., **Little S.R.** Engineering Sustained Release in Therapeutics. University of

Pittsburgh Science Technology Showcase, Pittsburgh, PA, October 2010.

30) Roy, A., Jhunjhunwala, S., **Little, S.R.,** Kumta, P. Calcium Phosphate-Poly(lactic-co-glyolic) Acid Composite Cements for Bone Regeneration. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

29) Tengood, J., Russell, A.J., **Little, S.R.** Temporal Delivery of Angiogenic Growth Factors. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

28) Hofer, H., Sfeir, C.S., **Little, S.R.** Biocompatibility of a Gene Delivery Vehicle for Bone Tissue Engineering. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

27) Glowacki, A.J., Jhunjhunwala, S., Garlet, G., Sfeir, C.S., **Little, S.R.** Regenerating Periodontal Structures Through Recruitment of Regulatory Lymphocytes. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

26) Karunanidhi, A., **Little, S.R.** Evaluation of PDGF-BB for Osteo-Angiogenic Effects Using 3D-Speroidial Co-culture Model. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

25) Kamalasanan, K., **Little, S.R.** Dual Protein Patterning of Microspheres for Therapeutics, Biosensor, and Photonic Applications. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

24) Jhunjhunwala, S., Hall, S., Raimondi, G., Thorne, S., Garlet, G., Thomson, A.W., **Little, S.R.** Developing Controlled Release Formulations for Regulatory T-cell Recruitment. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

23) Rothstein, S.N., **Little, S.R.** Translation of *In Silico* Controlled Release Predictions into Rationally Designed Therapeutic Formulations. Biomedical Engineering Society Annual Meeting, Pittsburgh, PA, October 2009.

22) Jhunjhunwala, S., Raimondi, G., Thomson, A.W., **Little, S.R.** Controlled Release for Recruitment of Regulatory T cells. Keystone Regulatory T-cell Conference, Keystone, CO, March 2009.

21) Yadav, S., van Vlerken, L., **Little, S.R.**, Langer, R., Amiji, M. Multifunctional Nanosystems for MDR-1 Gene Silencing and Chemotherapy Administration to Overcome Drug Resistance. Bio International Convention, Boston, MA, May 8, 2008.

20) Tengood, J., Russell, A.J., Wagner, W.R., **Little, S.R**. Sequential Delivery of Growth Factors to Improve Angiogenesis. 8th World Biomaterials Congress, Amsterdam, The Netherlands, May 28 – June 1, 2008.

19) **Little, S.R.** Non-Viral Delivery of Genetic Vaccines to Dendritic Cells. Drug and Nucleic Acid Delivery Symposium, Pittsburgh, PA, June 2, 2008.

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14) **Little, S.R.** High-Throughput Fabrication of Polymeric Microparticles. AIChE Annual Meeting, San Francisco, CA, November 2006.

13) **Little, S.R.**, Anderson D.G., Langer R. High-Throughput Fabrication of Polymeric Microparticles. US-Japan Symposium on Drug Delivery Systems, Lahaina, HI, December 2005.

12) Wood, K.C., **Little, S.R.,** Langer, R., Hammond, P.T. A New Family of Hierarchically Self-Assembling Linear-Dendritic Hybrid Polymers for Targeted Gene Delivery. US-Japan Symposium on Drug Delivery Systems, Lahaina, HI, December 2005.

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10) Zugates, G.T., Anderson, D.G., **Little, S.R.,** Langer, R. Synthesis of Functionalized Poly(Beta-Amino Ester)s for Targeted Gene Delivery. US-Japan Symposium on Drug Delivery Systems, Lahaina, HI, December 2005.

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PROFESSIONAL ORGANIZATIONS (WITH SELECT LEADERSHIP ROLES)

- American Institute for Medical and Biological Engineering (AIMBE)
- American Association for the Advancement of Science (AAAS)
- American Association of Pharmaceutical Scientists (AAPS)
    - *Selected as a Member of the Awards Committee*, 2022-2024
- American Chemical Society (ACS)
- American Institute of Chemical Engineers (AIChE)
    - *Co-Organizer* of the Symposium on "Polymers for Immunology and Immunotherapy" for the 2011 Spring Meeting
    - *Organizer* of the Multi-Session (4) Drug Delivery Program at the 2009 Annual Meeting in Nashville, TN
    - *Primary Organizer* of the Topical Conference on "Biomedical Applications of Chemical Engineering" for the 2012 Annual Meeting, Pittsburgh, PA.
        - *Thirteen (13) sessions, 84 scientific talks, 18 invited speakers, Plenary by Nicholas Peppas (UT Austin)*
- American Society for Engineering Education (ASEE)
- Association for Research in Vision and Ophthalmology (ARVO)
- BioMedical Engineering Society (BMES)
    - *Organizer* of the Session on "Biomaterial Immunoengineering" for the 2012 Annual Meeting, Atlanta, GA
- Controlled Release Society (CRS)
    - *Member, President's Task Force for Connectivity, 2016*
    - *Appointed Representative to the Board of Directors for Focus Groups*
        - *Led the effort in 2017/2018 to establish Focus Groups in the CRS in the areas of: Biomimetic Drug Delivery, Nanomedicine and Nanoscale Drug Delivery, Ophthalmic Drug Delivery, Oral Drug Delivery and Gene Delivery and Gene Editing*
    - *CRS Young Investigator Award Winner, 2018*
    - *Elected to the Board of Directors (Director-At-Large), 2018-2021*
    - *Elected by the Board of Directors to Chair the Programming Committee for the 2020 Annual Meeting*
- Council for Chemical Research (CCR)

- Hilton Head Regenerative Medicine Alliance (Georgia Tech & University of Pittsburgh)
  - *Organizing Committee for the 2013 Meeting – Technologies Enabling Novel Therapies*
- International Association for Dental Research (IADR)
- Materials Research Society (MRS)
  - *Co-Organizer* of the Symposium on "Biomimetic Engineering of Particles" for 2011 Spring Meeting
  - Was later turned into a full issue of *Advanced Materials* with each speaker contributing a manuscript (Editor: Lorna Stimson).
- Society for Biomaterials (SFB)
  - *Elected to the Board of Directors (SIG Representative)*, 2013 - 2015
  - *Society for Biomaterials Young Investigator Award Winner*, 2012
  - *Member*, Web Redesign Task Force, 2011-2012
  - *Elected Chair*, Drug Delivery Special Interest Group, 2011
  - *Organizer* of the Panel for Bridging Academic and Industry Gaps for 2011 National Meeting
  - *Elected Vice-Chair*, Drug Delivery Special Interest Group, 2010
  - *Organizer* of the Panel for Translation of Nano-Medicine for 2009 National Meeting
  - *Organizer* of the Symposium on Micro and Nano Particulate Delivery for 2008 National Meeting
- Society for Leukocyte Biology (SLB)
- Tissue Engineering and Regenerative Medicine International Society (TERMIS)

Reviewer for Journals:

AAPS Journal

Advanced Functional Materials

Advanced Healthcare Materials

Advanced Materials

ACS Applied Materials and Interfaces

ACS Nano

Acta Biomaterialia

Angewandte Chemie

Archives of Oral Biology

Arnold and Mabel Beckman Foundation

Biomacromolecules

Biomaterials

Biomaterials Science

Biomedical Materials

Biotechnology and Bioengineering

BMC Cancer

Cell Reports, Medicine

Chemical Communications

Chemical Product and Process Modeling

Clinical and Translational Medicine

Cogent Medicine

Colloids and Surfaces B: Biointerfaces

Drug Design, Development and Therapy

Drug Development and Industrial Pharmacy

Environmental Science and Pollution Research

European Journal of Pharmaceutics and Biopharmaceutics

Experimental Dermatology

Expert Opinion on Drug Delivery

Gene Therapy

Gordon Research Conference Proposals

Integrative Biology

International Journal of Pharmaceutics

Journal of Applied Polymer Science

Journal of Biomedical Materials Research: Part A

Journal of Controlled Release

Journal of Dental Research

Journal of Drug Delivery Science and Technology

Journal of Drug Targeting

Journal of Liquid Chromatography & Related Technologies

Journal of Molecular Medicine

Journal of Pharmaceutical Science

Journal of the American Chemical Society

Journal of Tissue Engineering and Regenerative Medicine

Journal of Tissue Science and Engineering

Macromolecular Rapid Communications

Mini Reviews in Medicinal Chemistry

Molecular Pharmaceutics

Molecular Therapy

Nanobiomedicine

Nanomedicine

Nanomedicine: Nanotechnology, Biology, and Medicine

National Institutes of Health (NIH)

National Science Foundation (NSF)

National Science Centre, Poland (NCN)

Nature Materials

Nature Methods

Nature Scientific Reports

Ocular Immunology and Inflammation

Oncotarget

Pharmaceutical Research

Proceedings of the National Academy of Sciences

Recent Patents on Drug Delivery Formulation

Rejuvenation Research

Science, Advances

Science, Translational Medicine

Small

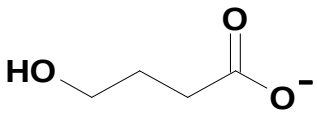
Trends in Biotechnology

Vaccines

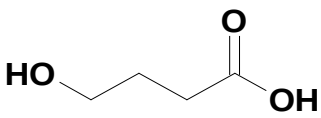
EXHIBIT 34

GAMMA-HYDROXYBUTYRATE / BUTYRIC ACID

Latest Revision: May 16, 2005



gamma-hydroxybutyrate



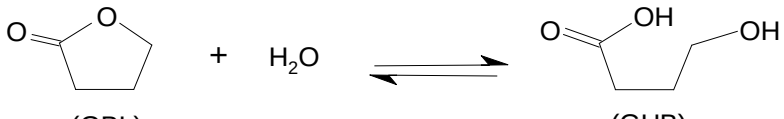
gamma-hydroxybutyric acid

1. SYNONYMS

CFR:	*Gamma*-Hydroxybutyric acid
CAS #:	Sodium: 502-85-2
Other Names:	Sodium oxybate Sodium gamma-hydroxybutyrate 4-Hydroxy butyrate, sodium 4-Hydroxybutanoic acid monosodium salt GHB Anetamin Somsanit *Gamma* OH Somatomax PM

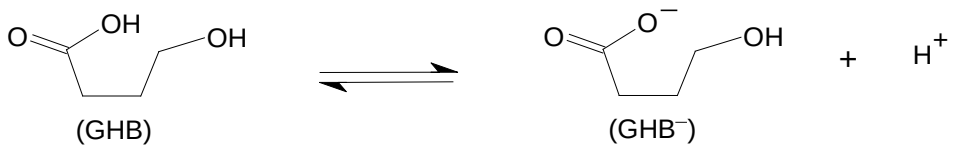
2. CHEMICAL AND PHYSICAL DATA

Gamma-hydroxybutyrate / butyric acid, ambiguously called GHB, presents some unique challenges for analysis due in part to its acidity, high polarity, and high solubility in aqueous solution. Its chemistry is complicated by its conversion into the corresponding lactone compound, where the GHB molecule condenses to form a cyclic ester with a five-membered ring. This compound, *gamma*-butyrolactone (GBL), is particularly stable among the family of lactones (Streitwieser and Heathcock, 1976), and exists in equilibrium with GHB in aqueous solution:



(GBL) (GHB) (2.1)

Here the term GHB specifically refers to *gamma*-hydroxybutyric acid, or the free acid form of GHB. The equilibrium constant for this reaction is 0.39. The solution chemistry of GHB is also described by the dissociation of the free acid into the *gamma*-hydroxybutyrate anion (GHB^-):



(2.2)

The dissociation constant for this reaction is estimated at 2.0 x 10^{-5}moles per liter (pK_a~4.71). Historically, the term GHB has been used to describe both the free acid and anion since the two species readily interconvert in aqueous solution depending upon the solution pH. However, in a chemical discussion it is important to distinguish between the two species since they are distinct molecular entities. The salt forms of GHB when dissolved into water are chemically equivalent to the anion species in aqueous solution.

The three distinct species of lactone, free acid and anion may all coexist in an aqueous sample containing GHB. The relative concentration, or distribution, of these species is a function of solution pH and may be determined from the equilibrium constants. At equilibrium, GHB exists predominantly as the anion under basic conditions (pH greater than 7), occurring as dissolved salts, commonly with sodium or potassium as the counter-ion. Under moderately acidic conditions (pH less than 4), the free acid and lactone predominate in aqueous solution in a proportion of approximately 30% GHB to 70% GBL. Most aqueous samples of GHB, though, fall in the intermediate region between pH 4 and 6 where a mixture of all three species occurs.

The actual composition for many aqueous solutions is, however, complicated by the lack of an established equilibrium among the species, since the interconversion of GBL and GHB may be a very slow process (Ciolino, *et al*., 2001). The kinetics of the reaction (Eq.2.1) are observed to be pseudo-first-order in aqueous solution, in which equilibrium is approached asymptotically in time, and may be quantified by a rate constant that is strongly dependent upon the solution pH (Long and Friedman, 1950; Frost and Pearson, 1961). This classic behavior for a hydrolysis reaction is due to mechanisms that are catalyzed by the relative acidity or basicity of the aqueous solution. In contrast, the dissociation equilibrium between the free acid and the anion (Eq.2.2) occurs rapidly (essentially instantaneous) between the dissolved species in aqueous solution.

The rate of conversion of GBL into GHB^- is observed to increase greatly as the solution pH spans the range from neutral to a basic pH of 12, where the rate constant increases by approximately one order of magnitude (10x) for each unit increase in the solution pH (Chappell, 2002). The hydrolysis of GBL into GHB^- is quite rapid at pH values greater than 12, with complete reaction occurring within several minutes. Conversely, the hydrolysis reaction is very slow at neutral pH, where complete conversion into GHB^- is indicated to require a period greater than one year.

The rate constant assumes a minimum value near a solution pH of 5, and increases in magnitude as the pH decreases for distinctly acidic solutions. An aqueous solution of GBL buffered to a pH of 2 requires approximately one week to attain an equilibrium proportion of GHB. At lower solution pH, GBL hydrolysis is naturally faster, and GHB may be detected after one hour, although equilibrium may not be achieved for over a day.

The interconversion of GBL and GHB is therefore extremely slow for solutions between pH values of 4 and 7, and based on the observed rate behavior, requires several months for significant reaction to occur. The solution chemistry may be further complicated by side reactions with other components in the sample, including alcohol (Hennessy, *et al*., 2004). This behavior has important implications for the analysis of illicit samples containing GHB since most samples are aqueous solutions that are prepared as drinks for human consumption. Illicit samples typically consist of tap water or familiar commercial beverages (soft drinks or juices), as well as alcoholic drinks, which are spiked with GHB or GBL and fall within the pH range of 3 to 7. Consequently, the

composition of most aqueous samples of GHB is not likely represented by an equilibrium distribution, but is dependent upon the pH, buffering capacity and other components of the solution, as well as its age. An analysis should therefore determine the solution pH and whether GBL is present in addition to GHB. Fortunately, the lactone and the free acid may be readily extracted from aqueous solutions for their separate identification.

2.1. CHEMICAL DATA

Form	Chemical Formula	Molecular Weight (g/mole)	Melting Point (°C)
Free acid	$C_4H_8O_3$	104.1	<-17
Sodium Salt	$C_4H_7O_3Na$	126.0	144-148
Potassium Salt	$C_4H_7O_3K$	142.2	137-139
Lithium Salt	$C_4H_7O_3Li$	110.0	177-178
Lactone	$C_4H_6O_2$	86.09	-42

2.2. SOLUBILITY

Form	A	C	E	H	M	W
Free Acid	S	I	S	I	S	S
Sodium Salt	I	I	I	I	S	VS
Potassium Salt	I	I	I	I	S	VS
Lithium Salt	I	I	I	I	FS	VS
Lactone	VS	VS	VS	SS	VS	VS

A = acetone, C = chloroform, E = ether, H = hexane, M = methanol and W = water, VS = very soluble, FS = freely soluble, S = soluble, PS = sparingly soluble, SS = slightly soluble, VSS = very slightly soluble and I = insoluble

3. SCREENING TECHNIQUES

3.1. COLOR TESTS

TEST	COLOR PRODUCED
GHB Test 1	Red
GHB Test 2	Purple
GHB Test 3	Dark Green

3.2. CRYSTAL TESTS

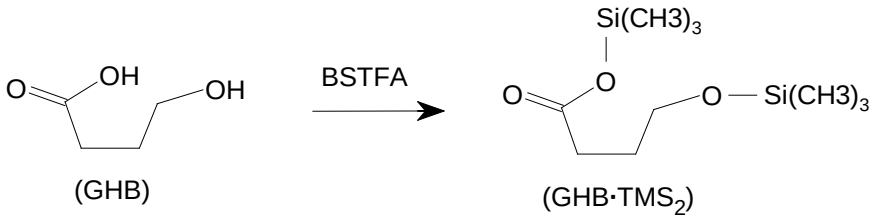
REAGENT	CRYSTALS FORMED
Silver nitrate	Rectangular crystals

3.3. GAS CHROMATOGRAPHY

Method GHB-GCS1

GHB is thermally unstable and may convert into GBL in the gas chromatograph injection port. Reaction with *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) allows for the analysis of the trimethylsilyl (TMS) derivative. GC/MS permits identification, and GC/FID is also amenable using a similar temperature program. Although it is possible to simultaneously detect GBL, possible formation from excess GHB warrants caution in interpreting data. Instead, GBL should be isolated for a separate analysis (see Section 4, Separation Techniques).

The TMS derivative compound is readily prepared by the reaction of the GHB with BSTFA,



where a trimethyl silyl group replaces the active proton at both the carboxylic acid and hydroxyl sites of the GHB molecule. A benefit to this approach is the conversion of GHB into a compound that is much less polar and sufficiently volatile for analysis by gas chromatography. The derivative compound GHB·TMS_2 also presents mass spectra (see both the electron-impact and chemical-ionization mass spectra of GHB·TMS_2) which may be suitable for the identification of GHB. Chemical-ionization produces a mass spectrum with a protonated molecular ion(249 amu) and a base peak of 159 amu. For the electron-impact mass spectrum, the molecular ion (248 amu) for GHB·TMS_2 is very weak, but the cleavage of a methyl group produces a distinctive fragment of 233 amu (Blackledge and Miller, 1991). The other prominent features of the electron-impact mass spectrum include a base peak at 147 amu and a significant fragment at 73 amu, both of which are common to di-O-substituted TMS derivatives.

Sample Preparation:
The derivative compound is prepared by the reaction of the BSTFA reagent with GHB or GHB^-, however, BSTFA reacts with protic solvents so the GHB specie must be isolated from any aqueous sample. An extraction scheme (see Section 4) is effective at isolating GHB as the free acid from aqueous solutions. A small aliquot (50 to 100 μL) of the BSTFA reagent is added directly to the extract solution (1 mL) containing GHB (approximately 1 to 3 mg). Heating the solution is generally unnecessary, especially if the reagent contains a silylation catalyst (for example, BSTFA with 1% TCMS). The extract solution with BSTFA may be examined directly by GC/MS.

The TMS derivative of GHB may also be prepared from a salt form of GHB, although the salt must be separated from aqueous samples and recovered in a relatively dry state. Derivatization of a GHB salt may be accomplished by heating a small portion of the dry salt (2 mg) with a small aliquot of the BSTFA reagent placed within a suitable solvent (1 mL chloroform). Initially the GHB salt will be insoluble within the solvent, but upon heating, GHB^- will convert into GHB·TMS_2 and dissolve into the solvent. Complete reaction may require approximately 20 minutes of heating at 70°C.

Instrument:	Gas chromatograph with electron-impact or chemical-ionization mass selective detector

Column: 100% polydimethylsiloxane, 12.0 m x 0.20 mm x 0.33µm film thickness

Carrier gas: Helium at 1.0 mL/min

Temperatures: Injector: 250°C
Transfer line: 280°C
Oven program:
70°C initial temperature for 1.20 min
Ramp to 280°C at 15°C/min
Hold final temperature for 5.00 min

Injection parameters: Split Ratio = 50:1, 1 µL injected

COMPOUND	RRT
GHB·TMS_2	1.00
GBL	0.33

3.4. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method GHB-LCS1

Sample Preparation:
Dissolve or dilute (if necessary) in mobile phase and filter (0.45 µm).

Instrument: High performance liquid chromatograph with diode array detector

Column: 5 µm ODS Hypersil, 4.6 mm x 100 mm

Detector: UV, 215 nm

Flow: 0.75 mL/min

Injection Volume: 5 µL

Buffer: 10 mM NaH_2PO_4 adjusted to pH 3 with H_3PO_4

Mobile Phase: Buffer:methanol (80:20)

COMPOUND	RRT
GHB	**1.000**
GBL	1.082

Method GHB-LCS2

GHB, GBL, and 1,4-butanediol can be identified in drinking water solutions by LC/MS (see the electrospray mass spectrum of the GHB sodium salt). The electrospray (+) mass spectrum is characterized by several protonated (M+1) species, including the sodium salt (127 amu), the free acid (105 amu) and the lactone (87 amu). The spectrum also displays a weaker peak for the protonated ammonium salt (122 amu) due to the presence of ammonium ions in the mobile phase, as well as a di-sodium GHB species (149 amu). Negative ion detection can be substituted for the GHB analysis, but comparatively poor sensitivity towards GBL and 1,4-butanediol is observed. Note that GHB (as GHB^-) shows no column retention with this buffer system.

Standard Solution Preparation:
Prepare a mixed standard of GHB sodium salt (1-10 mg per mL), GBL (5-10 mg/mL), and 1,4-butanediol (1-10 mg/mL) in methanol.

Instrument: High performance liquid chromatograph with atmospheric pressure ionization electrospray mass selective detector

Column: 5 µm Aqua C18, 100 mm x 4.6 mm

Detector: Scan mode, positive ion
Capillary voltage: 3000 V
Fragmentor: 30 eV
Nebulizer pressure: 60 psig
Drying gas flow: 13.0 L/min
Drying gas temperature: 350°C

Flow: 1.500 mL/min

Injection Volume: 5 µL

Buffer: 20 mM CH_3COONH_4 (~ pH 7.5)

Mobile Phase: 100% Buffer

Typical Retention Times: GHB: 2.00 min
1,4-Butanediol: 5.44 min
GBL: 6.46 min

COMPOUND	RRT
GHB	**1.000**
1,4-Butanediol	2.711
GBL	3.230

3.5. NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

GHB and GBL present proton (^{1}H) and carbon (^{13}C) NMR spectra with suitably distinct peaks, whereby mixtures of the two may be identified (see NMR spectra for GHB and GBL). Simple aqueous solutions of GHB and GBL may be examined with minimal sample preparation that allows the relative proportions of the two substances to be assessed directly from the composite NMR spectrum. Complex aqueous mixtures that arise from commercial beverages require GHB and GBL to be separated prior to analysis (see Section 4, Separation Techniques).

Method GHB-NMRS1

Sample Preparation:
Simple aqueous samples (typically 10 to 20 mg GHB /mL), may be diluted in deuterium oxide (D_2O) with the external reference standard 2,2-dimethyl-2-silapentane-5-sulfonate (DDS). GHB (or GBL) isolated by extraction may be prepared in D_2O with DDS, or in deuterated chloroform ($CDCl_3$) with the internal reference standard tetramethylsilane (TMS). Residual solvent peaks from the extraction solvent may be detected but do not interfere with the identification of GHB. Filter all preparation solutions before analysis.

Instrument: Nuclear magnetic resonance spectrometer

Probe: 5-mm dual channel, room temperature

Parameters:

^{1}H NMR:
Observation frequency: 300 MHz
Pulse angle: 30°
Acquisition time: 1.998 s
Spectral window: 4500 Hz
Filter bandwidth: 2250 Hz
Delay: 0 - 1 s
Frequency offset: 0 Hz
Number of transients: 16

^{13}C NMR:
Observation frequency: 75 MHz
Pulse angle: 45°
Acquisition time: 1.706 s
Spectral window: 18761.7 Hz
Filter bandwidth: 9500 Hz
Delay: 0 s
Frequency offset: 0 Hz
Number of transients: 512 (minimum)
Proton decoupler: on
Decoupler modulation frequency: 3233 Hz

4. SEPARATION TECHNIQUES

Aqueous samples containing GHB may also contain GBL due to the equilibrium between the two species (see Section 2). The following extraction scheme can isolate the two species from aqueous solutions for subsequent identification by IR, GC-MS or NMR.

GBL is readily removed from an aqueous sample by direct extraction with chlorinated solvents like methylene chloride (CH_2Cl_2) or chloroform ($CHCl_3$). Following the extraction, the extraction solvent should be passed over a column of drying agent (e.g., anhydrous sodium sulfate) in order to remove residual water that may be suspended or dissolved in the extract solvent. The extract solution may be examined directly by GC/MS to identify the presence of GBL. If sufficient GBL is present, evaporation of the solvent from the extract solution may also yield a clear, oily residue, which may be suitably pure for an infrared identification (the oily liquid may be simply examined neat as a liquid film between KBr disks). A second extraction of the aqueous sample with a chlorinated solvent is recommended to remove any residual GBL prior to the extraction of GHB.

During the CH_2Cl_2 or $CHCl_3$ extraction, the GHB species remains dissolved within the original aqueous sample. GHB may next be extracted in the form of the free acid after the sample has been acidified (with dilute HCl) to a pH between 1 and 4. The adjustment of the sample pH converts essentially all of the GHB present to the form of the free acid, which will predominate in the sample for a minimum period of one hour before a significant conversion to GBL occurs. The aqueous sample is saturated with sodium chloride and promptly extracted with ethyl acetate (Dardoize, *et al*., 1989; Couper and Logan, 2000). The partition coefficient for this extraction is relatively low, such that a quantitative removal of the free acid is not feasible, although the partition allows sufficient GHB to be extracted for identification. The extraction of a sample aliquot with a 3-times greater volume of ethyl acetate can remove approximately 50% of the free acid that is present in the aqueous sample. The extract solution should be passed over a column of drying agent to remove residual water. Preparation of the trimethylsilyl (TMS) derivative of GHB may be performed directly on the extract solution and examined by GC/MS (see Section 3.3). Alternatively, a relatively pure residue of GHB may be obtained and examined neat by infrared spectrometry following evaporation of the solvent. The evaporation of ethyl acetate is best accomplished on a steam bath under a stream of dry air or nitrogen until a clear, oily residue is obtained. Care should be taken to avoid overheating the residue for an extended period of time since GHB is subject to converting into GBL. The spectrum of GHB displays very broad features that are characteristic of a strongly hydrogen-bonded carboxylic acid (see the infrared spectrum of GHB). This extraction scheme has proved effective for a variety of samples prepared from different beverages, including soft drinks, juices and sport drinks (Chappell, Meyn and Ngim, 2004).

One limitation to the extraction scheme is the non-identification of the salt form of GHB since acidification of the original sample converts any GHB present as a salt (GHB^-) into the form of the free acid. However, this issue is moot for many samples encountered. Samples prepared with fairly acidic beverages (i.e., carbonated drinks or citrus juices) will generally have a pH value less than 5, in which case the GHB present in the sample predominates as the free acid. In addition, some beverages consist of a complex solution of electrolyte cations (sport drinks), which can obscure the identity of the original salt form of the GHB introduced into the drink. Only for samples prepared from tap water or a beverage with low levels of dissolved minerals can the GHB be confidently recovered in its original salt form.

The salt form of GHB may be recovered from simple aqueous solutions provided that the pH is greater than 6. A portion (greater than 5 mL) of the aqueous sample is evaporated on a steam bath (assisted under a stream of air) until a damp residue remains. The residue should be washed with acetone to remove excess water and other potential contaminants, and then dried under vacuum or at 100°C until a solid residue is obtained. If the original sample is relatively free of any other components, the recovered be suitable for infrared identification. Often the salts of GHB will initially give a poor infrared spectrum that is characterized by broad features due to a poorly crystallized solid and residual moisture. Heating the solid to 100°C for a few minutes will generally dry the material and promote crystallization, and the solid may then present a suitably resolved spectrum (see the infrared spectra for the sodium, potassium and lithium salts of GHB). This procedure may also be applied

to the solid that has been pressed within a KBr matrix since ion exchange between the alkali salts of GHB and KBr is not observed to occur, even after heating the mixture of the solids for an extended period (several days).

5. QUANTITATIVE PROCEDURES

5.1. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method GHB-LCQ1

Standard Solution Preparation:
Prepare a standard solution of GHB sodium salt in water at approximately 1.0 mg per mL.

Sample Preparation:
Accurately weigh an amount of sample into a volumetric flask and dilute with water. If necessary, dilute the sample so the final concentration approximates the standard concentration or falls within the linear range. Filter the sample (0.45 µm).

Instrument:	High performance liquid chromatograph with diode array detector
Column:	5 µm Aqua C18, 100 mm x 4.6 mm; 25°C
Detector:	UV, 195 nm (450 nm reference)
Flow:	1.0 mL/min
Injection Volume:	2 µL
Buffer:	25 mM KH_2PO_4, pH 6.5
Mobile Phase:	100% Buffer
Typical Retention Time:	GHB: 3.30 min GBL: 8.90 min
Linear Range:	0.32 - 5.04 mg/mL
Repeatability:	RSD less than 3.0%
Correlation Coefficient:	0.9998
Accuracy:	Error less than 5%

COMPOUND	RRT
GHB	**1.00**
GBL	5.59

6. QUALITATIVE DATA

See spectra on the following pages for Infrared Spectroscopy, Mass Spectrometry, and Nuclear Magnetic Resonance.

7. REFERENCES

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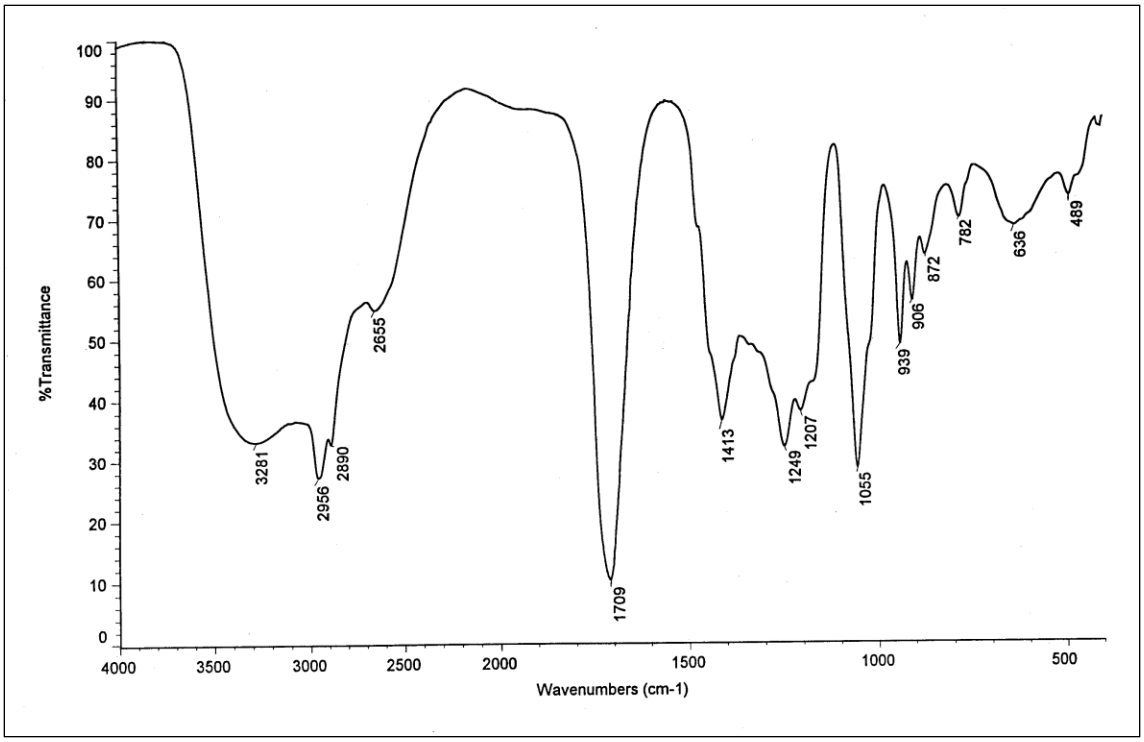
8. ADDITIONAL RESOURCES

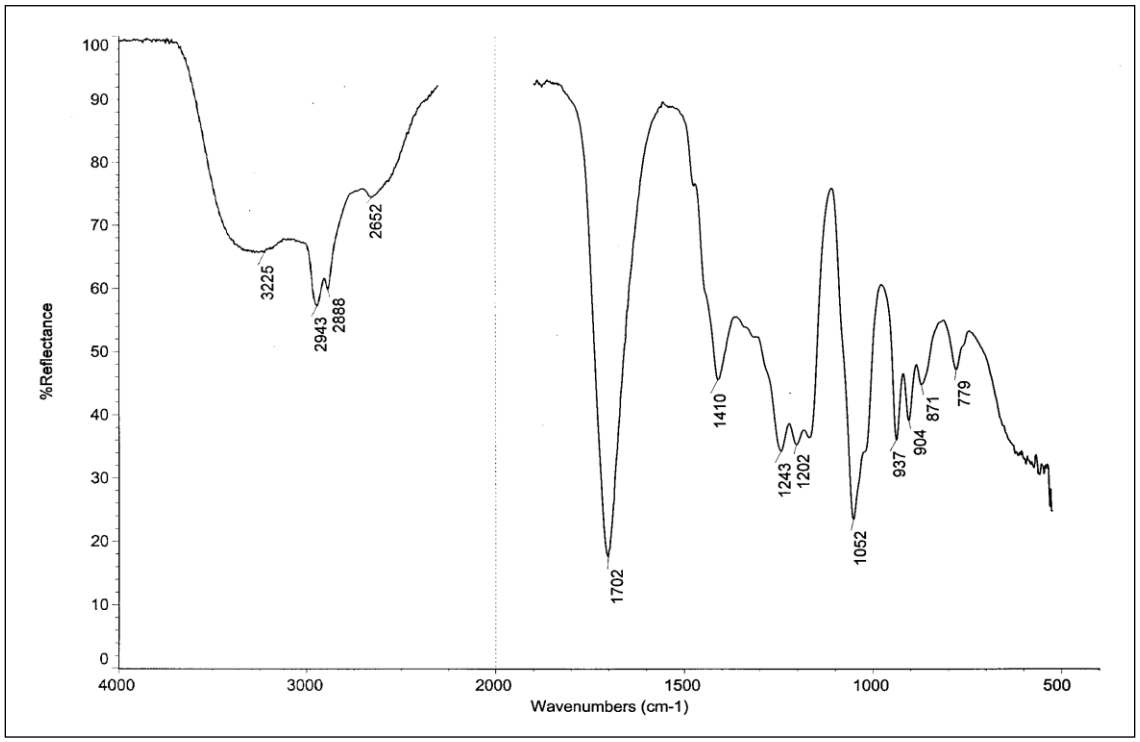
Forendex

Wikipedia

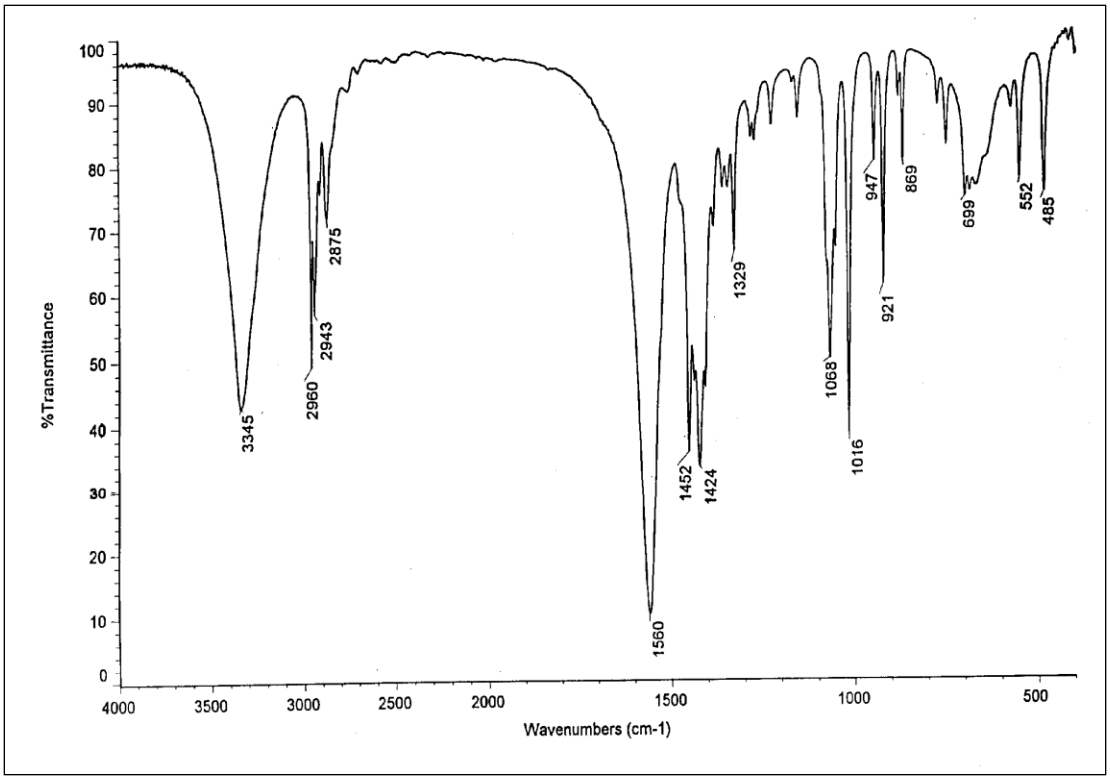
Acid, Transmission IR: *gamma*-Hydroxybutyric acid, sample neat between KBr disks
16 scans, 4.0 cm^{-1} resolution



IR (ATR bounce, diamond device): *gamma*-Hydroxybutyric acid
16 scans, 4.0 cm^{-1} resolution



Transmission IR: *gamma*-Hydroxybutyrate, sodium salt sample in KBr matrix
16 scans, 4.0 cm^{-1} resolution



IR (ATR, 3-bounce, diamond device): *gamma*-Hydroxybutyrate, sodium salt
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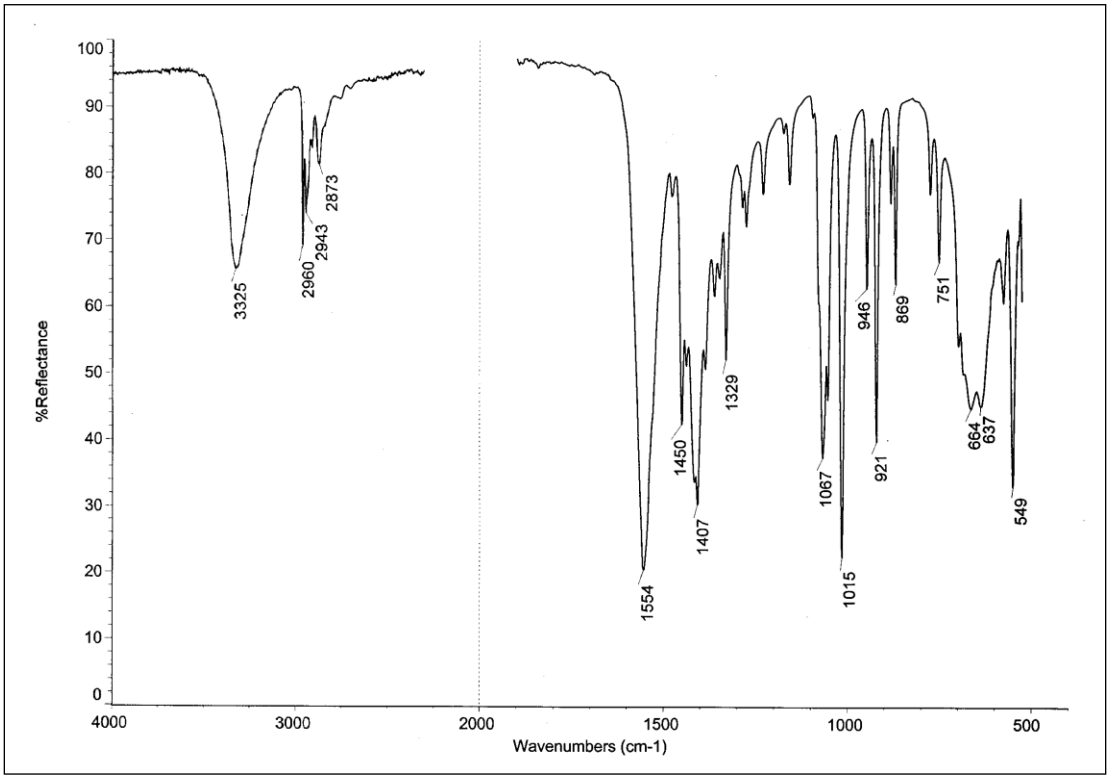

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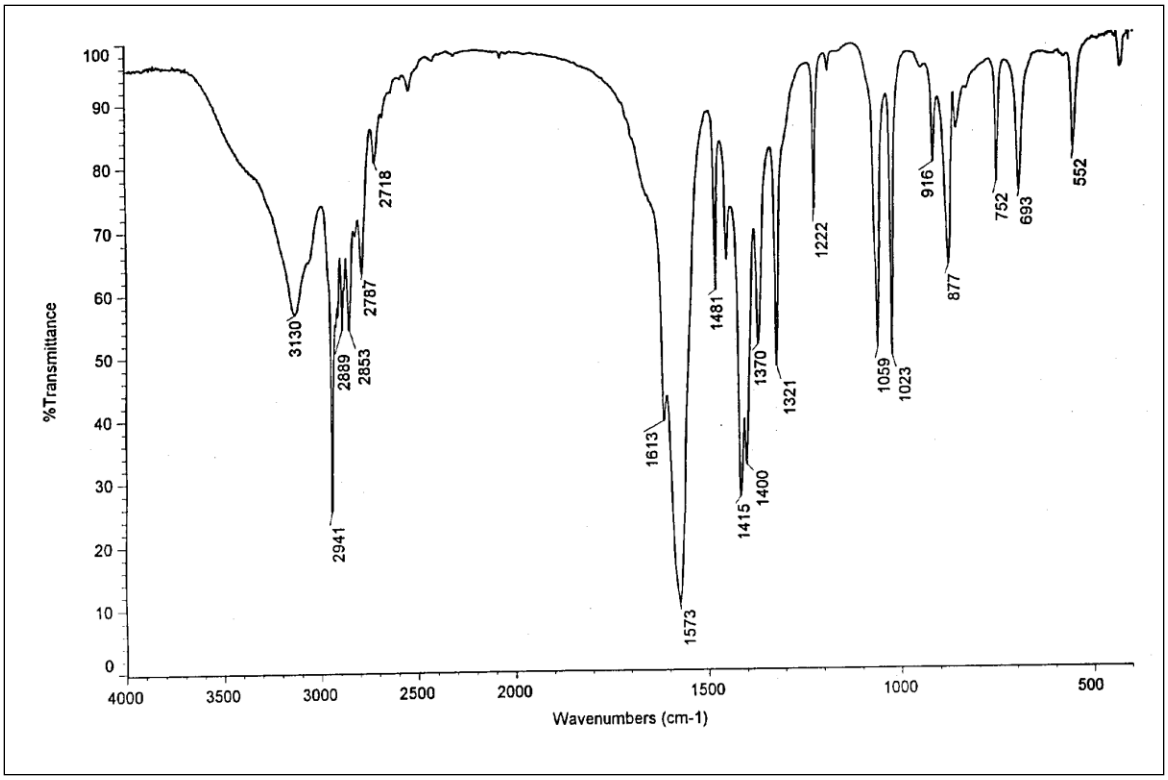
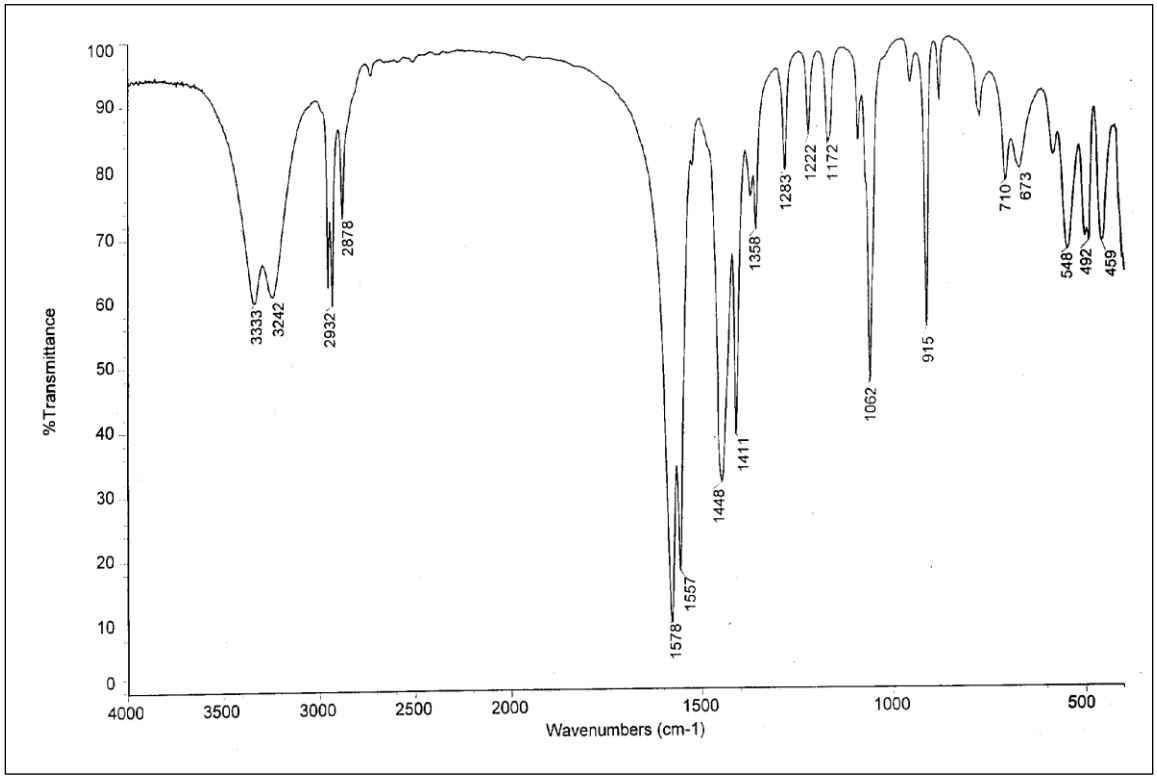
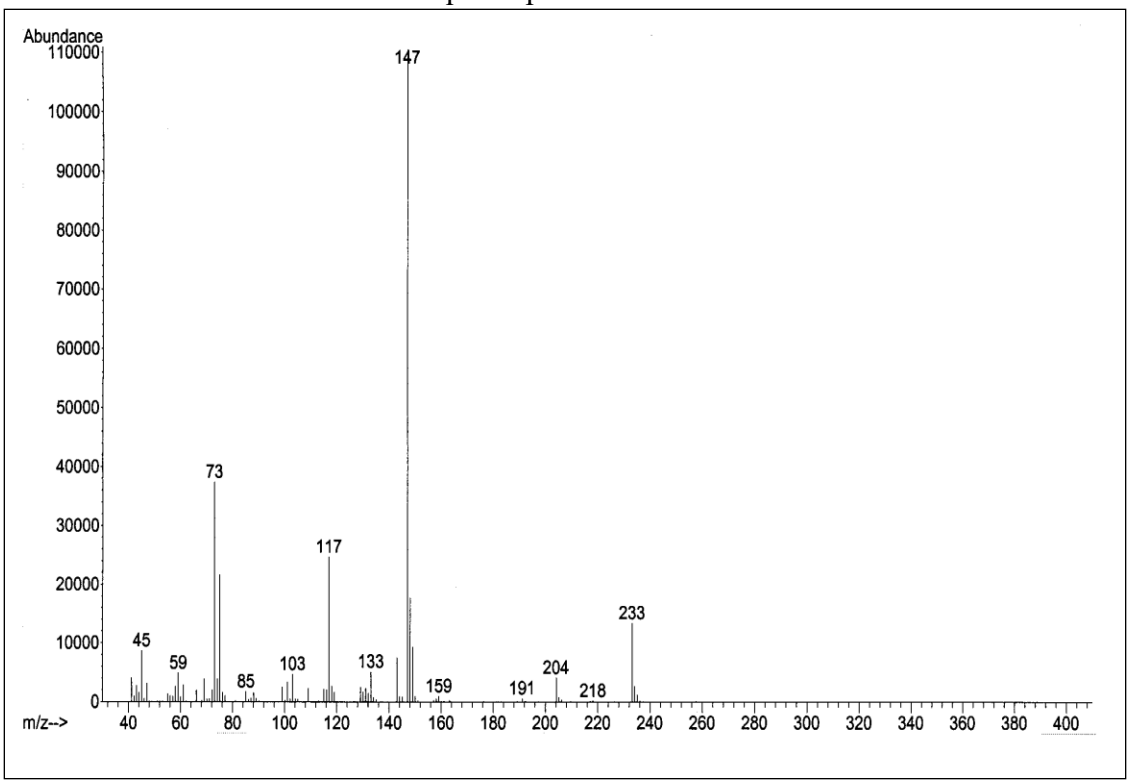


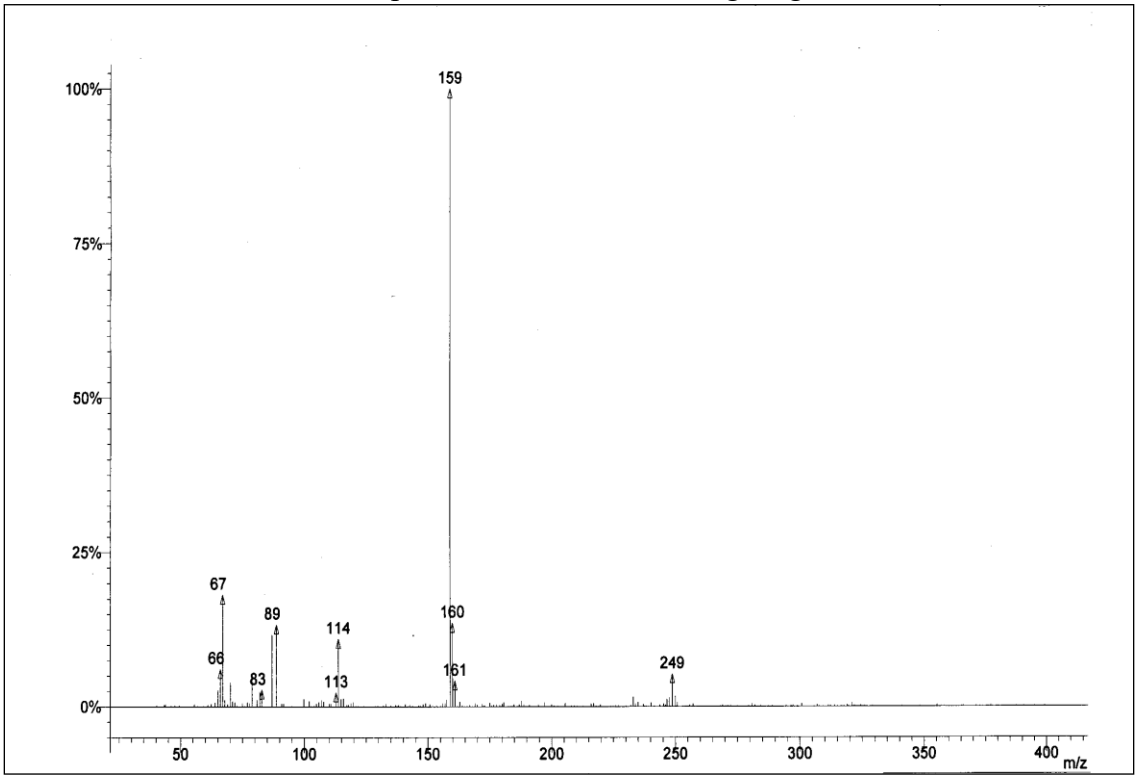
Transmission IR: *gamma*-Hydroxybutyrate, lithium salt sample in KBr matrix
16 scans, 4.0 cm^{-1} resolution



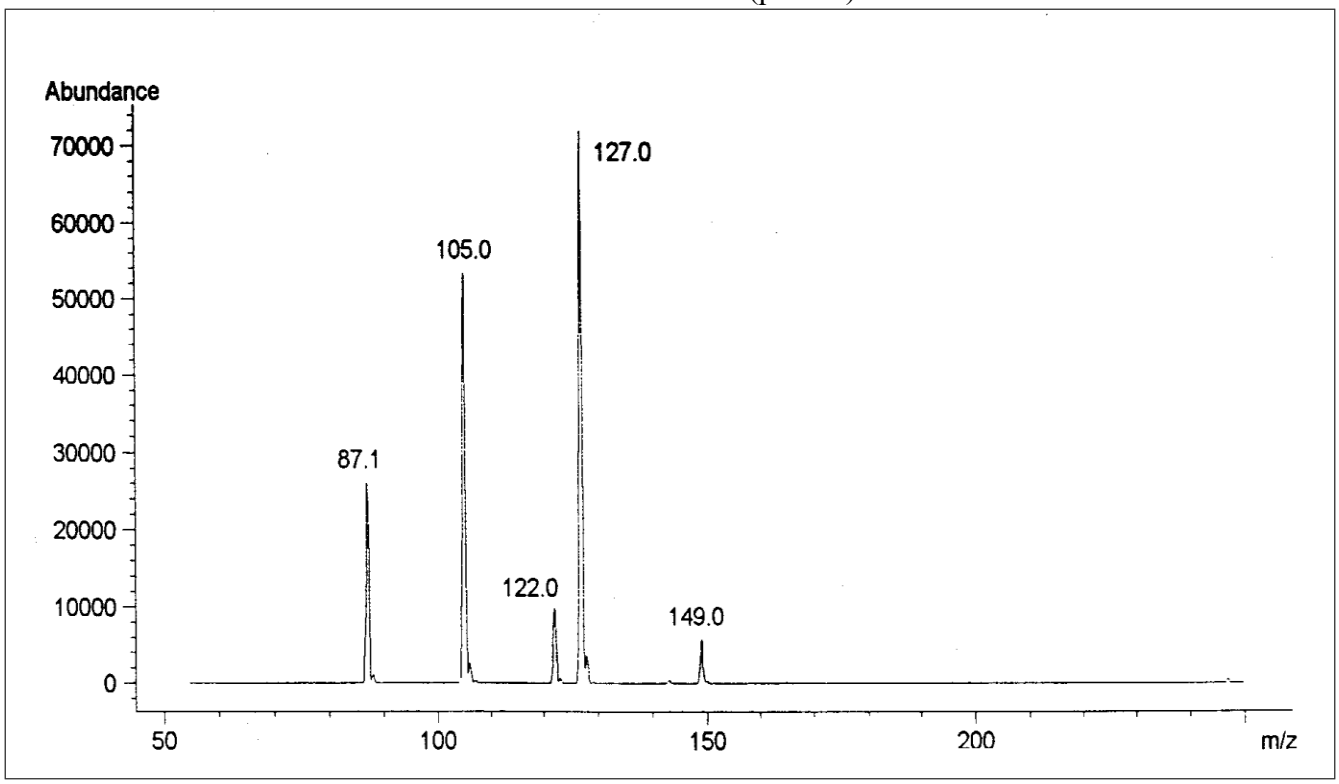
MS (EI): *gamma*-Hydroxybutyric acid, trimethylsilyl derivative
quadrupole detector



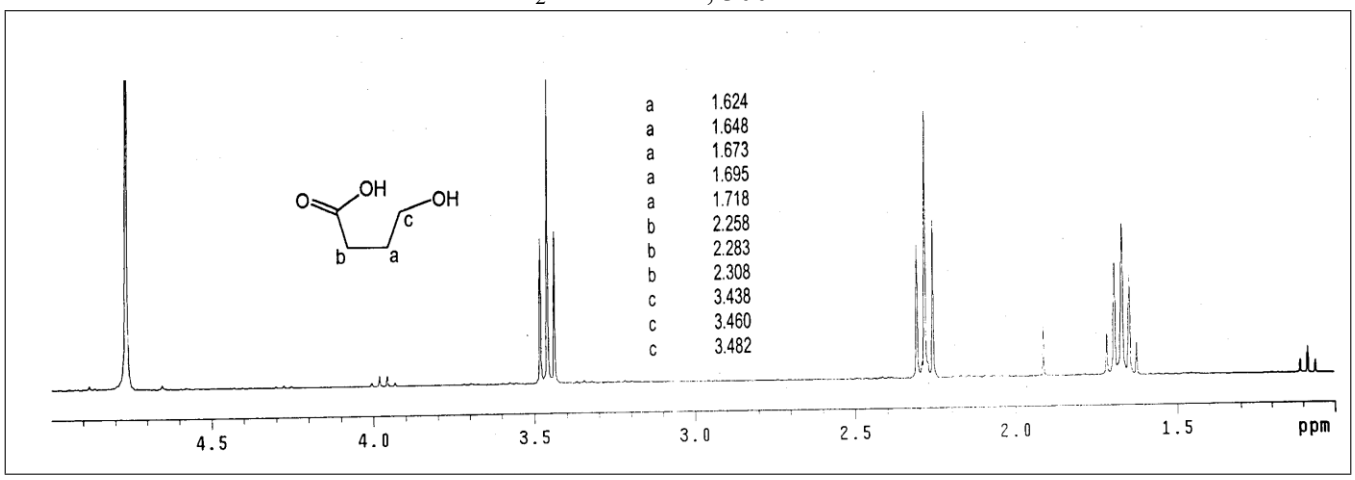
MS (CI): *gamma*-Hydroxybutyric acid, trimethylsilyl derivative
ion-trap detector, acetonitrile reagent gas



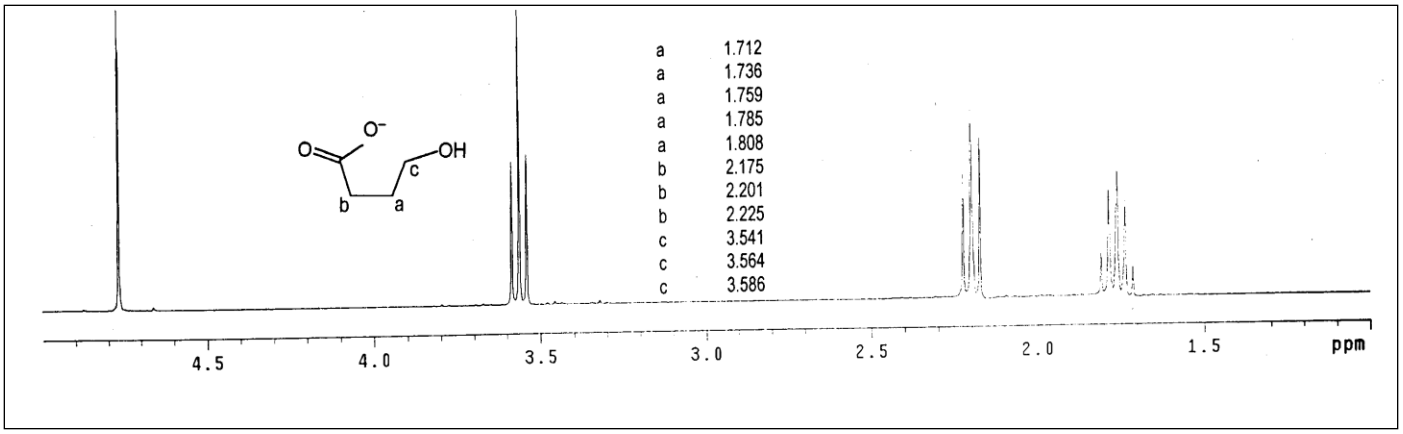
MS (Electrospray (+)): *gamma*-Hydroxybutyrate, sodium salt
0.02 M ammonium acetate (pH 7.5) buffer



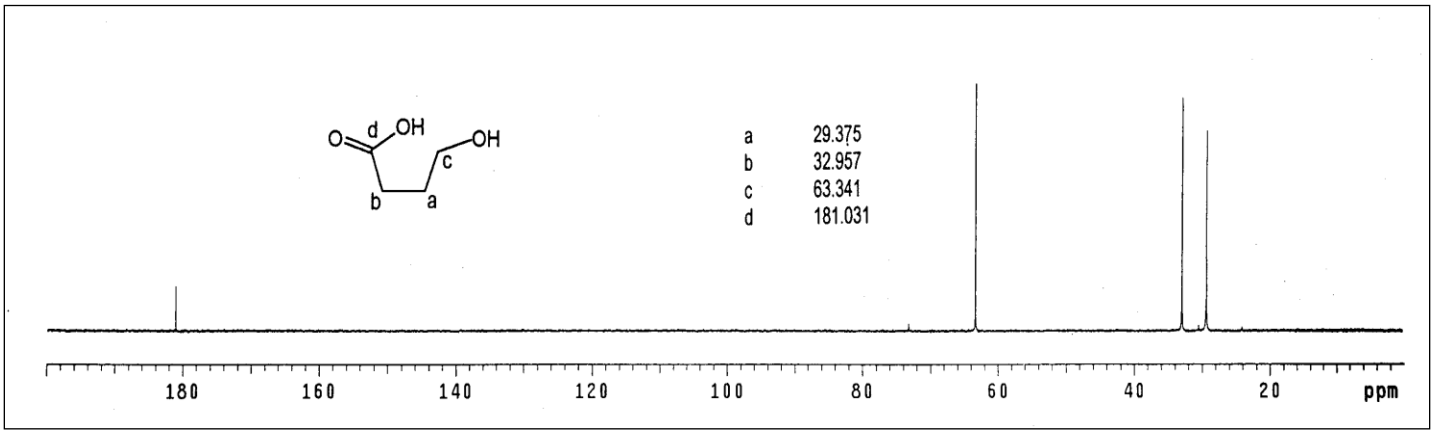
Nuclear Magnetic Resonance (^{1}H): *gamma*-Hydroxybutyric acid
D_2O with DDS, 300 MHz



Nuclear Magnetic Resonance (^{1}H): *gamma*-Hydroxybutyrate, sodium salt
D_2O with DDS, 300 MHz



Nuclear Magnetic Resonance (^{13}C): *gamma*-Hydroxybutyric acid
$CDCl_3$ with TMS, 75 MHz



Nuclear Magnetic Resonance (^{13}C): *gamma*-Hydroxybutyrate, sodium salt
$CDCl_3$ with TMS, 75 MHZ

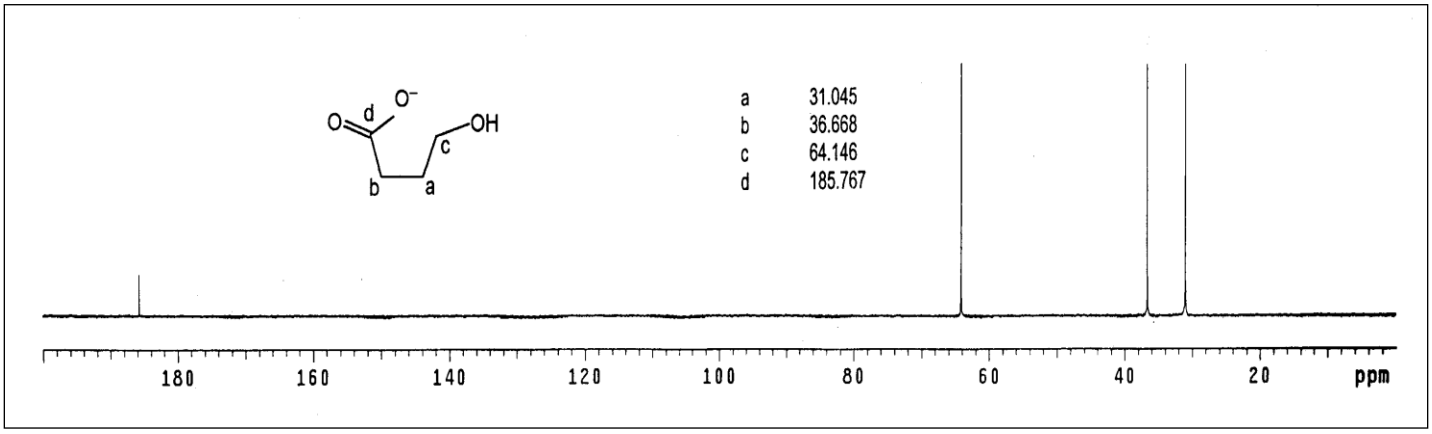


EXHIBIT 35

acicular [SCI TECH] Needlelike; slender and pointed. { ə'sik·yə·lər }

acicular ice [HYD] Fresh-water ice composed of many long crystals and layered hollow tubes of varying shape containing air bubbles. Also known as fibrous ice; satin ice. { ə'sik·yə·lər 'īs }

acicular powder [MET] A metal powder whose grains are needle-shaped. { ə'sik·yə·lər 'paůd·ər }

aciculignosa [ECOL] Narrow sclerophyll or coniferous vegetation that is mostly subalpine, subarctic, or continental. { ə,sik·yə·lig'nōs·ə }

acid [CHEM] **1.** Any of a class of chemical compounds whose aqueous solutions turn blue litmus paper red, react with and dissolve certain metals to form salts, and react with bases to form salts. **2.** A compound capable of transferring a hydrogen ion in solution. **3.** A substance that ionizes in solution to yield the positive ion of the solvent. **4.** A molecule or ion that combines with another molecule or ion by forming a covalent bond with two electrons from the other species. { 'as·əd }

π-acid [ORG CHEM] An acid that readily forms stable complexes with aromatic systems. { 'pī 'as·əd }

acid acceptor [ORG CHEM] A stabilizer compound added to plastic and resin polymers to combine with trace amounts of acids formed by decomposition of the polymers. { 'as·əd ək'sep·tər }

acid alcohol [ORG CHEM] A compound containing both a carboxyl group (—COOH) and an alcohol group ($—CH_2OH$, $=CHOH$, or $≡COH$). { 'as·əd 'al·kə·hōl }

acid amide [ORG CHEM] A compound derived from an acid in which the hydroxyl group (—OH) of the carboxyl group (—COOH) has been replaced by an amino group ($—NH_2$) or a substituted amino group (—NHR or $—NHR_2$). { 'as·əd 'a,mīd }

Acidaminococcus [MICROBIO] A genus of bacteria in the family Veillonellaceae; cells are often oval or kidney-shaped and occur in pairs; amino acids can supply the single energy source. { ,as·əd,a·mə·nō'käk·əs }

acid anhydride [CHEM] An acid with one or more molecules of water removed; for example, SO_3 is the acid anhydride of H_2SO_4, sulfuric acid. { 'as·əd ,an'hīd,rīd }

acid azide [ORG CHEM] **1.** A compound in which the hydroxy group of a carboxylic acid is replaced by the azido group ($—N_3$). **2.** An acyl or aroyl derivative of hydrazoic acid. Also known as acyl azide. { 'as·əd 'ā,zīd }

acid-base balance [PHYSIO] Physiologically maintained equilibrium of acids and bases in the body. { 'as·əd 'bās 'bal·əns }

acid-base catalysis [CHEM] The increase in speed of certain chemical reactions due to the presence of acids and bases. { 'as·əd 'bās kə'tal·ə·sis }

acid-base equilibrium [CHEM] The condition when acidic and basic ions in a solution exactly neutralize each other; that is, the pH is 7. { 'as·əd 'bās ,ik·wə'lib·rē·əm }

acid-base indicator [ANALY CHEM] A substance that reveals, through characteristic color changes, the degree of acidity or basicity of solutions. { 'as·əd 'bās 'in·də,kād·ər }

acid-base pair [CHEM] A concept in the Brauonsted theory of acids and bases; the pair consists of the source of the proton (acid) and the base generated by the transfer of the proton. { 'as·əd 'bās 'par }

acid-base titration [ANALY CHEM] A titration in which an acid of known concentration is added to a solution of base of unknown concentration, or the converse. { 'as·əd 'bās tī'trā·shən }

acid blowcase *See* blowcase. { 'as·əd 'blō·kās }

acid bottom and lining [MET] A melting furnace's inner bottom and lining composed of materials that at operating temperatures of the furnace react with the melt and slag to give an acid reaction; examples of materials are sand, siliceous rock, and silica brick. { 'as·əd 'bäd·əm an 'līn·iŋ }

acid brittleness [MET] Low ductility of a metal due to its absorption of hydrogen gas, which may occur during an electrolytic process or during cleaning. Also known as hydrogen embrittlement. { 'as·əd 'brit·əl·nəs }

acid bronze [MET] A copper-tin alloy containing lead and nickel; used in pumping equipment. { 'as·əd 'bränz }

acid calcium phosphate *See* calcium phosphate. { 'as·əd 'kal·sē·əm 'fās,fāt }

acid cell [HISTOL] A parietal cell of the stomach. [PHYS CHEM] An electrolytic cell whose electrolyte is an acid. { 'as·əd ,sel }

acid chloride [ORG CHEM] A compound containing the radical —COCl; an example is benzoyl chloride. { 'as·əd 'klȯr,īd }

acid clay [GEOL] A type of clay that gives off hydrogen ions when it dissolves in water. { 'as·əd 'klā }

acid cleaning [ENG] The use of circulating acid to remove dirt, scale, or other foreign matter from the interior of a pipe. { 'as·əd 'klēn·iŋ }

acid conductor [CHEM ENG] A vessel designed for refortification of hydrolyzed acid by heating and evaporation of water, or sometimes by distillation of water under partial vacuum. { 'as·əd kən'dək·tər }

acid cure [MET] The removal of some gangue carbonates from uranium ore by agitation with sulfuric acid prior to the leaching process. { 'as·əd ,kyůr }

acid dilution [PETRO ENG] Dilution of concentrated hydrochloric acid with water prior to oil-well acidizing. { 'as·əd də'lü·shən }

acid disproportionation [CHEM] The self-oxidation of a sample of an oxidized element to the next higher oxidation state and then a corresponding reduction to lower oxidation states. { 'as·əd ,dis·prə,pȯr·shə'nā·shən }

acid dye [ORG CHEM] Any of a group of sodium salts of sulfonic and carboxylic acids used to dye natural and synthetic fibers, leather, and paper. { 'as·əd ,dī }

acid egg *See* blowcase. { 'as·əd ,eg }

acid electrolyte [INORG CHEM] A compound, such as sulfuric acid, that dissociates into ions when dissolved, forming an acidic solution that conducts an electric current. { 'as·əd ə'lek·trə,līt }

acidemia [MED] A condition in which the pH of the blood falls below normal. { ,as·ə'dē·mē·ə }

acid-fast bacteria [MICROBIO] Bacteria, especially mycobacteria, that stain with basic dyes and fluorochromes and resist decoloration by acid solutions. { 'as·əd ,fast bak'tir·ē·ə }

acid-fast stain [MICROBIO] A differential stain used in identifying species of *Mycobacterium* and one species of *Nocardia*. { 'as·əd ,fast 'stān }

acid-fracture [PETRO ENG] To open or enlarge a fracture in a productive, hard limestone formation by using a mixture of oil and acid or of water and acid under high pressure. { 'as·əd ,frak·chər }

acid gases [CHEM ENG] The hydrogen sulfide and carbon dioxide found in natural and refinery gases which, when combined with moisture, form corrosive acids; known as sour gases when hydrogen sulfide and mercaptans are present. { 'as·əd 'gas·əz }

acid halide [ORG CHEM] A compound of the type RCOX, where R is an alkyl or aryl radical and X is a halogen. { 'as·əd 'hā,līd }

acid heat test [ANALY CHEM] The determination of degree of unsaturation of organic compounds by reacting with sulfuric acid and measuring the heat of reaction. { 'as·əd 'hēt ,test }

acidic [CHEM] **1.** Pertaining to an acid or to its properties. **2.** Forming an acid during a chemical process. { ə'sid·ik }

acidic dye [ORG CHEM] An organic anion that binds to and stains positively charged macromolecules. { ə,sid·ik 'dī }

acidic group [ORG CHEM] The radical COOH, present in organic acids. { ə'sid·ik 'grüp }

acidic lava [GEOL] Extruded felsic igneous magma which is rich in silica (SiO_2 content exceeds 65). { ə'sid·ik 'lä·və }

acidic oxide [INORG CHEM] An oxygen compound of a nonmetal, for example, SO_2 or P_2O_5, which yields an oxyacid with water. { ə'sid·ik 'äk,sīd }

acidic rock [PETR] Igneous rock containing more than 66% SiO_2, making it silicic. { ə'sid·ik 'räk }

acidic titrant [ANALY CHEM] An acid solution of known concentration used to determine the basicity of another solution by titration. { ə'sid·ik 'tī·trənt }

acidification [CHEM] Addition of an acid to a solution until the pH falls below 7. { ə,sid·ə·fə'kā·shən }

acidimeter [ANALY CHEM] An apparatus or a standard solution used to determine the amount of acid in a sample. { ,as·ə'dim·ə·tər }

acidimetry [ANALY CHEM] The titration of an acid with a standard solution of base. { ,as·ə'dim·ə·trē }

aciding [ENG] A light etching of a building surface of cast stone. { 'as·əd·iŋ }

acidity [CHEM] The state of being acid. { ə'sid·ə·tē }

McGraw-Hill Dictionary of Scientific and Technical Terms

Fifth Edition

Sybil P. Parker
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On the cover: Photomicrograph of crystals of vitamin B_1.
(*Dennis Kunkel, University of Hawaii*)

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EXHIBIT 36

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC. and
JAZZ PHARMACEUTICALS IRELAND LIMITED,
Plaintiff,
v.
AVADEL PHARMACEUTICALS PLC,
AVADEL US HOLDINGS, INC., AVADEL
SPECIALTY PHARMACEUTICALS, LLC,
AVADEL LEGACY PHARMACEUTICALS,
LLC, AVADEL MANAGEMENT
CORPORATION and AVADEL CNS
PHARMACEUTICALS LLC,
Defendants.

CASE NO.21-691-MN; 21-1138-MN; 21-1594-MN

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Alexander Klibanov, Ph.D.
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San Diego, California
Lead: Frank Calvosa, Esquire
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Washington CRR #21035137
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TABLE OF CONTENTS

EXHIBITS

INFORMATION TO BE SUPPLIED

Page	Line
(None)	

QUESTIONS INSTRUCTED NOT TO ANSWER

Page	Line
93	15
94	1
95	10
96	24
97	7

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10:07 A.M.
* * *

THE VIDEOGRAPHER: We are on the record. My name is Elijah Ochoa, and I'm a notary public contracted by Jane Rose Reporting.

I'm not financially interested in this action, nor am I a relative or an employee of any of the attorneys or any of the parties.

Today is April 6th, 2023, and the time, it's 10:07 a.m.

This video deposition is taken at 12670 High Bluff Drive, San Diego, California 92130.

The name of the case is Jazz Pharmaceuticals, Inc., versus Avadel CNS Pharmaceuticals, LLC, filed in the United States District Court for the District of Delaware, the Case No. 21-691-GBW.

This is the video-recorded deposition of Dr. Alexander Klibanov.

Would the attorneys please introduce yourselves and state who you represent.

MR. CALVOSA: Frank Calvosa from Quinn Emanuel Urquhart & Sullivan on behalf of Plaintiffs. Also with me is Gabe Brier from Quinn Emanuel.

MR. YUE: Herman Yue from Latham & Watkins on

behalf of Avadel and the witness.

THE VIDEOGRAPHER: We are ready to proceed.

The court reporter today is Kayla Lotstein with Jane Rose Reporting.

Would the reporter please swear in the witness.

Alexander Klibanov, PhD,
called as a witness on behalf of the Plaintiffs, and having been duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. CALVOSA:

Q Good morning, Dr. Klibanov.

A Morning, Mr. Calvosa.

Q Thank you for joining us today.

We've worked together a couple times before and also averse from one another, so I know you've been deposed before.

Right?

A Correct.

Q And you've been deposed many times before; right?

A I don't know what you mean by "many times," but I certainly have been deposed more than once.

Q Sure. I'll ask you, do you know about how

Page 9

many times you've been deposed?
A Over the last 30, 35 years, maybe three, four dozen times.
Q Okay. So you generally understand the rules for a deposition?
A I think I do, but I would certainly appreciate whatever guidance you care to provide.
Q Sure. So, number one, do you understand you have to tell the truth today?
A Yes.
Q Any reason you can't do so?
A Not to my knowledge.
Q And you understand I'll be asking you a series of questions today?
A I do. And I hope that when you do that, you will -- you will be speaking slower than you're speaking now.
Q I'll slow down for you. Thank you for pointing that out.
So along that line, let's both talk slowly, not speak over one another, and all verbal answers, so that way the court reporter can take stuff down.
A Understood.
Q If you need a break at any time, just please ask for one.

Page 10

You understand?
A Yes.
Q And if there's -- the only thing I ask is if there's a question pending, you answer that question before we go to break.
A Understood.
Q I've given you some documents in front of you. We'll go through all them in order at some point today, but those are all the declarations that you've put in in this case so far.
If you need any other document at any point today, feel free to ask me. I'll be more than happy to provide it for you.
A That's fine. I just want to correct you that, in fact, some of them are not declarations but expert reports.
Q Oh, okay. Thank you for that correction.
The first one you have in front of you, do you see it? It has an "Exhibit C" on it.
A Yes.
Q This was Exhibit C to Avadel's supplemental responsive claim construction brief.
And is this the declaration that you provided in support of that brief?
A I mean, it looks like my declaration and is

Page 11

certainly my signature on page 14.
Q If I could ask you to please turn to page 3 of the declaration. And I'm looking at the paragraphs 6 through 7 that follow from page 3 to page 4.
A Okay. Sir, a couple of things, with your permission. I apologize for interrupting.
Q Sure.
A Okay?
So, first of all, whenever is a good time, when I was rereviewing my declaration yesterday, I found one typographical -- clerical, actually -- error that I would like to correct at a time when it's convenient for you.
Okay?
And, second, as far as referring me to certain paragraphs, I would like to establish a routine with you, if that's okay, that when you direct me to a certain paragraph, I'd like to read it to myself first just to put it in, you know, context, and then I'll be happy to try to answer your questions.
Q Sure. So would it be more helpful for you if I tell you what paragraphs I want you to look at and then wait until you read it to ask the question?
A Exactly. Yes.
Q Okay. That's perfectly fine with me.

Page 12

A Yeah. And as far as the correction, whenever it's convenient for you.
Q We can do that now.
A Okay. So there's just one clerical error. It refers to paragraph 25 of my declaration. First line of paragraph 25, the fifth word from the end of that line, which is "that," should be deleted. I incorrectly copied what Dr. Little said in his declaration.
Q Okay. Any other corrections to the declaration?
A No. This is the only clerical error that I found, and everything else, I stand by.
Q Thank you for pointing that out.
If we could go back to paragraphs 6 through 7, and just let me know when you've had a chance to review those.
A Sure.
Yes, sir.
Q Okay. I'd like to better understand your opinion on the claim term "gamma-hydroxybutyrate/oxybate."
So, first, let me ask you, is it okay if I just refer to "gamma-hydroxybutyrate" today to encompass both gamma-hydroxybutyrate and oxybate?
A Yes.

Page 13

Q Is your opinion that the term "gamma-hydroxybutyrate," as used in Jazz's patents means the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid, unbound to anything else?
A So, first of all, when you're saying the term, I'm making a judgment with respect to the claim term specifically, not the term "gamma-hydroxybutyrate," but the claim term "gamma-hydroxybutyrate".
Q Can you --
A Okay?
Q Can you explain what you mean there.
A What I mean is that the meaning of the word "gamma-hydroxybutyrate" when it is used in the claims of the asserted patents.
Q Is it your opinion that the -- that the term gamma-hydroxybutyrate has a different meaning within the claims than it does in other places of Jazz's patents, like the specification?
A I'm opining on what this claim term means in the -- what this term means in the claims of -- of the patents. Whatever meaning may take place elsewhere, that's just not something that I have focused on.
Q Okay. Do you have an opinion on what the plain and ordinary meaning of gamma-hydroxybutyrate is to a person of skill in the art? Just in general.

Page 14

A Well, I mean, that will depend on the context in which it is used.
Q Okay. So it's your opinion that there is no plain and ordinary meaning of gamma-hydroxybutyrate in the art?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: That's not what I said. I said that it would depend on what the context of this term is.
And, as you know, in the case of the Resinate patents, the claim term "gamma-hydroxybutyrate" is expressly defined. That is not the case with respect to the Sustained Release patents, but the constructions that are proposed are those -- by the parties here are those listed in paragraph 6 of my declaration.
BY MR. CALVOSA:
Q So let's just unpack that a bit.
You would agree that in what you call -- let's -- let's establish them first. In what you call the Resinate patents, is that Jazz's '079 and '782 patents?
A Yes.
Q Okay. The other patents that are asserted in this case, is it fair if I just call them the Sustained Release patents?

Page 15

A It is as fair as calling the other two the Resinate patents.
Q So it's your opinion that in what you call the Resinate patents, there is a definition for gamma-hydroxybutyrate; right?
A That is correct. The lexi- -- the patentees use their right to be their own lexicographers and defined that term.
Q In the Sustained Release patents, there is no definition for gamma-hydroxybutyrate.
A There is no express definition for gamma-hydroxybutyrate.
Q Do you have an opinion on what the plain and ordinary meaning of gamma-hydroxybutyrate is, as it's used in the Sustained Release patent in total?
MR. YUE: Objection. Vague.
THE WITNESS: Yeah. I agree with Avadel's proposal; namely, that the -- that the meaning -- I don't know whether you call it a plain and ordinary meaning, but the meaning of "gamma-hydroxybutyrate" -- the meaning of the claim term "gamma-hydroxybutyrate" in the Sustained Release patents is -- and I quote -- "the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid."
BY MR. CALVOSA:

Page 16

Q Is that the plain and ordinary meaning of "gamma-hydroxybutyrate" to a person of ordinary skill in the art?
A As I said, the plain and ordinary meaning would depend on the context. But, in general, I think that will be reasonable to say that that -- that is a plain and ordinary meaning.
Q And is it okay if I refer to that longer construction as the "negative anion"?
A Well, the term "negative anion" is nonsensical --
Q Okay.
A -- because "anion" means a negative ion. So "negative anion" would mean negative-negative ion. Okay? Which is exactly why both parties in this case say a negatively charged or -- o-r -- anionic form.
Q Okay. May I just call it, then, the anionic form?
A I think that would be potentially misleading because the negatively charged or anionic form (conjugate base) refers not to just any negatively -- not just to a negatively charged ion, but an ion or anion that has a negative charge, electrostatic negative charge of minus 1.
Q Okay.

Page 17

A So not just a partial negative charge, but the electrostatic charge of minus 1.
Q Where does it say that in the Sustained Release patents?
A I mean, that's what the term "conjugate base" means. The conjugate base is a species -- a molecular species that has the electrostatic charge of minus 1.
Q Okay. It's not possible for a conjugate base to have any other electrostatic charge other than minus 1?
A If we're talking about gamma-hydroxybutyrate specifically, there are other anions that have electrostatic charges of minus 2 or minus 3 or whatever; but if we are talking about gamma-hydroxybutyrate specifically, the conjugate base is a species that has the electrostatic charge of minus 1.
Q Okay. Is your opinion that the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid unbound to any other atom?
A It is unbound to anything else that's -- you can call it unbound. You can call it freestanding. You can call it standalone. But that's what it is. And it has the electrostatic charge of minus 1.
Q Okay. And I think we all agree that an unbound -- or the -- an unbound negatively charged or

Page 18

anionic form (conjugate base) of gamma-hydroxybutyric acid cannot exist in solid form; right?
A I don't know about all of us, but that is certainly my opinion, and I know that's Dr. Little's opinion.
Q Are you offering an opinion that there's any disclaimer or disavowal of claim scope for gamma-hydroxybutyrate in the Sustained Release patents?
A I mean, I'm not -- I mean, it sounds to me like a legal question.
The opinions that I'm offering with respect to the claim construction are those that are in the four corners of my declaration. That's -- that's Exhibit C to Avadel's brief.
Q Okay. I didn't see the words "disclaimer" or "disavowal" appear anywhere in your declaration.
Is that consistent with your -- your memory of its preparation?
A It is --
MR. YUE: Objection.
THE WITNESS: I'm sorry.
MR. YUE: Document speaks for itself.
But go ahead.
THE WITNESS: That is consistent with my recollection, and if it's not there, then I'm offering

Page 19

no opinions on that.
BY MR. CALVOSA:
Q Do you know a person named Dan Nocera?
A Yes.
Q Did you ever collaborate with Dr. Nocera?
A No.
Q He was also a professor at MIT?
A Correct. In my department, yes.
Q Yes. He left for Harvard about ten years ago now?
A He left for Harvard. I -- I don't remember when it was.
Q Do you have any opinion on whether he is a good chemist?
A He's an excellent chemist.
Q Good in spectroscopy?
A I mean, that's his area of research, so I have to believe that he's good at that.
Q Okay. And just one more question on the clarification of your opinions.
Are you offering any opinions on what the term "gamma-hydroxybutyrate" or "oxybate" means within the specifications -- not the claims -- of the Sustained Release and what you call the Resinate patents?

Page 20

A Well, with respect to the Resinate patents, the claim term "gamma-hydroxybutyrate" is defined, if I recall, in column 3 of the Resinate patents, and I believe that that definition applies both to the claims and to the specification.
In the case of the Sustained Release patents, as we discussed earlier, "gamma-hydroxybutyrate" is not expressly defined in the specification.
I agree with Avadel's proposal as to what it means as a claim term. I haven't given really much thought to all the possible shades, if you will, of that meaning in the specification.
Q Okay. So your opinions in the Sustained Release patent are limited to what "gamma-hydroxybutyrate" means in the claims?
MR. YUE: Objection. Asked and answered. Misstates witness's testimony.
THE WITNESS: I don't think it's limited to that, but that certainly was the focus of my analysis.
BY MR. CALVOSA:
Q Is it your opinion that "gamma-hydroxybutyrate" has the same meaning each time it appears in the Sustained Release patents, both in the specification and in the claims?
A Well, with respect to the claims, I already

Page 21

said that every time it is used in the claims, I already said that I agree with Avadel's proposal as to what that meaning is.

With respect to the specification, it is listed many times. I would have to take a look at every time that is listed, and then I might be able to answer your question for each of those instances.

Q Okay. You didn't do that before today?

A I may have done it before today. I don't remember whether -- it certainly was not an exhaustive analysis of every single instance where this term is used in the specification.

So if your question is whether I have systematically analyzed every single instance, that wasn't what I have done. But I certainly have reviewed the specification, and, you know, I've seen instances, but I have read the specification without that particular question in mind.

Q Understood.

You refer to the '079 and '782 patents as the Resinate patents.

Why is that?

A Because, as I recall, the thrust of that patent, including, I think, all of the examples, involve gamma-hydroxybutyrate deposited or bound to ion exchange

Page 22

resins.

(Reporter clarification.)

THE WITNESS: Resins. The word resins. Resins is plural from resin, r-e-s-i-n.

BY MR. CALVOSA:

Q So all of the examples of what you call the Resinate patents are the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid ionically bound to a resin?

A It is bound to the resin. So in the bound state, it is no longer gamma-hydroxybutyrate as it is defined in the parties' construction.

So they are -- it's essentially a salt, but it is basically a -- the active is on the resin, or is bound to the resin. So I would just say "the active" to avoid this confusion of what gamma-hydroxybutyrate means.

Q Okay. So all of the examples of what you call the Resinate patents are the active bounds in salt form?

A I'm not even sure about that. I think there was also -- there was at least one example, as I recall -- I mean, I may have to take a look at the '079 patent. But I think in one case, actually, they used a prodrug. It was gamma-hydroxy-butyrolactone, which is not a charged species at all.

Page 23

But my recollection is that the examples are essentially -- the examples of the '079 patent are all -- and if you ask that question once again, I will literally have to verify it, take you up on your offer to take a look at the documents that I need to see -- that the examples are limited to act as associated with ion exchange resins.

Q And when gamma-hydroxybutyrate is in the form of sodium gamma-hydroxybutyrate, it's also associated with a salt; right? Or a metal cation?

MR. YUE: Objection. Form.

THE WITNESS: It is not associated with a salt. It is a salt. And in that salt, it is associated with a sodium cation.

BY MR. CALVOSA:

Q So let me ask that again.

In -- when gamma-hydroxybutyrate is in the form of sodium gamma-hydroxybutyrate, it is a salt; right?

MR. YUE: Objection. Form.

THE WITNESS: I want to avoid confusion -- potential confusion between the claim term "gamma-hydroxybutyrate," which is defined by both parties, as stated in paragraph 6 of my declaration, for example, and the term -- not the claim term, but the

Page 24

term "gamma-hydroxybutyrate" as it was in your question.

BY MR. CALVOSA:

Q What's the difference?

A The difference is, as I already pointed out, is that in the case of the claim term "gamma-hydroxybutyrate," the electrostatic charge of the species is minus 1, as I pointed out already.

In the case of a salt, such as sodium gamma-hydroxybutyrate, the electrostatic charge on the anion is less, meaning not minus 1, but less than minus .1 -- I'm sorry. Less than minus 1. And I'm saying -- when I'm saying "less," I mean the absolute value is less than 1.

Q Okay. And what is that value?

A It is somewhere between what the cation is. It is somewhere between zero and 1.

Q You could figure that out for sodium oxybate; right?

A It may be possible to do it using some spectroscopic technique, but, you know, I haven't done it because it wasn't necessary. But we know for a fact that it is less than minus 1.

And, again, when I'm saying "less than minus 1," I mean the absolute value is less than 1. So whether it is 0. -- minus 0.9 or 0.95, that, I do not

Page 25

know. But it is not minus 1.
Q It is still -- the anion is still negatively charged when associated with the sodium cation in sodium oxybate; right?
A Yes. It has a partial negative charge. So the word "partial" reflects the fact that the absolute value is less than minus -- less than 1.
Q Would the absolute value ever be exactly minus 1 when the anion is associated with a cation?
A No.
MR. YUE: Objection. Vague.
THE WITNESS: I'm sorry. No.
BY MR. CALVOSA:
Q The negatively charged or anionic form "conjugate base" of gamma-hydroxybutyric acid is highly soluble; right?
MR. YUE: Objection. Vague.
THE WITNESS: I have a couple of issues -- three issues with the question, as stated.
BY MR. CALVOSA:
Q Sure.
A So, first of all, you asked were they soluble, but didn't say soluble in what.
Q Okay.
A Second of all, you said "highly soluble." I

Page 26

don't know what you mean by "highly."
And, thirdly, typically, we talk about the solubility -- chemists talk about solubility of solid substances or liquid substances. And an anion is not -- cannot be as a solid substance -- cannot be a solid substance, as we already discussed.
Q Okay. So a chemist wouldn't say, then, that the anion is water-soluble?
A It will be an imprecise way of saying it, because how would you determine whether it's water-soluble or not?
Typically, the way you determine whether something is water-soluble or not, you take that substance that you want to know the solubility of and you place it in water.
But since both Dr. Little and I -- and it seemed to me that you placed yourself in the same category -- our opinion is that this conjugate base of gamma-hydroxybutyrate cannot exist in a solid form, how would you know what its solubility is?
Q So then it would be more precise to say that the salt form of this anion is water-soluble?
A Yeah. You can say that the sodium gamma-hydroxybutyrate is water-soluble.
Q But you wouldn't say that the anion alone is

Page 27

water-soluble?
A How would you know whether it's, you know, water-soluble? How would you experiment in a test the solubility in water of something that does not exist in a solid form?
Q What about hygroscopicity? Would your answers be the same for hygroscopicity as for solubility?
A Yes, because hygroscopicity is a propensity of a solid substance to attract water.
So if gamma-hydroxybutyrate -- the anion was the electrostatic charge of minus 1 does not exist in a solid form, how would you assess its hygroscopicity?
Q Before I do that, can you please turn to paragraph 5 of your declaration.
A Sure. Let me read it to myself.
Yes, sir.
Q That's -- paragraph 5 of your declaration is your opinion of who the person of ordinary skill in the art would be for Jazz's patents; is that right?
A That's correct.
Q Okay. Did you take a --
A And I'm sorry for interrupting.
If by "Jazz's patents," you mean the Sustained Release and Resinate patents. I'm sure Jazz may have some other patents. I'm not opining on a definition of

Page 28

a person of ordinary skill in the art with respect to those.
Q Okay. So let me be more specific. You're correct.
Your opinion in paragraph 5 is who the person of ordinary skill in the art would be for the Sustained Release patents and for what you call the Resinate patents; is that right?
A Yes.
Q Did you see -- did you review Dr. Little's declaration in support of Jazz's claims construction brief?
A Of course.
Q Did you review who his person of ordinary skill in the art was?
A I reviewed the entire declaration.
Q Would you like to see a copy of his declaration to remind yourself of that person of ordinary skill?
A Sure.
Q And we're going to mark this as Klibanov 4.
A Thank you.
Q You're welcome, sir.
(Whereupon Exhibit 4 was marked for identification.)

Page 29

BY MR. CALVOSA:
Q And what I've marked as Klibanov 4 is Exhibit 2 to Jazz's opening claim construction brief, and it's the declaration of Dr. Steven R. Little, Ph.D.
And if you could please turn to paragraph 17 of Dr. Little's declaration, and let me know when you've had a chance to review his person of ordinary skill in the art.
A Sure.
Yes, sir.
Q Dr. Little's definition of a person of ordinary skill in the art is different than your definition.
Is that fair?
MR. YUE: Objection. Vague.
THE WITNESS: I don't know whether it's fair, but it is correct.
BY MR. CALVOSA:
Q Okay. Would your opinions change if the Court adopted Dr. Little's definition of the person of ordinary skill in the art instead of your definition?
A I don't think so.
Q Okay. Do you see anything you consider to be a meaningful difference between Dr. Little's definition of the person of ordinary skill in the art and your

Page 30

definition?
A I do.
Q And what is that?
A In the last sentence of paragraph 17, Dr. -- Dr. Little opines, "It is further my opinion that a POSA may rely on individuals with knowledge and experience in the treatment of narcolepsy."
So to the extent that Dr. Little suggests that these individuals may not be people with ordinary skill but instead experts, I disagree.
Q Okay. Do you disagree with anything else or see any other meaningful differences?
A I mean, I don't know what you call "meaningful differences." There are clearly differences.
But, as I indicated a moment ago, with the proviso that I just put forth in my previous answer, my opinions, with respect at least to the claim construction issues, would be the same, even if the Court accepts Dr. Little's definition of a person of ordinary skill in the art, which --
THE WITNESS: This is just for Kayla. Sometimes both counsel and I will be using an abbreviation, which is four capital letters: POSA.
BY MR. CALVOSA:
Q When you were -- reviewed Dr. Little's

Page 31

opinions regarding the meaning of the term "gamma-hydroxybutyrate" in the Sustained Release and what you call the Resinate patents' claims, did you think that Dr. Little's opinion was unreasonable?
MR. YUE: Objection. Vague.
THE WITNESS: I don't understand what you mean by "unreasonable."
BY MR. CALVOSA:
Q Did you think it was unreasonable?
MR. YUE: Same objection.
THE WITNESS: If, by "unreasonable," you mean that it was not based on any reason or any reasoning, then, no, I didn't think that. I just think that Dr. -- Dr. Little's reasoning was incorrect.
BY MR. CALVOSA:
Q Why do you say you don't think it -- it wasn't your thought that it was not based on any reason or reasoning?
MR. YUE: Objection. Form.
THE WITNESS: I think Dr. Little reasoned his opinions. He provide reasons for his opinions. I just don't agree with his analysis.
(Whereupon Exhibit 5 was marked for identification.)
BY MR. CALVOSA:

Page 32

Q I'm now going to hand you the '079 patent, which is Exhibit 24 to Jazz's opening brief, and I've marked it as Klibanov 5.
A Okay.
Q You have reviewed this patent before; right?
A Certainly.
Q Do you remember the first time you reviewed it?
A A long time ago.
Q Do you know how many times you reviewed it?
A I think over the last -- more than a year, at least a couple of times.
Q What do you mean by "a couple"?
A I mean, I would say at least two or three.
Q In your pile to the left there, I want you to go to the very last document there. It's what's marked Klibanov 3.
(Whereupon Exhibit 3 was marked for identification.)
BY MR. CALVOSA:
Q This is a declaration that you submitted or signed on February 28th, 2023; is that right?
A Yes.
Q And do you know what this declaration was used for by Avadel?

Page 33

MR. YUE: Objection. Caution the witness not to disclose the content of any discussions he's had with counsel.
THE WITNESS: Well, again, I'm sure that I will not be necessarily using correct, sort of, legal terminology; but my understanding is that Avadel used it in its petition to the Court to continue the claim construction process.
And, again, I'm sure that I stated loosely some procedural facts here, but that's sort of my -- I'm a scientist, obviously, not a lawyer -- so that's my understanding.
BY MR. CALVOSA:
Q And if you turn to paragraph 4 -- and you could read all the way through paragraph 6, or the entire declaration, if you want. Whatever is easiest for you.
A Well, it's not a question of what I want. I mean, you know, I -- I will read whatever you're going to ask me questions about. So you tell me what you will ask me questions about, what paragraphs, and I'll be happy to read it.
Q Okay. Let's start with paragraph 4.
A Just a sec.
Yes, sir.

Page 34

Q Okay. When Ms. Sawyer sent you Dr. Little's reports, along with copies of Jazz's Sustained Release patents, including the '488 patent, on February 4, 2023, had you read them before?
Let me ask you, had you read the Sustained Release patents before Ms. Sawyer sent you Dr. Little's report on February 4, 2023?
MR. YUE: And I'll just caution the witness, you can answer "yes" or "no," but not to disclose the content of any privileged communications with Avadel's attorneys.
THE WITNESS: Yes.
BY MR. CALVOSA:
Q Okay. And had you read them carefully before that time?
MR. YUE: Same caution.
And objection. Vague.
THE WITNESS: I read them carefully, but an old lawyer, who was one of the first lawyers I ever worked with some 30, 35 years ago, once told me something that I find to be profoundly wise, which is you cannot read the patent in suit too many times because, you know, every time you read it, you notice some things that may have escaped, sort of, your, at least, emphasis before.
But yes, I -- I read them, I thought was

Page 35

careful, yeah.
BY MR. CALVOSA:
Q Okay. And, again, you read them, in total, about two or three times --
MR. YUE: Objection.
BY MR. CALVOSA:
Q -- up until today?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: Well, when I said two -- at least two or three times, that's as of today.
BY MR. CALVOSA:
Q Yes.
A In paragraph 4, the date there is February 4, 2023, so that's more than two months ago. At that time, it may have been fewer times.
Q Sure. It's -- I was asking you, as of today, you've said you've read the Sustained Release patents and what you call the Resinate patents about two or three times?
A At least two or three times, yes.
Q After February 4th, did you have an in-person meeting with the attorneys from Latham & Watkins?
MR. YUE: And caution the witness, you can answer "yes" or "no," but not to disclose the content of any

Page 36

privileged communications.
THE WITNESS: Yes.
BY MR. CALVOSA:
Q Okay. That in-person meeting -- was that at Latham & Watkins' office?
MR. YUE: Same caution.
THE WITNESS: Yes.
BY MR. CALVOSA:
Q That in-person meeting, was that a Latham & Watkins office in New York City?
A No.
Q Where was it?
A It was in the Latham & Watkins office here, in Del Mar.
Q Okay. Did you talk to anybody else besides your attorneys about that meeting?
A Let me just clarify a couple of things.
So, first of all, you said "your attorneys." I have tremendous respect for Dr. Yue here. I, sadly, cannot count him to be my attorney, although he represents me today.
I have only discussed the matters -- the matters that I cover in my declarations with counsel for Avadel, meaning with various attorneys from Latham & Watkins --

Page 37

Q So you didn't talk about --
A I'm sorry. I apologize. I just want to finish.
Latham & Watkins as well as Morrison & Foerster.
Q Is it okay --
THE WITNESS: And I'm sorry, Kayla. I cannot spell Morrison & Foerster. I just call them MoFo.
BY MR. CALVOSA:
Q MoFo.
A And this is with no disrespect.
Q No. My wife works for them. It's fine. Is it okay if I refer to the Latham attorneys and the MoFo attorneys as "Avadel's attorneys"?
Would you be more comfortable with that?
A Sure. If you -- I mean, I'm -- I'm fine. If that's legally proper, that's fine.
Q Did you talk to anybody about your meeting that you had at the Latham & Watkins -- Watkins office with anyone other than MoFo attorneys?
A And Latham & Watkins attorneys?
Q I don't know what I said. Let me ask it again.
A Okay.
Q Did you talk to anyone other than Avadel's

Page 38

attorneys, Latham & Watkins and MoFo, about the meeting you had at the Latham & Watkins office?
A Well, I told my wife where I was going. I mean, she expressed an interest. She's not a scientist, so I wouldn't worry about her. And we certainly didn't talk about the substance, which she, not being a scientist, would have absolutely no interest in.
Q Other than your wife, did you speak with anybody else about that meeting?
A No.
Q You're 100 percent sure of that?
A I mean, a hundred percent is a theoretical and abstract sort of thing. But, yeah, I'm as certain as I can be about anything --
Q Okay.
A -- that I haven't -- I cannot imagine who I would be talking about it with.
Q Do you know of somebody by the name of Anthony Lagalante?
A Anthony who?
Q Lagalante.
A Doesn't -- doesn't ring a bell at all.
Q Okay. Do you know if he ever collaborated with Dan Nocera?
A I don't even know who that person is, so I --

Page 39

would you spell the last name slowly.
Q Lagalante, L-a-g-a-l-a-n-t-e.
A I don't know this person at all.
Q Okay. Going back to what I've marked as Klibanov 5, the '079 patent.
A Okay.
Q And I'd like you to turn to the claims.
A All right. Are you aware of the fact that there's highlighting in this copy?
Q Yeah. So what happens is when we submit it to the Court, the parties put highlighting in there, so I'm using the copy that's been submitted to the Court. So the exhibits you'll see today will have highlighting in them.
A Okay. I just want to make sure that you know.
Q I appreciate that.
And if you turn to column 24, claim 1.
A Okay.
Q As a -- I guess, a understanding of the legal principles that you experts use, do you understand that the claim construction opinions are supposed to be given from the view of a person of ordinary skill in the art?
A At the time of the invention, yes.
Q Do you understand that the person of ordinary skill in the art should analyze not just the claim term

Page 40

alone, but within the context of the claim in which it appears?
A Among other things, yes.
Q Okay. Do you also understand that the person of ordinary skill should analyze the claim term in light of the specification in which it appears?
A Among other things, yes.
Q If you look at claim 1 -- and you can take the time to read it for yourself, and then I'll ask you a question.
A Okay.
Yes, sir.
Q If you go to about line 63 of column 24 in the '079 patent --
A Okay.
Q -- do you see a step in the claim as "opening a sachet containing a solid oxybate formulation"?
A Yes.
Q Okay. In your opinion, the word "oxybate" there means the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid unbound to any cation; right?
A That's what the claim term "oxybate" means, in my opinion.
Q Okay. With using your opinion of what the

Page 41

claim term "oxybate" means, a POSA would understand that you could never have a solid oxybate formulation as the claim requires; correct?
A Not necessarily, no.
Q Okay. How can you have a solid oxybate formulation with your interpretation of the word "oxybate"?
A Well, "oxybate," as I understand and have defined this claim term, clearly can exist in an aqueous solution; and it can also exist in an aqueous gel, g-e-l, and that will be a solid substance.
Q So an aqueous solution, in your opinion, is a solid substance?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: Certainly not, and that's not what I just said. I just -- sort of, to explain my opinion, I first said that it can exist in an aqueous solution, which is undeniably not a solid substance; and it can also exist -- can exist in a gel, which is a solid substance.
BY MR. CALVOSA:
Q And, in your opinion, the '079 patent talks about having the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyrate as a solid

Page 42

gel?
A A gel is a solid substance, so you -- you know, there is no reason -- there is no sensible reason to say "solid gel." Gel is a solid substance.
And, I mean, that certainly is one example of how oxybate can be in a solid form and an example that is actually rooted in the specification of the Resinate patents.
Q Can you show me where, in what you call the Resinate patents, the gel example is what you call "rooted."
MR. YUE: Objection. Misstates the witness's testimony.
But go ahead.
THE WITNESS: I mean, I can just give you something that I remember now.
For instance, if you go to the summary of the invention and specifically column 2, and there is a paragraph that starts in line 20. So the last sentence of this paragraph reads, "Finely ground resin beads may also be encapsulated within polysaccharide gel structures that confer enteric protection, through ionotropic gelation as with calcium alginate encapsulation."
So, for example, this sentence expressly talks

Page 43

about gels.
BY MR. CALVOSA:
Q And it talks about gels of oxybate?
A It talks about gels as a -- as a possible medium. I mean, obviously, it says what it says. I'm just saying that the concept of a gel as a solid substance is rooted in the specification of the Resinate patents.
Q Sir, that sentence there, it's your opinion that that's talking about gel formulation of oxybate?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: The sentence speaks for itself. Obviously, the sentence contains no words like "oxybate" or "gamma-hydroxybutyrate." I can just repeat what I said a moment ago, that the sentence illustrates that gels, as a solid form, is contemplated in the specification of the Resinate patents.
BY MR. CALVOSA:
Q Sir, do you know what ionotropic gelation is?
A I think it's just a gelation that results in -- it's a gelation that involves ionic gelling agents.
Q And when the oxybate, as you've defined it, is in an ionotropic gelation, you understand it's

Page 44

associated with a positive cation; right?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: I don't understand the question.
BY MR. CALVOSA:
Q Ionotropic gelation, for the oxybate to go through that process, it would necessarily be associated with a positively charged cation.
MR. YUE: Objection. Form.
THE WITNESS: I mean, are you suggesting that oxybate would have to be bound to the component of the gel?
Is that what you're saying?
BY MR. CALVOSA:
Q To be within the gel?
Have you ever performed ionic -- ionotropic gelation?
A Many times.
Q Yes. And for the oxybate to be in a formulation with ionotropic gelation, the oxybate would be associated with a cation, as you've defined oxybate.
A Which cation?
Q That forms the ionotropic gelation.
A No. It doesn't have to be associated with it at all.

Page 45

Q Tell me why not.
A Well, tell me why yes.
Q You're the expert, sir. Tell me why not.
A Well, you cannot say something that's nonsensical and then just expect me to explain why it is nonsensical.
Q Tell me why it's nonsensical.
A The specific gel that is referred to here in this sentence that I just read is calcium alginate. Okay?
I have done a lot of work with calcium alginate. I have published papers on calcium alginate. So calcium alginate is a gel whereby the network of the gel is formed when calcium ions react with alginic acid.
So, typically, the way to form a calcium alginate is you have a solution of, for example, calcium chloride -- an aqueous solution of calcium chloride. Okay? And then you add, drop by drop, sodium alginate in that aqueous solution of calcium chloride.
When the droplet -- now, sodium alginate is soluble in water. Calcium alginate is not.
So when you drop an aqueous solution of sodium alginate into calcium chloride, as soon as the droplet hits the calcium chloride solution, the precipitate forms, which encapsulates this droplet, and then calcium

Page 46

chloride further diffuses into the droplet, thereby creating a solid calcium chloride -- I'm sorry -- calcium alginate bead.
Okay?
So formation of calcium alginate is in no way dependent on the presence of gamma-hydroxybutyrate or -- or anything else. It only requires alginate and calcium.
Q Okay. Well, then how do I put the oxybate, as you've defined it, into the calcium alginate gel?
A It's very simple. So I just explained to you how you form the calcium alginate gel.
So you drop a aqueous solution -- drop by drop, aqueous solution of sodium alginate into calcium chloride. If you want to put -- if you put -- if you want to put oxybate into that gel, then the aqueous solution of sodium alginate that you intend to drop into calcium chloride contains a salt of oxybate, for example, sodium oxybate.
And then when you do what I just described, you will have a gel that will contain oxybate.
Q The process you just described is not what's described in the examples of the '079 patent.
Is that fair?
A Well, I would -- I doubt that it's described

Page 47

there. At least that's not my recollection. But to be absolutely sure, I would need to rereview the -- the examples.
Q Sure. Go ahead.
A Thank you.
Yeah. So I briefly looked at the example. In the -- in the -- in the interest of time, that's what many of the examples actually start with the lactone of a gamma-hydroxybutyric acid, but that's not what these examples, which, of course, by necessity and by definition nonlimiting, they use different processes.
Q Different processes than the calcium alginate processes -- process that you talked about; right?
A They use different methodologies. These are examples, and these examples use different methodologies. Yes.
Q Different methodologies than the calcium alginate methodology you talked about; right?
A These methodologies, they are different from each other, and they're also different from what I described, yes.
Q Okay. The oxybate resins that are described in the examples, in your opinion, they would not fit within the solid oxybate formulation that's discussed in claim 1?

Page 48

MR. YUE: Objection. Form.
THE WITNESS: I have not analyzed this question. I would just need to -- to rereview the examples once again and to think about whether or not they are -- they meet the -- all the requirements of the claims of the '079 patent and preferably do so not under the stress of a deposition.
BY MR. CALVOSA:
Q Sure.
So, sitting here today, you have not considered whether the examples in the '079 patent fall within the scope of claim 1?
MR. YUE: Objection. Form. Calls for a legal conclusion.
THE WITNESS: I mean, I may have considered it at some point, but certainly not recently.
But, I mean, I can tell you that, for example, with respect to the Sustained Release patents, I do remember that, for example, the claims of the Sustained Release patents -- I'm sorry -- the examples in the Sustained Release patents do not meet all the claim limitations of the claims of those patents.
BY MR. CALVOSA:
Q Well --
A So, again, since we're talking about sort of

Page 49

these two families of Jazz's patents, I may have analyzed it at some point. I certainly haven't done it recently because my focus has been on the claim construction, not on, you know, other patent issues. So I certainly have not considered it recently.
Q Okay. So is it fair to say, in offering your opinions in support of Avadel's claim construction, you did not consider whether your interpretation of oxybate within the -- what you call the Resinate patents' claims would exclude the examples?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: I would not put it this way. I -- as I said, I -- in -- in the past, I -- I have looked at the -- at the examples, obviously have looked at the claims many times. I just have not specifically analyzed whether the examples of the '079 patent meet all the claim limitations of the claims of that patent.
BY MR. CALVOSA:
Q Let me ask you a simpler question, and you could look at Example 1, if you want.
Example 1 discusses forming GHB resin.
A Just a second. Let me just read Example 1 to myself.
Yes, sir. I read Example 1.

Page 50

Q Example 1 describes the process of formulating a GHB resin?
MR. YUE: Objection. Form.
THE WITNESS: I mean, it describes what it describes. It speaks for itself.
BY MR. CALVOSA:
Q That's your answer, sir?
A That's my answer, yes.
Q You can't tell me whether Example 1 describes the formation -- the formulation of a GHB resin?
MR. YUE: Objection. Form.
THE WITNESS: I mean, it describes the formation of GHB resin, whereby the resin is a strong ion exchange resin, namely Dowex, D-o-w-e-x, 1X2 of certain size in a certain way.
BY MR. CALVOSA:
Q Okay. As we established earlier, GHB resin is a salt; right?
MR. YUE: Objection. Form.
THE WITNESS: A GHB resin is a solid, yes.
BY MR. CALVOSA:
Q "A salt" was my question.
A Oh, a salt. I'm sorry. I thought you said "a solid." I apologize.
Yes, it is a salt.

Page 51

Q Based on your opinion that "oxybate" means the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid unbound to anything, a GHB resin would not meet your definition of "oxybate"; right?
MR. YUE: Hold on one sec.
Objection. Form.
THE WITNESS: It would not, yes. It would not have the -- a gamma-hydroxybutyrate in the salt will not have the electrostatic charge of minus 1.
BY MR. CALVOSA:
Q Were you aware that the parties previously went through a claim construction process last year?
MR. YUE: Objection. Just caution the witness, he can answer "yes" or "no," but not disclose the content of any conversations he may have had with counsel.
THE WITNESS: That's my recollection, yes.
BY MR. CALVOSA:
Q Okay. Were you aware that Avadel previously argued that the claims of what you're calling the Resinate patents covered only GHB resins?
MR. YUE: Objection. Again, caution the witness not to disclose the content of any privileged communications he's had with Avadel.
THE WITNESS: I have no firm recollection of that.

Page 52

MR. CALVOSA: Okay. We can take a break.
THE VIDEOGRAPHER: We are off the record. The time is 11:18 a.m.
(Recess was taken at 11:18 a.m. until 11:32 a.m.)
THE VIDEOGRAPHER: We are back on the record. The time is 11:32 a.m.
BY MR. CALVOSA:
Q Dr. Klibanov, going back to that calcium alginate encapsulation and the gel you talked about from column 2 -- can you go back to that in the '079 patent.
A Yes, sir.
Q If you read that full paragraph beginning on line 20 in column 2 through line 36, that's referring to carrying out that encapsulation process for a GHB resin; right?
A Okay. First of all, let me read it to myself, and then, you know, I'll be happy to entertain your question.
Yes, sir. Will you repeat your question, please.
Q Sure.
The -- the gel encapsulation process you were talking about, that refers to a GHB resin, not the negatively charged or anionic form (conjugate base) of

Page 53

gamma-hydroxybutyric acid; right?
MR. YUE: Objection. Form.
THE WITNESS: Yes. I think I already answered that question repeatedly before the break.
And, as I said, this just talks about -- the only reason I mention this passage in the specification of the '079 patent is just to illustrate that the concept of working with gels is well-rooted in the specification of the '079 patent.
BY MR. CALVOSA:
Q Could you have a powder formulation of the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid?
MR. YUE: Objection. Form.
THE WITNESS: I'm sorry. Could you repeat your question, please.
BY MR. CALVOSA:
Q Could you have a powder formulation of the negatively charge or anionic form (conjugate base) of gamma-hydroxybutyric acid?
MR. YUE: Objection. Form. Vague.
THE WITNESS: Yes. You can grind a gel, for example, and it will look like a powder.
So, you know, you can take a gel and, for example, cut it into small pieces or just grind it. It

Page 54

will look like a powder, but it would still be gel particles.
BY MR. CALVOSA:
Q Okay. So, in your opinion, all of the formulations claimed are limited to a gel?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: Certainly it's not my opinion, and I already said that it's not my opinion.
I just gave you one possible example of how you can have the existence of solid oxybate. There may be many other scenarios. I have not considered this question exhaustively, but, you know, one possible example is having an aqueous gel.
BY MR. CALVOSA:
Q If you turn to column 5 of the '079 patent --
A Okay.
Q -- and I'm looking at the paragraph that begins on line 49 and ends over on line 60.
A Okay. So let me read it to myself.
Yes, sir.
Q Okay. Do you see, about line, I guess, 54, it reads, "Those skilled in the art will appreciate that these factors complicate and, in many cases, limit conventional approaches for modified release, such as

Page 55

core/shell or matrix formulations, as the high solubility and mobility of GHB would tend to significantly reduce the number of viable approaches using such conventional solubility and diffusivity control technologies"?
A I do see it.
Q The word "GHB" there, is it your opinion that that's referring to the negatively charged or anionic form of (conjugate base) of gamma-hydroxybutyric acid?
MR. YUE: Objection. Form. The document speaks for itself.
THE WITNESS: Yes. My -- yes. And my opinion is based on the express definition that is found in column 3 of the '079 patent and, specifically, in lines 61 through -- I'm sorry, in line 59 through 61.
BY MR. CALVOSA:
Q I thought you told me earlier that you wouldn't talk about the solubility of the negatively charged or anionic form of gamma-hydroxybutyric acid unbound to anything.
A Well, first of all, I wouldn't talk about it and one of skill in the art wouldn't talk about it.
And, second of all, if you go to the very first line of the very paragraph that you directed me to, the first sentence there reads, "The solubility of

Page 56

sodium oxybate is unusually high."
So it's not the solubility of oxybate. The solubility of sodium oxybate is unusually high, which is exactly what I told you earlier before the break.
Q But if you go down to line 58, it doesn't say "sodium GHB" there, sir. It just says "GHB"; right?
A Yeah. But the sentence that you directed me to says, "Those skilled in the art will appreciate that these factors," and "these factors" are solubility of sodium oxybate that's unusually high. That is what it refers to.
Q So here in column 5, line 58, the inventors are using "gamma-hydroxybutyrate" to refer to sodium oxybate?
A I'm just telling you that the "high solubility" term that is used here clearly refers to the solubility in water of sodium oxybate.
Q So your testimony is that a POSA would understand that the use of "gamma-hydroxybutyrate" in line 58 refers to sodium oxybate?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: A person of ordinary skill in the art would understand that this paragraph that we're discussing in column 5 may not be the paragon of

Page 57

clarity, but the solubility refers to the solubility of sodium oxybate.
BY MR. CALVOSA:
Q And even when it just says "gamma-hydroxybutyrate" alone, without sodium in front of it, it's referring to sodium oxybate?
A It must refer to sodium oxybate because otherwise it makes no sense.
Q And if you go to column 6 and read lines 12 through 19 --
A Okay. Let me do it.
Yes, sir.
Q There in column 6, lines 12 through 19, when it's referring to the soluble drug oxybate, the oxybate there is necessarily referring to a salt of oxybate; right?
MR. YUE: Objection. The document speaks for itself. Form.
THE WITNESS: What -- are you talking about the last sentence in that paragraph?
BY MR. CALVOSA:
Q Yes, sir.
A They -- one of skill in the art would understand that -- again, that they refer to sodium oxybate, which is what I already indicated when we

Page 58

talked about the paragraph in column 5.
Q Okay. So in column 6, line 19 -- or 18 through 19, a person of ordinary skill in the art would understand that the use of "oxybate" there refers to sodium oxybate?
A In order to make sense of that sentence, in order to make it scientifically precise, that's what a person of ordinary skill in the art would -- would understand.
Q Okay.
MR. YUE: Is that --
MR. CALVOSA: No. That's the wrong one.
MR. YUE: Thank you.
BY MR. CALVOSA:
Q All right. Dr. Klibanov, I've just handed you what I've marked as Klibanov 7.
Do you recognize this to be one of the Sustained Release patents, specifically, the '488 patent that you provide opinions on?
A Actually, what I have in front of me, it says Klibanov 6, not Klibanov 7.
Q Oh, Klibanov 7.
A No, not 7. Klibanov 6. That's what I have. That's what you gave me. It says Klibanov 6.
Q Okay. Klibanov 6.

Page 59

A I thought you said "Klibanov 7."
Q I -- I did twice. So yeah. I said -- meant Klibanov 6.
A Ah, okay.
MR. YUE: Just for the record, Klibanov 6 is --
MR. CALVOSA: Is the '488 patent.
MR. YUE: -- the '488 patent. Okay.
(Whereupon Exhibit 6 was marked for identification.)
THE WITNESS: I'm sorry. Is there a question pending?
BY MR. CALVOSA:
Q I'm asking if you recognize this as one of the patents you provided opinions on.
A Yes.
Q If you turn to the title of that patent, do you see it says, "Controlled Release Dosage Forms for High-dose, Water-soluble and Hygroscopic Drug Substances"?
A I do.
MR. YUE: I'm just -- you meant "hygroscopic."
MR. CALVOSA: Hygroscopic, yeah.
MR. YUE: Okay.
BY MR. CALVOSA:
Q Based on what you told me earlier about

Page 60

solubility and hygroscopicity, this necessarily must be referring to salts and not the anionic form on its own, unbound to everything; right?
A Well, first of all, I -- I don't think that one skill in the art would just read the title of a patent, ignore the rest of the patent, and make any judgments on that. Obviously, a title has to be read in a -- in the context of the entire patent.
Second of all, as I said earlier, hygroscopic substances are solid substances that have a propensity to absorb moisture.
Q And that -- that would not include the negatively charged or anionic form of gamma-hydroxybutyric acid; right?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: The gamma-hydroxy -- the gamma-hydroxybutyrate anion with an electrostatic charge of minus 1 is -- cannot exist as a solid substance, as has been discussed by me on numerous occasions, as agreed by Dr. Little.
And, therefore, strictly speaking, you would not be talking about -- you should not -- one should not be talking about hygroscopicity of components of substances. You have to talk about the substance

Page 61

itself.
And the solid substance is a salt of -- the solid drug substance is a salt in this particular case of something like gamma-hydroxybutyrate.
BY MR. CALVOSA:
Q What did you mean by "component"?
A You -- a component would be an ion, for example. You're not referring -- you should not be referring to whether an ion is hygroscopic. The substance is hygroscopic.
Q So the anion is a component of the salt?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: The anion of a partial negative charge is a component of a salt. A salt consists of two ionic components: a cation and an anion.
BY MR. CALVOSA:
Q If you could turn to --
A As, by the way, I -- I state in my declaration.
Q If you could turn to column 1.
A Of?
Q The '488 patent, sir.
A Yes, sir.
Q And I'd like you to read lines 38 through 41.

Page 62

A Yes, sir.
Q The use -- a person of ordinary skill in the art would understand that the use of gamma-hydroxybutyrate in those lines cannot mean what you opine that gamma-hydroxybutyrate means within the context of the Sustained Release patents; right?
MR. YUE: Objection. Form.
THE WITNESS: Well, it -- at the end of this sentence, it specifically says, "Particularly the sodium salt of GHB."
So it certainly fully applies to the sodium salt of GHB, the statement that's made here.
BY MR. CALVOSA:
Q So what does "gamma-hydroxybutyrate" mean before the comma, sir?
A Gamma-hydroxybutyrate, as such, means what I described previously. In this particular case, you know, they -- they -- I don't know what form -- this is in the "Background" section, so I don't know what form of -- for instance, if sodium -- sodium salt of GHB is dissolved in water, if they're talking about the liquid form, you will have gamma-hydroxybutyrate present in that aqueous solution. You will have that unbound, freestanding anion. So that would mean that.
Q So the gamma-hydroxybutyrate there means --

Page 63

when it says its "high water solubility," it's referring to the freestanding anion.
That's your opinion?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: That's not my opinion, and by now, you should know that it's not my opinion because I stated it repeatedly.
I already told you that the solubility can refer to a substance that can exist in a solid form, and gamma-hydroxybutyrate, as I define it, cannot. Okay?
So it cannot be my opinion possibly. You asked me that question before, and I answered it before. Okay?
BY MR. CALVOSA:
Q We're going to do this for each time it appears in conjunction with solubility or hygroscopicity within the patents that you opined on.
Your opinion will be the same every time, that it can't possibly be referring to the negatively charged or anionic form of gamma-hydroxybutyrate on its own?
MR. YUE: Objection. Form. Vague.
You can answer if you can.
THE WITNESS: My opinion is that, strictly speaking, it is improper to talk about hygroscopicity or

Page 64

solubility of an ion. Okay?
Now, people often speak imprecisely, speak loosely; and when they do so, then, obviously, their hope is that people read what they said with a mind willing to understand.
But strictly speaking -- and I just want to be very clear about that -- solubility in water and hygroscopicity refer to a property of a solid substance.
And gamma-hydroxybutyrate anion, as I define it in terms of the claim term, cannot be a solid substance.
BY MR. CALVOSA:
Q Okay. So if you go to column 4, beginning on line 63, and continuing on to the column 5 --
A Just a second.
Q Read as much as you need to, sir, but I'm going to ask you about the bottom of column 4.
A Yeah.
Yes, sir.
Q In the bottom of column 4 of the '488 patent where it says, "For instance, GHB is very soluble," what would a POSA understand "GHB" there to mean?
A A POSA would understand that this is yet another example of loose talk on the part of the patentees, and that what they're really referring to is

Page 65

salts, and probably -- most likely a sodium salt of gamma-hydroxybutyrate --
Q So --
A -- or sodium salt or, to be precise, sodium salt of gamma-hydroxybutyric acid.
Q So it's your opinion that the inventors are using the term "gamma-hydroxybutyrate" within their patent loosely?
MR. YUE: Objection. Misstates the witness's testimony.
THE WITNESS: They -- in the specification, they use it somewhat inconsistently.
But, thankfully, it doesn't affect the claim construction because the language of the claims is quite clear.
BY MR. CALVOSA:
Q Within the specification, you agree with me, then, that the inventors use "GHB" inconsistently refer to both salts of GHB, such as sodium oxybate, and gamma-hydroxybutyric acid; right?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: I don't see where -- at least what we have read so far, I don't see where they're referring to it as gamma-hydroxybutyric acid.

Page 66

BY MR. CALVOSA:
Q Okay. Do you agree with me that the inventors use the term "gamma-hydroxybutyrate" within the specification of the Sustained Release patents to mean salts of gamma-hydroxybutyrate, including sodium oxybate?
Right?
MR. YUE: Hold on.
Objection. Form. Vague. Misstates the witness's testimony.
THE WITNESS: Could you repeat this question slowly, please.
BY MR. CALVOSA:
Q I apologize.
You agree with me that the inventors use the term "gamma-hydroxybutyrate" within the Sustained Release patent specification to mean salts of gamma-hydroxybutyric acid, including sodium oxybate?
MR. YUE: Objection. Form. Vague. Misstates the witness's testimony.
THE WITNESS: I would not put it that way.
BY MR. CALVOSA:
Q How would you put it, sir?
A I would say -- and I think that what -- my opinion is illustrated by the passage in column 1 that

Page 67

we read earlier, namely, that there is sort of a somewhat imprecise formulation of the sentences.
But, for example, if we go back to what we read in column 1 -- and this is lines 38 through 41 -- they specifically -- they talk about gamma-hydroxybutyrate, that, for example -- you know, I'm just explaining what I think they mean here -- sodium salt of GHB that is dissolved in water.
Q When it refers to a "sodium salt of GHB," would you also say that's an imprecise usage of GHB?
A Yes, it is.
Q What would be -- how would a POSA understand "salt of GHB"?
A I actually explained this -- this issue in some detail in my declaration.
Q So let me just ask you a shortcut, then.
It's your opinion that a person of ordinary skill in the art would understand salt of gamma-hydroxybutyrate to actually mean salt of gamma-hydroxybutyric acid?
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: One would understand that, in fact, it's a -- for example, if it's a sodium salt, it's a sodium salt of gamma-hydroxybutyric acid. Correct.

Page 68

BY MR. CALVOSA:
Q So there, it's your -- there, it's your opinion that the inventors are using "gamma-hydroxybutyrate" loosely when they actually mean "gamma-hydroxybutyric acid"?
A I don't think -- I wouldn't use here "loosely." I mean, this is sort of -- strictly speaking, it is imprecise. But, again, people, as we all know, don't always, you know, speak in a totally precise manner.
I see nothing wrong -- again, given the proper context, I see nothing wrong with saying that "sodium salt of gamma-hydroxybutyrate." It's not wrong. Okay? Strictly speaking, you know, there is a more precise way of stating it.
But, certainly, I see no problem with, for example, Avadel's claim -- claim construction that says, you know, "salt of gamma-hydroxybutyrate." It's not wrong to say it. It's just -- you know, there is a more precise way of stating that.
Q As part of your review of Dr. Little's declaration, did you review articles that he attached to the declaration from the prior art?
A I did.
Q Okay. And did you see in those articles that

Page 69

many of them used the term "gamma-hydroxybutyrate" to refer to sodium gamma-hydroxybutyrate?
MR. YUE: Hold on one second.
Objection. Misstates the documents. They speak for themselves.
You can answer.
THE WITNESS: Yeah. I would need to take a look at the specific publications. Actually, most of them, as I recall, they use the abbreviation "GHB." That's what they actually use, not the term "gamma-hydroxybutyrate," as Dr. Little suggests.
But I'll be happy to take a look at any specific publication that you would like to discuss.
BY MR. CALVOSA:
Q Okay. I'm just trying to shortcut it. We'll go through each one individually.
In your opinion, is there a difference between the abbreviation "GHB" and "gamma-hydroxybutyrate" -- and "gamma-hydroxybutyrate"?
MR. YUE: Objection. Vague.
THE WITNESS: Some of those publications, as I recall, actually abbreviate "gamma-hydroxybutyric acid" as "GHB."
So you can introduce your own abbreviation. I mean -- and many people do, including in those

Page 70

publications cited by Dr. Little.
BY MR. CALVOSA:
Q All right. We'll go through each one individually.
Back to the '488.
A Sure.
Q Column 5, starting around line 16. And read as far as you need to through 27.
A So we're talking about that paragraph; correct?
Q Yes, sir.
A Yes, sir.
Q When it says there that "Some forms of GHB, such as the sodium salt of GHB, sodium oxybate, are extremely hygroscopic," the use -- a person of ordinary skill in the art would understand that the use of "GHB" in Jazz's patents was not limited to just the negatively charged or anionic form of gamma-hydroxybutyric acid unbound to anything else; right?
MR. YUE: Objection. Form. Vague.
THE WITNESS: Okay. I can only talk about one passage at a time. Okay?
So in this particular case, they are talking about sodium salt of gamma-hydroxybutyrate, or GHB.
BY MR. CALVOSA:

Page 71

Q They're not -- so they said "some forms of GHB."
A They say, "Some forms of GHB, such as sodium salt of GHB, sodium oxybate, are extremely hygroscopic."
So it's clear that they're talking about here the salts of GHB. And when they say "some forms of GHB," they're talking about salts of GHB.
Q Would a POSA understand "forms of GHB, such as the sodium salt of GHB," to mean that the "sodium salt" is included within the term "gamma-hydroxybutyrate"?
MR. YUE: Objection. Form.
THE WITNESS: No.
BY MR. CALVOSA:
Q That's not what "forms of" something means to you?
A Well, forms -- what "forms of" means to me depends on the context in which it is used.
In this particular case -- if you, at the very least, read the sentence as a whole rather than just cherrypicking portions or words from the sentence, it's very clear that, in this particular case, when they talk about "forms of GHB," they are talking about various salts of GHB.
Q So salt -- a POSA would understand that the salts of GHB are forms of GHB?

Page 72

MR. YUE: Objection. Vague.
THE WITNESS: You can say that it's a form of GHB. Again, it's -- there is -- it's not wrong to say that. And, indeed, the claim constructions that are -- that are in paragraph 6 of my declarations, for example, if we go to Avadel's, it's negatively charged or anionic form of GHB.
So the word "form" can apply to different things. And, as I said, it depends on the context. In the context of column 5, here, in this context, as is clear from reading the sentence as a whole, it refers to different salts of GHB.
BY MR. CALVOSA:
Q Sir, in your answer, you just referred to gamma-hydroxybutyric acid as "GHB."
A Pardon me?
Q In your answer, you just referred to gamma-hydroxybutyric acid as "GHB."
A I don't think I did. Why don't we ask the -- Kayla here to read my answer back.
MR. CALVOSA: Please.
THE WITNESS: If I did, I misspoke, and I will then correct myself.
MR. CALVOSA: I don't think you misspoke, sir.
THE WITNESS: It's possible. I mean, I'm certainly

Page 73

not a perfect man, and my wife reminds me about that on a daily basis. And we've been married for 30 -- for 51 years, so she should know.

MR. CALVOSA: Can you please read that answer back.

THE WITNESS: Slowly please, Kayla.

THE STENOGRAPHER: Yes.

(The following was read from the record:

"Answer: You can say that it's a form of GHB. Again, it's -- there is -- it's not wrong to say that. And, indeed, the claim constructions that are -- that are in paragraph 6 of my declarations, for example, if we go to Avadel's, it's negatively charged or anionic form of GHB.

So the word "form" can apply to different things. And, as I said, it depends on the context. In the context of column 5, here, in this context, as is clear from reading the sentence as a whole, it refers to different salts of GHB.")

THE WITNESS: Thank you very much.

You are correct. I misspoke, and I apologize. Avadel's proposal -- proposed construction of the claim term "gamma-hydroxybutyrate" is, as I already mentioned

Page 74

before the break, the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid.

BY MR. CALVOSA:

Q And you would not refer to gamma-hydroxybutyric acid -- let me ask a different question.

A POSA would not refer to gamma-hydroxybutyric acid as gamma -- as "GHB"?

MR. YUE: Objection. Vague.

THE WITNESS: A POSA can introduce whatever abbreviation a POSA wants.

And, in fact, as I already mentioned to you a few minutes ago, in some of the publications cited by Dr. Little, people, for whatever reason, abbreviated "gamma-hydroxybutyric acid" as "GHB."

But I certainly don't want to make matters more confusing than they already may seem to. And, therefore, I, in the context of this case, certainly would not refer to gamma-hydroxybutyric acid. I would not abbreviate it as "GHB" because I think it would just create unnecessary confusion.

BY MR. CALVOSA:

Q But you agree that people of ordinary skill in the art in the prior art refer to gamma-hydroxybutyric acid as "GHB"?

Page 75

MR. YUE: Objection. Form.

THE WITNESS: I don't know whether those people were of ordinary skill in the art or not. I haven't examined their background.

Some people -- you know, you can introduce any abbreviation you want as long as you clearly state what -- what it is that you're abbreviating. There is nothing wrong with that. All right?

So, you know, there's no rule as to what abbreviations you can introduce. Okay?

In the context of this case, in particular, in the context of the claim construction phase of this case, I would note -- and I don't think it will be reasonable to abbreviate gamma-hydroxybutyric acid as "GHB," in particular, because it directly contradicts the express definition that is provided in column 3 of the Resinate patents.

BY MR. CALVOSA:

Q You understand that the Sustained Release patents issued before what you call the Resinate patents issued; right?

A I don't specifically recall. It's possible. I don't remember.

Q Okay. Did they have an earlier priority date?

A I -- I don't know specifically. I didn't

Page 76

commit it to memory.

Q Okay. I'll represent to you that they do.

Show me where in the Sustained Release patents it says that gamma-hydroxybutyrate means the negatively charged or anionic form of gamma-hydroxybutyric acid unbound to anything else.

MR. YUE: Objection. Form.

THE WITNESS: I certainly will need, at the very least, to review -- rereview the specification of the '488 patent, for example, and then I may be able to show you if I find it.

But the first step would be to rereview the specification of the '488 patent, which I'll be glad to do if you want me to.

BY MR. CALVOSA:

Q Don't you think if it actually said that in there, you would have cited it in your declaration?

MR. YUE: Objection. Form.

THE WITNESS: I don't want to speculate on coulda, woulda, shoulda.

I -- as I said, you asked me a specific question. As a first step toward possibly answering this question, I would need to rereview the specification of the '488 patent.

BY MR. CALVOSA:

Page 77

Q Okay. We're going to have enough time, so let's do that at the last point of the day. That way, we'll take the time for you to read it, and you can show me where it says it. Because I don't see it.
A Is there a question pending?
Q No. I'm just saying --
A Okay.
Q -- we're going to do that later.
A Okay.
Q You would agree with me that the references that you reviewed that were attached to Dr. Little's declaration, some of those refer to gamma-hydroxybutyric acid as "GHB"; right?
MR. YUE: Objection. Documents speak for themselves.
THE WITNESS: I would not put it that way.
The way I would put it is that my recollection is that some of those references -- in some of those references, the authors chose to use the abbreviation GHB for gamma-hydroxybutyric acid.
BY MR. CALVOSA:
Q Okay. And in some of the references that you reviewed that were attached to Dr. Little's declaration, the authors chose to use the abbreviation GHB for sodium oxybate; right?

Page 78

MR. YUE: Objection. The documents speak for themselves.
THE WITNESS: I would need to refresh my memory with respect to that.
BY MR. CALVOSA:
Q You don't recall?
A I do not specifically recall, no.
Q When you've published on gamma-hydroxybutyrate, how have you used that term?
A I'm not sure I have ever published on gamma-hydroxybutyric acid.
Q Okay. When you were conducting research on gamma-hydroxybutyrate, how did you use that term?
MR. YUE: Objection. Vague.
THE WITNESS: I mean, with all due respect, sir, the question as you ask it makes no sense at all.
BY MR. CALVOSA:
Q Why is that?
A Because you said when you researched the literature, how did you use this term?
Q No, sir.
A Well, when I --
Q That wasn't my question, so why don't I --
THE WITNESS: Excuse me. Could you please read counsel's question back.

Page 79

(The following was read from the record:
"Question: Okay. When you were conducting research on gamma-hydroxybutyrate, how did you use that term?")
THE WITNESS: So it was your question.
BY MR. CALVOSA:
Q You misinterpreted it. Let me ask again.
In your laboratory --
A I -- excuse me. I misinterpreted it? What was there to misinterpret?
Q Sir, I don't know why you're arguing with me.
A No. No. Because I -- no, you're just saying things that are demonstrably untrue.
Q My question was unclear, then.
A Okay. That's -- that's fine.
Q Okay.
A That's fine.
Q This reminds me of us working together in the past.
When you --
A These are not happy memories, then, because I have no memories like that. But anyway.
Q When you conducted laboratory work, actual chemistry, on gamma-hydroxybutyrate, how did you use

Page 80

that term?
MR. YUE: Objection. Vague. Assumes facts not in evidence.
THE WITNESS: I don't think I ever conducted laboratory work on gamma-hydroxybutyric acid.
BY MR. CALVOSA:
Q You've never published on gamma-hydroxybutyrate; right?
A I'm not sure. I -- you know, I just don't recall. I -- I have several hundred publications, and I don't -- don't specifically recall.
Q Okay. Sitting here today, you can't recall ever publishing on gamma-hydroxybutyrate?
A I recall that I published on a number of other hydroxycarboxylic acids. Whether gamma-hydroxybutyric acid was among them, I don't specifically recall one way or the other.
Q Would it surprise you to learn that I couldn't find any publications from you on gamma-hydroxybutyrate?
A I -- it wouldn't surprise me because I don't know what kind of search you have conducted, how you -- careful you've done it, and all that.
I -- as I said, sitting here today, I do not recall one way or the other whether I have published specifically on gamma-hydroxybutyrate.

Page 81

What I do recall is that I published papers on what is involving other hydroxycarboxylic acids.
Q You understand the dispute here is about gamma-hydroxybutyrate; right?
A The dispute here is about the meaning of the claim term "gamma-hydroxybutyrate." Correct.
Q And, sitting here today, you cannot recall ever publishing, one way or the other, on gamma-hydroxybutyrate?
A Sitting here today, I cannot recall, one way or the other, publishing papers on gamma-hydroxybutyric acid or its derivatives.
Q Sitting here today, you can't recall, one way or another, whether you've ever conducted laboratory research on gamma-hydroxybutyrate?
A I cannot recall, one way or the other, whether I have conducted laboratory research on gamma-hydroxybutyric acid or its derivatives.
Q Okay. Do you know of a doctor named Martin Scharf.
A Spell the last name --
Q Scharf --
A -- slowly.
Q -- S-c-h-a-r-f.
A For some reason, the name Martin Scharf seems

Page 82

familiar, but I cannot place it specifically.
(Whereupon Exhibit 7 was marked for identification.)
BY MR. CALVOSA:
Q Here you are.
A Thank you.
Q And what I've just marked as Klibanov 7 is a publication called "Pharmacokinetics of Gamma-hydroxybutyrate (GHB) in Narcoleptic Patients," and the lead author on this publication is Martin B. Scharf.
A Yeah. I don't think that I ever met this particular gentleman, Martin B. Scharf.
Q Okay. And do you see right in the summary section, the first thing it says is "sodium gamma-hydroxybutyrate," and then in parentheses "GHB"?
A I do. And it also says that -- see that in the title of the paper, it says just "gamma-hydroxybutyrate" and also says in parentheses "GHB."
So there is an inconsistency sort of jumping out of the page, if you will.
Q Okay. Do you see in the first line of the body of the text, again, it says "sodium gamma-hydroxybutyrate" and then "GHB" in parentheses?

Page 83

A I do see that.
Q Okay. So this paper uses gamma-hydroxybutyrate and sodium gamma-hydroxybutyrate interchangeably?
MR. YUE: Objection. The document speaks for itself. That misrepresents the document.
THE WITNESS: I mean, I -- I -- I don't know. At the very least, I would need to read the entire paper.
But what I can tell you is that there is a clear inconsistency that I can immediately see by comparing the title of the paper with the first sentence of the summary and the first sentence of the introduction.
BY MR. CALVOSA:
Q Would you say that this is an imprecise usage of "gamma-hydroxybutyrate," like you say of other publications in your declaration?
MR. YUE: Objection. The document speaks for itself. Vague.
THE WITNESS: When you're saying "it," what is "it"?
BY MR. CALVOSA:
Q I didn't say "it" at all in that question, so let me ask it again.
A Just -- would you like -- I mean, again, sir,

Page 84

you can say that you misspoke or that you --
MR. CALVOSA: You can read the question back.
THE WITNESS: Please. Slowly, please, Kayla.
(The following was read from the record:
"Question: Would you say that this is an imprecise usage" --)
THE WITNESS: Thank you. "This is." So I -- I was wrong. I thought you said "it is," but you said "this is."
So what is "this"?
BY MR. CALVOSA:
Q Would you say that the use of gamma-hydroxybutyrate in this publication is an imprecise usage of that term, like you do with the other publications that you discuss in your declaration?
MR. YUE: Objection. Vague. The document speaks for itself.
THE WITNESS: First, I cannot speak for this publication as a whole because -- because I would need to rereview it.
Second of all, what I can say is that certainly, the use of the term "GHB" is inconsistent, which is evident by looking -- by comparing its use in the title of the paper with its use in the first sentence of the summary and the first sentence of the

Page 85

introduction.
BY MR. CALVOSA:
Q Wouldn't a person of ordinary skill in the art understand that gamma-hydroxybutyrate was used, as you call it, inconsistently in the prior art?
MR. YUE: Objection. Form. Vague.
THE WITNESS: Well, I would need to see some examples that you're referring to with respect to this inconsistency.
It's certainly possible, and, in fact, I specifically say in my declaration that, you know, there has been some loose or imprecise use of terminology. But if you -- again, if you are talking about specific publications, I would need to take a look at those publications.
BY MR. CALVOSA:
Q Do you know if Dr. Scharf would be a person of ordinary skill in the art?
MR. YUE: Objection. Vague. Lacks foundation.
THE WITNESS: I don't know Dr. Scharf, and I don't know what his background -- professional background is.
BY MR. CALVOSA:
Q What if I told you he was one of Avadel's experts?
MR. YUE: Same objection.

Page 86

THE WITNESS: My answer doesn't change. I don't know Dr. Scharf, and I don't know what his professional background is.
BY MR. CALVOSA:
Q Handing you what I'll mark as Klibanov 8.
(Whereupon Exhibit 8 was marked for identification.)
BY MR. CALVOSA:
Q This is a -- this is a publication, again, by Martin Scharf, titled "Sodium Oxybate for Narcolepsy."
And do you see in the first sentence of the abstract there, he says, "Sodium oxybate," then "Xyrem" in parentheses, "also known as gamma-hydroxybutyric acid"?
A I do see that portion of the first sentence of the abstract.
Q In your opinion, is that a correct usage of gamma-hydroxybutyric acid?
A I mean, I think that this statement there is scientifically imprecise for at least two reasons.
First of all, because it says "sodium oxybate in (Xyrem)," trademark. Okay?
Sodium oxidate is a molecule that exists as such. It doesn't only exist in the drug Xyrem. Okay? So that's imprecise use of the English language and

Page 87

scientific terminology.
And, likewise, I don't think it's correct to say that sodium oxybate is known as gamma-hydroxybutyric acid. These are two different substances. So that's all I can tell you.
Q Where is gamma-hydroxybutyrate found within the human body?
MR. YUE: Objection. Vague. Lacks foundation. He's not here to testify about human physiology.
THE WITNESS: Well, my recollection is that it's a neurotransmitter, so it reacts with -- it can react with neurons. So it can be found, for instance, in the brain tissues.
BY MR. CALVOSA:
Q Okay. And in the brain tissue, it's present as the negatively charged or anionic form of gamma-hydroxybutyric acid?
MR. YUE: Objection. Vague. It's outside -- outside the scope of Dr. Klibanov's opinions.
THE WITNESS: In any -- in an aqueous solution, it will be present as a gamma-hydroxybutyric anion with the electrostatic charge of minus 1, yes.
BY MR. CALVOSA:
Q Okay. So you're saying if I dissolve even sodium oxybate in water, it then becomes the negatively

Page 88

charged or anionic form of gamma-hydroxybutyric acid?
A If you dissolve sodium gamma-hydroxybutyrate in water, three events will occur in sequence.
First, there will be the release of gamma-hydroxybutyrate from the solid. Then there will be a dissolution of that salt in water. And, finally, there will be a dissociation of that salt into the cation of sodium and the anion of gamma-hydroxy- -- the anion of gamma-hydroxybutyrate.
Q How long does that process take?
A It's a fairly -- a fairly quick process.
Q Less than a minute?
A It depends on conditions, so, you know, how exactly it is done, under what conditions, and so forth. But it doesn't change the fact that these are three distinct events that occur in sequence in the order that I just mentioned.
Q Why is that important?
A I think it's important chemically to understand how things -- sort of how things take place in chemistry. So understanding a mechanism of chemical phenomena is fundamentally important to pass a judgment on this phenomena.
Q Okay. When you said "fairly quick process," can you put a time on that at all?

Page 89

A As I just said, it very much depends on conditions, but it's generally fast -- these are fast processes.
Q And the anionic form -- the anion fully negative 1, that comes from the sodium oxybate.
MR. YUE: Objection. Form. Misstates the witness's testimony.
THE WITNESS: It comes from dissociation of sodium oxybate in aqueous solution to form NA+ and the anion of gamma-hydroxybutyric acid, or the anion which is gamma-hydroxybutyrate.
BY MR. CALVOSA:
Q Does the ionic solid of sodium oxybate exist in aqueous form?
MR. YUE: Objection. Vague.
THE WITNESS: I'm sorry. Sorry. The question makes no sense to me.
BY MR. CALVOSA:
Q Why doesn't it make sense?
A It's just a nonsensical question.
Could you read it back and -- but it just sort of -- when I heard it, it didn't make sense to me. Could you please read it back, Kayla. I'm sorry for troubling you.
(The following was read from the record:

Page 90

"Does the anionic solid of sodium oxybate exist" --)
THE WITNESS: That's it. You said "the anionic solid," and that was -- that's what was nonsensical to me.
BY MR. CALVOSA:
Q Does the ionic salt, sodium oxybate, exist when it's dissolved in water?
A Saying ionic salt makes -- doesn't make a lot of sense either.
Q Let me ask it again.
A Please.
Q Does the salt solid exist when it's dissolved in water?
MR. YUE: Objection. Vague.
THE WITNESS: What do you mean, "salt solid"?
BY MR. CALVOSA:
Q How would you put it?
A Put what?
Q Does the salt gamma- -- sorry.
Does sodium oxybate exist when it's dissolved in water?
MR. YUE: Objection. Form. Vague.
THE WITNESS: Yes, as I just explained to you three consecutive steps that take place in aqueous solution.

Page 91

After the first step and after the second step, you still have the undissociated salt sodium oxybate or sodium gamma-hydroxybutyrate.
In the third step, that salt -- that salt dissociates into the corresponding cation and the corresponding anion.
MR. CALVOSA: Now's a good time for a break if you want to take one.
THE WITNESS: That's fine.
MR. YUE: Sure.
THE VIDEOGRAPHER: We are off the record. The time is 12:31 p.m.
(Recess was taken at 12:32 p.m. until 12:42 p.m.)
THE VIDEOGRAPHER: We are back on the record. The time is 12:42 p.m.
BY MR. CALVOSA:
Q Dr. Klibanov, can you please go to the '488 patent, column 27, and read claim 1 to yourself, please.
A Which claim?
Q Claim 1.
A Okay. Of the '488 patent?
Q Yes.
A All right.
Q I want to focus on the Element A to begin

Page 92

with.
A Element A.
Q Yes, sir.
A Okay.
Q When it's talking about a "sustained release portion comprises a functional coating and a core, wherein the functional coating is deposited over the core," is that referring to a solid formulation?
MR. YUE: Objection. Vague.
THE WITNESS: That's how I understand it. And, of course, as I mentioned earlier, that solid could be a gel. But, yes, that's -- that's how I understand it.
BY MR. CALVOSA:
Q So this one, too, you say it -- it's talking about a gel?
A No. The answer is yes. It -- the -- the answer to your question is yes. It's a solid -- it's a solid substance, which could be a gel.
Q Could it be a tablet?
MR. YUE: Objection --
THE WITNESS: A tablet --
MR. YUE: -- form --
THE WITNESS: I'm sorry. A tablet --
(Reporter clarification.)
MR. YUE: Form. Vague.

Page 93

THE WITNESS: Tablet is a dosage form. Okay? So, you know, you can have a tablet, inside of which you will have a gel.

So, I mean, I don't see -- you know, I am not sure I understand exactly what the point of the question is.

BY MR. CALVOSA:

Q The gel that you're referring to, is that discussed anywhere in the '488 patent?

A There are publications that, even judging by their names, refer to gels.

So, again, the concept of gels is certainly within the intrinsic evidence with respect to the '488 patent.

Q When did you come up with this gel theory for the solid? Because it's not in your declaration.

MR. YUE: I'm going to object. You're asking for the timing?

I'm going to object on the grounds that this invades the providence of attorney work product. I instruct the witness not to answer.

BY MR. CALVOSA:

Q Are you going to follow your attorney's instruction?

A Certainly.

Page 94

Q Did you come up with this theory before you submitted your declaration?

MR. YUE: Same objection.

BY MR. CALVOSA:

Q You're going to follow --

MR. YUE: And -- sorry. Same instruction for the witness not to answer.

BY MR. CALVOSA:

Q You're going to follow your attorney's instruction?

A Yes.

And to save you time today, I will follow attorney's instructions not to answer whenever they are given.

Q I'm still going to do it for the record, sir, but thank you.

Did you come up with this gel theory during your -- well, let me ask you this:

Did you prepare with Avadel's attorneys for your deposition today?

MR. YUE: And you can answer that "yes" or "no" without disclosing the contents of any privileged communications.

THE WITNESS: Yes.

BY MR. CALVOSA:

Page 95

Q When did you prepare?

MR. YUE: Same caution.

THE WITNESS: If, by that question, you mean when did I prepare with the attorneys --

BY MR. CALVOSA:

Q With the attorneys.

A -- for Avadel, then the answer is yesterday.

Q Any other day other than yesterday?

A No. Prior to that, I was preparing myself.

Q Did you come up with this new gel theory during the preparation with your attorneys yesterday?

MR. YUE: Objection. You know, again, same question, asking the timing of when he came up with this theory. So instruct the witness not to answer.

BY MR. CALVOSA:

Q Are you going to follow your attorney's instructions?

A Yes.

Q Did you yourself come up with this gel theory, or was it told to you by Avadel's attorneys?

MR. YUE: Without any waiver, I'll let the witness answer.

THE WITNESS: Say again?

MR. YUE: Without any waiver of privilege, on that understanding, I'll let you answer.

Page 96

THE WITNESS: I don't know what you mean by "this gel theory."

BY MR. CALVOSA:

Q That the inventions could cover gels of the anionic form, as you understand that term.

A I mean, I think --

MR. YUE: Hold on. I'll just say object to the form -- to the form of the question because I don't believe that accurately represents what Dr. Klibanov has been testifying about.

But to the extent you're able to answer, you can answer.

THE WITNESS: I think that it can be a gel has been my opinion for quite some time.

I -- as I mentioned earlier, I have a lot of experience working with gels. I am of the view that gels are solid substances, so it has been my opinion for quite some time.

MR. CALVOSA: I think he just answered all the questions that you objected to on privilege, so let's explore that.

MR. YUE: Well --

BY MR. CALVOSA:

Q Why did you not include that in your declaration if that's been your opinion for some time?

Page 97

MR. YUE: Objection. I'm going to instruct the witness not answer on privilege grounds.
BY MR. CALVOSA:
Q Are you going to follow your attorney's instructions?
A Yes.
Q Did you want to put the gel opinion in and your attorneys told you not to?
MR. YUE: Instruct the witness not to answer on privilege grounds.
BY MR. CALVOSA:
Q And I assume you're going to follow your attorney's instructions?
A Yes.
Q For portion A, it says that the sustained release portion can comprise a pharmaceutically acceptable salt of gamma-hydroxybutyrate.
A Are you reading the claim language?
Q Yes, sir.
A In what line?
Q It says, "Active ingredient selected from" --
A What line, sir?
Q 40 through 40 -- just portion A. Read the whole of portion A. That way, we don't have any issue.
A I'm not sure I understand.

Page 98

Q There's an A, sir, on line 29.
Do you see it?
A I'm well aware of that, and line 29, for example, which is why I asked you whether you're reading it, doesn't read the way that you just read, which is why I asked you, where do you read it?
Q The entire portion A. You can read it to yourself.
A I already read it to myself.
Q Do you not see the words "pharmaceutically acceptable salts of gamma-hydroxybutyrate" anywhere in portion A?
MR. YUE: Objection. Form. Not what you asked previously.
But go ahead.
THE WITNESS: I do see the phrase "pharmaceutically acceptable salts of gamma-hydroxybutyrate."
BY MR. CALVOSA:
Q And there, it's your opinion that a person of ordinary skill in the art would understand "gamma-hydroxybutyrate" to mean "gamma-hydroxybutyric acid"?
MR. YUE: Misstates the witness's testimony. Vague. Form.
THE WITNESS: As I already testified at least

Page 99

twice, if you want to, there is nothing wrong with saying "salt of gamma-hydroxybutyrate." But a more precise way of stating that would be "salts of gamma-hydroxybutyric acid." But there's nothing wrong with saying "salts of gamma-hydroxybutyrate."
BY MR. CALVOSA:
Q How do you have a salt of the negatively charged or anionic form of gamma-hydroxybutyric acid?
MR. YUE: Objection. Form. Vague.
THE WITNESS: Strictly speaking, you have a salt of gamma-hydroxybutyric acid, as I explain in my declaration; but it is understood that when the statement is a salt of gamma-hydroxybutyrate, that's what that means.
BY MR. CALVOSA:
Q Even though it says "gamma-hydroxybutyrate" and not "gamma-hydroxybutyric acid"?
MR. YUE: Objection. Form and vague.
THE WITNESS: Well, if it said "salt of gamma-hydroxybutyric acid," there would be nothing to understand there. Okay?
But since it says "salt of gamma-hydroxybutyrate," it is understood that that is synonymous with "salts of gamma-hydroxybutyric acid."
BY MR. CALVOSA:

Page 100

Q And if you --
A And, by the way, I might add that this is the expression that is used both by Jazz and by Avadel in their respective proposed claim constructions --
Q If --
A -- and by Dr. Little in his declaration, repeatedly.
Q Well, you understand it's Dr. Little's opinion that the term "gamma-hydroxybutyrate," the plain and ordinary meaning, refers to more than just the negatively charged or anionic form of gamma-hydroxybutyric acid unbound; right?
A I do. But, nevertheless, he agrees with the use of the term -- he doesn't disagree with the use of the terms of "salts" -- in fact, uses himself terms such as "salts of gamma-hydroxybutyrate."
Q If you were to have -- if you selected the sodium oxybate as your sustained release portion, is it your opinion, then, that there could never be a release of gamma-hydroxybutyrate?
MR. YUE: Objection. Vague.
THE WITNESS: They could never be a release of its, i-t-s, gamma-hydroxybutyrate. There is a claim term "its."
So in my view, as I state in my declaration,

Page 101

formulation cannot release something that it doesn't have in the first place; and, therefore, it wouldn't meet the "its" claim limitation.
BY MR. CALVOSA:
Q So there would be a release of gamma-hydroxybutyrate, just not its gamma-hydroxybutyrate?
A There will be ultimately -- no. There will ultimately be a formation of a gamma-hydroxybutyrate in the third step of the process that I outlined, but the -- but the gamma-hydroxybutyrate formed in that third process would not meet the "its" claim limitation.
Q Where does the "gamma-hydroxybutyrate," as you've defined the term, come from?
A It comes from sodium gamma-hydroxybutyrate, from its dissociation in the third step of the three-step process that I previously outlined.
Q Do you know what Xyrem is?
MR. YUE: Objection. Scope.
You can answer.
THE WITNESS: It's a pharmaceutical product, yes.
BY MR. CALVOSA:
Q Had you ever heard of Xyrem before your engagement on this case?
A I think so.

Page 102

Q In what context?
A I don't remember.
Q Why did you say "I think so"?
A Just as I sort of dig into my memory, I mean, that sort of seems to be my recollection, that I've heard of it before.
Q You don't prescribe any pharmaceutical products; right?
A I'm not a physician, so therefore, I'm not allowed to prescribe any pharmaceutical products, nor would I ever violate that rule.
Q Okay. Would you agree with me that Xyrem is an oxybate drug?
MR. YUE: Objection. Vague.
THE WITNESS: Xyrem is a drug where the active ingredient is sodium oxybate dissolved in water.
BY MR. CALVOSA:
Q Okay. Do you think it would be imprecise to say that Xyrem is an oxybate drug, as you understand that term?
A I mean, since it's an aqueous solution of sodium oxybate in which sodium oxybate dissociates into the corresponding cation and anion, I don't necessarily think that it will be imprecise, but I think it's just more descriptive to say that it's an aqueous solution of

Page 103

sodium oxybate.
Q Are you familiar with Avadel's FT218 product?
MR. YUE: Objection. Scope.
THE WITNESS: I mean, I have some familiarity with it from my prior discussions with counsel. Certainly not from recent discussions with counsel.
BY MR. CALVOSA:
Q Do you have an opinion on whether FT218 is an oxybate drug?
MR. YUE: Objection. Vague. Scope.
THE WITNESS: I have only -- I'm sorry. I have only a vague recollection of that, so I have no opinion.
BY MR. CALVOSA:
Q Okay.
A Perhaps I would form an opinion if I continue my involvement in this case and continue my investigation, but at this time, I have no particular opinion.
Q Did you see in Dr. Little's declaration, which you have, top left-hand corner there if you'd like to look at it, his discussion of the file histories or the patent prosecution of the Sustained Release patents and what you call the Resinate patents?
A Yes, I recall that.
Q You did not provide any response to

Page 104

Dr. Little's discussion of the file histories in your declaration; is that right?
A Not expressly, no, as I recall.
Q Did you implicitly reply?
MR. YUE: Objection. Vague.
THE WITNESS: I mean, some of the statements that I made in my declaration are, at least to some extent, responsive to what Dr. Little said, but I don't believe that I expressly discussed the prosecution histories.
BY MR. CALVOSA:
Q Why not?
A I didn't see any need for that.
Q Do you understand that the prosecution histories should be considered by a POSA as part of the claim construction process?
A Yes, and I did consider it. But in this particular case, in my judgment, the meaning of the claim term "gamma-hydroxybutyrate" was quite clear from the clear language of the claims and the specification; and, therefore, there was no need to invoke anything that I saw in the prosecution histories.
Q Do you remember reviewing from the prosecution history a declaration of one of the inventors, Clark Allphin?
A Yes, I do.

Page 105

Q And do you remember that when he was talking about the Sustained Release portion, he said the Sustained Release portion contains GHB as sodium oxybate?
MR. YUE: And I'll just note for the record, if the witness would like to --
MR. CALVOSA: Sure.
MR. YUE: If you'd like to, sort of, direct the witness to where it is, that would be helpful --
THE WITNESS: Yeah.
MR. YUE: -- to answer the question.
THE WITNESS: Yeah. I remember that I reviewed his declaration. I certainly don't remember the content of his declaration. So if you intend to ask me any questions about it, I would need to rereview it.
(Whereupon Exhibit 9 was marked for identification.)
BY MR. CALVOSA:
Q There you are.
And what I've marked as Klibanov 9 is Exhibit 23 to Jazz's opening brief, and it is the March 5th, 2020 declaration of Clark Allphin from the '488 patent file history.
A Okay. So you -- are you instructing me to read this declaration?

Page 106

Q Whatever you need to read. I'm referring to paragraph 13 specifically, but feel free to read whatever you need to.
A Okay. Well, I'll start with paragraph 15, and we'll take it from there.
Okay. I briefly reviewed paragraph 13.
Q Do you see at the beginning he's referring to the dissolution profile of the sustained release portion of a GHB formulation meeting the limitations of the claims?
A Yes.
Q And then he says, "The sustained release portion contains GHB (as sodium oxybate)"?
A Yes.
Q Okay. So he's using "GHB" there to refer to sodium oxybate?
MR. YUE: Objection. Form. The document speaks for itself.
THE WITNESS: He says what -- what he says. He says, "The sustained release portion contains GHB (as sodium oxybate)." That's what he says.
BY MR. YUE:
Q And that's how a POSA would understand it?
MR. YUE: Objection. Misstates the witness's testimony. Form.

Page 107

THE WITNESS: I think a POSA at least would read the -- Mr. Allphin's declaration in its entirety and then would think about it.
BY MR. YUE:
Q Well, sir, you had the opportunity to read this declaration in its entirety and respond to it as part of your declaration in this case.
You understand that?
A I do understand that, and I just explained to you why I didn't do it, because there was no need for me to do it since the meaning of the claim term "oxybate" or "gamma-hydroxybutyrate" was clear from the plain language of the claims of the asserted patents and the definition that was provided in the Resinate patents and the specifications of the asserted patents. And, therefore, there is no need to invoke anything from the prosecution history, of which I understand Mr. Allphin's declaration is a part.
Q Okay. So your opinion is that the Court shouldn't look to the prosecution history at all?
MR. YUE: Objection. Misstates the witness's testimony. Form.
THE WITNESS: We both know that that's not my opinion, and I just find it offensive that you would state the question the way you stated it.

Page 108

I don't give advice -- I mean, I don't give directions to the Court, sir. Okay? The Court will do what the Court sees fit.
BY MR. YUE:
Q I agree.
A Well, but you just said -- you just implied in your question that I'm directing the Court to do something, and I think it's offensive. Okay?
Q If it's offensive to you, that's fine.
A That's fine. Okay?
I -- I don't give any -- the Court knows what to do. Okay?
Q Okay.
A The Court doesn't need me --
Q So let me ask you --
A No, excuse me.
Q -- another question.
A Let me just finish -- unless you want to withdraw your question, let me finish the question that you did ask.
Q Go ahead.
A Okay? Do you --
Q No. No. No. Come on.
A Okay. Yeah.
The -- everything should be considered, okay,

Page 109

the -- the claim -- in the order of the claim language. If there is any lexicographic definition that's provided, then the specification and the prosecution history. So everything should be considered, and then the judgment should be made based on those.

And if the meaning of the claim terms, such as the claim term "gamma-hydroxybutyrate," is clear from the plain language of the claim, the lexicographic definition, and this specification, then there is no need to invoke anything. And in this particular case, I didn't see anything in the prosecution history that would need to be invoked in addition to that.

Q Okay. My question is:

Do you have an opinion on how a POSA would understand the inventor to be using GHB when he says "as sodium oxybate"?

MR. YUE: Objection. Form. Outside the scope of his testimony.

THE WITNESS: In my answer that I already provided once, but will be happy to provide again just to be helpful, is that as a first step towards answering this question, I would need to reread at least the entirety of Mr. Allphin's declaration.

BY MR. YUE:

Q Sir, you had the opportunity to do that before

Page 110

today.

A I did, and I did not -- and I did not commit it to memory.

Q Okay. You see later in that paragraph where Mr. Allphin then says, "The sustained release portion released less than 10 percent of its GHB," as you put it, and it's referring back to the sodium oxybate?

A What do you mean, its GHB, as I put it? I didn't say --

Q You emphasized its GHB --

A -- its GHB --

THE STENOGRAPHER: Please speak one at a time.

BY MR. YUE:

Q -- when we were talking about the claim, sir.

A You said in the very beginning -- I am grateful for that -- that we should not talk over each other.

Q Sir, I don't need a lecture. I would like an answer to my question.

A Are you done?

Q Sir, will you answer my question?

A I will answer your question. But, first of all, I will say that it's disrespectful to interrupt -- to interrupt, and it is certainly not helpful to Kayla here, who has a difficult job to do.

Page 111

And, now, to answer your question, I did not say "its GHB." I said "its gamma-hydroxybutyrate."

Q Sir, your opinion is, is that GHB and gamma-hydroxybutyrate have different meanings?

MR. YUE: Objection. Misstates the witness's testimony. Vague.

THE WITNESS: If you are talking about the context of Mr. Allphin's declaration to -- as I already indicated now three times, in order to opine on the meaning of things in Mr. Allphin's declaration, I would, at the very least, need to review -- rereview Mr. Allphin's declaration, which I did review at some point, did not commit to memory, and which, in my judgment, is not immediately germane to the meaning of the claim term "gamma-hydroxybutyrate."

BY MR. YUE:

Q Would you be willing to come testify live at a claim construction hearing in Delaware?

MR. YUE: You -- you can answer the question.

THE WITNESS: I have not thought about it. If asked to do so, I don't see why not.

BY MR. YUE:

Q Okay.

A And when I said when -- "if asked to do so," I didn't mean by you. I meant by either invited to do so

Page 112

by the Court or asked to do so by counsel for Avadel.

Q Okay. We'll subpoena you. That's fine.

Do you know if a court has ever critiqued your opinions?

MR. YUE: Objection. Vague.

THE WITNESS: I mean, over the entire period of time that I have served as an expert witness, so the last 30, 35 years?

Is that what you're referring to?

BY MR. YUE:

Q Yeah. That's what "ever" means, sir.

A I know that on -- in some instances, the courts have disagreed with my opinion, which is certainly fine. I am not an attorney. I respect the court's opinion, whatever it is.

Q Have you ever read any opinions -- court opinions that discuss your testimony as being unsupported?

A I don't remember.

Q Have you ever read any opinions that describe your testimony as being not credible?

A I certainly don't remember that. I -- and I would have remembered if I read something like that.

Q Why don't you take time now to review the entire declaration, and then I have a couple more

Page 113

questions on it.
A Sure.
Okay. I briefly reviewed it.
Q Do you see in paragraph 1 where the inventor says, "At Jazz, I have been working on gamma-hydroxybutyrate/GHB-related projects for more than ten years and attend GHB-related U.S. patents"?
A Yes.
Q And a POSA would understand there that the inventor's abbreviating gamma-hydroxybutyrate as "GHB"?
A Not the anion.
Q Okay.
A Not the -- the anion of the electrostatic charge of minus 1.
Q Okay. So the inventor there is not using gamma-hydroxybutyrate to mean the anion of the electrostatic charge of minus 1; right?
A The --
MR. YUE: Objection. Form.
THE WITNESS: The inventor, Mr. Allphin, throughout his declaration that I just briefly reviewed, uses the term "GHB" inconsistently.
In some cases, it appears he uses it to mean the gamma-hydroxybutyrate anion of the electrostatic charge of minus 1. In some other cases, he demonstrably

Page 114

does not do that.
BY MR. YUE:
Q Okay. And one of the cases he demonstrably does not do that is paragraph 13, when he's talking about a dissolution profile of a sustained release portion of a GHB formulation, meaning the limitations of the claims; right?
A It's possible, but when I said that he demonstrably does not do that, I actually specifically referred to paragraph 7 --
Q Okay.
A -- of his declaration.
Q And where in paragraph 7 does he demonstrably not do that?
A In paragraph 7, in the fifth line, he says 900 -- I'm sorry. Hold on a sec.
He talks about 900 milligrams of GHB. And as both Dr. Little and I agree, you cannot have a solid that is the gamma-hydroxybutyrate anion with the electrostatic charge of minus 1; and, therefore, you cannot weigh it out.
Q So if it's being weighed out in milligrams or grams, then it's a solid that can't be the negatively charged or anionic form of gamma-hydroxybutyric acid?
MR. YUE: Objection. Vague. Form.

Page 115

THE WITNESS: The anion of the electrostatic charge of minus 1 cannot exist in a solid form, and, therefore, cannot be weighted out.
BY MR. YUE:
Q Not in milligram amounts?
A Pardon?
Q Not in milligram amounts?
A You cannot weigh it out, including in milligram amounts or gram amounts or whatever.
Q And if you turn to paragraph 13, there, the inventor's using "GHB" refer to sodium oxybate again; right?
MR. YUE: Objection. Form. Document speaks for itself.
THE WITNESS: No. It says, "The sustained release portion contains GHB (as sodium oxybate)."
So it's not clear, actually, what -- given the inconsistent use that -- prior inconsistent use that I just explained, it's not entirely clear what he means by "GHB" -- excuse me -- by "GHB" in this particular case.
BY MR. YUE:
Q How would a POSA understand it?
A I think that the POSA would be equally confused because the POSA would also see the inconsistent use of the term "GHB" in the prior portions

Page 116

of Mr. Allphin's declaration.
Q And your opinion is a POSA would not know, when it says he puts sodium oxybate in the sustained release portion, whether its GHB -- in paragraph 13, second-to-last line -- refers to the sodium oxybate that was put into the sustained release portion?
MR. YUE: Sorry. Sorry. Frank, where are you reading?
MR. CALVOSA: In paragraph 13.
MR. YUE: Where in the paragraph? Just --
MR. CALVOSA: Second-to-last line.
THE WITNESS: I'm sorry. Which one?
BY MR. YUE:
Q Second-to-last line of paragraph 13.
A I think that, again, given the inconsistent use of the term "GHB" in Mr. Allphin's declaration, a POSA would not be clear on that and, therefore, would not have a clear understanding of what exactly Mr. Allphin is referring to here.
Q Isn't it possible that you're just wrong, and that all the prior art inconsistent usages and all the patent inconsistent usages and all the declaration inconsistent usages is just how a person of ordinary skill in the art used the term "GHB" at the time?

Page 117

MR. YUE: Objection. Vague. Form.
THE WITNESS: Okay. I already explained that nobody's inviolable. Okay? I'm -- I'll be the first to admit that I'm not perfect.
So to me, frankly, the question, isn't it just possible that you're wrong, doesn't make a lot of sense. I don't believe that I am wrong. I clearly explained the reasons for my opinions in my declaration.
And, regardless, whatever common usage may have been and whatever confusion may have existed in the literature, the claims have to be clear to a person of ordinary skill in the art.
I'm specifically opining, as I made very clear in the beginning, I hope, that my opinions are limited to the meaning of the claim term "gamma-hydroxybutyrate."
I'm not opining necessarily on the meaning of the term "gamma-hydroxybutyrate" as it has been used by various individuals. I'm specifically opining on what the meaning of the claim term "gamma-hydroxybutyrate" or "oxybate" is in the context of the asserted patents.
MR. YUE: Okay. And with that, why don't we break for lunch.
THE VIDEOGRAPHER: We are off the record. The time is 1:27 p.m.

Page 118

(Recess was taken at 1:27 p.m. until 2:04 p.m.)
THE VIDEOGRAPHER: We are back on the record. The time is 2:04 p.m.
BY MR. CALVOSA:
Q Welcome back, Dr. Klibanov.
A Thank you, sir.
Q Hopefully you had a nice lunch.
If I could ask you now to go to what I had marked earlier as Klibanov 1. It's that big document to your left.
A Oh, okay.
(Whereupon Exhibit 1 was marked for identification.)
BY MR. CALVOSA:
Q And is that the -- or do you recognize as the opening expert report that you submitted in this case for what you call the Resinate patents?
A It seems to be my opening expert report in this case, and on page 95, there's what seems to be a facsimile of my signature.
Q Okay. Did you review this report in preparation for your deposition today?
A I did not.
Q Okay. When is the last time you looked at

Page 119

this report?
A Well, it was signed -- it was signed on January -- January 17th, 2023. I certainly haven't looked at it since.
Q Do you have any reason to believe that there's any inaccurate opinions from you in this report?
MR. YUE: Objection. Vague.
THE WITNESS: I mean, I'm sure that the opinions expressed there were to the best of my knowledge as of January 17, 2023.
BY MR. CALVOSA:
Q Okay. If you turn to -- you can actually stay almost where you were -- to page 94 and read paragraph 313. And you might need to read 312 for context, so feel free to do so.
A I may need to read a lot more than just 312 for context, but I will start there.
Okay.
Q Do you see in paragraph 313, about the third line down to the fourth line, you say, "As of the time" of those -- or "As of the time those references were published, GHB was known to be a hygroscopic drug"?
A I do see that sentence, yes.
Q Your use of "GHB" there refers to not the negatively charged on anionic form of

Page 120

gamma-hydroxybutyric acid; right?
A I don't remember. I would need to take a look at some other portions of my expert report. I don't remember. I submitted this expert report many weeks ago. I haven't looked at it since. I just really don't recall.
Q Well, given what you said about GHB, as you understand the term and you offer the opinion in your claim construction declaration, that it's a negatively charged or anionic form of gamma-hydroxybutyric acid, this statement wouldn't be correct; right? Because you say, "GHB was known to be a hygroscopic drug."
A Well, I don't know how I define -- I don't remember now how I define "GHB" in the context of my January 17 expert report.
So the opinions that I expressed previously concern the claim term "gamma-hydroxybutyrate" in the context of the asserted patents, but I don't remember right now, just -- looking just at paragraph 313 on page 94, what abbreviation "GHB" was referring to.
Q Okay. "GHB," as you use it in paragraph 313, based on your repeated testimony earlier today, cannot mean the negatively charged or anionic form of gamma-hydroxybutyric acid; right?
A As I mentioned earlier, strictly speaking,

Page 121

hygroscopicity refers to solid substances, and the gamma-hydroxybutyrate anion with an electrostatic charge of minus 1 cannot exist in a solid form.
Q Okay. So then as you use "GHB" in that paragraph, it cannot be referring to gamma-hydroxybutyrate anion with an electrostatic charge of minus 1?
A It certainly would not be precise and -- but, again, I would need to take a look at, at least, what I use this abbreviation, "GHB," in my opening expert report for.
Q If you turn to page -- sorry -- to paragraph 168. And you might need to look at paragraph 167 and whatever else you need for context.
Does that tell you what you're using the abbreviation "GHB" for?
A I'm sorry. What paragraph?
Q 168, when you talked about the claim formulation of GHB disclosed in claim 1.
A No. I mean, I don't -- it doesn't say what the abbreviation "GHB" refers to here.
Q Sir, it refers to the claim formulation of GHB disclosed in claim 1. And do you see the paragraph immediately preceding that is claim 1, where it says "a formulation of gamma-hydroxybutyrate"?

Page 122

A Let me just -- this is the formulation of claim 1 of what patent?
Q This is the '782 patent, sir.
A So it's the second one of the Resinate patents; is that correct?
Q The second one of what you call the Resinate patents. Yes, sir.
A I mean, I -- I just really don't remember the -- the whole context of -- of the discussions -- discussion in my opening expert report, and I would need to rereview it to refresh my memory and ideally not under the stress of a deposition.
Q You don't think you used "GHB" as an abbreviation for "gamma-hydroxybutyrate" in your opening report?
A It very well may be that I have, but I -- I just don't specifically recall the -- the context of that and if there were any conditions imposed on that. I mean, I just don't recall the -- certainly, paragraph 168 says what it says. I see no reason to suspect that it's inaccurate in any way, but I would really need to put it in the proper context, as I said. I have not looked at this report in many weeks.
Q I think we should have some time at the end. And I'm happy to have you start reading from the

Page 123

beginning. I think that's actually more important than the '488.
A Okay.
Q But let's just go through some other questions first and see if you can answer.
In paragraph 169, you say Liang 2006 is directed to an oral solid dosage form of GHB, and then you quote "containing an immediate release component of" -- and in brackets, you put "GHB -- "and one or more delayed/controlled release components of" -- again, brackets, "GHB." And you cite the abstract of Liang 2006.
Do you see that?
A I do.
Q Based on your opinion of what gamma-hydroxybutyrate means, if we look at the abstract of Liang, we should see it say there "the negatively charged or anionic form of gamma-hydroxybutyric acid."
Is that fair?
A It's --
MR. YUE: Objection. Form.
THE WITNESS: It's actually unfair because you said based upon your opinion of what gamma-hydroxybutyrate means. Okay? And that's a -- a -- that's not an accurate representation of my opinion.

Page 124

I have an opinion of what the claim term "gamma-hydroxybutyrate" means in the context of the claims of the asserted patents. That is what my opinion is. Okay?
I do not opine on what the term "gamma-hydroxybutyrate" means because, as we discussed previously, it's been used by different people to mean some different things.
BY MR. CALVOSA:
Q I'm happy to go through each individual one, but before I do, do you know, sitting here today, whether you used the term "gamma-hydroxybutyrate" repeatedly within your reports to refer to gamma-hydroxybutyric acid?
A I don't -- do not recall one way or the other.
Q Okay. Sitting here today, do you know whether you used the term "gamma-hydroxybutyrate" in your report to refer repeatedly to sodium gamma-hydroxybutyrate?
A I do not recall one way or the other. As I just said, I haven't looked at this report in many weeks.
Q When you say in your report that a prior art reference explicitly discloses claim limitations, what do you mean by that?
A Where -- where are you reading?

Page 125

Q Sure. In paragraph 170.
A Okay. Well, for starters, let me read paragraph 170 to myself.
Okay. So what was the question?
Q When you say that Liang 2006 explicitly discloses all of the claim limitations in claim 1 other than the viscosity-enhancing agent and acid that are separate from the immediate release particles and modified release particles, what do you mean by "explicitly discloses"?
A Expressly discloses.
Q And what do you mean by that?
A It says exactly that.
Q Okay.
A But, again, that's just meaning of the word "explicitly." But, you know, in terms of what that particular statement means, again, I would need to see the context of that.
Q Sure.
And claim 1 requires -- and you can look at paragraph 167 -- a formulation that has a plurality of immediate release particles comprising gamma-hydroxybutyrate and a plurality of modified release particles comprising gamma-hydroxybutyrate.
Do you see that?

Page 126

A I do see that. Right.
Q And your opinion is that "gamma-hydroxybutyrate" within that claim means the negatively charged or anionic form of gamma-hydroxybutyric acid unbound to anything; right?
A Since this is a claim in the Resinate -- in one of the Resinate patents, my opinion is that the meaning of this claim term "gamma-hydroxybutyrate" is that it is the gamma-hydroxybutyrate anion with an electrostatic charge of minus 1.
(Whereupon Exhibit 10 was marked for identification.)
BY MR. CALVOSA:
Q Okay. I'm going to hand you what I've marked as Klibanov 10. This is Liang 2006.
A Okay.
Q Okay. As support for this explicit disclosure of a GHB formulation in paragraph 169, you cite the abstract, "For an immediate release component of [GHB] and one or more delayed/controlled release components of [GHB]."
A That's what it says. That's what the first sentence of paragraph 169 says.
Q Okay. Can you please look at Liang 2006, what I've marked as Klibanov 11, the abstract.

Page 127

A Okay.
Q What you have bracketed as gamma-hydroxybutyrate in your report, what does it actually say in the abstract of Liang 2006?
A On two occasions, it uses the term "gamma-hydroxybutyric acid."
Q Nowhere in there does it say "the negatively charged or anionic form of gamma-hydroxybutyric acid"; right?
A The abstract does not talk about charges.
Q So when you prepared this report, you weren't using the term "gamma-hydroxybutyrate" then as you are today?
MR. YUE: Objection. Form.
THE WITNESS: I don't remember how I used it. And, as I just said, I haven't looked at this -- my opening expert report in many weeks, and I have not looked at Liang in as many weeks.
So I really cannot pass any judgment beyond just saying whether paragraph, let's say, 169, says what it says or does not say what it says.
BY MR. CALVOSA:
Q And if you could go to paragraph 207 of your report and take a look at that, please.
A Just a second. Paragraph what?

Page 128

Q 207.
A Okay. Let me just read it to myself.
Okay. I read it.
Q And there, you say, "It would have been obvious for a POSA to use an acid in a GHB formulation because it was disclosed in the prior art."
Do you see that?
A I do see that sentence, yes.
Q And for that disclosure in a GHB formulation, you're citing to salts of gamma-hydroxybutyric acid in paragraph 72 of Liang 2006; right?
MR. YUE: Objection. Document speaks for itself.
THE WITNESS: I mean, it says what it says. You obviously paraphrased what I say there.
But, again, I cannot go beyond what I expressly stated in this paragraph because I just don't remember the context, and it's a paragraph that's lifted out of a middle of a section.
BY MR. CALVOSA:
Q In that paragraph, it does not say for the GHB formulation a negatively charged or anionic form of gamma-hydroxybutyric acid?
MR. YUE: Objection. Document speaks for itself.
THE WITNESS: It says what it says. It doesn't say what it doesn't say.

Page 129

That's all I can tell you.
BY MR. CALVOSA:
Q Okay. Sir, I cannot find one instance of you referring to the negatively charged or anionic form of gamma-hydroxybutyric acid as gamma-hydroxybutyrate in your opening expert report that's 95 pages.
Does that sound accurate?
A Is there a question pending, or you're just sharing your -- your memory?
Q It's not my memory, sir. It's the fact of it. But I'm asking you, does that sound accurate, as I just did?
MR. YUE: Objection. Form.
THE WITNESS: I mean, I cannot tell you that without rereviewing the opening expert report.
BY MR. CALVOSA:
Q Sitting here today, you don't know one way or another whether you use the term "gamma-hydroxybutyrate" to refer to the negatively charged or anionic form of gamma-hydroxybutyric acid in your 95-page opening expert report?
MR. YUE: Objection. Form.
THE WITNESS: You're saying the term or the claim term?

Page 130

BY MR. CALVOSA:
Q The claim term, sir, which you repeatedly refer to in your report.
A The -- the claim -- the claim term of the asserted patents?
Q Of the asserted patents. The ones you said that those elements were disclosed in the prior art --
A Yeah.
Q -- do you know, sitting here today -- let me -- let me tell you something.
Do you know what's in your opening report at all?
A As I -- as I already told you repeatedly, I have a very vague recollection of what's in my opening report because I haven't looked at it in many weeks.
Q Okay.
A And I said it, like, at least four times.
Q Do you recall whether you opined that certain of the '079 and '782 claim limitations, including the gamma-hydroxybutyrate and oxybate claim limitations, were disclosed in the prior art?
MR. YUE: Objection. Form.
THE WITNESS: I do not recall one way or the other.
BY MR. CALVOSA:
Q So you can't recall one way or another whether

Page 131

you ever refer to "gamma-hydroxybutyrate," whether the claim term or just the term itself, as the negatively charged or anionic form of gamma-hydroxybutyric acid in your report?
MR. YUE: Objection. Form.
THE WITNESS: I do not recall that one way or the other because I haven't looked at my opening expert report in many weeks.
BY MR. CALVOSA:
Q If you could turn to paragraph 40 through 41 of your report.
A 40 or 41?
Q 40 through 41, sir, referring to Allphin 2012, and read those paragraphs to yourself, please.
A Sure.
Yes, sir.
Q And in paragraph 41, you say, "Allphin 2012 discusses various difficulties with formulating GHB to 'provide prolonged delivery.'"
Do you see that?
A I do, but you didn't read it correctly.
Q Okay. Let me try it again.
"Allphin 2012 discusses various difficulties with formulating GHB to 'provide prolonged delivery.'"
A I do see it, and now you did read it

Page 132

correctly.
Q When you used "GHB" there, were you referring to the negatively charged or anionic form of gamma-hydroxybutyric acid?
A As I indicated on a number of occasions already, I haven't looked at my opening expert report in many weeks; and I, therefore, am not in a position to opine on what I meant in a particular paragraph on a particular page of that expert report at this time.
Q Sir, if that's what "gamma-hydroxybutyrate" means to you, wouldn't that be how you would use it in your report?
MR. YUE: Objection. Argumentative. Vague.
THE WITNESS: I have nothing to add to what I just said.
BY MR. CALVOSA:
Q Next sentence, you write, "It teaches that 'GHB is very soluble, generally requires a relatively high dose, has a low molecular weight, and exhibits a short circulating halflife once administered.'"
Do you see that, sir?
A I do.
Q Being that's discussing GHB being very soluble, and based on your repeated answers earlier today, that would not be referring to the negatively

Page 133

charged or anionic form of gamma-hydroxybutyric acid; correct?
MR. YUE: Objection. Vague.
THE WITNESS: Okay. So, first of all, the term "GHB" that I use in this sentence that you just read, it was taken directly from Allphin 2012, so it's not my language. It's the language that Mr. Allphin used in his application.
And, second of all, as I already indicated with respect to your previous question, I haven't reviewed my opening expert report in many weeks; and, therefore, I am not in the position right now to opine one way or the other what I meant by a particular statement or sentence.
BY MR. CALVOSA:
Q How would a POSA understand that gamma-hydroxybutyrate and GHB is very soluble taken from Allphin 2012, as you pointed out?
MR. YUE: Objection. Scope. Vague.
THE WITNESS: I mean, in the case of -- both gamma-hydroxybutyric acid and sodium gamma-hydroxybutyrate are both very soluble.
BY MR. CALVOSA:
Q And as we established earlier, a POSA would not understand that the negatively charged or anionic

Page 134

form of gamma-hydroxybutyric acid is "very soluble"; right?
MR. YUE: Objection. Vague.
THE WITNESS: Strictly speaking, a person of ordinary skill in the art would not refer to water solubility of an ion -- two words, an ion. One would refer to water solubility of a particular compound, such as, for instance, sodium gamma-hydroxybutyrate.
BY MR. CALVOSA:
Q Next sentence in paragraph 41 of your report, "Allphin" -- you say, "Allphin 2012 also teaches that single dose of GHB can have 'a range of about 500 milligrams to about 12 grams of drug.'"
Do you see that, sir?
A I do.
Q And based on your testimony earlier today about weighing out GHB, that there cannot refer to the negatively charged or anionic form of gamma-hydroxybutyric acid; right?
A Not necessarily. As I said, people use -- sometimes use terms loosely, imprecisely. So I don't know what it refers to, so I certainly would not say it cannot possibly refer to that. It depends on what -- you know, what the context is here and whether the term is used precisely or loosely.

Page 135

Q Do you have any opinions on how Allphin 2012 uses the term "gamma-hydroxybutyrate"?
A I --
MR. YUE: Objection. Oh, sorry.
THE WITNESS: Sorry.
MR. YUE: Objection. Scope. Vague.
THE WITNESS: I have not looked at Allphin 2012 in many weeks, so I -- I don't specifically recall one way or the other.
BY MR. CALVOSA:
Q When's the last time you looked at the specification of the '488 patent?
A Of which patent?
Q The '488 patent.
A I don't think I reviewed it in its entirety, but I looked at it maybe a few weeks ago -- I'm sorry -- a few days ago.
Q When's the last time you reviewed the specification of the '488 patent in its entirety?
A I don't remember.
Q When is the last time you reviewed Allphin 2012 in its entirety?
A I don't remember.
Q Do you know that Allphin 2012 is the published patent application that's the specification of the '488

Page 136

patent?
A Yes.
Q Okay. If I go through and ask you about your use of "gamma-hydroxybutyrate" or "oxybate" in your expert report, would your answer be the same, that you don't remember how you used it, for each time I ask?
A If you're referring to my opening expert report, then, yes, I will just say that it's been many weeks since I even looked at it; I certainly haven't thought about it in connection with this deposition; and, therefore, I cannot offer any opinion without reading the entirety of the document and thinking about it.
Q Okay. Can you go now to your declaration in support of Avadel's claim construction?
A That's Exhibit C; correct?
Q Exhibit C. Yes, sir.
A Yes, sir.
Q And I misplaced mine, so just give me one second.
A Take your time.
Q While I'm looking for that, I want to ask you a couple questions about sodium gamma-hydroxybutyrate.
A Please.
Q The sodium cation, is that a very strong

Page 137

cation?
MR. YUE: Objection. Vague.
THE WITNESS: The expression "strong cation" makes no scientific sense.
BY MR. CALVOSA:
Q Okay. Would you call it a heavy cation?
A Heavy compared --
MR. YUE: Same -- same objection.
THE WITNESS: I'm sorry.
Heavy compared to what?
BY MR. CALVOSA:
Q Just in general, in absolute terms.
MR. YUE: Objection. Vague.
THE WITNESS: Again, question makes no sense to me.
BY MR. CALVOSA:
Q Okay. Is oxybate, as you've defined it, a weak anion?
MR. YUE: Objection. Vague.
THE WITNESS: I didn't -- I defined the claim term "gamma-hydroxybutyrate." Okay? That's the first thing.
And, second of all, I don't know what you mean by "weak anion."
BY MR. CALVOSA:
Q You've never heard the term "weak anion"?
A I've heard the term "weak acid." I've heard

Page 138

the term "weak base." But I don't think I've heard the term "weak anion."
Q Have you ever heard the term "strong anion"?
A I don't think so.
Q Okay. Same thing. No "strong cation"?
A Same -- exactly. Same answer.
Q No "weak cation"?
A Yeah. There are weak bases. There are strong bases. There are weak acids. There are strong acids. But not anions or cations.
Q If you could look at paragraph 10 in your declaration.
A Reading it to myself.
Okay.
Q Do you see you provided a -- I'll call it a picture, just to make it easier for the Court, of sodium oxybate?
A I wouldn't call it a picture. I would say that it's a depiction of the chemical structure of sodium oxybate.
Q Okay. So in paragraph 10 of your declaration, you've provided a depiction of the chemical structure of sodium oxybate.
A Correct.
Q Where did you get that depiction from? I see

Page 139

no citation.
MR. YUE: Objection. Form.
THE WITNESS: I mean, that's what the chemical structure -- that's what the chemical structure of this compound is. I didn't think it will be a controversial issue. So I -- I don't remember where I got it, but that's what -- that's what it is.
BY MR. CALVOSA:
Q So, sitting here today, you can't tell me where that depiction of the chemical structure of sodium oxybate came from?
MR. YUE: Objection --
THE WITNESS: No.
MR. YUE: -- form.
THE WITNESS: Just like I cannot tell you if I were to depict the structure of water, of H20, I cannot tell where it comes from. It just is.
BY MR. CALVOSA:
Q That is the depiction of sodium oxybate --
A It's not the depiction. It's a depiction of sodium oxybate, and another possible depiction of sodium oxybate is provided, for example, by Dr. Little in his declaration, and yet another one is provided in the -- just a second -- and yet another one is provided in the specification of the '488 patent, for example.

Page 140

These are all different depictions. And when a person of skill -- of skill in the art reads -- looks at these depictions, he or she would understand that they are -- these are all various equivalent depictions of sodium gamma-hydroxybutyrate.
Q Okay. The depiction of sodium gamma-hydroxybutyrate that's in column 4 of the '488 patent that you're referring to --
A Yeah.
Q -- that has a positive charge on the sodium and a negative charge on the anionic form of gamma-hydroxybutyric acid; right?
A It is expressly depicted there, and it is understood in the structure that I depicted in paragraph 10 of my declaration, yes.
Q But you didn't put the positive and the negative charge there -- right? -- in paragraph 10 of your declaration.
A Because a person of ordinary skill in the art would understand that that will be the case since the sodium atom has a very low electronegativity, and the oxygen atom has a very high electronegativity; and, therefore, the oxygen atom will pull much of sodium's outer shell -- outer shell electron density toward itself.

Page 141

Q And that's why the oxygen has the negative charge and the sodium has the positive charge?
A The --
MR. YUE: Objection. Vague.
THE WITNESS: Oxygen has a partial negative charge, and sodium has a partial positive charge, yes.
BY MR. CALVOSA:
Q Have you ever depicted the chemical structure of sodium oxybate before you did so in paragraph 10 of your declaration in support of Avadel's claim construction?
A It's very possible that I may have depicted it in my opening expert report. Let me take a look at it. That's what I -- something that I vaguely recall.
Q Paragraph 34. I can help you out.
A So why do you ask a question if you already know the answer?
Yes, I depicted it in paragraph 34 of Klibanov Exhibit 1.
Q And in that depiction, before this new claim construction theory, you depicted sodium oxybate with the negative charge on the oxygen and the positive charge on the sodium cation; right?
A With a partial negative charge on the oxygen and a partial positive charge on the sodium. Correct.

Page 142

And I also depicted the bond angles differently, so it's just a different depiction.
Q Well, sir, to be fair, you left out the negative charge and the positive charge in your declaration in support of Avadel's claim construction.
A Well, I just explained to you that these are equivalent depictions, because a person of ordinary skill in the art would know that sodium has a low electronegativity and oxygen has a high electronegativity, so some of the electron density will shift from sodium to oxygen, thereby making oxygen carry a partial negative charge and sodium carry a partial positive charge.
So one of skill in the art would understand that these are equivalent depictions.
Q When you saw ionic compounds, it's proper to draw them with a negative charge and a positive charge; right?
A Not necessarily, no.
Q Okay.
A If I -- if I, for example -- you asked me -- which you didn't. But if you asked me what the -- to write a structure of table salt, for example, which is sodium chloride, I would just write NaCl without any charges, and it will be very proper. I can assure you

Page 143

of that.
Q Okay. I haven't found a depiction anyplace else -- in the exhibits, the expert reports, the patents, evidence label -- that does not have the negative and positive charge for sodium oxybate, so I'll ask you one more time.
Do you know where that depiction that's in paragraph 10 of your report came from?
A And my answer will be the same as it was the previous time when you asked me that very question.
I don't specifically recall, and I, furthermore, reiterate my view that depictions in paragraph 10 my declaration, in column 4 of the '488 patent, in paragraph 34 of my opening expert report, and in Dr. Little's declaration -- declaration are all equivalent depictions of that salt.
Q Why did you put the negative charge on the depiction of the anionic form that follows sodium oxybate?
MR. YUE: Objection. Vague. Dr. Klibanov has answered this question multiple times at this point.
MR. CALVOSA: I'm asking him about a different picture now.
MR. YUE: I --
MR. CALVOSA: I know it's a bad day for you, but --

Page 144

MR. YUE: I disagree.
Go ahead, Dr. Klibanov.
THE WITNESS: Okay. Because in that particular case, it is the electrostatic negative charge of 1.
BY MR. CALVOSA:
Q Where does it say that?
A If you go to paragraph 9 of my declaration, the penultimate sentence of that paragraph specifically says, "Gamma-hydroxybutyrate is a negatively charged ion (also known as an 'anion')" -- the anion is in quotation marks -- "and having an electrostatic charge of minus 1."
And then just to make sure there is no misunderstanding, in parentheses, it says, "i.e., minus 1," closed parentheses. And then it continues.
Q You keep distinguishing between a partial negative charge and a negative charge of minus 1.
Where in any of the references is that distinction made?
A I mean, I -- I -- I don't -- I don't understand you -- what exactly you mean by that question.
I mean, I didn't think there will be any -- in fact, Dr. Little, reading his declaration, it's clear that a negative charge in the oxybate is minus 1, where

Page 145

it is minus 1 as opposed to minus fraction. Okay? It's clear even from Dr. Little's declaration.
Q Where in his declaration does it say minus 1 --
A It doesn't say that. I said -- excuse me, sir. You don't need to be sarcastic. I mean, you know, it's just --
Q Sir, you're taking an aggressive attitude. You get what you get.
Go ahead. Please continue.
A I just want to say that you conduct yourself in a way that I consider disrespectful. I just want to put it on the record.
Q I understand that, sir.
A Okay.
Q I feel the same way about you.
THE WITNESS: Let's take a short break because I -- I think that Mr. Calvosa here needs to calm down.
THE VIDEOGRAPHER: We are going off the record. The time is 2:49 p.m.
(Recess was taken at 2:49 p.m. until 3:01 p.m.)
THE VIDEOGRAPHER: We are back on the record. The time is 3:01 p.m.
BY MR. CALVOSA:

Page 146

Q If you could go to your declaration again --
A May I finish the answer that I started giving you before the break?
Q No. You took a break.
A I started giving you an answer. I said, for example, if we take a look at --
Q Sir, I'm going to ask you a question. You took a break. There's no answering on both sides of the break.
A Okay.
Q You signed your declaration in support of Avadel's claim construction on April 4th, 2023.
Do you see that?
A It is correct.
Q And you received the Little declaration that you respond to on March 24th of 2023; is that right?
A I don't recall when I received it.
Q Okay. Can you take a look at it right there in front of you and tell me what -- what's the date it's signed on?
A It is signed on March 24, 2023.
Q So you couldn't have received it until at least that date.
Is that fair?
A Yes. I certainly couldn't have received it

Page 147

before it was signed.
Q Okay. And in your declaration, you say -- this is paragraph 4 -- "The materials I have reviewed in support of my opinions presented herein include the asserted patents, Jazz's opening supplemental claim construction brief, Dr. Little's March 24, '23, declaration and accompanying exhibits, and all the exhibits to this declaration cited herein."
Is that right?
A That's what that says.
Q Did you review the '488 patent and the '079 and '782 patents between March 24th and the time you signed your declaration on April 4th?
MR. YUE: Objection. Vague.
THE WITNESS: I certainly reviewed at least the claims and some portions of the prosecution histories.
BY MR. CALVOSA:
Q Anything else?
A I'm sorry. And some portions of the specification. I apologize. So let me just repeat to make sure there is no confusion.
I certainly reviewed at least the claims and some portions of the specification of those patents.
Q So when you say you've reviewed the exhibits attached to Dr. Little's declaration, did you review

Page 148

them in full or only certain portions of that?
A No. I reviewed them in full.
Q Okay. So you reviewed the '488 patent in full?
A The '488 patent, I reviewed the claims in full. Since I previously reviewed the specification, I reviewed a substantial portion of the portions -- portion of the specification. I'm not sure it was the entirety of the specification because I -- as I said, I reviewed it repeatedly before.
Q And by "repeatedly," you mean at least two times or three times?
A Correct.
Q Can you go to -- back to Klibanov 1, your opening expert report. And I'd like to point you to paragraph 33.
A Yes, sir.
Q Okay. That's the first instance that we could find in your report of the use of "GHB."
Does that help you understand how you used it in your report?
A It does not. As I said, I have not seen this opening report in many weeks, and I don't have a clear recollection of the context of the statements that I made; therefore, it does not.

Page 149

Q Can you take out what I've marked as Klibanov 2. It should be to your left over there. Okay.
A Okay.
(Whereupon Exhibit 2 was marked for identification.)
MR. CALVOSA: No. That's --
MR. YUE: Is it this one?
MR. CALVOSA: Right.
THE WITNESS: Oh, sorry.
BY MR. CALVOSA:
Q And feel free to review this whole thing. It's short. And then let me know if it's your supplemental expert report that you submitted in this case on January 27, 2023.
A I can tell you, even without reviewing it, that, yes.
Q Okay. And now I'd like you to read the whole thing so I can ask you some questions about it.
A Okay.
MR. YUE: Sorry, Frank. Just before you ask questions --
MR. CALVOSA: Yeah.
MR. YUE: -- let me see if I can find my copy. I don't think you gave me one.

Page 150

MR. CALVOSA: I definitely gave you one.
MR. YUE: I may have given him mine, actually.
THE WITNESS: Okay.
Yes, sir.
BY MR. CALVOSA:
Q In paragraph 5, you're talking about the claim term "acid" within the claims of the '782 patent; is that right?
A Yes.
Q Okay. And then you quote some testimony from Mr. Allphin; is that correct?
A Yes.
Q And then you say, "Mr. Allphin's testimony supports my opinion that a POSA would have been motivated to add an acid separately from the immediate released particles and the modified release particles."
And I'll stop there. You're referring to the immediate release particles and the modified release particles of the claims of the '782 patent; right?
A That's my recollection.
Q And then you continue, "With a reasonable expectation of success, including to more quickly modify the pH surrounding the particles to counteract the strong alkalinity of sodium oxybate in the particles."
Do you see that, sir?

Page 151

A I do.
Q When you wrote this, it was your opinion that the immediate release and modified release particles of gamma-hydroxybutyrate in the '782 patent's claims included sodium oxybate?
A I don't -- again, I haven't looked at that in a number of weeks, so I don't specifically recall what my understanding or view was at that time; but I stand by what I said here, at least as of January 27, 2023.
Q Do you have a different opinion today?
A I have not thought about that. It wasn't relevant to the claim construction issues that I'm testifying on today.
Q Do you know or have you heard the term before "molecular compounds"?
MR. YUE: Objection. Vague.
THE WITNESS: I certainly have heard it. In fact, I've heard it in several different contexts, I think.
BY MR. CALVOSA:
Q Do you understand or have you heard of a molecular compound being a compound with a covalent bond.
A You mean only covalent bonds or containing, among others, covalent bonds?
Q The latter.

Page 152

A Well, if you have both ionic bonds and covalent bonds, I don't think it will be accurate to refer to this compound as a molecular compound because there are ionic bonds there as well.
Q Gamma-hydroxybutyric acid, is that a molecular compound?
A Gamma- --
MR. YUE: Objection. Vague.
THE WITNESS: I'm sorry.
Gamma-hydroxybutyric acid may be viewed as a molecular compound because it contains only covalent bonds.
BY MR. CALVOSA:
Q Is sodium oxybate a molecular compound?
A Sodium oxybate contains both covalent bonds and an ionic bond; and, therefore, I think it would not be proper to refer to it as a molecular compound.
Q Would it be proper -- I apologize.
Would it be proper to refer to sodium oxybate as an ionic compound?
A You can refer to it as an ionic compound as long as it's understood that, in addition to an ionic bond, it also contains a number of covalent bonds.
Q What is a covalent bond?
MR. YUE: Objection. Vague. Outside the scope of

Page 153

his -- of his expert report, but you can go ahead and answer.
THE WITNESS: A covalent bond is a bond created when, for example, two atoms donate an electron to create an electron pair that is shared by these two atoms. Sharing may be equal or unequal, as I say in my declaration, in extreme form of a covalent bond is an ionic bond, but that's what a covalent bond is.
BY MR. CALVOSA:
Q Is the bond that's present between the carboxylic acid and the hydrogen in gamma-hydroxybutyric acid a covalent bond or is it an ionic bond?
A There's no bond between a carboxylic acid and a hydrogen.
Q Okay. Where is the -- where is the bond between the oxygen and the hydrogen located in gamma-hydroxybutyric acid?
A Between -- it is between the -- one of the oxygens of the carboxyl group and the hydrogen.
Q Okay. Let me ask it that way, then.
Is the bond between one of the oxygens in the carboxylic group and the hydrogen a covalent bond or an ionic bond?
A It's a covalent bond.
Q Why isn't it somewhat of an ionic bond as

Page 154

well?
A When you're saying somewhat of an ionic bond, what do you mean by that?
Q Is it your opinion that there -- and I think it is -- that there's no clear distinction between a covalent bond and an ionic bond?
A Well, my opinion is stated in my declaration, so rather than -- and I specifically cite a -- a publication to support that opinion. Just a second. Let me find it for you.
Yes. So as I discuss in paragraph 13 of my declaration, the sentence that in the -- in the middle of that paragraph is, "In this respect, an ionic bond is akin to an extreme case of a covalent bond of the type present in gamma-hydroxybutyric acid that Dr. Little discusses."
And then I cite -- I provide a quote from a textbook, a chemistry textbook, and the quote is, "There is no sharp boundary between ionic bonding and covalent bonding."
Q Did you read the entire section of the textbook from which you quote?
A I did.
Q Okay. Does that discuss gamma-hydroxybutyric acid at all?

Page 155

A I don't think so, no.
Q Does it discuss sodium oxybate at all?
A No.
Q It does not discuss the covalent bond in gamma-hydroxybutyric acid, then?
A It just doesn't discuss anything related to gamma-hydroxybutyric acid or its salt. It's a general discussion of what a covalent bond is.
Q And that general discussion, you think, would be applicable to all ionic compounds?
MR. YUE: Objection. Scope. Vague.
THE WITNESS: I don't understand the question.
BY MR. CALVOSA:
Q Well, do you believe that what you've quoted here, "There is no sharp boundary between ionic bonding and covalent bonding," is applicable to all ionic compounds?
MR. YUE: Objection. Vague.
THE WITNESS: I don't see why it wouldn't be, and it certainly applies to salts of gamma-hydroxybutyric acid.
BY MR. CALVOSA:
Q Okay. Do you know what specific compounds or elements this portion of the text was discussing when it said there's no sharp boundary between ionic bonding and

Page 156

covalent bonding?
A I think it generally discusses it of inorganic chemical compounds.
Q Do you know if it discusses any relationship between the supposed no sharp boundary and the solubility of a compound?
A I don't recall that discussion.
Q Would that influence your opinion at all if it did?
A I don't see why it would. It discusses the nature of the chemical bond. It has nothing to do with the solubility. I mean, this fact -- I'm just citing this chemistry textbook as one, you know, possible source.
I -- what I say here about -- that an ionic bond is an extreme of a covalent bond, I didn't think would be controversial issue. I think it's -- a chemist, in fact, anybody who's taken freshman chemistry -- and I used to teach freshman chemistry at MIT, taught it for many years -- would understand that because that is something that immediately follows from the concept of electronegativity, which is, you know, very well-known and is commonly used and understood.
Q Do you know if that text discusses how the size of the charge on the cation, for example, affects

Page 157

this principle of there being "no sharp boundary between ionic bounding and covalent bonding"?
MR. YUE: Objection. Vague.
THE WITNESS: The principle that is stated there is a general principle. It is not affected by the sizes of the atoms involved.
The sizes of the atoms involved will only affect the extent of the sharing. It will not affect the basic notion that I explain in paragraph 13 of my declaration and substantiate by a representative statement from a chemistry textbook.
BY MR. CALVOSA:
Q My question, sir, was:
Do you know if that text discusses how the size of the charge on the cation, for example, affects the principle of there being "no sharp boundary between ionic bonding and covalent bond"?
MR. YUE: Objection. Vague. Document speaks for itself.
THE WITNESS: And I don't -- my answer is that I don't specifically recall. But even if it's there, it would not affect that general notion.
BY MR. CALVOSA:
Q When did you last read that text?
A I mean, I read that textbook many years ago,

Page 158

but I -- the last time I took a -- took a look at the -- at that chapter, just a few days ago.
Q And you can't recall whether the things I just asked you about are in that textbook or not?
MR. YUE: Objection. Vague. Asked and answered.
THE WITNESS: I don't specifically recall. I mean, my focus was on finding a proper -- finding a statement that would just illustrate the general point that I explained in paragraph 13, and that's what my focus was.
BY MR. CALVOSA:
Q Can you turn to paragraph 15 of your declaration.
A Sure. Yes, sir.
Q What did you mean here when you said "the common usage of gamma-hydroxybutyrate"?
A Which sentence are you referring to?
Q It's the last sentence in there, starts about halfway through, "however."
A And so -- I'm sorry -- what's the question?
Q What were you referring to when you say "the common usage of gamma-hydroxybutyrate"?
A Usage that has been common, meaning that -- something that has been used, for example, some of the publications that we discussed here earlier today. So common usage meaning that's something that has been

Page 159

used.
Q Okay. And what did you -- what did you mean when you were talking about the common usage of gamma-hydroxybutyrate?
A People use this term to mean different things.
Q Like what?
A Like, for example, we talked earlier today about -- so it's Klibanov Exhibit 8, which is the Scharf paper. Sorry. Klibanov Exhibit 7, rather, which is a paper where the first author is Martin Scharf, and -- so he uses "gamma-hydroxybutyrate" inconsistently, and the same is true for -- the same is true for the other paper by Dr. Scharf.
So people sometimes use -- in -- in the literature use "gamma-hydroxybutyrate" to refer to sodium gamma-hydroxybutyrate and sometimes, again, commonly use it in the literature to refer to gamma-hydroxybutyric acid.
Q Sitting here today, have you seen one reference, either Dr. Little's declaration or in what you submitted in this case, other than the Sustained Release patents and -- and the -- what you call the Resinate patents -- I know your opinions on those -- but that uses "gamma-hydroxybutyrate" or "oxybate" to mean the negatively charged or anionic form of

Page 160

gamma-hydroxybutyric acid unbound to anything else?
MR. YUE: Objection. Vague.
THE WITNESS: Yes. I saw a statement in Dr. Little's declaration that essentially states that.
BY MR. CALVOSA:
Q Okay. Can you show me where in Dr. Little's declaration that is.
A Of course.
So let me preface it by saying that, as you know, and both Dr. Little and I specifically stated in our respective declarations, that the negatively charged or anionic -- or anionic form is the same thing as a conjugate base, because conjugate base is in parentheses.
So with that in mind, I would like to invite your attention to footnote 3, which is on page 7 of Dr. Little's declaration, which helpfully defines what a conjugate base is. And it specifically says, "A conjugate base is a reaction product that results when a hydrogen is donated from an acid (here, gamma-hydroxybutyric acid)."
And, of course, when Dr. Little says a hydrogen, more precisely, it is a proton that is donated because an acid cannot donate hydrogen. It can only donate a proton.

Page 161

And when a proton is donated, the proton is a hydrogen ion that is devoid of its sole electron, so it has the electrostatic charge of plus 1. Then, by definition, what is left, which is the conjugate base, has the electrostatic charge of minus 1.

And Dr. Little correctly points out that that specifically applies to gamma-hydroxybutyric acid, meaning that when gamma-hydroxybutyric acid donates its proton, for example, to water or something else, what is left and what is a conjugate base is a species that has an electrostatic charge of minus 1.

Q You understand it's Dr. Little's opinion that a person of ordinary skill in the art would understand that when you talk about that negatively charged or anionic form of gamma-hydroxybutyric acid, that includes when it's within an ionic compound, such as sodium oxybate, as the people in the art say; right?

MR. YUE: Objection. Misstates --

THE WITNESS: I mean --

MR. CALVOSA: If it misstates Dr. Little's opinion, I'm not sure what we're doing here.

MR. YUE: No. No. No. I -- objection that I think it misstates the field, in general, but -- and vague.

But go ahead, Dr. Klibanov.

Page 162

THE WITNESS: I mean, Dr. Little has put it in several different ways. But the definition of conjugate base, which, as I said, he helpfully provides in footnote 3 on -- on page 7, clearly indicates to a person of ordinary skill in the art that a conjugate base, including the conjugate base form of gamma-hydroxybutyric acid, has an electrostatic charge of minus 1.

BY MR. CALVOSA:

Q Have you seen it referred to as that anywhere in any reference that we have in this case?

A I don't specifically recall that, nor would it matter to the meaning of the claim term "gamma-hydroxybutyric acid," where this meaning is very clear from the plain language of the claims, the lexicographic definition in the Resinate patents, and the specification of the asserted patents.

Q Given the specification of the '079 patent, for example -- we could call it both -- we could call it Resinate patents -- would it make sense to a POSA that the claims would be drafted to cover only the negatively charged or anionic form of gamma-hydroxybutyric acid unbound to anything else?

MR. YUE: Objection. Form. Vague.

THE WITNESS: I don't understand the question. I

Page 163

heard the question. I just don't understand what you mean.

BY MR. CALVOSA:

Q Given the specification of what you call the Resinate patents --

A Yeah.

Q -- would it make sense to a POSA that the claims were meant to cover only the unbound anionic form of gamma-hydroxybutyric acid?

MR. YUE: Same objection.

THE WITNESS: When the claim term in question is "oxybate" or "gamma-hydroxybutyrate," yes, it would make sense. Yes.

BY MR. CALVOSA:

Q Even though the specification, all the examples, are of oxybate resins?

A I don't see what -- any -- the claims -- the examples of the Resinate patents don't list -- don't contain some other things that they would have to contain in order to meet the -- just a second. No.

Could you repeat your question, please.

Q Sure.

My question was, even though the specification, all the examples, are of oxybate resins?

A Yeah.

Page 164

The example -- one of skill in the art would understand that examples are nonlimiting and are just that, the examples.

But there is a clear lexicographic definition of the term "oxybate" and "gamma-hydroxybutyrate," and that lexicographic definition, unequivocal definition, specifically says "as used herein," as I recall, in the third -- in column 3, clearly controls the meaning.

Q But you understand that you and Dr. Little disagree on how a POSA would understand that definition in what you call the Resinate patents; right?

MR. YUE: Objection. Form. Vague.

THE WITNESS: There is a disagreement between us on what that means, but that doesn't change the fact that the specific -- that the definition that is provided -- just a second -- that the definition that is provided in column 3, lines 59 through 61, of the '079 patent controls what the meaning of the claim term "gamma-hydroxybutyrate" or "oxybate" is.

BY MR. CALVOSA:

Q Yes. But I'm saying you understand that you and Dr. Little understand that definition differently.

A That's -- as I said, yes, there is a disagreement here, but I believe that Dr. Little -- and I say it respectfully -- is mistaken.

Page 165

And, furthermore, I think that his own discussion in paragraph 22 of his declaration, I think, shows, as I just tried to explain, that, in fact, the gamma-hydroxybutyrate anion has a negative charge of -- electrostatic charge of minus 1. And I see no, what I consider, credible support for Dr. Little's opinion that gamma-hydroxybutyrate includes the salts, or the acid for that matter.

Q Have you worked with Dr. Little before?

A No.

Q Have you worked against Dr. Little before?

A I don't work against anybody.

Q Okay. Have you been on opposite sides of a case from Dr. Little?

A It's possible.

Q Okay. Do you know who Dr. Little is?

A Yes.

Q How do you know him?

A I remember Steve Little, Dr. Steve Little, from the time when he was a postdoctoral scientist in Professor Robert Langer's laboratory at MIT.

Q Do you have any reason to believe that Dr. Langer didn't give him good training?

MR. YUE: Objection. There's no way Dr. Klibanov could know one way or the other.

Page 166

THE WITNESS: I mean, I can tell you that I -- I'm sure that Dr. Little's training was very good even before he joined Dr. Langer's laboratory.

Dr. Langer is the most brilliant scientist I have ever met in my life, so I certainly have absolutely no, you know, negative views of the training that Dr. Little received. But that doesn't make Dr. Little or -- or any of us God.

And I believe that Dr. Little is a good scientist, but I believe that he is mistaken in the views that he expresses in his recent claim construction declaration.

BY MR. CALVOSA:

Q Okay. Is he so mistaken, in your view, that no other POSA would agree with him?

MR. YUE: Objection. Vague. Form. Lack of -- lacks foundation.

THE WITNESS: I don't -- I have not surveyed all the POSAs in the world, so I do not know.

I can point out that Dr. Little is not a chemist. He's a chemical engineer. The views that I express here in his declaration, at least in the background section, are primarily chemistry views.

And, as I said, I believe that his opinion is mistaken, but that's my view. I -- again, I -- I'm

Page 167

certainly -- you know, I don't have a monopoly on the truth; and, you know, that's just my view.

And I try to explain that view. So, in other words, I'm not just saying that Dr. Little's mistaken. I say that, and then I explain in my declaration, in as much detail as I felt is appropriate, why that is my view.

And I also, by the way, would like to point out that, for whatever reason, Dr. Little, as I also say in my declaration, just simply ignored some claims of the Sustained Release patents that directly contradict his views, in my opinion.

BY MR. CALVOSA:

Q The field of sustained release formulation, does that fall within the field of chemical engineering?

MR. YUE: Objection. Vague.

THE WITNESS: Somewhere between chemistry and chemical engineering and pharmaceutical sciences. It's -- it's some -- it's somewhere there. Right.

I was specifically talking about the "Background" section, where chemistry is discussed. The "Background" section of Dr. Little's declaration, not the entirety of his declaration. I think that he's a very good expert in this case.

BY MR. CALVOSA:

Page 168

Q So you think he's well-qualified to be offering opinions for claim construction?

MR. YUE: Objection. Vague. Misstates the witness's testimony.

THE WITNESS: I certainly don't see why he would not be qualified. I was specifically commenting on some of the chemistry issues that are covered in the background section of his declaration.

MR. CALVOSA: Why don't we take a five-minute break.

MR. YUE: Okay.

THE VIDEOGRAPHER: We are off the record. The time is 3:45 p.m.

(Recess was taken at 3:45 p.m. until 4:07 p.m.)

THE VIDEOGRAPHER: We are back on the record. The time is 4:07 p.m.

MR. CALVOSA: And pending any questions from opposing counsel, I have nothing else, but I think opposing counsel does.

MR. YUE: I have a few questions for the witness.

EXAMINATION

BY MR. YUE:

Q Good afternoon, Dr. Klibanov.

A Good afternoon.

Page 169

Q If you could grab Klibanov -- what's been marked as Klibanov Exhibit 7 and Klibanov Exhibit 8 and put those in front of you. Those are the two publications by Dr. Scharf.
A Yeah.
Q Okay. Do you recall providing testimony about these two articles during today's deposition?
A I do.
Q And before today's deposition, had you ever seen either of these articles?
A I have no recollection, so I don't know.
Q Okay. And --
A I'm not sure.
Q Okay. But, sitting here today, you don't have any specific recollection of having either seen these articles or reviewed them, read them, anything like that; is that correct?
MR. CALVOSA: Objection. Leading.
THE WITNESS: I have no --
MR. CALVOSA: Objection --
One second, sir.
(Reporter interruption of simultaneous speakers and clarification of the record.)
MR. CALVOSA: Objection. Leading. Objection. Asked and answered.

Page 170

THE WITNESS: I have no specific recollection of ever reading them.
BY MR. YUE:
Q Okay. Just to make sure that we are clear, you understand that -- let me ask you this:
What do you understand are the two terms -- the two claim terms at dispute in the parties' claim construction disagreement?
MR. CALVOSA: Objection to form.
THE WITNESS: The two claim terms are "gamma-hydroxybutyrate" and "oxybate."
BY MR. YUE:
Q Okay. Is the acronym GHB -- is that a claim term that is part of the parties' claim construction dispute? Strike -- let me rephrase that question.
Is the acronym "GHB" a part of either the Sustained Release or the Resinate patent claims?
A No, it is not.
Q And it's your understanding that the parties' claim construction dispute does not involve the acronym "GHB"; is that correct?
A That is correct.
Q Okay. So let's take a look at Klibanov -- well, before we get there, do you recall that you may have testified during today's deposition that Dr. Scharf

Page 171

was using the term "gamma-hydroxybutyrate" inconsistently in Klibanov Exhibit 7 and Klibanov Exhibit 8?
A Yes, that's my recollection.
Q Okay. So let's go ahead and take a look at Klibanov Exhibit 8 to begin with.
A Okay.
Q Okay. And I think you were directed by counsel for Jazz to the abstract of this article.
Do you recall that?
A Yes. And, in fact, counsel even highlighted a portion of the first sentence of the abstract --
Q Okay.
A -- in -- in pink.
Q Okay. And that's -- in taking a look at that first sentence, does that first sentence contain the term "gamma-hydroxybutyrate" or "oxybate"?
A Certainly not "gamma-hydroxybutyrate."
As far as "oxybate," it doesn't have "oxybate" by itself. It has the term "sodium oxybate." So it does not have a freestanding term "oxybate."
Q Okay. And with that clarification that there is nowhere in this abstract -- or sorry -- the first sentence of the abstract that counsel for Jazz pointed you to, there's nowhere in there the term "oxybate" by

Page 172

itself or "gamma-hydroxybutyrate," does it change your views as to whether or not Dr. Scharf was using the term "gamma-hydroxybutyrate" inconsistently in this publication?
MR. CALVOSA: Objection. Form.
THE WITNESS: I mean, he's talking about -- Dr. Scharf is talking about -- is equating sodium oxybate to Xyrem, which I think is improper, and it also says that sodium oxybate is known as gamma-hydroxybutyric acid, which is also, strictly speaking, scientifically improper, so that's sort of the part of the inconsistencies that I was referring to.
BY MR. YUE:
Q Okay. But were you referring to his inconsistent usage of either the term "oxybate" by itself or "gamma-hydroxybutyrate"?
A No, I was not referring to that.
Q We can go to Klibanov -- you can put that to the side.
We can go to Klibanov Exhibit 7.
A Okay.
Q And do you recall that you were directed towards the title of this article as well as the first sentence in the body of the text of this article?
A Actually, my recollection is that I directed

Page 173

myself to the title of the article, but I was directed by opposing counsel to the first sentence of the summary.
Q Okay. And the title uses the term "gamma-hydroxybutyrate"; correct?
A Yes. Which it abbreviates as "GHB."
Q Okay. And if we look at the first sentence in the body of the text, which counsel directed you -- directed you towards, does that first sentence ever use the term "gamma-hydroxybutyrate" standing alone?
MR. CALVOSA: Objection. Form.
THE WITNESS: No, it does not.
BY MR. YUE:
Q Okay. And reviewing the title and the first sentence of the body of Klibanov Exhibit 7, does that change your views as to whether or not Dr. Scharf was using the term "gamma-hydroxybutyrate" inconsistently?
MR. CALVOSA: Objection. Form.
THE WITNESS: Not the term "gamma-hydroxybutyrate" by itself, with nothing more defining it.
MR. YUE: Okay. No further questions.
MR. CALVOSA: Okay. I just have a couple for you, sir.

Page 174

EXAMINATION
BY MR. CALVOSA:
Q If you take out that first one you had with the orange -- sorry -- the pink highlighting, and that's Klibanov 8, I believe.
A Yes, Klibanov 8.
Q Okay. You see there it says "sodium oxybate." Right?
A Yes.
Q That suffix "-ate," what does that signify?
A I mean, I specifically discussed that issue with citations and sort of documentation in my declaration, so let me find it for you.
Yes. As I describe in paragraph 8 of my declaration, which is Exhibit C, the third sentence, I say, "As a matter of naming convention, as set forth in the nomenclature guide of the International Union of Pure and Applied Chemistry ('IUPAC'), the '-ate' suffix is used in chemistry in reference to anions, not acids."
And then I provide the citation to the IUPAC recommendation and provide the quote from those recommendation. And the quote reads, in quotation marks, "(the endings" -- another set of quotation marks -- "'-ate' or '-ite'" -- also in quotation marks, i-t-e -- "are used to name anions derived from acids.)"

Page 175

MR. CALVOSA: I have no further questions.
Thank you for your time today.
THE WITNESS: You're welcome.
THE VIDEOGRAPHER: We are off the record. The time is 4:15 p.m.
(A discussion was held off the record.)
THE STENOGRAPHER: For the stenographic record, would anyone like to order a rough draft or certified copy, including expedited?
MR. CALVOSA: Me.
MR. YUE: We would like both the rough and the expedited final.
(Proceedings concluded at 4:18 p.m.)

Page 176

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ACKNOWLEDGMENT OF THE DEPONENT

I, ALEXANDER KLIBANOV, PH.D., do hereby certify that I have read the foregoing pages and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

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(DATE) ALEXANDER KLIBANOV, PH.D.

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_____ day of _____, 2023.

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PAGE	LINE	CHANGE	REASON

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I, ALEXANDER KLIBANOV, PH.D., do hereby certify that I have read the foregoing pages 87-88 and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

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_____ day of _____, 2023.

_____
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PAGE	LINE	CHANGE	REASON
88	4	"release of" to "release of sodium"	misspoke
88	21	"a mechanism" to "mechanisms"	misspoke
88	23	"this" to "these"	misspoke

EXHIBIT 37

Pharmacokinetics of Gammahydroxybutyrate (GHB) in Narcoleptic Patients

Martin B. Scharf, Allen A. Lai, Barb Branigan, Robin Stover, and David B. Berkowitz

The Center For Research In Sleep Disorders, Cincinnati, Ohio; The Tri-State Sleep Disorders Center, Cincinnati, Ohio

Summary: Sodium gamma-hydroxybutyrate (GHB) is an endogenous compound that has been under investigation in the management of narcolepsy for about two decades. The data confirm that GHB treatment decreases daytime sleepiness and episodes of cataplexy, sleep paralysis, and hypnagogic hallucinations. The current study evaluated the pharmacokinetics of GHB, given twice in one night to six narcoleptic patients who had been chronically taking GHB nightly on a similar basis. Results confirmed earlier reports and showed nonlinear pharmacokinetics. Maximum concentrations were reached in 40±6.2 and 35.7±7 minutes after the first and second dose respectively. Mean AUC_{inf} was 17731.6±4867 mg/mL/m. Mean GHB $T_{1/2}$ was 53±19 minutes. GHB elimination appears to be capacity-limited in some patients when administered at a fixed dose of 3 g twice nightly at a 4-hour interval.
Key words: Cataplexy; narcolepsy; GHB; pharmacokinetics

SODIUM GAMMA-HYDROXYBUTYRATE (GHB), or sodium 4-hydroxybutyrate, is an endogenous compound with hypnotic properties that is found in many tissues of the body. The neuropharmacologic effects of GHB include increases in brain acetylcholine, increases in brain dopamine, inhibition of GABA ketoglutarate transaminase, and depression of glucose utilization but not oxygen consumption in the brain. GHB is converted to succinate and then metabolized via the Krebs cycle by a dehydrogenase.[1-4] Clinical trials have shown that GHB increases delta sleep and improves the continuity of sleep in normal and narcoleptic subjects. A variety of neuropharmacologic mechanics of action have been reported, but none has been conclusively established.[1]

Studies have evaluated the effects of GHB in the treatment of narcolepsy.[5-10] The results of these studies all confirm that GHB treatment substantially reduces the signs and symptoms of narcolepsy, ie, daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. Our own experience with GHB has resulted in over 15 years of nightly clinical use in over 120 narcoleptic patients, and has provided over 750 patient years of safety and efficacy data attesting to the value of this compound in the management of narcolepsy.

The pharmacokinetics of GHB have been investigated in normal healthy males and in alcohol-dependent patients after oral administration.[11,12] In alcohol-dependent patients, consistent with its rapid onset and short pharmacological effect, the data indicated that both GHB absorption into and elimination from the systemic circulation were rapid processes.[11]

Virtually no unchanged drug could be recovered in the urine. There were preliminary indications that the pharmacokinetics of GHB might be nonlinear or dose-dependent.[11] In the healthy volunteers study, the pharmacokinetics of three rising GHB doses (12.5, 25, and 50 mg/kg) were investigated. The apparent area under the curve (AUC) increased disproportionately with dose; the dose-normal-

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ized peak concentrations, however, decreased with increasing doses, while the corresponding peak times increased.[12] These findings confirmed that both the oral absorption and elimination processes of GHB were capacity-limited, though the degree of dose dependency was moderate. The present study was designed to investigate the pharmacokinetics of two consecutive doses of GHB in narcoleptic patients (who on a regular basis ingested the first dose of this medication prior to bedtime and the second dose from 2.5 to 4.9 hours later).

The objective of this study was to assess the pharmacokinetics of GHB after oral administration of two consecutive single doses of GHB (3 g/dose, 4 hours apart) to narcoleptic patients who have been chronically maintained on a similar regimen of nightly GHB use.

METHODS

This pharmacokinetics study was conducted as an open-label, single-center investigation in six narcoleptic patients. Each patient was determined to be in stable health, and had previously received a diagnosis of narcolepsy (1 or more years of medical history based on a nocturnal polysomnogram [PSG]and a valid score from a multiple sleep latency test [MSLT]). Each had a longstanding history of moderate-to-severe cataplexy, and had been receiving GHB nightly on a chronic basis. None were taking antidepressants, hypnotics, sedatives, antihistamines, or anticonvulsants, though a stable regimen of methylphenidate (immediate-release or sustained-release) was allowed. The investigator ensured that there would be at least an 8-hour washout period for GHB prior to the treatment period. Patients were screened at least 1 day prior to the treatment phase, and passed a prestudy physical examination which included hematology, blood chemistry, urinalysis, and vital signs measurements prior to the commencement of the treatment phase. All patients were hospitalized from approximately 4 hours prior to first GHB dosing (around 20:00) until the end of the treatment period (around 10:00 the next morning). Patients ate their dinner at the clinical research unit soon after arrival and fasted until breakfast next morning. The investigator or his designee prepared the oral solution for dosing within 30 minutes prior to the first oral administration to individual patients. The contents of one twin-pouch containing 3 g of GHB in powder and excipient form was emptied into a dosing cup (provided by the sponsor) to which 2 ounces of water was added. After replacing the lid of the dosing cup (also provided by the sponsor), the dosing cup was gently shaken to dissolve the GHB and excipient in water. The GHB solution was ingested in its entirety. Likewise, the second GHB dosing solution was prepared in the same manner and was ingested in entirety 4 hours after the first GHB dose. Before oral administration of the first GHB dose, an indwelling catheter was placed in an arm vein, and a baseline blood sample was collected. Each patient then ingested a 3 g dose of GHB right at bedtime. Another 3 g GHB dose was administered 4 hours after the first dose. Twenty-one sequential blood samples were collected over 12 hours (starting at 10 minutes after the first dose and ending at 8 hours after the second dose). Upon completion of the treatment phase, a follow-up physical examination which included the measurement of vital signs was performed on each patient within 48 hours after the last blood sample.

All six patients took some nonstudy medications (Synthyroid, Premarin, Lovastatin, Fluvastatin, furosemide, potassium, hydrochlorothiazide, lansoprazole, and verapamil). None of these were expected to interfere with the metabolism of GHB or effect the results of the study.

Plasma samples were analyzed for GHB by the Department of Bioanalytical Chemistry, Covance (previously known as Hazleton Corning), Madison, Wis. A gas chromatographic method with mass selective detection (GC-MSD) was used in the analysis. This method has a limit of quantification (LOQ) of 7.02 mg/mL.

Pharmacokinetic parameters were determined for individual sets of plasma GHB concentration vs time data using the noncompartmental routine in WinNonlin Version 1.1. The peak GHB concentrations (C_{max}) were observed values. Apparent terminal half-life ($T_{1/2}$) was obtained by log-linear regression analysis of the terminal phase of concentration vs time curves. The apparent area under the curve (AUC_{inf}) and the area under the first moment curve ($AUMC_{inf}$) were calculated by the linear trapezoidal rule up to the last determined concentration and included extrapolated areas to time infinity. Apparent oral clearance (CL/F) was calculated as dose/AUC_{inf}. Volume of distribution ($V_{\lambda z}$/F) was determined by taking the ratio between CL/F and z (elimination rate constant). Mean residence time (MRT) was estimated from the ratio between $AUMC_{inf}$ and AUC_{inf}.

RESULTS

Six narcoleptic patients completed the study. Four patients were male and two were female; all six patients were Caucasian. Their mean age was 50.7 years. Their mean body weight was 87.6 kg. Five patients had been maintained on GHB nightly for over 10 years, and one patient had been receiving GHB nightly for 2 years. One patient had multiple sclerosis; however, the attending physician judged that it would not interfere with the objective of this study. All patients ingested the two GHB doses as scheduled. The GHB doses per kg body weight ranged from 26.4 to 52.4 mg/kg.

Individual patient plasma-GHB concentration data sets following two consecutive 3 g GHB doses at a 4-hour interval are depicted graphically in Figs. 1-6. It is of interest to

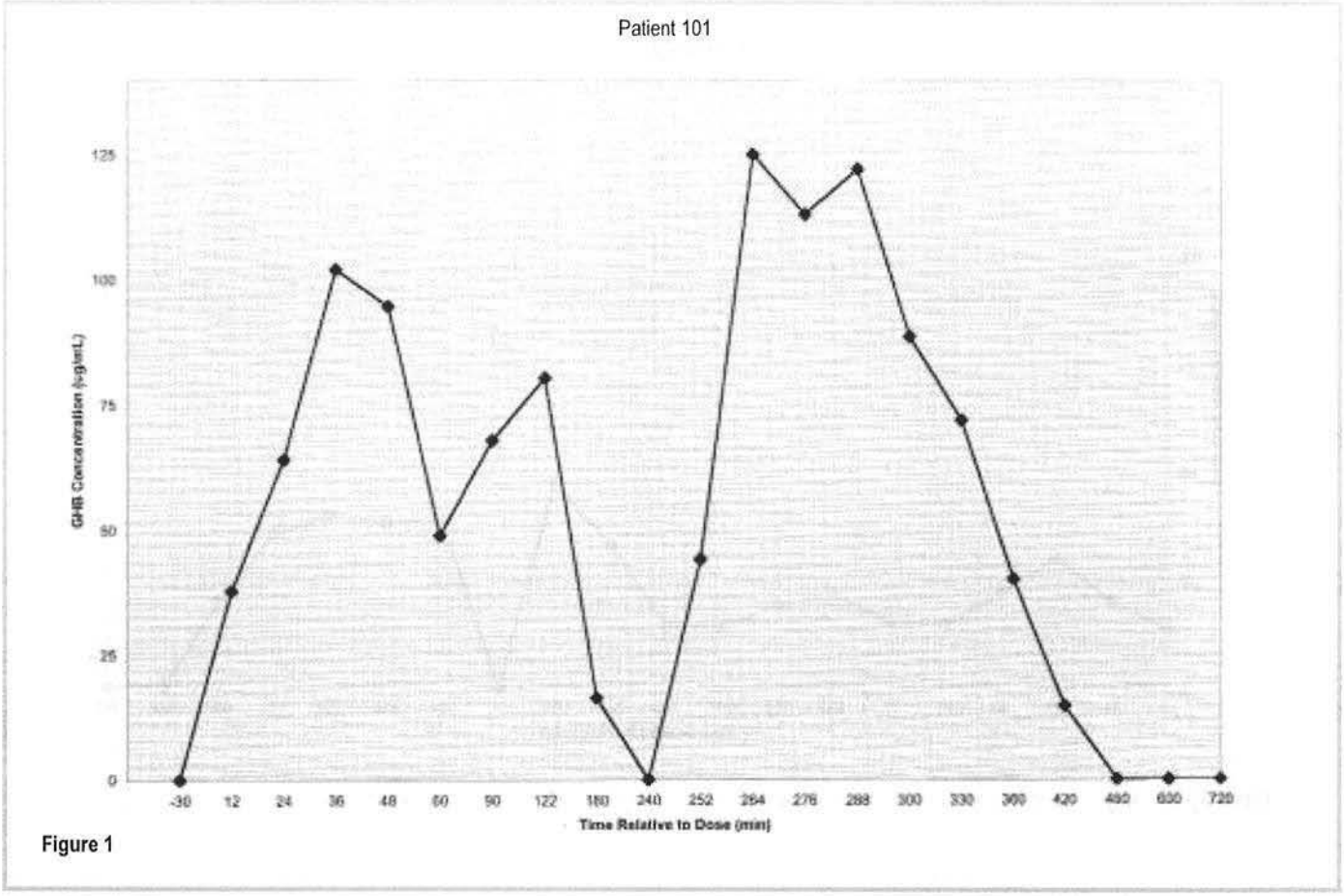

Figure 1

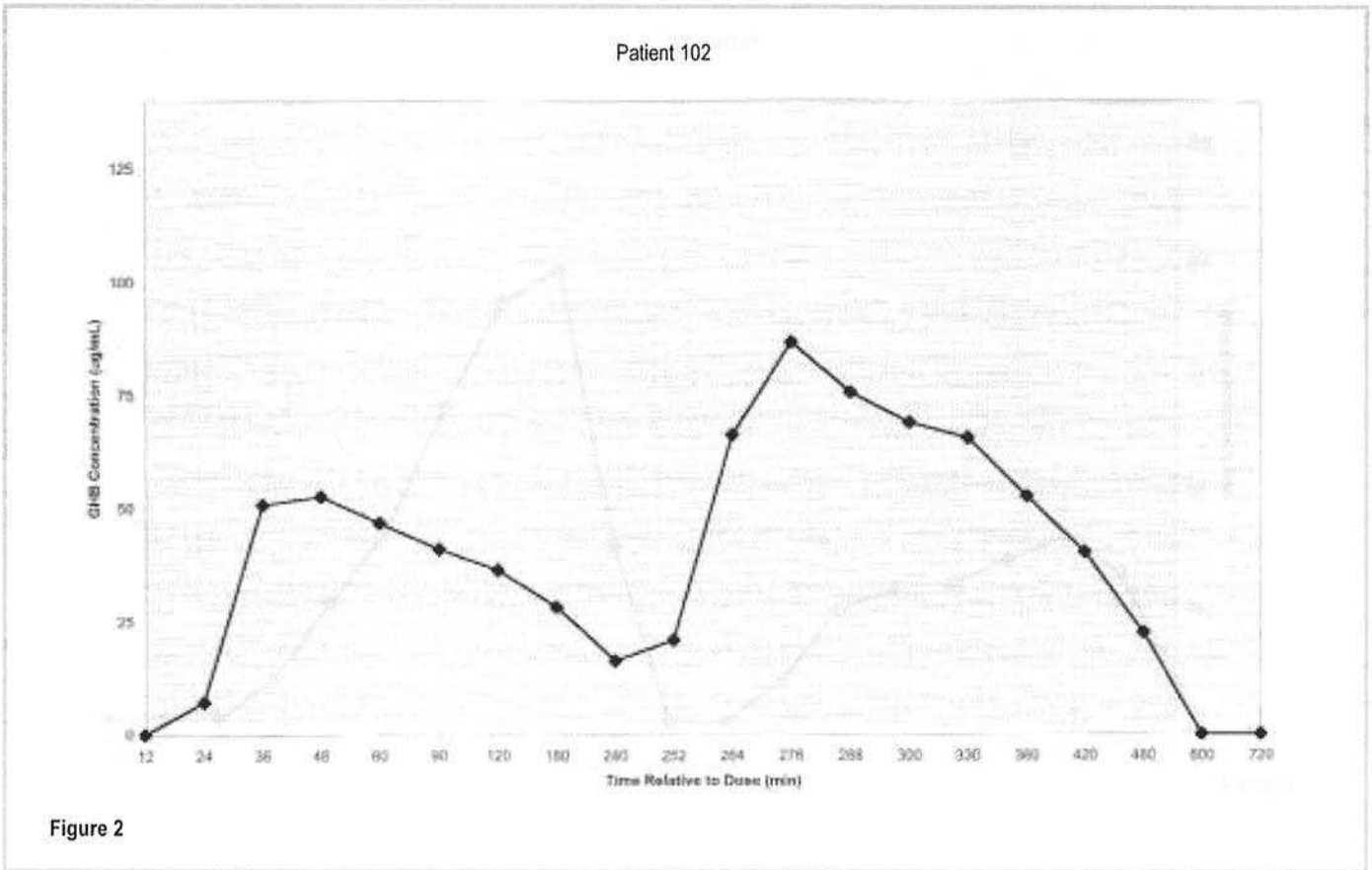

Figure 2

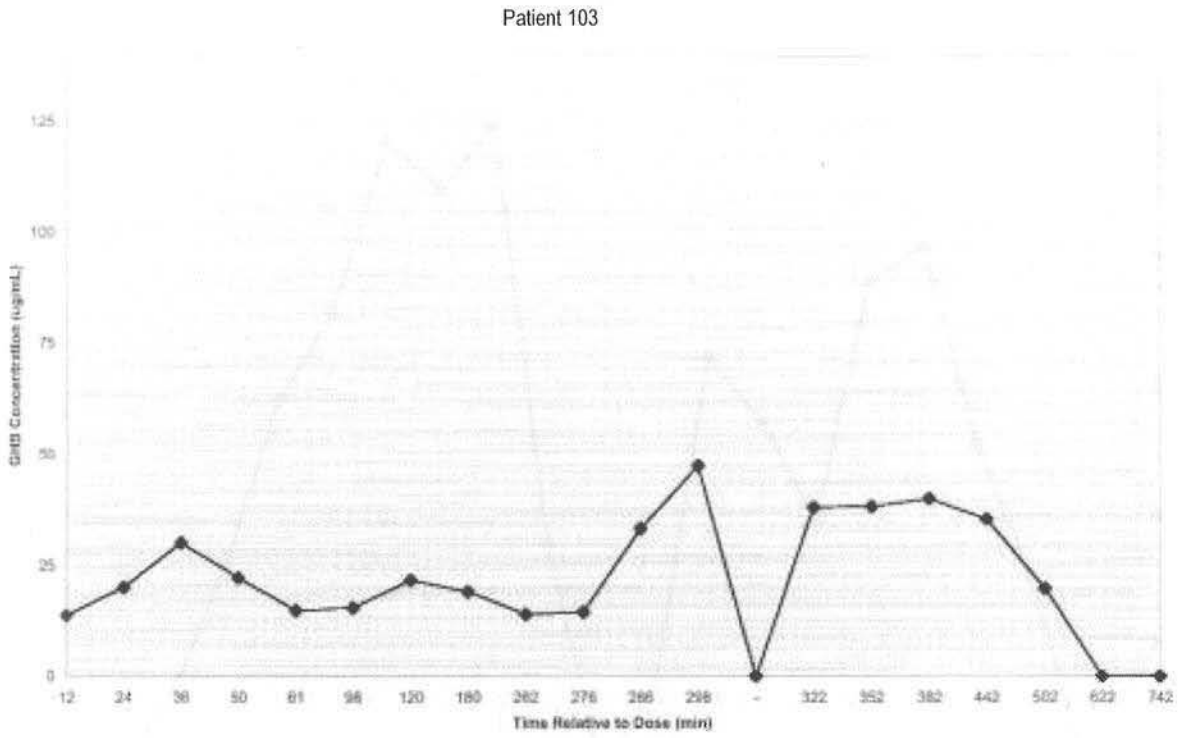

Figure 3

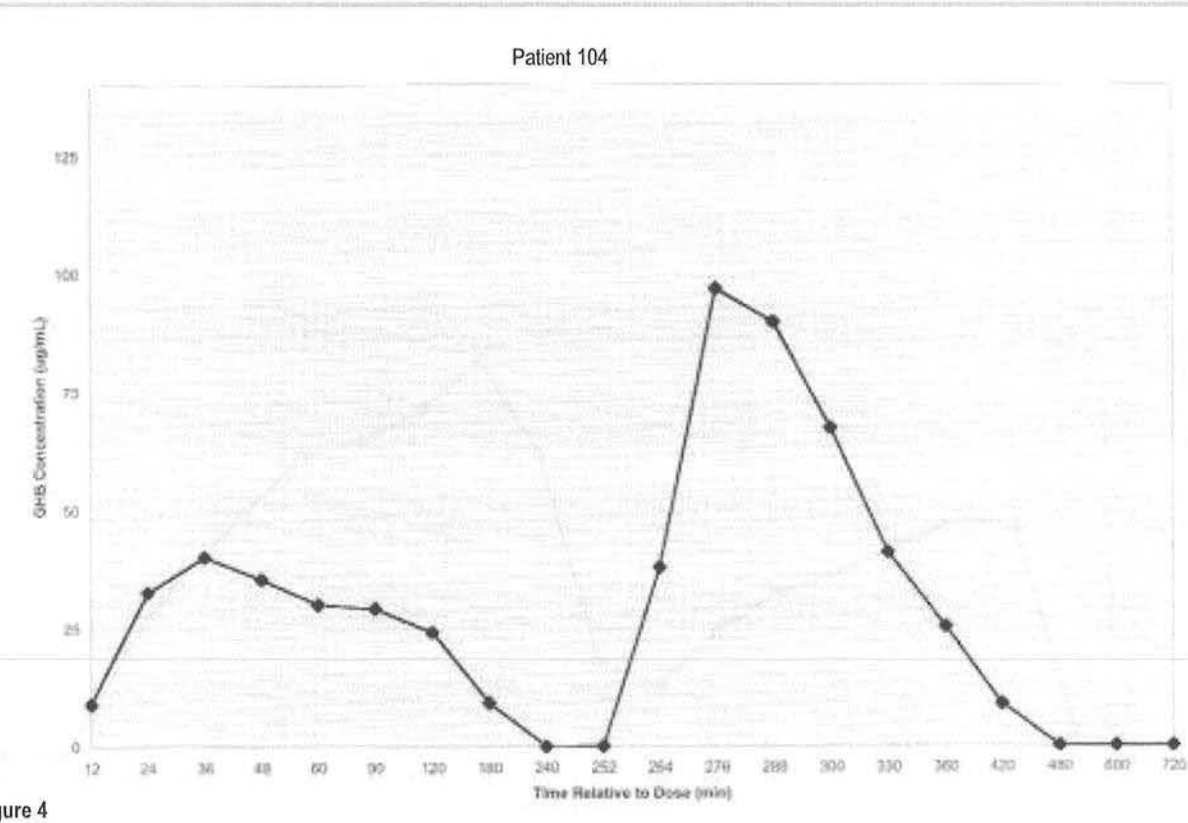

Figure 4

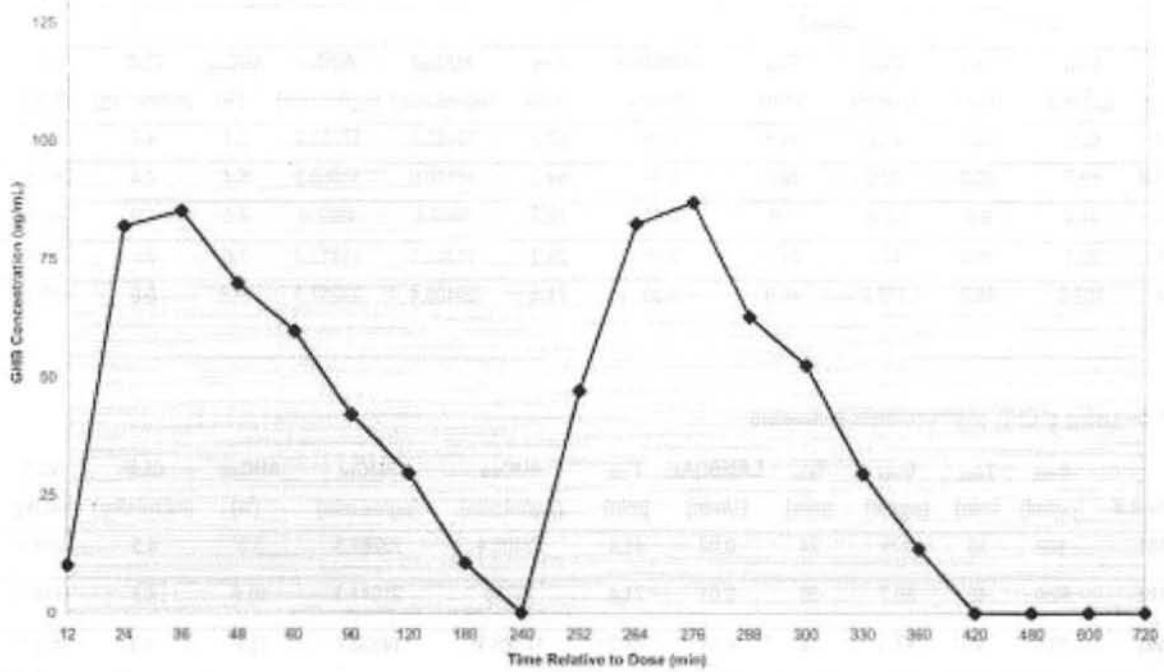

Figure 5

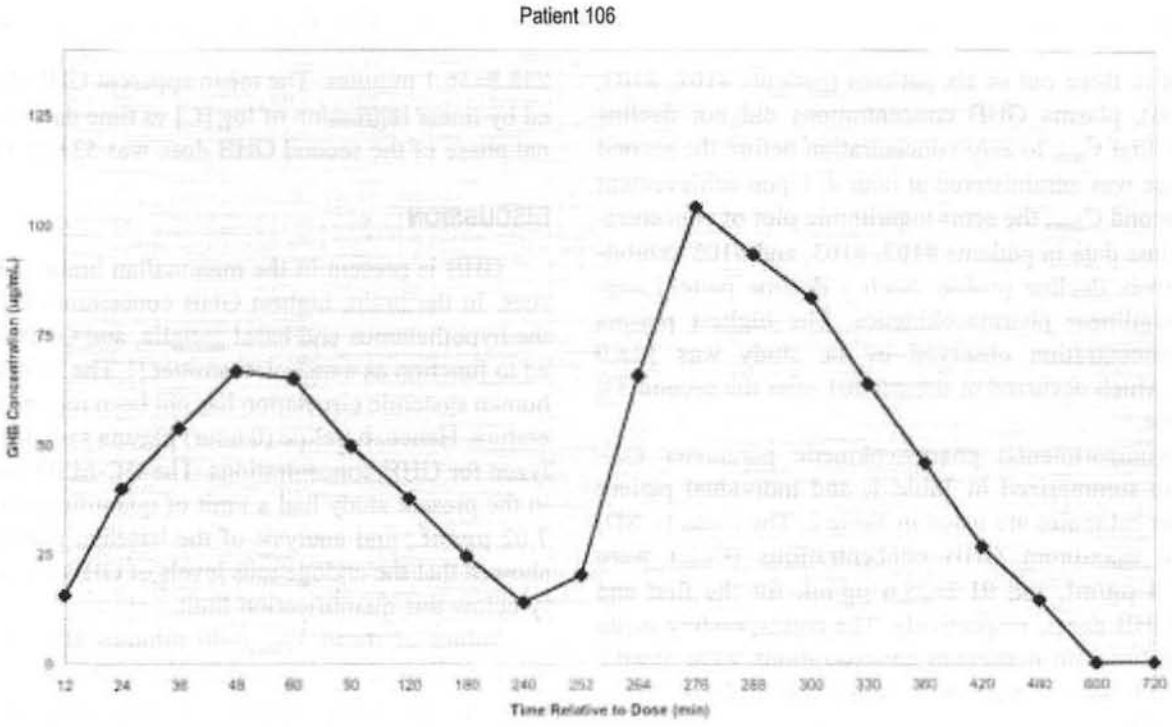

Figure 6

Table 1.—Summary of GHB pharmacokinetic parameters

	N=6											
	Dose 1		Dose 2									
Statistic	C_{max} (μg/ml)	T_{max} (min)	C_{max} (μg/ml)	T_{max} (min)	LAMBDAz (1/min)	$T_{1/2}$ (min)	AUC_{last} (μg/ml.min)	AUC_{inf} (μg/ml.min)	AUC_{ext} (%)	CL/F (ml/min/kg)	Vz/F mL/kg	MRT (min)
MEAN	62.8	40.0	91.2	35.7	0.15	53.0	16455.8	17731.6	7.1	4.2	307.0	248.8
MEDIAN	59.7	36.0	92.0	36.0	0.14	54.2	16170.6	18050.2	5.4	4.4	262.8	243.3
STD	27.4	6.2	25.6	7.0	0.01	19.3	4602.8	4867.0	4.1	1.0	96.2	56.1
MIN	30.1	36.0	47.5	24.0	0.01	26.9	11302.1	11813.2	3.8	2.5	216.0	176.0
MAX	102.0	48.0	125.0	46.0	0.03	71.4	22408.4	23287.3	13.6	5.6	439.1	330.3

Table 2.—Listing of GHB pharmacokinetic parameters

Patient #	C_{max} (μg/ml)	T_{max} (min)	C_{max} (μg/ml)	T_{max} (min)	LAMBDAz (1/min)	$T_{1/2}$ (min)	AUC_{last} (μg/ml.min)	AUC_{inf} (μg/ml.min)	AUC_{ext} (%)	CL/F (ml/min/kg)	Vz/F mL/kg	MRT (min)
101	102	36	125	24	0.02	41.4	22408.4	23287.3	3.8	4.5	268.8	207.9
102	52.6	48	86.7	36	0.01	71.4	19325	21641.3	10.7	4.1	418.5	291.7
103	30.1	36	47.5	46	0.01	71.2	12888.9	14923.7	13.6	4.3	439.1	330.3
104	40.1	36	96.9	36	0.02	39.8	11302.1	11813.2	4.3	4.5	256.8	232.2
105	85.2	36	87.1	36	0.03	36.9	13016.1	13547.3	3.9	5.6	216	176.2
106	66.8	48	104	36	0.01	67	19794.3	21176.7	6.5	2.5	243	254.4

note that in three out of six patients (patients #102, #103, and #106), plasma GHB concentrations did not decline from the first C_{max} to zero concentration before the second GHB dose was administered at hour 4. Upon achievement of the second C_{max}, the semi-logarithmic plot of concentration vs time data in patients #102, #103, and #105 exhibited a convex decline profile. Such a decline pattern suggested nonlinear pharmacokinetics. The highest plasma GHB concentration observed in the study was 125.0 mg/mL, which occurred in subject 101 after the second 3 g GHB dose.

Noncompartmental pharmacokinetic parameter estimates are summarized in Table 1, and individual patient parameter estimates are listed in Table 2. The mean (± SD) observed maximum GHB concentrations (C_{max}) were 62.8±27.4 μg/mL and 91.2±25.6 μg/mL for the first and second GHB doses, respectively. The corresponding mean observed times to maximum concentrations were 40±6.2 and 35.7±7 minutes after the first and second GHB doses, respectively.

The mean apparent AUC_{inf} was 17731.6±4867 μg/mL.min. The mean CL/F was 4.2±1 mL/min/kg and the mean $V_{\lambda z}/F$ was 307±96.2 mL/kg. The mean MRT_{inf} was 248.8±56.1 minutes. The mean apparent GHB $T_{1/2}$ estimated by linear regression of log [C] vs time data of the terminal phase of the second GHB dose was 53±19.3 minutes.

DISCUSSION

GHB is present in the mammalian brain and other tissues. In the brain, highest GHB concentration is found in the hypothalamus and basal ganglia, and GHB is postulated to function as a neurotransmitter.[13] The level of GHB in human systemic circulation has not been reported in the literature. Hence, baseline (0 hour) plasma samples were analyzed for GHB concentrations. The GC-MSD method used in the present study had a limit of quantification (LOQ) of 7.02 μg/mL, and analysis of the baseline plasma samples showed that the endogenous levels of GHB are substantially below this quantification limit.

Values of mean T_{max} (~40 minutes after dosing) and $T_{1/2}$ (~50 minutes) suggest that the GHB solution administered to narcoleptic patients in this study was readily absorbed and rapidly eliminated. In three out of six patients, the drug was essentially gone from the systemic circulation by hour 4 after the first GHB dose, whereas in the remaining three patients, residual GHB levels of 15

μg/mL were still detected at hour 4.

The convex nature of the decline of plasma GHB concentrations in three patients after achievement of the second C_{max} indicated that elimination of GHB from the systemic circulation in these three patients is capacity limited. Nevertheless, it should be noted that plasma GHB concentrations were no longer detectable by hour 6 after the second GHB dose (10 hours after the first GHB dose). The mean apparent oral clearance found in this study was 4.2 ±1.0 mL/min/kg and appeared to be comparable to the apparent oral clearance of 5.3±2.2 mL/min/kg reported in the literature for a group of alcohol-dependent patients who were administered a dose of 50 mg/kg.[11] While it appeared that the GHB dose (ranging from 26.4 to 52.4 mg/kg with a mean of 36.5 mg/kg) in the present study was lower than the comparison GHB dose (50 mg/kg) administered to the alcohol-dependent patients, it should be noted that each patient in the present study was administered two consecutive GHB doses at 4-hour interval, and residual GHB levels were detected in three out of six patients immediately prior to the second GHB dose. The GHB pharmacokinetic nonlinearity in alcohol-dependent patients easily can be observed from the apparent oral clearance, which increased to 8.1±4.8 mL/min/kg when the GHB dose is reduced to 25 mg/kg dose.[11] In the present study, the nonlinearity was less obvious because each narcoleptic patient received two consecutive fixed 3 g doses regardless of body weight.

The mean apparent elimination half-life of GHB in the six narcoleptic patients was determined to be 53±19 minutes, longer than that in alcohol dependent patients after a 50 mg/kg GHB dose.[11] The lengthening of GHB elimination half-life observed in this study was partially caused by the wider spacing in sampling time points. However, capacity limited elimination of this drug in some of the narcoleptic patients also could have contributed to this prolongation.

GHB appears to have a pharmacokinetic shortcoming in that its elimination from the body is capacity limited in some patients when the drug is administered at a fixed regimen of 3 g twice nightly at 4-hour intervals. However, from a therapeutic perspective, GHB offers an advantage in the treatment of narcolepsy because by the time a patient wakes up in the morning (ie, 8 to 10 hours after the first GHB dose), all GHB, including that from the second dose, will have been eliminated from the systemic circulation. GHB was well tolerated by narcoleptic patients in this study. No adverse experience was reported.

The results of this study may help explain the unique side effect profile seen with this compound. To date, the most prominent side effect observed has been episodes of sleepwalking. While quite rare, no other side effect has appeared to be directly due to the drug's effects. The fact that sleepwalking normally occurs out of slow-wave sleep and is most prevalent in children (in whom slow-wave sleep is quite prominent) suggests that the event may be secondary to the induction of this sleep stage. However, in our clinical experiences, the vast majority of sleepwalking events have tended to occur with the second dose rather than the first, despite the fact that both clearly induce slow-wave sleep. The possibility that capacity-limited elimination contributes to higher blood levels after the second dose may explain the phenomenon.

Finally, the extremely short half-life of GHB may explain why patients generally awaken fully alert and refreshed. A clear rebound insomnia or alertness occurs with drug elimination, which can be quite positive for patients with narcolepsy. Unfortunately, however, with some patients, drug effects may wear off prematurely, leaving the patient wide awake either long before their second scheduled dose or before their planned awakening time. We have dealt with this clinically by either adjusting the dose, adding a third dose, or adding a sedating short-acting hypnotic.

The results of this study confirm and extend the findings of GHB kinetics in alcoholic patients. Despite the fact that these patients had a long history of nightly GHB use, these kinetics of the drug were similar to GHB-naïve patients. Despite this, further studies should be carried out in naïve narcoleptic patients.

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Sodium oxybate for narcolepsy

Martin B Scharf

Sodium oxybate (Xyrem™), also known as γ-hydroxybutyric acid, is the only therapeutic specifically approved in the USA for the treatment of cataplexy in narcolepsy. The US FDA has recently expanded its indication to include excessive daytime sleepiness associated with narcolepsy. In contrast to the antidepressants and stimulants commonly used to treat the disorder, sodium oxybate is the only compound that addresses both sets of symptoms and, when used properly, is less likely to lead to the development of tolerance and other undesirable side effects. In this review, the results of clinical trials and the place of sodium oxybate in narcolepsy treatment are discussed.

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CONTENTS

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KEYWORDS:
cataleptic cataplexy, narcolepsy, sodium oxybate

Narcolepsy is a syndrome characterized by sleep abnormalities including excessive daytime sleepiness, disturbed night-time sleep and manifestations of cataplexy, sleep paralysis and hypnagogic hallucinations. There are two distinct classes of the syndrome: narcolepsy with and without cataplexy [1]. Prevalence studies for narcolepsy with cataplexy in Europe and the USA have reported frequency rates of the disorder in the general population that range 0.013–0.067% [2–4]. The prevalence of narcolepsy without cataplexy is more uncertain due to the greater probability of individuals with the condition remaining undiagnosed.

The first symptoms of the disorder typically develop near puberty. The peak age range of onset is 15–25 years of age, with smaller peaks of onset at 35–45 years and near menopause for women [5].

Pathophysiology of narcolepsy

Recent discoveries have linked narcolepsy with cataplexy to the human leukocyte antigen (HLA) DQB1*0602 and to a deficiency in the neuropeptide hypocretin (Hcrt) system. Narcolepsy was first associated with HLAs (also called major histocompatability complex) in the 1980s [6–9]. Soon after, it was found that narcolepsy patients with cataplexy who are DQB1*0602 positive have undetectable levels of Hcrt-1 peptides in their cerebrospinal fluid (CSF) [10–12]. This linkage led to the hypothesis that a CNS autoimmune insult, resulting in Hcrt cell loss might be the trigger for the development of narcolepsy. Subsequent attempts to verify this hypothesis have not proved successful [13–15].

Since the initial discovery of the HLA-narcolepsy association, testing technology has advanced considerably to include molecular typing at the DNA level. These more advanced techniques further narrowed the antigen subtypes definitively involved in narcolepsy. At present, the subtype HLA DQB1*0602 is the best known marker for the disease. This marker has proven to be especially important in African-American patients, who often test positive for DQB1*0602, while testing negatively for other common markers, such as HLA DR2 [16–18].

Diagnosis

The use of HLA typing to diagnose narcolepsy is limited in several respects. In patients with clear-cut cataplexy, the HLA association is greater than 90% [7]. In contrast, patients with atypical or absent cataplexy demonstrate HLA association only 40% of the time – a level that is hardly definitive for these patients [7]. Furthermore, many individuals without narcolepsy also have this marker. Estimates of the

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frequency of the DQB1*0602 subtype in the general population vary with ethnicity (approximately 22% of American Caucasians and 33% of African-Americans [16,17,19]) and are high enough to produce a significant number of false positives if used to diagnose narcolepsy in isolation from other factors.

Observations of Hrct-1 levels in the CSF of narcoleptic patients and control subjects have led to the establishment of a specific cut-off value for diagnosis (110 pg/ml). This level of Hrct-1 is highly predictive of narcolepsy in patients with definitive cataplexy (99% specificity, 87% sensitivity) [1]. Unfortunately, in patients without cataplexy or with doubtful cataplexy, this test proves less useful, as most of these cases present with normal results (99% specificity, 16% sensitivity) [11,12,20]. Further complicating the diagnostic value of this test, the lumbar puncture necessary to obtain the CSF, while generally safe, presents some trauma to the patient and is often associated with debilitating postpuncture headaches [21].

A third diagnostic tool, the multiple sleep latency test (MSLT), is currently the most predictive tool available, especially for cases presenting without definite cataplexy. The MSLT consists of five scheduled daytime naps during which the subject is monitored using polysomnography (PSG) to measure physiologic sleep tendencies in the absences of alerting factors [5,22]. A mean sleep latency of less than 8 min and two or more sleep-onset rapid eye movement (REM) periods during the MSLT, are considered necessary to support the diagnosis of narcolepsy. The MSLT is not necessary for diagnosis in patients with definite cataplexy, but is potentially the most useful diagnostic tool available for patients without this common symptom.

The Maintenance of Wakefulness Test (MWT) can also be used to investigate the degree of excessive daytime sleepiness experienced by a narcoleptic patient [23]. This test involves a PSG evaluation of a patient's ability to maintain wakefulness in a quiet, darkened room, while in a reclined position. A total of four 20 min tests are conducted at 2-h intervals beginning approximately 2 h after the patient awakens from a night of sleep. The MWT does not provide a diagnosis of narcolepsy itself, but can be useful for assessing the patient's degree of alertness and tendency to fall asleep at inappropriate times after a diagnosis of narcolepsy has been made.

Current treatment options

Traditionally, narcolepsy patients have often been prescribed two sets of medication to treat their disorder. The first group, typically antidepressants, is used to address cataplexy symptoms, while the second, typically amphetamines, is used to address symptoms associated with excessive daytime sleepiness (EDS).

Cataplexy treatment options

Tricyclic antidepressants (TCAs) were first used to treat narcolepsy with cataplexy in the 1960s [24] and, until recently, have been the most common type of antidepressant used to treat the disorder. TCAs (e.g., including protriptyline, desipramine, and viloxazine) and the serotonin norepinephrine reuptake inhibitor atomoxetine act as noradrenergic reuptake inhibitors to produce potent anticataplectic effects [25–27]. TCAs have also been shown to reduce the severity of other narcolepsy symptoms, specifically sleep paralysis and hypnagogic hallucinations. Unfortunately, the anticholinergic effects of these medications have been shown to produce impotence in male patients, with one evaluation discovering this effect in over 40% of males surveyed [5], making these drugs unacceptable for many patients. Common side effects of the TCAs include dry mouth, urinary retention, constipation and tachycardia, with male patients also reporting decreases in libido, impotence and delayed ejaculation [28–31].

Abrupt discontinuation of TCAs, especially at high doses, has been shown to produce rebound cataplexy that may last anywhere from a few days to several months [32–34]. Unlike normal cataplexy, rebound cataplexy can be spontaneous and unprovoked. Occurrences are often more frequent, severe and can be precipitated by mild emotional stimuli and normal daily events.

Today, selective serotonin reuptake inhibitors (SSRIs) are more frequently used to treat narcolepsy than the older TCAs. The metabolites of several SSRIs (e.g., fluoxetine and zimeldine) have noradrenergic reuptake inhibition effects [35]. However, of note there is some evidence that the SSRIs must be prescribed at higher doses to sufficiently treat cataplexy symptoms owing to these noradrenergic effects being weaker than those of the TCAs [26,27]. Side effects common to therapeutic doses of SSRIs include headache, nausea, epigastic discomfort, weight gain, dry mouth and delayed ejaculation [36–39]. Rebound cataplexy may also occur when SSRIs are withdrawn abruptly, but limited evidence suggests that these effects may be less severe than with the TCAs [40]. Neither the TCAs or the SSRIs have been shown to impact EDS [29,41–43].

A final treatment option, sodium oxybate (Xyrem®, Jazz Pharmaceuticals, Inc.) is the only medication specifically approved by the US FDA for the treatment of cataplexy symptoms.

EDS treatment options

Amphetamine-like medications (e.g., dextroamphetamine, methamphetamine and methylphenidate) and modafinil are the stimulants most widely used to treat EDS associated with narcolepsy. Amphetamines were first used for wake promotion in narcoleptics in 1935 and the first case of addiction was reported soon after in 1939 [44]. Concerns regarding abuse of these medications and tolerance development remain very prevalent today. With the exception of modafinil, the wake promoting effects of the amphetamine-like compounds appear to be related to dopamine release stimulation and reuptake inhibition, which in turn have the effect of reducing total sleep time and slow wave sleep [45,46].

Modafinil's mechanism of action is under debate, although it has been demonstrated to selectively inhibit dopamine uptake [47]. Unlike other wake promoting compounds, modafinil is believed to have a low addiction liability, even though it is a schedule IV drug. Furthermore, it is reported

to be safe in patients with hypertension – all qualities that have recently made it the first choice of stimulants for newly diagnosed narcoleptics.

Amphetamine-like compounds selective for dopamine transmission have no effect on cataplexy symptoms. However, those with combined dopaminergic and noradrenergic effects have been shown to produce some anticataplectic effects at high doses [1,26,48]. Modafinil has not been shown to impact cataplexy and REM-sleep symptoms [5].

Sodium oxybate

Sodium oxybate, also known as γ-hydroxybutyric acid (GHB), is the focus of this drug profile. Sodium oxybate is a naturally occurring CNS metabolite that acts as a sedative to consolidate sleep and increase slow wave sleep [25]. Dopaminergic regions of the CNS contain high concentrations of this compound, suggesting that it may modulate the activity of dopamine neurons [49]. At pharmacological doses, sodium oxybate increases serotonin turnover, interacts with endogenous opioid systems and may act as a γ-aminobutyric $acid_B$ receptor agonist [50–52].

Sodium oxybate is rapidly metabolized to succinic semialdehyde and then to succinic acid. This metabolite enters the Krebs cycle, producing the final metabolic products of CO_2 and H_2O [53]. Sodium oxybate's half-life of 0.5–1 h is so short that 4–6 h after ingestion, it may be impossible to measure its concentration in urine [54,55].

Clinical efficacy

Sodium oxybate was first used in narcolepsy trials in the late 1970s [56–62]. It was approved by the US FDA in 2002 to treat cataplexy symptoms largely based on the results of two randomized, double-blind, placebo controlled trials. Approval for the treatment of EDS in narcoleptics was followed in 2005 and was based on the results of Phase IV clinical trials. The first study leading to the initial FDA approval evaluated the effects of sodium oxybate on the frequency of cataleptic attacks and measures of daytime alertness in 136 narcoleptic patients [57,63]. The second study leading to initial approval evaluated the long-term effects of the drug by following 55 patients who took sodium oxybate to treat narcolepsy symptoms for an average of 21 months [64–66].

In the first study [57], adult patients with a current diagnosis of narcolepsy gradually withdrew from all medications used to treat cataplexy symptoms. Following a washout period, patients exhibiting at least three cataleptic attacks/week then received two equally divided nightly doses of sodium oxybate (totaling 3, 6, or 9 g/night) for a period of 4 weeks. Narcolepsy and cataplexy symptoms were assessed using patient diaries, while daytime somnolence was evaluated at 2 and 4 weeks using the Epworth Sleepiness Scale (ESS) and a clinical global impressions (CGI) scale.

Patients demonstrated dose-related responses to all measures. There was a marked decrease in the frequency of cataplexy attacks for all groups, including a 49% reduction in both the 3 and 6 g groups and a 69% reduction in the 9 g group. The ESS and CGI measures improved for all groups, becoming significant versus placebo at 9 g. Furthermore, the number of inadvertent daytime naps significantly decreased at both the 6 and 9 g dose levels. Relative to placebo, improvements were also seen in the frequency of sleep paralysis and hypnagogic hallucinations with all doses. Importantly, the improvements in daytime functioning were achieved, while 83% of patients remained stable on stimulant medication, indicating that sodium oxybate provided both anticataplectic and wake promotion benefits to these narcoleptic sufferers.

This study was continued for an additional 12 months as an open-label extension [63]. As part of the original study of 136 patients, sodium oxybate was discontinued for 3–5 days to evaluate the potential for withdrawal symptoms, then 117 patients elected to continue with sodium oxybate therapy. All of these patients were placed on an initial dose of 6 g and were individually titrated up or down in increments of 1.5 g until an optimal dose was reached. As treatment was maintained over a longer period, there was a significant reduction in cataplexy attacks as compared with baseline levels, even at the lowest dose (3 g). This reduction in attacks increased over time for all dose levels, potentially indicating that several months are needed for sodium oxybate to reach full therapeutic efficacy. Therefore, the improvements in cataplexy seen at lower dose levels than predicted by the first phase of this trial may suggest that some patients are receiving higher doses of sodium oxybate than necessary to control cataplexy.

The second trial addressed concerns a rising from anecdotal reports of withdrawal symptoms following chronic abuse of illicit GHB [65]. This study involved 55 narcolepsy patients who had taken sodium oxybate (3–9 g/night) for between 7 to 44 months (mean: 21 months). These patients remained stable on all medications for a 2-week, single-blind baseline period. Subsequently, approximately half continued with their current level of sodium oxybate and half were switched to placebo for a 2-week, double-blind treatment period. Patients remaining on sodium oxybate continued to demonstrate a stable number of cataleptic attacks, while those on placebo demonstrated a gradual return of symptoms over the 2-week period of observation. No significant withdrawal symptoms or rebound effects were seen.

Postmarketing studies: efficacy for EDS

More recently, sodium oxybate was evaluated in a small-scale, dose-escalation trial [67] and in two large, double-blind, placebo-controlled studies [68–70].

Patients were eligible for the dose-escalation study if they had a positive diagnosis of narcolepsy and were stable on TCAs, SSRIs and/or stimulants for at least 3 weeks prior to trial entry [67]. A total of 25 patients (22 of whom completed the trial) gradually withdrew from their antidepressant and sedative-hypnotic therapies and then underwent a washout period. Subsequently, they were given sodium oxybate 4.5 g/night (via two doses) for 4 weeks, and then titrated up to 6.0, 7.5 and 9.0 g/night, spending 2 weeks at each dose level. PSG was used

to evaluate sleep architecture at key points and the MWT and ESS were used to evaluate EDS symptoms. Each dose level was shown to significantly increase sleep latency (vs baseline) in both halves of the night and a significant decrease in nocturnal awakenings and increase in the amount of slow wave sleep in the second half of the night was seen with both 7.5 and 9.0 g. Furthermore, the amount of REM sleep in the second half of the night decreased significantly at all dose levels.

In the MWT evaluation, patients exhibited a significant increase in mean sleep latency versus baseline at both 4.5 and 9.0 g dose levels indicating that sodium oxybate has wake promotion effects. Significant improvement in ESS were seen at all three doses (6.0, 7.5 and 9.0 g), and the 7.5 and 9.0 g doses also showed significant improvement relative to scores from the initial evaluation under stable antidepressant usage. The increase in slow wave sleep and daytime sleep latency combined with the decrease in nocturnal awakenings seen with sodium oxybate may partially explain the marked improvement in daytime functioning observed in these patients. Peaking at the 9 g dose level, most patients also reported decreases in cataleptic attacks (86%), hypnagogic hallucinations (76%), sleep paralysis (76%), inadvertent daytime naps (76%) and daytime sleepiness (76%) and improvements in both their overall condition (81%) and in their ability to concentrate (67%).

The largest postmarketing study conducted to date evaluated sodium oxybates impact on both cataleptic symptoms and daytime functional outcomes [68,69]. This study involved 228 narcolepsy patients who were gradually withdrawn from their current cataleptic medications. Following a washout period, patients were treated with placebo, or sodium oxybate 4.5, 6 or 9 g for 8 weeks. After 4 weeks of treatment, the frequency of cataleptic attacks significantly decreased versus placebo by 44.3, 51.9 and 61.8% in the 4.5, 6 and 9 g dose groups, respectively. At the end of 8 weeks decreases of 57.0, 65.0 and 84.7% were reported.

The ESS, MWT, subjective patient reports and an investigator CGI score were used to assess changes in daytime function. By the end of 8 weeks, both ESS scores and the frequency of inadvertent daytime naps at all dose levels had significantly improved versus baseline, and the 6 and 9 g dose levels were also significantly improved relative to placebo. The MWT found a significant improvement relative to baseline for the 4.5 and 9 g groups, and a significant improvement relative to placebo for the 9 g group. Finally, using the CGI, investigators characterized 50.0, 51.7 and 63.8% of the patients in the 4.5, 6 and 9 g dose groups, respectively, as either much improved or very much improved.

A second large-scale, double-blind, placebo-controlled trial evaluated 222 narcoleptic patients who were stable on modafinil for at least 1 month [70]. These patients were randomized to 8 weeks of treatment in one out of four treatment arms: placebo, sodium oxybate only (6 g/night for 4 weeks, followed by 9 g/night for 4 weeks), modafinil only (patients current dosage) or sodium oxybate plus modafinil (same dosing schedule for each drug as in groups two and three, respectively). Significant improvements relative to placebo were seen in the MWT for both the group treated with sodium oxybate and the group receiving sodium oxybate plus modafinil.

Sodium oxybate was originally approved specifically for the treatment of cataplexy. Interestingly, the results from all clinical trials discussed here indicate that it also has a significant impact on both subjective and objective measures of excessive daytime sleepiness when stimulant medication is held constant. Earlier studies have also demonstrated that patients could control daytime sleepiness with sodium oxybate by actually reducing stimulant usage [71]. These findings recently led to US FDA approval of sodium oxybate for the treatment of EDS in narcoleptics.

Reduction of EDS may be owing to either rebound alertness, resulting from withdrawal from the second nightly dose of sodium oxybate or the increase in quality and quantity of night-time sleep resulting from treatment. In the studies discussed here, these improvements were usually significant at the 9 g dose level. Therefore, if sodium oxybate is intended-to-treat EDS symptoms, clinicians must be sure that patients receive a high enough dose to accrue this benefit. Thus, whereas cataplexy control may be reached over time at lower doses, higher doses are needed to control EDS.

Several studies have begun to evaluate the efficacy of sodium oxybate in other patient populations, including those with fibromyalgia. Work by Moldofsky demonstrated that aspects of the pain and mood symptoms experienced by these patients were correlated with an α (7.5–11 Hz) electroencephalogram non-REM sleep anomaly [72–74]. The early open-label study of fibromyalgia patients carried out by this author's group found that, over a 4-week period, sodium oxybate treatment significantly increased the percentage of time spent in slow wave sleep and significantly decreased the percentage of non-REM sleep with α intrusion [75]. Patients also reported significant improvements in subject measures of pain, fatigue and wellness. A subsequent double-blind, placebo-controlled study confirmed these findings [76]. Additional efforts in this patient population are on-going.

An interesting finding with sodium oxybate is the dose-related increase in slow wave sleep. This has been shown to be accompanied by a dose-related increase in growth hormone [79]. The majority of growth hormone secretion tends to occur at night during slow wave sleep and shifts with the temporal movement of sleep. Patients with fibromyalgia have been shown to have a decrease in growth hormone and clinically respond to sodium oxybate treatment with improvements in pain and fatigue. Thus, a potential mechanism for the effects of sodium oxybate in fibromyalgia patients may be through its effects on growth hormone.

Safety & tolerability

Sodium oxybate has been classified as a schedule III controlled substance because of concerns regarding its abuse potential. In the past, GHB has been used inappropriately as a date rape drug and by athletes using it to induce human growth hormone release, in order to enhance performance [77–79]. When used as

directed in narcolepsy patients, therapeutic doses of sodium oxybate have proven to be safe and well tolerated. Patients are instructed to take anywhere from 3 to 9 g of sodium oxybate in equally divided doses, with the first dose to be administered at bedtime and the second dose to follow 1.2–4 h later. Adverse events observed in clinical trials have been relatively few and mostly mild in severity. Overall, the most commonly reported side effects associated with the use of the drug are dizziness, headaches, nausea, pain, sleep disorder, confusion, infection, vomiting and enuresis [80]. The most recent update of the package insert has included an additional discussion concerning emergent depression and confusion as potential side effects. Furthermore, given the high sodium content of the drug, patient renal function and blood pressure should be closely monitored while using sodium oxybate. Long-term use of sodium oxybate has not been associated with addiction or the development of tolerance, and abrupt cessation has not been demonstrated to produce withdrawal symptoms.

Sodium oxybate is only available to patients through a program called the Xyrem Success Program. This program requires that a physician send patient and prescription information to a central pharmacy that controls sodium oxybate distribution. Patients are then sent educational information and required to confirm understanding of this material before distribution is initiated. This program has proven to be highly effective at restricting sodium oxybate access to the intended population and should be considered as a model for the medical distribution of other scheduled pharmaceuticals with abuse potential.

Conclusion

The results of large-scale and long-term usage studies of sodium oxybate have consistently shown that this compound is safe and effective in reducing narcolepsy symptoms. Unlike alternate therapeutic choices, sodium oxybate reduces both the frequency of catalepsy attacks and the extent of daytime sleepiness, while demonstrating no development of tolerance with long-term usage. The data from studies on cataplexy, as well as on daytime sleepiness suggest that sodium oxybate can effectively be used as a single agent to control all narcoleptic symptoms. Data on sodium oxybate usage patterns, treatment efficacy and diversion for abuse outside of clinical trials need to be collected to further support the recommendation for its use in narcolepsy and to strengthen existing risk management programs.

Expert commentary

Based on the evidence reviewed in this article, sodium oxybate should be viewed as a first-line therapeutic option for patients diagnosed with, narcolepsy. This recommendation is driven by the compounds proven ability to reduce catalepsy attacks, its wake promotion effects and its mild safety and tolerability profile. Sodium oxybate is the only compound proven to positively impact night-time sleep quality, EDS and cataplexy, thus presenting the possibility of minimizing patient medication. Furthermore, other treatments commonly used in this population are strongly associated with tolerance development and highly undesirable side effects. Because of the potential for abuse as an athletic performance enhancing and party drug, continued efforts will be necessary to ensure that sodium oxybate is not diverted to individuals other than the intended population of therapeutic users.

In my groups experience, the short half-life of sodium oxybate can result in premature awakenings, such that patients are often unable to sleep for more than 2.5 h with each dose. Common sense suggests that this could result in sleep deprivation in narcoleptics. My group initial response to this phenomenon was to increase each dose of medication or to add a third dose. However, since the side effects are dose related, my group subsequently elected to add a low dose of either zolpidem or eszopiclone to each dose of sodium oxybate. This enabled patients to sleep for a full 4 h with each dose. Patients have been on this regimen for over 10 years without difficulties. It has enabled the utilization of lower doses of sodium oxybate than might be utilized otherwise. In addition, a common complaint of patients taking sodium oxybate is the fact that they have more difficulty falling asleep with the first dose, but do better with the second dose. It should be noted that sleep is essential to the effectiveness of the medication. As such, in instances when patients experience this complaint, rather than increasing the dose of sodium oxybate, the use of either zolpidem (5 mg) or eszopiclone (1–2 mg) has been added.

Five-year view

The following areas are likely to produce major advances over the coming years or are areas where there is a strong need for additional research:

- Further exploration of sodium oxybate in other patient populations, including fibromyalgia;
- Development of a controlled-release formulation to eliminate the need for twice-nightly dosing;
- The mode of action of sodium oxybate in narcolepsy;
- Further evaluation of sodium oxybate in narcoleptic patients without cataplexy.

Key issues

- Large-scale trials indicate that sodium oxybate (Xyrem®) reduces the frequency of cataplexy attacks and improves daytime functional outcomes in narcolepsy patients.
- Sodium oxybate is unique among narcolepsy therapies in that it addresses both cataplexy and daytime sleepiness symptoms.
- Long-term treatment with therapeutic doses of sodium oxybate is generally safe and well tolerated.
- Sodium oxybate's history as a party drug and athletic performance enhancer necessitate continued risk management efforts to protect the general population, while ensuring its availability for narcoleptic patients.

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- • of interest
- •• of considerable interest

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EXHIBIT 38

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

SUPPLEMENTED OPENING EXPERT REPORT OF WILLIAM CHARMAN

HIGHLY CONFIDENTIAL

GHB would pose additional challenges if one sought to apply the teachings regarding tablet or capsule dosage forms to other dosage forms. As a result, a POSA would not view the Sustained Release patents' specification's disclosures and descriptions of tablet and capsule GHB forms as evidence that the inventors were in possession of other GHB dosage forms. This would be particularly true for formulations using microparticles in a sachet, where the difficulties associated with working with GHB due to its high solubility, hygroscopicity, and permeability through films and matrices would be exacerbated due to microparticles having greater surface area, as described above.

221. In light of the many challenges associated with developing a sustained release formulation of GHB, a POSA would have expected the inventors, had they actually developed once-nightly GHB formulations other than tablets and capsules, to have provided detailed descriptions of those formulations. Put differently, the specification lacks any description of how the inventors had allegedly achieved formulations other than the tablets and capsules mentioned in the specification having the claimed sustained release feature. The specification therefore would not have reasonably conveyed to the POSA that the inventors were in possession of the claimed subject matter and, indeed, would have led a POSA to doubt the inventors had actually developed such formulations other than tablet and capsules.

4. The Specification Lacks Any Mention of Other Dosage Forms for the Sustained Release Component

222. The specification does mention other dosage forms, such as a dry powder formulation, an encapsulated formulation, or a liquid solution or suspension. However, these formulations are only mentioned in passing in connection with an immediate release formulation. They are notably not mentioned as options for sustained release formulations (or any formulations containing a sustained release component). *See* '488 patent at 4:14-17. Indeed, the specific

I declare under penalty of perjury under the laws of the United States that the foregoing is true and correct.

Jan 26, 2023
Date

William N. Charman

EXHIBIT 39

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

OPENING EXPERT REPORT OF ALEXANDER M. KLIBANOV, PH.D.

TABLE OF CONTENTS

I. QUALIFICATIONS

1. I, Alexander M. Klibanov, Ph.D., expect to testify on behalf of the Defendant Avadel CNS Pharmaceuticals, LLC ("Avadel") in the above-captioned litigation against Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (together, "Jazz") as an expert witness regarding the validity of certain claims of U.S. Patent Nos. 11,077,079 (the "'079 Patent") and 11,147,782 (the "'782 Patent").

2. I am currently a Professor Emeritus of Chemistry and Bioengineering at the Massachusetts Institute of Technology ("M.I.T."), where I taught and conducted research for over 40 years. From 2014 to 2019 (and also from 2007 to 2012), I held the Novartis Endowed Chair Professorship at M.I.T. From 2012 to 2014, I held the Roger and Georges Firmenich Endowed Chair Professorship in Chemistry. Prior to that, I was a Professor of Chemistry and a Professor of Bioengineering at M.I.T., positions I held from 1988 and 2000, respectively. From 1979 to 1988, I was an Assistant Professor, then Associate Professor, and thereafter a Full Professor of Applied Biochemistry in the Department of Applied Biological Sciences (formerly the Department of Nutrition and Food Science) at M.I.T.

3. I obtained my M.S. degree in Chemistry from Moscow University in Russia in 1971 and my Ph.D. in Chemical Enzymology from the same University in 1974. Thereafter, I was a Research Chemist at Moscow University's Department of Chemistry for three years. From 1977 to 1979, following my immigration to the United States, I was a Post-Doctoral Associate at the Department of Chemistry, University of California in San Diego.

4. Over the last 50+ years as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of chemistry, including biological, pharmaceutical formulation, general, and medicinal.

5. During my career, I have earned numerous prestigious professional awards and distinctions for my work. For example, I was elected to the U.S. National Academy of Sciences (considered among the highest honors that can be given to an American scientist) and also to the U.S. National Academy of Engineering (considered among the highest honors that can be given to an American engineer). I am also a Founding Fellow of the American Institute for Medical and Biological Engineering and a Corresponding Fellow of the Royal Society of Edinburgh (Scotland's National Academy of Science and Letters). In addition, I have received the Arthur C. Cope Scholar Award, the Marvin J. Johnson Award, the Ipatieff Prize, and the Leo Friend Award, all from the American Chemical Society, as well as the International Enzyme Engineering Prize.

6. I currently serve on the Editorial Boards of a dozen scientific journals, including "Open Journal of Pharmacology," "Applied Biochemistry and Biotechnology," "Nanocarriers," "Open Access Academic Books in Chemistry," "Biotechnology and Bioengineering," "Journal of Biological Chemistry and Molecular Pharmacology," "Recent Patents in Biotechnology," "Current Pharmaceutical Biotechnology," "Archives of Medical Biotechnology," and "International Journal of Drug Design, Delivery, and Safety."

7. I have published over 315 scientific papers in various areas of chemistry and am also a named inventor of 32 issued United States patents plus many pending ones. I have given over 370 invited lectures at professional conferences, universities, and corporations all over the world, many dealing with pharmaceutical formulations and medicinal chemistry. Of particular relevance to the technical issues in the present litigations is my extensive experience with oral dosage forms of various drugs, including their both immediate and modified release formulations. According to a recent Stanford University-led study, the overall impact of my published work, places me in the top 0.01% of all scientists in the world.

8. In addition to my research and teaching activities at M.I.T., I have consulted for numerous pharmaceutical, medical device, and biotechnology companies. I have also founded six pharmaceutical companies and have been on the scientific advisory boards and/or boards of directors of those companies and of many others. A number of these industrial and corporate activities have dealt specifically with oral dosage forms and/or controlled release pharmaceutical formulations.

9. My curriculum vitae, attached hereto as Exhibit 1, summarizes my education and professional experience. Included in it is a list of my publications and patents.

10. Exhibit 2 is a list of all other lawsuits in which, during the previous five years, I testified as an expert at trial and/or by deposition.

11. I am being compensated at the rate of $975 per hour for time spent working on this engagement. Neither the amount of my compensation nor the fact that I am being compensated for my time has affected the opinions that I have given in this expert report. My compensation is in no way dependent on the outcome of these litigations.

II. SUMMARY OF OPINIONS

12. Counsel for Avadel ("Counsel") has asked me to form and provide opinions regarding the validity of the asserted claims of the '079 and '782 Patents (collectively, the "Resinate Patents"). Specifically, I have been asked to analyze the issue of obviousness of those asserted claims. Jazz addressed the following claims in its Final Infringement Contentions for the Resinate Patents: claims 1-3, 5-12, and 14-18 of the '079 Patent, and claims 1-24 of the '782 Patent (collectively, the "Asserted Claims of the Resinate Patents.").

13. The opinions presented herein have been formed by me to a reasonable degree of scientific certainty based on my education, training, and professional knowledge and experience,

as well as my review of numerous documents, including various patents and publications in peer-reviewed publicly available journals, as identified throughout this report and in Exhibit 3 hereto.

14. At trial, I may rely on visual aids and demonstratives related to the substance of my expert report(s). If asked by Counsel and allowed by the Court, I will supplement and/or amend my expert report(s) in connection with developments in this case, intervening orders by the Court, and/or opinions set forth by other experts in this case bearing on the substance of my expert report(s).

III. LEGAL STANDARDS AND LEVEL OF SKILL

15. I have been informed of the legal standards applicable to patent validity. I have relied upon these legal standards, as explained by Counsel, in forming my opinions set forth in this report.

A. Person of Ordinary Skill in the Art ("POSA")

16. I understand that for the '079 Patent, Jazz has claimed priority to February 18, 2015. I also understand that during prosecution, the Examiner informed the Applicant that the patent is entitled at most to a priority date of February 18, 2016. Unless stated otherwise below, my opinion regarding the level of skill in the art would not change regardless of which of the dates is considered the proper priority date and thus the time of the purported invention of the '079 Patent.

17. I understand that for the '782 Patent, Jazz has claimed priority to February 18, 2015. Unless stated otherwise below, my opinion regarding the level of skill in the art would be the same regardless of which date is considered the priority date and thus the time of the purported invention of the '782 Patent.

18. In my opinion, a POSA at the time of filing of the Resinate Patents would have had a doctorate degree (Ph.D. or Pharm.D.) in pharmaceutical sciences or a related field and around one year of relevant experience, or a Master's Degree with several years of experience in the

pharmaceutical or related industries. A POSA would typically have been a member of an inter-disciplinary team of ordinarily skilled scientists involved in drug research and development, and would have had direct access to other scientists with ordinary skills in, among other things, pharmacokinetics, pharmacodynamics, drug delivery, and other pharmaceutical characteristics. The team also would have included, or had access to, an ordinarily skilled individual with a medical degree with experience in treating sleep disorders, and particularly of narcolepsy with cataplexy.

19. At the time of filing of the Resinate Patents, I was at least a POSA, and I worked directly with and supervised others in the field of pharmaceutical sciences. For this expert report, I have been asked by Counsel to opine on issues related to pharmaceutical formulation and pharmaceutical sciences.

20. In addition, I reserve the right to supplement the aforementioned definition of a POSA to address any arguments presented by Jazz's experts.

21. I have been informed that a POSA is presumed to be aware of all relevant prior art publicly available as of the priority date. A POSA is also presumed to possess average creativity. Where applicable, I note whether there would be any difference in the understanding of a POSA based on the different possible priority dates.

B. Law of Obviousness

22. The following legal instructions have been explained to me by Counsel. A patent claim is invalid if the claimed subject matter, as a whole, would have been obvious to a POSA prior to the filing date. I understand that such a showing must be made by clear and convincing evidence. The following three factors are to be considered in an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the asserted claims; and (3) the level of ordinary skill in the pertinent art. I also understand that when a patent claims a

genus, that claim is obvious if even a single embodiment falling within the scope of the claims is obvious. Genus claim covers not just one specific invention but a class of related inventions.

23. A patent claim is invalid for obviousness if the differences between the claimed subject matter and the prior art are such that the claimed subject matter as a whole would have been obvious to a POSA prior to the filing date. Prior art includes relevant patents or patent applications, journal publications, public statements, or products before the priority date of the patent-in-suit, as well as knowledge available to a POSA before the priority date of the patent-in-suit.

24. Prior art is pertinent to the obviousness inquiry where it is from the same field of endeavor as the claimed invention (even if it addresses a different problem) or, alternatively, if the reference in question is reasonably pertinent to the problem faced by the inventor(s).

25. In order to find obviousness based on combining prior art references, a POSA must have been motivated to combine the known elements therein in the way the alleged invention does. Motivation may come from the prior art, background knowledge of a POSA, the nature of the problem to be solved, market demand, or common sense. The subject matter of a patent is obvious if the prior art creates a reasonable expectation of success in producing the claimed subject matter from the viewpoint of a POSA prior to the filing date. A reasonable expectation of success does not require a certainty of success.

26. When there is a finite number of identified, predictable solutions, it would have been obvious for a POSA to pursue those options within his or her technical grasp, and each of those options would be deemed obvious.

27. Yet another factor to be considered in an obviousness inquiry is sometimes referred to as objective indicia of nonobviousness (also called secondary considerations), i.e., certain real-world practical considerations.

IV. CLAIM CONSTRUCTION

28. I understand from Counsel that a claim construction order has been issued by the Court in this case. My opinions in this report are based on the Court's ruling to the construction of the following claim terms in the Resinate Patents:

Claim Term	Patent and Claims	Adopted Construction
"controlled release component"	'079 Patent, Claims 1, 10	Compositions characterized by having at least one of the active components having a release over a period of at least about 2 to about 8 hours
"modified release particles"	'782 Patent, Claims 1, 14	Plain and ordinary meaning, i.e., particles containing an active pharmaceutical ingredient with a release profile that is different from that of an immediate release particle

V. THE ASSERTED '079 PATENT CLAIMS ARE INVALID AS OBVIOUS

29. I understand from Counsel that it is Jazz's position that the priority date for the asserted claims of the '079 Patent is February 18, 2015. However, I am informed that during prosecution the Examiner informed the Applicant that the patent is entitled at best to a priority date of February 18, 2016. For purposes of this section of my report, my opinions are from the standpoint that the claims of the '079 Patent are entitled to a priority date of February 18, 2016. But my opinion would not change even if the claims of the '079 Patent were entitled to the priority date of February 18, 2015, as insisted by Jazz.

30. I understand from Counsel that Jazz has asserted claims 1-3, 5-12, and 14-18 of the '079 Patent against Avadel ("Asserted Claims of the '079 Patent"). Claims 1 and 10 of the '079 Patent are independent. Claims 2-3, 5-9, 11-12, and 14-18 depend on claim 1 or claim 10.

31. Claim 1 is:

> "A method of treating narcolepsy in a patient in need thereof, the method comprising:
>
> (a) administering a single daily dose to the patient,
>
> (b) the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate,
>
> (c) wherein the administering comprises: opening a sachet containing a solid oxybate formulation,
>
> (d) mixing the formulation with water, and orally administering the mixture to the patient,
>
> (e) wherein the oxybate formulation comprises an immediate release component and a controlled release component."

32. Claim 10 is:

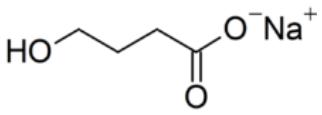
> "A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:
>
> administering a single daily dose to the patient,
>
> the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate,
>
> wherein the administering comprises: opening a sachet containing a solid oxybate formulation, mixing the formulation with water, and orally administering the mixture to the patient,
>
> wherein the oxybate formulation comprises an immediate release component and a controlled release component."

A. Scope and Content of the Prior Art

33. As stated in the legal section above, I understand from Counsel that prior art may be in the form of, among other things, a patent or patent application, a journal publication, a public

statement, or a product. The references below are pertinent prior art because they are within the field of endeavor of the Resinate Patents and, as described in detail below, the Liang 2006, Lebon 2013, and Allphin 2012 references address the problem facing the inventors of the '079 Patent, which was to have a single nightly dose of GHB that would include "a sufficient amount of GHB [] present in the blood to initiate the sleep function of GHB and then the controlled release component may engage to maintain the blood concentration above the threshold for a complete sleep of sufficient duration." '079 Patent at col. 4, ll. 20-24.

34. A POSA would have known at the time of the '079 Patent's priority date that Xyrem [i.e., sodium gamma-hydroxybutyrate or Na GHB, whose chemical structure is depicted at the end of this paragraph] was the only sodium oxybate drug approved by the United States Food and Drug Administration ("FDA") for the treatment for cataplexy and excessive daytime sleepiness (EDS) in narcolepsy. Xyrem is a sodium oxybate aqueous solution to be administered orally twice nightly. XYREM® (sodium oxybate) oral solution label was revised in April 2014 ("Xyrem 2014 Label"). However, a POSA would also have been aware of additional prior art references that discuss formulating sodium oxybate, or oxybate salts in general, some in a single daily dose, as discussed below.



1. Liang 2006

35. Liang 2006 is U.S. Patent Application Publication 2006/0210630 titled "Controlled Release Compositions of Gamma-Hydroxybutyrate." The publication is cited on the face of the '079 Patent. In Liang 2006, the inventors Likan Liang et al. report on the results from altering the delivery profile of GHB to provide for a "convenient once nightly or once daily dosing regiment

[sic] for the oral delivery of one or more gamma-hydroxybutyric acid salts to an animal." Liang 2006 at ¶ 12.

36. Liang 2006 discusses a variety of challenges known to affect GHB formulation. It states that "[s]odium gamma-hydroxybutyrate is highly [water-]soluble, hygroscopic, and strongly alkaline." *Id.* at ¶ 5. It also states that "the therapeutic dose [of Na GBH] is normally very high," "[f]or example, a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients." *Id.* Liang 2006 also states that the current twice-nightly dosing regimen requires patients to "take an initial dose of sodium gamma-hydroxybutyrate around bedtime and [] wake up four hours later to take a second dose. Such a dose regimen is rather inconvenient." *Id.* at ¶ 3.

37. Liang 2006 discloses that "[i]n one of the preferred embodiments, the composition comprises multiple delayed release pellets or beads (used interchangeably herein) and an immediate release component." *Id.* at ¶ 29. An immediate release component combined with pH sensitive delayed/controlled release particles "can conveniently replace the nightly multidose regimen of the existing commercial product," which eliminates the need for a patient "to wake up and take a second dose during the night." *Id.* at ¶ 36. The immediate release component can be in the form of, for example, "a sachet." *Id.* at ¶ 45. The immediate release and controlled release components can also be pre-mixed. *Id.* at ¶ 47 ("[T]he immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed/controlled release particles"); *id.* at ¶ 48 ("[T]he immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion.").

2. Lebon 2013

38. Lebon 2013 is U.S. Patent No. 8,529,954, titled "Composition based on gamma-hydroxybutyric acid." In Lebon 2013, the inventors Christophe Lebon and Pascal Suplie describe granules of "gamma-hydroxybutyric acid" or "its pharmaceutically acceptable salt[]." Lebon

2013, at Abstract. Lebon 2013 notes that the "major drawback" of GHB is that it "has a short half-life, a high plasma concentration peak, with fast elimination and variable (low) bioavailability as a function of feeding." *Id.* at col. 1, ll. 36-40. Because of this particular pharmacokinetic profile, Lebon 2013 states that the drug administration involves a "substantial daily dose of 4 to 9 g, in doses repeated every 3 to 4 hours, and in particular in the middle of the night for narcoleptic patients, which results in a limited effectiveness due to the wide variations in plasma concentration as well as a risk of intolerance due to these same variations." *Id.* at col. 1, ll. 46-51. Lebon 2013 further warns against using oral solution (the dosage form of Xyrem, the only sodium oxybate product on the market) to achieve an altered release profile: "The existing galenic forms do not allow this profile to be improved. For example, oral solutions are restrictive in terms of observance and can give rise to problems of stability and preservation." *Id.* at col. 1, ll. 53-57.

39. Lebon 2013 discloses a "novel galenic form based on gamma-hydroxybutyric acid or one of its salts" to reduce the number of daily doses, and in particular avoid taking a second dose at night. *Id.* at col. 1, ll. 64-67; col. 2, ll. 1-5, 11-16; col. 3, ll. 3-6. Lebon 2013 describes granulates that "may be packaged in individual containers, for example in sachets, sticks, paper bags, or bottles, and preferably in plastic ampoules." *Id.* at col. 5, ll. 49-51; *see also* col. 8, ll. 7-8.

3. Allphin 2012

40. Allphin 2012 is U.S. Patent Application Publication 2012/0076865 to Allphin et al., published on March 29, 2012, and titled "Controlled release dosage forms for high dose, water soluble, and hygroscopic drug substances." This patent publication is cited on the face of the '079 Patent.

41. Allphin 2012 discusses various difficulties with formulating GHB to "provide prolonged delivery." Allphin 2012 at Abstract. It teaches that "GHB is very soluble, generally

requires a relatively high dose, has a low molecular weight, and exhibits a short circulating half-life once administered." *Id.* at ¶ 29. Allphin 2012 also teaches that single dose of GHB can have "a range of about 500 mg to about 12 g of drug." *Id.* at ¶ 42.

B. The Asserted Claims of the '079 Patent Would Have Been Obvious in Light of the Prior Art and the Knowledge of a POSA

42. I have reviewed Jazz's Final Validity Contentions as to whether the Asserted Claims of the '079 Patent have written description support and are enabled. *See* Jazz's Responses to Defendant's Invalidity Contentions ("Jazz's Final Validity Contentions") at 94-98, 203-206. I have not been asked to consider whether the Asserted Claims of the '079 Patent indeed have adequate written description support in, or are enabled by, the '079 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified in Jazz's Final Validity Contentions. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '079 Patent. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

43. I have also reviewed Jazz's Final Validity Contentions that the Asserted Claims of the '079 Patent are not obvious. *See* Jazz's Final Validity Contentions at 105-49. Based on my review, I understand that Jazz only disputes whether the following two claim limitations of the Asserted Claims of the '079 Patent would have been non-obvious: "opening a sachet containing an oxybate formulation" and "mixing the formulation with water." *Id.* at 138-49.

1. Claim 1

a. "A method of treating narcolepsy in a patient in need thereof, the method comprising:"

44. To the extent that this preamble is limiting (i.e., acts as a claim limitation), it is my opinion that a POSA would have found that both Liang 2006 and Lebon 2013 disclose "[a] method of treating narcolepsy in a patient in need thereof." I note that Jazz does not challenge the obviousness of this claim preamble in its Final Validity Contentions. Jazz's Final Validity Contentions at 138-49.

45. Liang 2006 discloses that GHB can be used "in the treatment of narcolepsy." *Id.* at ¶ 1; *see also id.* at ¶ 2 ("Sodium gamma-hydroxybutyrate (GHB or sodium oxybate) . . . has broad indications including narcolepsy."); ¶ 5 ("Xyrem® is prescribed to narcolepsy patients."). Lebon 2013 similarly discloses that Xyrem (sodium oxybate), "is used for the treatment of narcolepsy in adult patients exhibiting cataplexy." *Id.* at col. 1, ll. 28-31. But Lebon 2013 explains that "the major drawback of GHB in terms of effectiveness is linked to its pharmacokinetic profile," limiting the effectiveness of GHB and requiring the administration of multiple doses repeated every few hours. *Id.* at col. 1, ll. 36-52. Lebon 2013 states that the "object of the present invention" was to provide a "novel galenic form based on gamma-hydroxybutyric acid or one of its salts (in particular sodium) which makes it possible to circumvent the aforementioned drawbacks" associated with the administration of GHB. *Id.* at col. 1, ll. 64-67.

46. Since this preamble was disclosed by both Liang 2006 and Lebon 2013, a POSA would have found this claim preamble to be obvious.

b. "(a) administering a single daily dose to the patient"

47. I note that Jazz does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz's Final Validity Contentions at 138-49.

48. I have reviewed Jazz's Final Validity Contentions as to whether the "administering a single daily dose to the patient" claim limitation has written description support in, and is enabled by, the '079 Patent specification. *See* Jazz's Final Validity Contentions at 203-06.

49. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, or is enabled by, the '079 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '079 Patent. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

50. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '079 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to achieve a single daily dose of GHB as claimed with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

51. Liang 2006 describes a single daily dosage of GHB that is convenient because "a patient does not need to wake up and take a second dose during the night." Liang 2006 at ¶ 36. Liang 2006 discloses a way to achieve a "single daily dose" by combining immediate release and "delayed/controlled release particles" of GHB, which it teaches "can constitute a complete once-nightly or once-daily dose." *Id.* at ¶ 32. Liang 2006 clarifies that the term "combining" can mean

supplying and consuming all components "simultaneously in the same presentation or dosage form." *Id.* Liang 2006 further discloses that the "delayed/controlled release" particles and immediate release component can be "supplied as pre-mixed doses," thus comprising a single dosage. *Id.* at ¶ 33.

52. Likewise, Lebon 2013 teaches that its invention "reduce[s] . . . the number of times it [i.e., gamma-hydroxybutyric acid or its salt] is taken per day." *Id.* at col. 2, ll. 1-4. Lebon 2013 further describes the current dosing regimen for narcolepsy as "repeated every 3 to 4 hours. . . in the middle of the night." *Id.* at col. 1, ll. 46-48.

53. Based on the disclosures in Liang 2006 and Lebon 2013, and given the aforementioned assumption that the '079 Patent has adequate written description and enablement for this claim limitation, a POSA would have been motivated to achieve a method of administering a single daily dose to a patient with a reasonable expectation of success.

54. I have also reviewed, and rely on, the opinion of Bruce Corser, M.D., who opined that, as of 2010, physicians specializing in sleep recognized shortcomings of twice-nightly forms of oxybate, and consequently recognized the need for once-nightly forms of oxybate. *See* Corser Report at ¶¶ 56-65.

55. Thus, it is my opinion that a POSA would have found this claim limitation to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

c. "(b) the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate,"

56. This claim limitation would have been obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge available to a POSA. Liang 2006 and Lebon 2013 both disclose "an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate." I note that Jazz

does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz's Final Validity Contentions at 138-49.

57. Liang 2006 discloses a single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate. Liang 2006 discloses that "a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients." *Id.* at ¶ 5. Liang 2006 also discloses that Xyrem is composed of sodium GHB. *Id.* at ¶ 3. In addition, Liang 2006 discloses that the GHB dosage can be adjusted beyond the daily dose expressly recited in Liang 2006: "the immediate release component can be at a slightly higher than normal dose, and the delayed release dose can be at a normal dose or at a reduced dose." *Id.* at ¶ 41.

58. In addition, Lebon 2013 discloses a daily dose within the range of 4 to 12 grams. It states that the current dosing regimen involves "a substantial daily dose of 4 to 9 g." *Id.* at col. 1, ll. 46-47. Moreover, the '079 Patent identifies no unique or unexpected properties associated with the recited range of oxybate amount. I understand from Counsel that where the claimed invention has an overlapping range with a disclosure in the prior art, the burden shifts to the patentee to establish non-obviousness either by a showing that the prior art taught away from the invention or by a showing of new and unexpected results relative to the prior art.

59. Further, at the '079 Patent's priority date, it was known in the art that a single dose of GHB can have "a range of about 500 mg to about 12 g of drug." Allphin 2012 at ¶ 42. Thus, a POSA would have also been motivated to modify the amount of sodium oxybate in the single daily dose described in Liang 2006 and/or Lebon 2013 to arrive at the claimed range of "from 4.0 g to 12.0 g of sodium oxybate."

60. Thus, based on my review of Lebon 2013 and Liang 2006, this claim limitation would have been obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

d. "(c) wherein the administering comprises: opening a sachet containing a solid oxybate formulation,"

61. I have reviewed Jazz's Final Validity Contentions as to whether the "wherein the administering comprises: opening a sachet containing a solid oxybate formulation" claim limitation has written description support in, and is enabled by, the '079 Patent specification. *See* Jazz's Final Validity Contentions at 205-06. Jazz contends that the written description legal requirement is satisfied because "[t]he specification of the '079 Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10." *Id.*

62. I have also reviewed Jazz's Final Validity Contentions concerning enablement of the Asserted Claims of the '079 Patent. *See* Jazz's Final Validity Contentions at 206. I understand based on my review that Jazz asserts that the '079 Patent specification enables the full scope of the Asserted Claims of the '079 Patent.

63. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, or is enabled by, the '079 Patent specification. Instead, for purposes of this report I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to

demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '079 Patent (including both resinate and non-resinate sachet formulations). Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

64. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '079 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to achieve a sachet formulation as claimed with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

65. Liang 2006 discloses "opening a sachet." In particular, Liang 2006 discloses that "[t]he dosage forms of the current invention comprise an immediate release component in the form of a solid, a semi-solid or a liquid. It can be a . . . sachet . . . or the like." Liang 2006 at ¶ 45. It would have been obvious to a POSA from its disclosures that a pre-mixed powder comprising both immediate release and controlled release components disclosed by Liang 2006 can be administered in a sachet. *Id.* at ¶ 47 ("[T]he immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed/controlled release particles"); *id.* at ¶ 48 ("[T]he immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion."). Further, a POSA would have understood that administration of the GHB formulation in a sachet requires opening the sachet.

66. As discussed above, Jazz contends that written description is satisfied because "[t]he specification of the '079 Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate

containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10." Jazz's Final Validity Contentions at 205-06. The disclosure in Liang 2006 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '079 Patent.

67. Lebon 2013 likewise discloses the use of a sachet to store the GHB formulation and indeed lists a sachet as very first among a handful of allowed choices. *Id.* at col. 5, ll. 49-51 ("The granulates according to the invention may be packaged in individual containers, for example in sachets, sticks, paper bags or bottles, and preferably in plastic ampoules."). Opening the sachet would be a characteristic that is necessarily present based on the disclosures in Lebon 2013 of a sachet. For example, the 46th Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations - TRS, No. 970 (June 1, 2012) ("WHO 2012") is a World Health Organization report on common strategies for pharmaceutical dosage forms. It teaches that "[p]owders and multiparticulates are provided in sachets or in hard capsules that allow the contents to be taken directly or after manipulation," thereby implying that it must be opened. *Id.* at 213.

68. As discussed above, Jazz contends that written description is satisfied because "[t]he specification of the '079 Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10." Jazz's Final Validity Contentions at 205-06. The disclosure in Lebon 2013 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '079 Patent.

69. A powder for suspension is a well-known multiparticulate dosage form where the formulation is made up of multiple small particles. The drug is administered by adding a liquid or a drink to form a suspension to be orally ingested. A POSA would have been motivated to arrive at such a dosage form because it is expressly taught by Liang 2006 and because a POSA would have recognized that a sachet resolves various challenges with administrating a GHB formulation for narcolepsy, namely the high dose and the related challenge of swallowability. The benefits and methods of administrating a drug in a multiparticulate form as an oral suspension were well known in the art (i.e., a powder for oral suspension). It was known in the art that treating narcolepsy using GHB requires a "high" dose. *See, e.g.*, Liang 2006 at ¶ 31 (disclosing that the dosage needed for oxybate is preferably "high"); Allphin 2012 at ¶ 29 (disclosing that Na GHB "requires a relatively high dose" and, therefore, "should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration"). For drugs at a high dose, such dosage forms as tablets or capsules may not be appropriate, as it would present a swallowability difficulty to the patient. *See, e.g.*, Liang 2006 at ¶ 31 ("Preferably, due to the high dosage of GHB, the immediate release component is a liquid."). The advantages of administrating a multiparticulate drug as a powder for oral suspension include increasing swallowability and reduce the challenges of food compatibility or choking. *See, e.g.*, Alexandra F. Bowles, *Development of A Multiparticulate-Based Platform for Delivering Functionalized Capability as An Oral Liquid Dosage Form* 64 (2013) (Ph.D. thesis, Univ. Coll. London Sch. of Pharm.) ("Bowles 2013") ("By using a suspension form, we allow for swallowability and reduce the challenges of other multiparticulate administration methods such as food compatibility, choking or the use of expensive proprietary technologies."). Given the background knowledge of a POSA, it is thus my opinion that a POSA would have been motivated by Liang 2006 and/or Lebon 2013

to use a powder for suspension dosage form to facilitate administration of the large dose of GHB known to be needed in the art for the treatment of narcolepsy.

70. Further, a POSA would have been motivated to store a powder for suspension formulation of GHB in a sachet as directed by Liang 2006 and Lebon 2013 because of the well-known advantages a sachet can provide, including a flexible method of drug administration. WHO 2012 teaches that "powders and multiparticulates [] provided in sachets" "possess great flexibility." *Id.* at 213. *See also* Bowles 2013 at 77 (explaining that liquid dosage forms require many different excipients and in higher levels compared to solid dosage form).

71. Finally, a POSA would have been motivated to use a sachet for use with the powder for suspension dosage form of the GHB formulation of Liang 2006 and Lebon 2013 in light of their teachings with a reasonable expectation of success because sachets were routinely used in the art for formulations at the priority date of the '079 Patent. For example, Robert J. Balch & Andrea Trescot, *Extended-Release Morphine Sulfate in Treatment of Severe Acute and Chronic Pain*, 3 J. PAIN RSC. 191, 195 (2010) ("Balch 2010") is an article that discusses the administration of a powder for suspension dosage forms by opening a sachet. *See also* Bowles 2013 at 57 ("It can be seen that commercially available multiparticulates are mainly supplied for administration in capsules, sachets, or multi-use containers."); WHO 2012 at 215 (describing sachets as a formulation dosage form for "sustained-release formulations"); Nexium (esomeprazole magnesium) delayed-release capsules for oral use and Nexium (esomeprazole magnesium) for delayed-release oral suspension 2014 label at 6 ("Nexium 2014 label") (Nexium, a delayed-release formulation of esomeprazole magnesium, has a sachet dosage form).

72. Jazz states that "a POSA would have known that GHB is a hygroscopic drug product that would not have been well-suited to formulation in a sachet." Jazz's Final Validity

Contentions at 145. I disagree with this conclusion. As of the time those references were published, GHB was known to be a hygroscopic drug. Liang 2006 at ¶ 5. But since both Liang 2006 and Lebon 2013 teach a sachet as a preferred dosage form, as well as the explicit disclosure in both Liang 2006 and Lebon 2013 of formulating GHB in a sachet, a POSA would have been motivated to make a sachet formulation of GHB with a reasonable expectation of success.

73. Thus, a POSA would have found this claim limitation obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

e. "(d) mixing the formulation with water and orally administering the mixture to the patient,"

74. I have reviewed Jazz's Final Validity Contentions as to whether the "mixing the formulation with water and orally administering the mixture to the patient" claim limitation has written description support in, and is enabled by, the '079 Patent specification. *See* Jazz's Final Validity Contentions at 205-06. Jazz contends that the written description legal requirement is satisfied because "[t]he specification of the '079 Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10." *Id.*

75. I have also reviewed Jazz's Final Validity Contentions concerning enablement of the Asserted Claims of the '079 Patent. *See* Jazz's Final Validity Contentions at 206. I understand based on my review that Jazz asserts that the '079 Patent specification enables the full scope of the Asserted Claims of the '079 Patent.

76. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, or is enabled by, the '079 Patent specification. Instead, for the

purposes of this report I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '079 Patent (including both resinate and non-resinate sachet formulations). Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

77. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '079 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to mix the sachet formulation with water and orally administer the mixture to the patient with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

78. Liang 2006 discloses that the immediate release component can be "an aqueous solution" with GHB. Liang 2006 at ¶ 49. Further, it discloses that the "delayed release particles are mixed with the liquid [that is the immediate release aqueous solution] and then ingested." *Id.* at ¶ 50. A POSA would have understood that there is necessarily water in an aqueous solution. A POSA, therefore, would have been motivated to mix the formulation with water before administering it to a patient with a reasonable expectation of success.

79. Lebon 2013 likewise discloses that "[t]he granulates according to the present invention may be ingested directly or may be dispersed in a solution, or mixed in a dietary support

such as a yoghurt or a compote." Lebon 2013 at col. 5, ll. 60-62. Since water is necessarily present in a drink, a POSA would have been motivated to mix the formulation with water and orally administer it to patient with a reasonable expectation of success.

80. As discussed above, Jazz contends that written description is satisfied because "[t]he specification of the '079 Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10." Jazz's Final Validity Contentions at 205-06. The disclosures in Liang 2006 and Lebon 2013 are substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '079 Patent.

81. Further, it was known to a POSA at the time that the lone commercial oxybate drug, Xyrem, "contain[ed] 0.5 g of sodium oxybate in USP Purified Water." *See* Xyrem 2014 label at 13. Therefore, a POSA would have been motivated to use water by this sole existing commercial drug with GHB as the active moiety.

82. In addition, mixing the contents of a sachet with water and orally administering the mixture to the patient was a routine method of administrating a powder for suspension dosage form well known in the field. *See* PHARMACEUTICAL SUSPENSIONS: FROM FORMULATION DEVELOPMENT TO MANUFACTURING 45 (Kulshreshtha et al., eds., 2010) ("PHARMACEUTICAL SUSPENSIONS 2010") ("Suspensions are prepared by insoluble solids in dispersion medium, mostly water."). For example, WHO 2012 teaches that a sachet can be used as a single-dose administration, and that one way of administering it is to "reconstitute the product, [] with boiled and cooled water." *Id.* at 212. Similarly, Bowles 2013 provides an overview of ways of

administering multiparticulate formulations, including a sachet, one of which is "administering a multiparticulate in a suspension." *Id.* at 59. Fang Liu et al., *Patient-Centered Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations*, 74 DRUGS, 1871, 1881 (2014) ("Liu 2014") further teaches that "[m]ultiparticulates . . . presented in sachets or capsules [] can be reconstituted in a drink to provide solutions or suspensions." A POSA would have recognized that the multiparticulate formulations discussed in WHO 2012, Bowles 2013, and Liu 2014 are all intended for oral administration.

83. As of the priority date of the '079 Patent, a POSA would also have been familiar with commercial examples that include instructions on how to administer a powder for oral suspension dosage form. For example, the Nexium 2014 label taught administrating the drug by suspending it in water and drinking it within 30 minutes. *Id.* at 6. *See also* Nina Bladh et al., *A New Esomeprazole Packet (Sachet) Formulation for Suspension: In Vitro Characteristics and Comparative Pharmacokinetics Versus Intact Capsules/Tablets in Healthy Volunteers*, 29 CLINICAL THERAPEUTICS 640 (2007) ("Bladh 2007") (discussing the results of a clinical study for Nexium delayed-release capsules, including a description of the method for its administration).

84. Thus, in view of the disclosures in the art teaching administering a drug formulation stored in a sachet by mixing it with water, and in light of the teachings of Liang 2006 and Lebon 2013, a POSA would have been motivated to arrive at a method of administering the GHB formulation stored in a sachet by mixing it with water and administering it orally. As discussed above, a known challenge to formulating GHB for treatment of narcolepsy is the required large doses of the drug. *See, e.g.*, Liang 2006 at ¶ 31 (disclosing that the dosage needed for oxybate is "high"); Allphin 2012 at ¶ 29 (disclosing that GHB "requires a relatively high dose" and, therefore, "should be configured to deliver large doses of drug over a prolonged period of time, while being

acceptably sized for oral administration"). Prior art thus taught that drugs formulated for reconstitution as a suspension are more easily swallowed compared to other conventional solid dosage forms. *See, e.g.*, Bowles 2013 at 64 ("By using a suspension form, we allow for swallowability and reduce the challenges of other multiparticulate administration methods such as food compatibility, choking or the use of expensive proprietary technologies."); Bladh 2007 at 640 ("A packet (sachet) formulation of esomeprazole for suspension has been developed for use in patients who have difficulty swallowing.").

85. Jazz states that "administering the claimed sachet formulation in water—as opposed to another vehicle like juice or applesauce—would do little to mask the salty taste of sodium oxybate. Therefore, a POSA would not have been motivated to use water as claimed." Jazz's Final Validity Contentions at 147. I disagree with this conclusion. The lone commercial sodium oxybate product used water despite the allegedly salty taste. Even taking as true Jazz's statement, the salty taste of sodium oxybate would have simply motivated a POSA to use a taste masking agent in addition to water, instead of deterring a POSA from using water. Moreover, given the aforementioned assumption that the '079 Patent has adequate written description and enablement for this claim limitation, as well as the explicit disclosures in Liang 2006, Lebon 2013, and the Xyrem label reciting the mixing of GHB in water, a POSA would have been motivated to mix the GHB formulation with water before administering to a patient with a reasonable expectation of success.

86. Thus, it is my opinion that it would have been obvious for a POSA to administer the formulation by mixing the formulation with water and orally administering the mixture.

f. "(e) wherein the oxybate formulation comprises an immediate release component and a controlled release component."

87. It is my opinion that a POSA would have found this claim limitation obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. I note that Jazz does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz's Final Validity Contentions at 138-49.

88. Liang 2006 discloses a GHB formulation with both an immediate release and a controlled release component. Liang 2006 states that "[t]he dosage forms of the current invention comprise an immediate release component . . . wherein the immediate release component is present together with (or separated [sic] contained from) one or more pH sensitive delayed/controlled release particles," *id.* at ¶ 27, "[i]n one of the preferred embodiments, the composition comprises multiple delayed release pellets or beads (used interchangeably herein) and an immediate release component," *id.* at ¶ 29, and "[c]ombining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete . . . dose," *id.* at ¶ 32. Liang 2006 also discloses that the "delayed/controlled release" particles and immediate release component can be "supplied as pre-mixed doses," thus comprising a single dosage. *Id.* at ¶ 33. Further, it discloses a preferred embodiment where "an immediate release component is combined with . . . delayed/ controlled release particles." *Id.* at ¶ 38.

89. Furthermore, it would have been obvious to combine the two components in view of Lebon 2013. Lebon 2013 discloses that "[t]he present invention relates to a granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2, ll. 25-29. Lebon 2013 further discloses that "[a]ccording to a particular embodiment [of its invention], the core of the granulates may however comprise particles of gamma-

hydroxybutyric acid or one of its salts." *Id.* at col. 2, ll. 51-53. A solid core supported by the gamma-hydroxybutyric acid or one of its salts, without any other excipients, would have been understood by a POSA to possess an immediate release profile. Lebon 2013 also discloses that "[d]ifferent types of coating may also be produced which each play a particular role, namely: consolidation, production of a hydrophobic layer, colouring, bitterisation, modification of the release of the active constituent . . . ." *Id.* at col. 7, ll. 66-67 to col. 8, ll. 1-2. A POSA would have understood the teachings of Lebon 2013 to describe granulates of both an immediate release and a controlled release variety: (i) if the applied coating does not modify the release of the active constituent, then the granulate would be an immediate release granulate, and (ii) if the applied coating modifies the release, then the granulate would be a controlled release granulate.

90. Lebon 2013 further discloses granulates of GHB having a controlled release profile. It discloses that adding a "sustained-release coating" "enable[s]a modified or delayed release of the active constituents (modified-release granulates)." Lebon 2013 at col. 4, ll. 34-37; *see also* Claims 5, 15. Lebon 2013 further discloses that the coating can consist of "copolymers of methacrylates and acrylates, Eudragit® S100, shellac, cellulose derivatives, in particular ethylcellulose, and acrylic derivatives." *Id.* at col. 4, ll. 38-41.

91. Furthermore, a POSA would have been motivated to combine the GHB granulates having an immediate release profile with the GHB granulates having a "modified or delayed release" profile to arrive at one oxybate formulation to treat narcolepsy given the express teachings of the prior art. Liang 2006 at ¶ 38 ("More preferably, an immediate release component is combined with a single type of pH sensitive delayed/controlled release particles."). Further, it would have been obvious to a POSA that, in order to treat narcolepsy, a patient would need to both fall asleep and stay asleep. An immediate release component would have been needed for the

patient to fall asleep, and a controlled release component would have been needed for the patient to stay asleep.

92. For the above-described reasons, a POSA would have found claim 1 of the '079 Patent obvious over Liang 2006 and Lebon 2013 in view of the general knowledge in the field.

2. Claim 2

a. "The method of claim 1, wherein the orally administering occurs at night."

93. Claim 2 depends directly on claim 1 and further recites "wherein the orally administering occurs at night." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

94. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

95. A POSA would have known that a treatment for narcolepsy should be administered at night. For example, the Xyrem 2014 Label discloses that the oral administration should occur at night. *See id.* at 3 (instructing patients to take the first dose at bedtime and the second dose 2.5 to 4 hours later), 4 ("Patients should take both doses of Xyrem while in bed and lie down immediately after dosing. . . . ").

96. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

3. Claim 3

a. "The method of claim 1, wherein the oxybate formulation is mixed with water immediately prior to administration."

97. Claim 3 depends directly on claim 1 and further recites "wherein the oxybate formulation is mixed with water immediately prior to administration." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

98. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

99. A POSA would have been motivated to obtain the recited subject matter given that, among other things, the oxybate formulation would need to be mixed immediately prior to administration to avoid the negative effects of the particles settling out of suspension. *See, e.g.*, PHARMACEUTICAL SUSPENSION at 110 ("When left undisturbed for a long period of time the suspension particles will aggregate, sediment, and eventually cake."); Bladh 2007 at 640 ("the packet formulation was stable for up to 60 minutes after reconstitution."); Nexium 2014 Label at 6 (instructing that the administration must happen "within 30 minutes" of the mixing with water).

100. Further, as noted above, a POSA would have had a reasonable expectation of success in mixing the formulation with water immediately before administration because of the general knowledge in the art describing that the suspension is often mixed with water immediately prior to administration.

101. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

4. Claim 5

a. "The method of claim 1, wherein the administering promotes the patient to sleep for 6 to 8 hours."

102. Claim 5 depends directly on claim 1 and further recites "wherein the administering promotes the patient to sleep for 6 to 8 hours." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

103. I have reviewed Jazz's Final Validity Contentions as to whether the "wherein the administering promotes the patient to sleep for 6 to 8 hours" claim limitation has written description support in, and is enabled by, the '079 Patent specification. *See* Jazz's Final Validity Contentions at 96-98. Jazz contends that the written description legal requirement is satisfied because: "One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. . . . Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities." ('079 Patent at col. 4, ll. 4-13). *Id.* at 96.

104. I have not been asked to consider whether this claim indeed has adequate written description support in, or is enabled by, the '079 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '079 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '079 Patent, and (b) the '079 Patent specification enables a POSA to practice the full

scope of the Asserted Claims of the '079 Patent. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

105. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '079 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to arrive at a formulation that promotes a patient to sleep for 6 to 8 hours with a reasonable expectation of success.

106. Liang 2006 discloses administering the dosage form so as to promote the patient to sleep for 6 to 8 hours. It teaches that the twice-nightly Xyrem solution was inconvenient because it required that the patient wake up after 4 hours to take a second dose. Liang 2006 at ¶ 3 ("Patients take an initial dose of sodium gamma-hydroxybutyrate around bedtime and must wake up four hours later to take a second dose. . . . Such a dose regimen is rather inconvenient."). A POSA would have therefore understood that it is desirable to arrive at a formulation that promotes a total of approximately eight hours of sleep with a single daily dose.

107. As discussed above, Jazz contends that written description is satisfied because: "One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. . . . Additionally, it is an object of the invention to ensure that the sleep-inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities." ('079 Patent at col. 4, ll. 4-13). Jazz's Final Validity Contentions at 96. The disclosure in Liang 2006 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '079 Patent.

108. Lebon 2013 provides a similar motivation. It teaches that the narcoleptic patient needed to take a commercially existing dose of GHB every 3-4 hours in the middle of the night.

Id. at col. 1, ll. 46-49. A POSA would have understood the disclosure in Lebon 2013 to mean that each dose of Xyrem only caused the patient to sleep for 3-4 hours per dose. *See* Xyrem 2014 Label at 3 (instructing patients to take the first dose at bedtime and the second dose 2.5 to 4 hours later).

109. As discussed above, Jazz contends that written description is satisfied because: "One object of the invention is to maintain the concentration of GHB in the blood at levels sufficient to promote sleep for up to 8, 7, 6, or 5 hours. . . . Additionally, it is an object of the invention to ensure that the sleep inducing effects of GHB do not remain for longer than the above periods as it would compromise a patient's ability to perform normal day to day activities." ('079 Patent at col. 4, ll. 4-13). Jazz's Final Validity Contentions at 96. The disclosure in Lebon 2013 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '079 Patent.

110. Further, it was well known in the art at the priority date of the '079 Patent that 6 to 8 hours of sleep per night was considered optimal for patients taking sodium oxybate. For example, Mignot provides a review of methods of administering sodium oxybate to narcolepsy patients so that the patient can "fully consolidate a six to eight hour night." Emmanuel J. M. Mignot, *A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes*, 9 NEUROTHERAPEUTICS 739, 746 (2012). Thus, Mignot would have provided a POSA with further motivation to promote the patient to sleep for 6 to 8 hours.

111. Given the aforementioned assumption that the '079 Patent has adequate written description and enablement for this claim limitation, both Liang 2006 and Lebon 2013 would have provided a POSA with the motivation and a reasonable expectation of success in obtaining such a dosage form. *See* Liang 2006 at ¶ 12 ("It provides a convenient once nightly or once daily dose regiment for the oral delivery of one or more gamma-hydroxybutyric acid salts to an animal."),

¶ 32 ("Combining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete once-nightly or once-daily dose."); ¶ 33 (clarifying "delayed/controlled release" particles and immediate release component can be "supplied as pre-mixed doses," thus comprising a single dosage); Lebon 2013 at col. 2, ll. 1-4 ("Thus an object of the present invention is to provide a novel galenic form based on gamma-hydroxybutyric acid or one of its salts which makes it possible to reduce the daily dose and the number of times it is taken per day…").

112. Therefore, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

5. Claim 6

a. "The method of claim 1, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate."

113. Claim 6 depends directly on claim 1 and further recites "wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

114. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

115. All of the dosages recited in this claim fall within the range disclosed by Liang 2006. A POSA would have understood that milliequivalent (mEq) measures the amount of solute in mg equal to 1/1000th of gram of the equivalent weight of the substance. It can be converted to weight for any given solute, such as sodium oxybate. (mEq = (mg/molecular weight) x valence).

According to this conversion, 35 mEq of oxybate is about 4.4 g, 45 mEq is about 5.7 g, 60 mEq is about 7.6 g, and 70 mEq is about 8.8 g. A POSA would have used the mEq units rather than grams for a resin-based dose form, which is described in the specification of the '079 Patent.

116. Liang 2006 discloses that "a daily dose of 4.5 to 9 grams of Xyrem® is prescribed to narcolepsy patients." *Id.* at ¶ 5. Lebon 2013 similarly discloses a dosing regimen for GHB of a "daily dose of 4 to 9 g." *Id.* at col. 1, ll. 46-47. Liang 2006 and Lebon 2013 therefore disclose dosing regimens for GHB falling within 4 g to 9 g.

117. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

6. Claim 7

a. "The method of claim 1, wherein the mixture is a suspension."

118. Claim 7 depends directly on claim 1 and further recites "wherein the mixture is a suspension." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

119. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

120. As discussed with respect to claim 1, Liang 2006 discloses a sachet dosage form of GHB that is mixed with water. A POSA would have understood that mixing the claimed formulation with water would necessarily result in a either a solution or a suspension. *See, e.g.*, Bowles 2013 at 59 ("Wet administration of a multiparticulate is being taken to be administering a multiparticulate in a suspension."); Liu 2014 at 1881 ("Multiparticulates . . . presented in sachets

or capsules [] can be reconstituted in a drink to provide solutions or suspensions."). Because it would have been extremely difficult, if not impossible, to formulate a once-nightly oxybate drug that will invariably result in a solution once mixed with water (depending on the quantity of the latter), it would have been obvious in light of the general knowledge of a POSA that the mixture would be a suspension. And it would necessarily be a suspension with resinate formulations, because ion-exchange resin beads are insoluble in water.

121. For the same reason, a POSA would have understood that the sachet form disclosed in Lebon 2013 would be mixed with water to create a suspension of the mixture of GHB particles. *See id.* at col. 5, ll. 49-51 (disclosing a sachet); col. 5, ll. 60-61 (disclosing that the granulates "may be dispersed in a solution").

122. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

7. Claim 8

a. "The method of claim 1, wherein the oxybate formulation further comprises an acid."

123. Claim 8 depends directly on claim 1 and further recites "wherein the oxybate formulation further comprises an acid." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

124. It is my opinion that a POSA would have been motivated to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

125. A POSA would have been motivated, and would have had a reasonable expectation of success, to modify the GHB formulation disclosed in Lebon 2013 through the addition of an

acid because it was disclosed in the prior art. *See, e.g.*, Liang 2006 at ¶ 72 (disclosing adding "acidifiers" to "prevent[] these alkalinic salt from reacting with the enteric coat material").

126. Further, Liang 2006 discloses and claims a dosage form comprising an acid, *i.e.*, "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *See, e.g.*, Liang 2006 at Claim 3. Liang 2006 teaches using these acids for numerous reasons, including to adjust the target release/dissolution pH, *id.* at ¶ 88, as well as for gastro-stability of the GHB formulations. *Id.* at ¶ 72. The use of such acids in the barrier coat of the GHB formulations prevents the "release [of] any sodium gamma-hydroxybutyrate at pH 1.1 and pH 6.0 for up to 3 hours," thus improving the gastro-stability of the GHB formulations. *Id.* at ¶ 111; *see also id.* at ¶ 114.

127. Liang 2006 also teaches that an acid can be formulated as a separate component. It teaches that "the immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion." *Id.* at ¶ 48. Further, Liang 2006 teaches that "[t]he immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can be . . . mixed/sprinkled with fluids, soft foods (i.e. yogurt, applesauce)." *Id.* at ¶ 43. Lebon 2013 likewise discloses that "[t]he granulates according to the present invention may be ingested directly or may be dispersed in a solution, or mixed in a dietary support such as a yoghurt or a compote." Lebon 2013 at col. 5, ll. 60-62. A POSA would have known that both yogurt and applesauce are acidic.

128. A POSA would have understood that Liang 2006 further teaches that excipients, including "buffers," can be separate from the modified release component. *See* Liang 2006 at ¶ 83 ("[O]ther suitable additives known in the art can also be used **together with** the pH sensitive

enteric coating materials.") (emphasis added); compare to Liang 2006 at ¶ 82 ("Materials suitable for use **in** the pH sensitive enteric coat of the current invention are pH sensitive coating materials known in the art."). These disclosures would have motivated a POSA to formulate using an acid as a separate component, and would have given a POSA a reasonable expectation of success in doing so.

129. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

8. Claim 9

a. "The method of claim 8, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid."

130. Claim 9 depends directly on claim 8 and depends indirectly on claim 1, and further recites "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

131. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

132. For the reasons set forth above for claim 8, a POSA would have been motivated to use an acid in a GHB formulation, including the acids recited in claim 9, all of which were well known in the art, and to do so with a reasonable expectation of success. A POSA would have found that prior art discloses the listed components to be acids routinely used for formulations for oral suspension and also specifically used for GHB. Liang 2006 discloses adding an acid to a

sodium oxybate formulation. Specifically, it claims a dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." Liang 2006 at Claim 3.

133. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field

9. Claim 10

134. Claim 10 is:

> "10. A method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof, the method comprising:
>
> administering a single daily dose to the patient, the single daily dose comprising an amount of oxybate equivalent to from 4.0 g to 12.0 g of sodium oxybate, wherein the administering comprises:
>
> opening a sachet containing a solid oxybate formulation,
>
> mixing the formulation with water, and
>
> orally administering the mixture to the patient, wherein the oxybate formulation comprises an immediate release component and a controlled release component."

135. Claim 10 is independent and identical to claim 1 other than the preamble, which is: "[a] method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy."

136. To the extent that this preamble is limiting (i.e., acts as a claim limitation), it is my opinion that a POSA would have been motivated to arrive at "[a] method of treating cataplexy or excessive daytime sleepiness associated with narcolepsy." I note that Jazz does not challenge the obviousness of this claim preamble in its Final Validity Contentions. *See* Jazz's Validity Contentions at 138-49. Further, the prior art taught that sodium oxybate was useful for the

treatment of cataplexy and excessive daytime sleepiness associated with narcolepsy. *See, e.g.*, Xyrem 2014 Label at 3 (teaching the use of sodium oxybate to treat cataplexy and excessive daytime sleepiness in narcolepsy).

137. Because the remaining limitations of claim 10 are identical to those of claim 1, it is my opinion that a POSA would have found this claim to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

10. Claim 11

a. "The method of claim 10, wherein the orally administering occurs at night."

138. Claim 11 depends directly on claim 10 and further recites "wherein the orally administering occurs at night." This claim limitation is also recited in claim 2. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

139. A POSA would have found this claim obvious for the same reasons as explained above for claims 2 and 10.

11. Claim 12

a. "The method of claim 10, wherein the oxybate formulation is mixed with water immediately prior to administration."

140. Claim 12 depends directly on Claim 10 and further recites "wherein the oxybate formulation is mixed with water immediately prior to administration." This claim limitation is also recited in claim 3. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

141. A POSA would have found this claim obvious for the same reasons as explained above for claims 3 and 10.

12. Claim 14

a. "The method of claim 10, wherein the administering promotes the patient to sleep for 6 to 8 hours."

142. Claim 14 depends directly on claim 10 and further recites "wherein the administering promotes the patient to sleep for 6 to 8 hours." This claim limitation is also recited in claim 5. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

143. A POSA would have found this claim obvious for the same reasons as explained above for claims 5 and 10.

13. Claim 15

a. "The method of claim 10, wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate."

144. Claim 15 depends directly on claim 10 and further recites "wherein the amount of oxybate administered to the patient is 35 mEq, 45 mEq, 60 mEq, or 70 mEq of oxybate." This claim limitation is also recited in claim 6. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

145. A POSA would have found this claim obvious for the same reasons as explained above for claims 6 and 10.

14. Claim 16

a. "The method of claim 10, wherein the mixture is a suspension."

146. Claim 16 depends directly on claim 10 and further recites "wherein the mixture is a suspension." This claim limitation is also recited in claim 7. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

147. A POSA would have found this claim obvious for the same reasons as explained above for claims 7 and 10.

15. Claim 17

a. "The method of claim 16, wherein the oxybate formulation further comprises an acid."

148. Claim 17 depends directly on claim 16 and depends indirectly on claim 10, and further recites "wherein the oxybate formulation further comprises an acid." This claim limitation is also recited in claim 8. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

149. A POSA would have found this claim obvious for the same reasons as explained above for claims 8 and 10.

16. Claim 18

a. "The method of claim 17, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid."

150. Claim 18 depends directly on claim 17 and depends indirectly on claim 10, and further recites "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid." This claim limitation is also recited in claim 9. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 138-49.

151. A POSA would have found this claim obvious for the same reasons as explained above for claims 9 and 17.

VI. THE ASSERTED '782 PATENT CLAIMS ARE INVALID AS OBVIOUS

152. I understand from Counsel that it is Jazz's position that the priority date for the claims of the '782 Patent is February 18, 2015. However, I am informed that during prosecution,

the Examiner informed the Applicant that the patent is entitled at most to a priority date of February 18, 2016. For purposes of this section of my report, my opinions are from the standpoint that the Asserted Claims of the '782 Patent are entitled to a priority date of February 18, 2016. But my opinion would not change even if the claims of the '782 Patent were entitled to the priority date of February 18, 2015, as insisted by Jazz.

153. I understand from Counsel that Jazz has asserted claims 1-24 of the '782 Patent (i.e., all of its claims) against Avadel ("Asserted Claims of the '782 Patent"). Claims 1 and 14 are independent claims. Claims 2-13 and 15-24 depend on claim 1 or claim 14, respectively.

154. Claim 1 is:

> A formulation of gamma-hydroxybutyrate comprising:
>
> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;
>
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

155. Claim 14 is:

> A unit dose comprising a formulation of gamma-hydroxybutyrate, wherein the formulation comprises:
>
> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;

> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

A. Scope and Content of the Prior Art

156. As stated in the legal section above, I understand from Counsel that prior art may be in the form of, among other things, a patent or patent application, a journal publication, a public statement, or a product. The references below are pertinent prior art because they are within the field of endeavor of the Resinate Patents and, as described in detail below, the Liang 2006, Lebon 2013, and Allphin 2012 references address the problem facing the inventors of the '782 Patent.

157. A POSA would have known at the time of '782 Patent's priority date that Xyrem was the only sodium oxybate drug approved by the FDA for the treatment for narcolepsy, cataplexy, and excessive daytime sleepiness (EDS) in narcolepsy. *See*, *e.g.*, Lebon 2013 at col. 1, ll. 28-32; Allphin 2012 at ¶ 9. Xyrem is a sodium oxybate aqueous solution to be administered orally twice nightly. Xyrem 2014 Label at 1. However, a POSA would also have been aware of additional prior art references that discuss formulating sodium oxybate, or oxybate salts in general, in alternative dosage forms.

1. Liang 2006

158. The Liang 2006 reference is discussed above in ¶¶ 35-37.

159. Additionally, Liang 2006 teaches an oral solid dosage form of GHB "comprising an immediate release component of [GHB], one or more delayed/controlled release components of [GHB]." *Id.* at Claim 1. One of the embodiments disclosed in Liang 2006 is "an immediate release component in the form of particles and one or more pH sensitive delayed/controlled release particles are supplied as pre-mixed doses." *Id.* at ¶ 33. Liang 2006 also teaches adding a viscosity enhancing agent, and specifically "suspending agents, thickening agents, [and] gelling agents," to a sodium oxybate formulation. *Id.* at ¶ 53. Further, it discloses adding acid to a sodium oxybate

formulation, specifically, "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *See, e.g.*, *id.* at Claim 3.

2. Lebon 2013

160. The Lebon 2013 reference is discussed above in ¶¶ 38-39.

161. Further, Lebon 2013 teaches "a granulate of gamma-hydroxybutyric acid or of one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2, ll. 25-29. It further describes that "the present invention also relates to a pharmaceutical composition, comprising granulates . . . ." *Id.* at col. 5, ll. 41-52.

3. Allphin 2012

162. The Allphin 2012 reference is discussed above in ¶¶ 40-41.

163. Additionally, Allphin 2012 notes that sodium oxybate is extremely hygroscopic and that "[t]he hygroscopic nature of sodium oxybate presents significant challenges to the formulation, production, and storage of dosage forms capable of delivering sodium oxybate over a sustained period of time." *Id.* at ¶ 30. Due to these difficulties, Allphin 2012 teaches that "a controlled release unit dosage form of GHB should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration." *Id.* at ¶ 29.

164. Allphin 2012 also presents the plasma concentration data of patients receiving 6 g doses of GHB. Specifically, the "administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 µg/mL." *Id.* at ¶ 35. It further specifies that the controlled release form can "provid[e] GHB plasma concentrations of at least 10 µg/mL over . . . up to about 8 hours." *Id.*

B. The Asserted Claims of the '782 Patent Would Have Been Obvious In Light of the Prior Art and the Knowledge of a POSA

165. I have reviewed Jazz's Final Validity Contentions as to whether the Asserted Claims of the '782 Patent have written description support and are enabled. *See* Jazz's Final Validity Contentions at 98-104, 206-210. I have not been asked to consider whether the Asserted Claims of the '782 Patent indeed have adequate written description support in, or are enabled by, the '782 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '782 Patent specification identified in Jazz's Final Validity Contentions. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '782 Patent, and (b) the '782 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '782 Patent. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

166. I have also reviewed Jazz's Final Validity Contentions that the Asserted Claims of the '782 Patent are not obvious. *See* Jazz's Final Validity Contentions at 149-203. Based on my review, I understand that Jazz only disputes whether the following claim limitations of the Asserted Claims of the '782 Patent would have been non-obvious: "a viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles" and "wherein the unit dose is a sachet." *Id.* at 184-203.

1. Claim 1

167. Claim 1 is:

1. A formulation of gamma-hydroxybutyrate comprising:

> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;
>
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

168. It is my opinion that a POSA would have had the requisite knowledge to develop the claimed formulation of GHB disclosed in claim 1, would have had the requisite motivation to do so, and would have had a reasonable expectation of success in doing so.

169. Liang 2006 is directed to an oral solid dosage form of GHB "containing an immediate release component of [GHB], and one or more delayed/controlled release components of [GHB]." Liang 2006 at Abstract. It states that "an immediate release component in the form of particles and one or more pH sensitive delayed/controlled release particles are supplied as pre-mixed doses." *Id.* at ¶ 33. Liang 2006 discloses adding a viscosity enhancing agent, and specifically "suspending agents, thickening agents, [and] gelling agents," to a sodium oxybate formulation. *Id.* at ¶ 53. It also discloses adding an acid to a sodium oxybate formulation. Specifically, Liang 2006 discloses and claims a dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *See, e.g.*, *id.* at Claim 3. A POSA would have understood that a viscosity enhancing agent can be a thickening agent and that a thickening agent by definition increases the viscosity of a suspension.

170. Thus, Liang 2006 explicitly discloses all of the claim limitations of claim 1 other than that the "viscosity enhancing agent and acid that are separate from the immediate release particles and modified release particles."

171. Lebon 2013 describes "granulate[s] of gamma-hydroxybutyric acid or of one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported gamma-hydroxybutyric acid or one of its salts is supported." Lebon 2013 at col. 2, ll. 25-29. It thus discloses granulates of GHB acid or one of its pharmaceutically acceptable salts, capable of immediate release of GHB. *Id.* It also describes granulates as "a shape which is quite regular, homogeneous and quasi-spherical," "intended for oral administration," and "hav[ing] a characteristic structure of the core/shell type, wherein the core is of a different nature from the active constituents which form the shell." *Id.* at col. 2, ll. 38-50. Lebon 2013 further discloses that granulates of GHB may optionally have modified-release characteristics. *Id*. at col. 4, ll. 23-44. Still further, it discloses the "development of a novel oral multi-particle form" that consists of granulates intended for oral administration. *Id.* at col. 2, ll. 63-64.

172. Thus, Lebon 2013 discloses all of the claim limitations of claim 1 other than the "viscosity enhancing agent and an acid that are separate from the immediate release particles" and modified release particles. Although Lebon 2013 is listed on the face of the '782 Patent, I am informed by Counsel that it was not cited or discussed by the Examiner during prosecution.

a. "A formulation of gamma-hydroxybutyrate"

173. To the extent that this preamble is limiting (i.e., acts as a clam limitation), it is my opinion that a POSA would have found that both Liang 2006 and Lebon 2013 disclose this claim preamble. I note that Jazz does not challenge the obviousness of this claim preamble in its Final Validity Contentions. Jazz's Final Validity Contentions at 184-203.

174. Liang 2006 is "directed to pulse-released formulations of oxybate, or gamma-hydroxybutyric acid, salts." Liang 2006 at ¶ 1.

175. Lebon 2013 is directed to "a granulate of gamma-hydroxybutyric acid or of one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts." Lebon 2013 at col. 2, ll. 25-29. Furthermore, it claims a "granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, comprising: a solid core; and a shell layer constituted of the gamma-hydroxybutyric acid or one of its salts that is deposited around and supported by the solid core . . . ." *Id.* at Claim 1.

176. Since this preamble was disclosed by both Liang 2006 and Lebon 2013, a POSA would have found this claim preamble to be obvious.

b. "a plurality of immediate release particles comprising gamma-hydroxybutyrate"

177. A POSA would have found this claim limitation to be disclosed in both Liang 2006 and in Lebon 2013. I note that Jazz does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz's Final Validity Contentions at 184-203.

178. Liang 2006 states that "[t]he dosage forms of the current invention comprise an immediate release component . . . wherein the immediate release component is present together with (or separated [sic] contained from) one or more pH sensitive delayed/controlled release particles," *id.* at ¶ 27, "[i]n one of the preferred embodiments, the composition comprises multiple delayed release pellets or beads (used interchangeably herein) and an immediate release component," *id.* at ¶ 29, and "[c]ombining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete . . . dose," *id.* at ¶ 32. Liang 2006 further discloses that "an immediate release

component in the form of particles and one or more pH sensitive delayed/controlled release particles are supplied as pre-mixed doses," thus comprising a single dosage. *Id.* at ¶ 33. Further, it discloses a preferred embodiment where "an immediate release component is combined with a single type of pH sensitive delayed/ controlled release particles." *Id.* at ¶ 38.

179. Lebon 2013 discloses that "[t]he present invention relates to a granulate of gamma-hydroxybutyric acid or one of its pharmaceutically acceptable salts, characterised in that it comprises a solid core on which is supported the gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2, ll. 25-29. It further discloses that "[a]ccording to a particular embodiment, the core of the granulates may however comprise particles of gamma-hydroxybutyric acid or one of its salts." *Id.* at col. 2, ll. 51-53. A solid core supported by the gamma-hydroxybutyric acid or one of its salts, without any other excipients, will be understood to display an immediate release profile. Lebon 2013 also discloses that the granulates are for "a novel oral multi-particle form," *id.* at col. 2, ll. 63-67; and that they can be packaged in individual containers, "such as in sachets, sticks, paper bags, or bottles," (*id.* at col. 5, ll. 49-51, col. 8, ll. 7-8). It therefore also describes having a plurality of the disclosed immediate release particles.

180. Therefore, a POSA would have found this claim limitation to be obvious in view of Liang 2006 and/or Lebon 2013.

c. "a plurality of modified release particles comprising gamma-hydroxybutyrate;"

181. A POSA would have found this claim limitation to be disclosed in both Liang 2006 and Lebon 2013. I note that Jazz does not challenge the obviousness of this claim limitation in its Final Validity Contentions. Jazz's Final Validity Contentions at 184-203.

182. Liang 2006 discloses that the "delayed/controlled release components are particles containing GHB." *See, e.g.*, Liang 2006 at Claim 2. "Specifically, at the essence of the present

invention is a dosage form comprising one or more pH sensitive delayed/controlled release particles (e.g., beads, granules, minitabs or pellets)." Liang 2006 at ¶ 26. Thus, a POSA would have understood that Liang 2006 disclosed a plurality of modified release particles.

183. Lebon 2013 teaches a granulate of GHB acid with a modified or delayed release characteristic. It discloses that adding a "sustained-release coating" "enable[s] a modified or delayed release of the active constituents (modified-release granulates)." Lebon 2013 at col. 4, ll. 34-37; *see also* Claims 5, 15. Lebon 2013 further discloses that the coating can consist of "copolymers of methacrylates and acrylates, Eudragit(R) S100, shellac, cellulose derivatives, in particular ethylcellulose, and acrylic derivatives." *Id.* at col. 4, ll. 38-41. It also discloses that the granulates are for "a novel oral multi-particle form," (*id.* at col. 2, ll. 63-64); and that they can be packaged in individual containers, such as "in sachets, sticks, paper bags, or bottles," (*id.* at col. 5, ll. 49-51, and col. 8, ll. 7-8). Lebon 2013, therefore, also discloses having a plurality of modified release particles.

184. Thus, a POSA would have found both Liang 2006 and Lebon 2013 to teach a plurality of modified release particles, and, consequently a POSA would have found this claim limitation to be obvious.

d. "a viscosity enhancing agent . . . wherein the viscosity enhancing agent [is] separate from the immediate release particles and the modified release particles"

185. I have reviewed Jazz's Final Validity Contentions as to whether the "viscosity enhancing agent . . . wherein the viscosity enhancing agent [is] separate from the immediate release particles and the modified release particles" claim limitation has written description support in, and is enabled by, the '782 Patent specification. *See* Jazz's Final Validity Contentions at 208-09. Jazz contends that the written description legal requirement is satisfied because "[t]he specification provides examples of 'viscosity enhancing agent[s]' found to be compatible with the

claimed formulations. *See id*. at col. 14, ll. 56-61. A POSA therefore would have understood that the claimed viscosity enhancing agents are to be included in the formulation, separate from the drug-containing particles." *Id*. Another cited portion of the '782 Patent specification states: "In some embodiments of the formulations of the present invention, the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof." '782 Patent at col. 14, ll. 56-61.

186. I have also reviewed Jazz's Final Validity Contentions concerning enablement of the Asserted Claims of the '782 Patent. *See* Jazz's Final Validity Contentions at 210. I understand based on my review that Jazz asserts that the '782 Patent specification enables the full scope of the Asserted Claims of the '782 Patent.

187. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, and is enabled by, the '782 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '782 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '782 Patent, and (b) the '782 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '782 Patent. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

188. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '782 Patent would have been obvious to a POSA as of the priority date,

including that a POSA would have been motivated to formulate with a viscosity enhancing agent wherein the viscosity enhancing agent is separate from both the immediate release particles and the modified release particles, with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

189. Liang 2006 discloses that pharmaceutically acceptable excipients such as "suspending agents/thickening agents/gelling agents" may be used in the formulations of GHB. *See* Liang 2006 at ¶¶ 53, 55. A POSA would have understood that thickening agents are viscosity enhancing agents. Liang 2006 also discloses the use of other common viscosity enhancing agents such as xanthan gum, microcrystalline cellulose, hydroxypropylmethylcellulose, and hydroxypropyl cellulose. Liang 2006 at ¶ 55; *see also* '782 Patent Claim 2 (identifying these excipients as viscosity enhancing agents). A POSA would have understood that a viscosity enhancing agent is a form of a thickening agent, and that a thickening agent by definition increases viscosity. As I understand it, Jazz does not contest in the Final Validity Contentions that Liang 2006 discloses viscosity enhancing agents. *See* Jazz's Final Validity Contentions at 184-203.

190. As discussed above, Jazz contends that written description is satisfied because "[t]he specification provides examples of 'viscosity enhancing agent[s]' found to be compatible with the claimed formulations. *See* ['782 Patent] at col. 14, ll. 56-61. The POSA therefore would have understood that the claimed viscosity enhancing agents are to be included in the formulation, separate from the drug-containing particles." Jazz's Final Validity Contentions at 208-09. The disclosure in Liang 2006 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '782 Patent.

191. Lebon 2013 teaches that "binders. . . give viscous solutions," and further discloses such common "binders" as methylcellulose, carboxymethylcellulose,

hydoxypropylmethylcellulose, and hydroxypropylcellulose. *See* Lebon 2013 at col. 3, ll. 35-48. A POSA would have understood that these binders can also serve as viscosity enhancing agents in aqueous liquids. Modifying drug release has been practiced and known for decades. In particular, formulating a multiparticulate drug to be orally administered as powder for suspension is well known in the art. Common excipients to a powder for suspension dosage forms including suspending/thickening agents or viscosity enhancing agents, buffering agents, and flavoring agents. Well-known prior art references a POSA would have been familiar with include such treatises as PHARMACEUTICAL SUSPENSIONS 2010, and PHARMACEUTICAL DOSAGE FORMS: DISPERSE SYSTEMS 153-154 (Herbert A. Lieberman et al., eds., 1996) ("PHARMACEUTICAL DOSAGE FORMS 1996"). .

192. As discussed above, Jazz contends that written description is satisfied because "[t]he specification provides examples of 'viscosity enhancing agent[s]' found to be compatible with the claimed formulations. *See* ['782 Patent] at col. 14, ll. 56-61. The POSA therefore would have understood that the claimed viscosity enhancing agents are to be included in the formulation, separate from the drug-containing particles." Jazz's Final Validity Contentions at 208-09. The disclosure in Lebon 2013 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '782 Patent.

193. Specifically, suspending/thickening agents and/or viscosity enhancing agents have been known in the art to be a typical ingredient in an oral suspension formulation due to its ability to increase viscosity, decrease sedimentation rate, and improve overall stability of the formulation. *See* PHARMACEUTICAL SUSPENSIONS 2010 at 110-12 (stating that viscosity enhancing agents are added to formulations containing a plurality of drug particles for oral suspension to improve the physical stability of an oral suspension and decrease sedimentation rate). *See* PHARMACEUTICAL

DOSAGE FORMS 1996 at 151, 161 (teaching that "a typical suspension" may contain a "suspending agent" and that "[s]uspending agents are used to impart increased viscosity and retard sedimentation" and can include "cellulose derivatives, clays, natural gums, synthetic gums, and miscellaneous agents"). These viscosity enhancing agents were often added to formulations containing a plurality of drug particles for oral suspension to improve the physical stability of an oral suspension and decrease sedimentation rate. PHARMACEUTICAL SUSPENSIONS 2010 at 110-12. For that reason, the inclusion of a viscosity enhancing agent was a well-established technique commonly used in the art.

194. Further, a POSA would have been motivated to add such a viscosity enhancing agent to increase viscosity and beneficially decrease the sedimentation rate of the oral suspension. *See, e.g.*, PHARMACEUTICAL SUSPENSIONS 2010 at 3 ("Greater viscosity of dispersion medium offers the advantage of slower sedimentation.").

195. For example, U.S. Patent No. 5,540,912 to Roorda et al. issued on July 30, 1996 ("Roorda 1996") is a patent that describes formulation of a controlled-release, anesthetic composition for localized application comprising a suspension prepared by mixing minipellets with an aqueous solution containing a viscosity-elevating solute. Roorda 1996 at Abstract, col. 7, ll. 43-62 (disclosing a formulation of a controlled-release, anesthetic composition for localized application comprising an even suspension prepared by mixing minipellets with an aqueous solution containing a viscosity-elevating solute). In another example, Farhan AlHusban et al., *Formulation of Multiparticulate Systems as Lyophilized Orally Disintegrating Tablets*, 79 EUROPEAN J. PHARM & BIOPHARMACEUTICS 627, 629 (2011) ("AlHusban 2011") describes adding the polysaccharide carrageenan as a "viscosity modifying agent" to "drastically increase[] the viscosity of the gelatin stock solution" to formulate the oral disintegrating tablet made of enteric

coated multiparticulate. In yet another example, U.S. Patent Application Publication 2007/0020330 to Dang et al. published on January 25, 2007 ("Dang 2007") describes formulations for intranasal or ocular pharmaceutical compositions with "one or more water soluble viscosity-increasing agents." Dang 2007 at ¶ 92.

196. It was also known in the art that adding a viscosity enhancing agent would decrease settling rate and decrease sedimentation residue, thereby raising the likelihood that a patient will take a full dose. PHARMACEUTICAL DOSAGE FORMS 1996 at 161. Viscosity enhancing agents were, therefore, routinely added to powders for suspension formulations. For example, U.S. Patent Application Publication 2014/0287038 to Mehta 2014 et al. published on September 25, 2014 ("Mehta 2014"), is directed to an oral methylphenidate powder consisting of immediate and modified release particles for reconstitution into an "oral aqueous sustained release formulation." Mehta 2014 at Abstract. Mehta 2014 also discloses that the powder blend can contain "suspending agents." *Id.* at ¶ 78. A POSA would have understood suspending agent to encompass viscosity enhancing agent.

197. Further, it would have been obvious to a POSA for the viscosity enhancing agent to be ***separate*** from both the immediate release and modified release particles. First, according to Jazz, the mere teaching of "examples of 'viscosity enhancing agent[s]' found to be compatible with the claimed formulations" alone is sufficient, as "[t]he POSA therefore would have understood that the claimed viscosity enhancing agents are to be included in the formulation, separate from the drug-containing particles." *See* Jazz's Final Validity Contentions at 208-09. Second, Lebon 2013 discloses that "an optional step of mixing with a lubricant and/or flavouring and/or a sweetener and/or a colouring, which may or may not be in the form of granulate." Lebon 2013 at col. 7, ll. 16-18. A POSA would have understood this teaching to disclose that excipients

in general (including, for example, viscosity enhancing agents), can be *separate* from the drug-containing particles, and (s)he would have been motivated to use a viscosity enhancing agent separate from the drug-containing particles.

198. Third, it was known that the addition of a viscosity enhancing agent can be separate from the particles containing the drug product, providing both a motivation and a reasonable expectation of success. Clyde M. Ofner and Roger I. Schnaare describe in *Suspensions in* FMC BIOPOLYMER, 2000, https://www.studocu.com/ph/document/lyceum-northwestern-university/chemistry/308042943-suspensions/8883081, at 11 ("Ofner 2000") the "Published Processing Guidelines," where suspending agents are added separately from the drug particles for formulating an aqueous suspension ("since the drug and suspending agent must be uniformly dispersed during suspension preparation, they can be combined in the dry state…"). *See id.* at 7-8 (providing several examples where the suspending agents are separate from the drug particles). Likewise, WO Patent Application Publication 2011/107865 to Gandhi et al. published on September 9, 2011 ("Gandhi 2011") is directed to a sustained release oral liquid suspension dosage form of pharmaceutical active ingredients ("APIs"). Gandhi 2011 at col. 1, ll. 3-5. It is directed specifically to APIs of high aqueous solubility and/or short half-life to be administered once daily or twice daily. *Id.* at col. 1, ll. 19-21; col. 3, ll. 16-18. Gandhi 2011 specifies that the viscosity enhancing agent is part of the aqueous media *separate* from the sustained release pellets. *See id.* at col. 5, ll. 13-18 ("Wherein the sustained release pellets are suspended with viscosity modifying agent or suspending agent. . . in a suspending media."); col. 5, ll. 27-29. It further teaches that "viscosity modifying agent" or "thickening agent" or "suspending agent" . . . are also called as [sic] suspension stabilizers and they are intended to ensure that the individual doses removed have constant active ingredient content." *Id.* at col. 10, ll. 13-16. In another example, Mehta 2014

describes an oral methylphenidate powder consisting of immediate and modified release particles for reconstitution into an "oral aqueous sustained release formulation." *Id.* at Abstract. It discloses that the powder blend can contain a diluent granule, ion exchange resin complex, and optionally "suspending agents." *Id.* at ¶ 78.

199. A POSA would have had the motivation to combine the prior art teaching of Liang 2006 and/or Lebon 2013 with the general knowledge in the field. A POSA would have known that a viscosity enhancing agent could be added as a suspension stabilizer. Thus, adding the viscosity enhancing agent as a separate component would have been an obvious choice for a POSA.

200. Fourth, it would have been obvious to try to formulate the viscosity enhancing agent to be separate from both the immediate release and modified release particles, because there is merely a finite number of, and especially only a few, ways to include the viscosity enhancing agent: as part of the modified release pellets, as part of the immediate release pellets, as part of both pellets, and as a separate component from the pellets. I have been informed by Counsel that when there is just a finite number of predictable options, any one of them is deemed obvious to a POSA.

201. Jazz argues in its Final Validity Contentions that Avadel has "not identified any problem(s) in the prior art specific to GHB suspension formulations that would have motivated a POSA to add a viscosity modifying agent to the claimed formulations." Jazz's Final Validity Contentions at 187. Jazz further argues that Avadel "ha[s] no evidence indicating that a POSA would have had reasonably expected the claimed formulation to solve a known problem. Nor have they shown a finite number of known solutions, let alone predictable ones." *Id.* at 193. I disagree with these arguments.

202. Given (i) the aforementioned assumption that the '782 Patent has adequate written description and enablement for this claim limitation by stating that "[i]n some embodiments of the formulations of the present invention, the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof," '782 Patent at col. 14, ll. 56-61, (ii) the explicit disclosure in Liang 2006 and Lebon 2013 of a viscosity enhancing agent in GHB formulations, (iii) the disclosure in Lebon 2013 that the viscosity enhancing agent can be separate from the GHB-containing particles, and (iv) the fact that there are only a handful of possibilities for formulating the viscosity enhancing agent as either together or separate with the immediate release and modified release particles (each of which would have been deemed obvious), a POSA would have been motivated to add a viscosity enhancing agent as a separate component with a reasonable expectation of success.

e. "an acid . . . wherein the acid [is] separate from the immediate release particles and the modified release particles"

203. I have reviewed Jazz's Final Validity Contentions as to whether the "acid . . . wherein the acid [is] separate from the immediate release particles and the modified release particles" claim limitation has written description support in, and is enabled by, the '782 Patent specification. *See* Jazz's Final Validity Contentions at 208-09. Jazz contends that the written description legal requirement is satisfied because:

> The specification expressly discloses that "the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids. . . . In certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alpha[-]hydroxy carboxylic acid." *See* '782 Patent at 14:1-6. The specification further discloses that, "[i]n other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH." *Id.* at 14:30-32. The specification further teaches that an "acid, pH-mediating, adjusting or buffering compound or agent . . . as would be known by one

> of skill in the art, is contemplated for use" in the formulation. *Id.* at 14:33-48. Thus, and contrary to Defendants' contention, the POSA would understand, by the disclosures of the specification, that an acid added to the disclosed embodiments could be separate from the "immediate release particles" and "modified release particles" and included in the formulation as a pH buffering agent.

Jazz's Final Validity Contentions at 209.

204. I have also reviewed Jazz's Final Validity Contentions concerning enablement of the Asserted Claims of the '782 Patent. *See* Jazz's Final Validity Contentions at 210. I understand based on my review that Jazz asserts that the '782 Patent specification enables the full scope of the Asserted Claims of the '782 Patent.

205. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, and is enabled by, the '782 Patent specification. Instead, for purposes of this report, I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '782 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '782 Patent, and (b) the of the '782 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '782 Patent. Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

206. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '782 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to formulate with an acid wherein the acid is separate from both the immediate release particles and the modified release particles with a

reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

207. It would have been obvious for a POSA to use an acid in a GHB formulation because it was disclosed in the prior art. *See, e.g.*, Liang 2006 at ¶ 72 (disclosing adding acidifiers to "prevent[] these alkalinic salts [of GHB] from reacting with the enteric coat material").

208. Further, Liang 2006 discloses and claims a dosage form comprising an acid, *i.e.*, "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." *See, e.g.*, Liang 2006 at Claim 3. Liang 2006 teaches using these acids for numerous reasons, including to adjust the target release/dissolution pH, (*id.* at ¶ 88), as well as for gastro-stability of the GHB formulations. *Id.* at ¶ 72. The use of such acids in the barrier coat of the GHB formulations prevents the "release [of] any sodium gamma-hydroxybutyrate at pH 1.1 and pH 6.0 for up to 3 hours," thus improving the gastro-stability of the GHB formulations. *Id.* at ¶ 111; *see also id.* at ¶ 114.

209. The separateness requirement likewise would have been obvious. First, according to Jazz, the mere teaching of the potential addition of an acid is sufficient, as "the POSA would have understood, by the disclosures of the specification, that an acid added to the disclosed embodiments could be separate from the 'immediate release particles' and 'modified release particles' and included in the formulation as a pH buffering agent." Jazz Final Validity Contentions at 209.

210. Second, Liang 2006 also teaches that the added acid can be formulated as a separate component. It teaches that "the immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion." *Id.* at ¶

48. Further, Liang 2006 teaches that "[t]he immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can be . . . mixed/sprinkled with fluids, soft foods (i.e. yogurt, applesauce)." *Id.* at ¶ 43. Lebon 2013 likewise discloses that "[t]he granulates according to the present invention may be ingested directly or may be dispersed in a solution, or mixed in a dietary support such as a yoghurt or a compote." Lebon 2013 at col. 5, ll. 60-62. A POSA would have known that both yogurt and applesauce are acidic drinkable liquids.

211. A POSA would have understood that Liang 2006 further teaches that excipients, including "buffers," can be separate from the modified release component. *Compare* Liang 2006 at ¶ 83 ("[O]ther suitable additives known in the art can also be used **together with** the pH sensitive enteric coating materials.") (emphases added) *with* Liang 2006 at ¶ 82 ("Materials suitable for use **in** the pH sensitive enteric coat of the current invention are pH sensitive coating materials known in the art."). These disclosures would have motivated a POSA to formulate using an acid as a separate component and would have provided a POSA with a reasonable expectation of success in doing so.

212. Third, the use of an acid as a separate component was disclosed in the art, providing both a motivation and an expectation of success. Ofner 2000 teaches that an acid can be added as a separate component to a suspension, and provides several examples where the formulation contains acid as a separate ingredient from the drug particles. Ofner 2000 at 7-8, 11. Gandhi 2011 teaches adding an acid separate from the immediate and modified release components. In one example, the suspension formulation consists of "extended release granules" and *separately* "citric acid monohydrate." Gandhi 2011 at Ex. 3. Another example is Mehta 2014, which discloses the buffering agent as separate from the immediate release and modified release ion-exchange

complex beads. *See* Mehta 2014 at Abstract ("a blend containing a combination of an uncoated methylphenidate-ion exchange resin complex, a barrier coated methylphenidate-ion exchange resin complex matrix, and a water-soluble buffering agent."); ¶ 42 ("In one embodiment, the powder blend further comprises water-soluble diluent granules which contain at a minimum, a water soluble buffering agent"). Mehta 2014 further discloses that the buffering agent is "selected from the group consisting of one or more of a pharmaceutically acceptable acid consisting of citric acid, ascorbic acid, acetic acid, tartartic acid, phosphoric acid, a pharmaceutically acceptable salt of citric acid, ascorbic acid, acetic acid, tartartic acid, phosphoric acid, or a mixture of said pharmaceutically acceptable acid or salt, and mixtures thereof." *Id.* at ¶ 42, claim 15. Finally, an acid is also incorporated separately from the immediate and modified release components of Nexium. *See* Nexium 2014 Label at 14.

213. Fourth, it would have been obvious to try to formulate the acidifying agent to be separate from both the immediate release and the modified release particles, because there is merely a finite number of, and especially only a few, ways to include the acidifying agent: as part of the modified release pellets, as part of the immediate release pellets, as part of both pellets, and as a separate component form the pellets. I have been informed by Counsel that when there is just a finite number of predictable options, any one of them is deemed obvious to a POSA.

214. Jazz argues that "the only three references . . . that discuss modified-release, GHB suspension formulations expressly teach that the acids ***would not (and need not) be separated*** from the drug-containing particles." Jazz's Final Validity Contentions at 198. I disagree with this argument. Given (i) the aforementioned assumption that the '782 Patent has adequate written description and enablement for this claim limitation by stating that "the pharmaceutical composition may comprise a pH adjusting or buffering agent. Such agents may be acids. . . . In

certain embodiments, the acid may be an organic acid, preferably a carboxylic acid or alphahydroxy carboxylic acid," '782 Patent at col. 14, ll. 1-6, that "[i]n other preferred embodiments, a weak acid and its conjugate base are used to form a buffering agent to help stabilize the composition's pH," *id.* at col. 14, ll. 30-32, and that "acid, pH-mediating, adjusting or buffering compound or agent . . . as would be known by one of skill in the art, is contemplated for use," *id.* at col. 14, ll. 33-48, (ii) the explicit disclosure in Liang 2006 that the acid can be separate from the GHB-containing particles, and (iii) the fact that there are only a handful of possibilities for formulating the acid as either together or separate with the immediate release and modified release particles (each of which would have been deemed obvious to a POSA), a POSA would have been motivated to add an acid as a separate component with a reasonable expectation of success.

i. A POSA would have been motivated to add an acid separately from the particles as a pH-modifier

215. A POSA would have determined that the Asserted Claims of the '782 Patent describe the addition of an acid as a pH-modifier: "[D]ue to the buffering effect of oxybate (pKa of 4.5), the immediate-release portion of the dose would cause the gastric pH to increase to about 6 . . . In particular, if delayed release via enteric coating is desired, then upon release of the immediate release portion of the dose, the concomitant rise in gastric pH could result in at least partial dissolution of the enteric coating, thereby compromising the delayed release function of the enteric coating." '782 Patent at col. 5, ll. 39-49. Prior art contains numerous examples of modified-release formulations with an acid in their formulation to modify the pH. For example, Allphin 2012 discloses the use of an acid to adjust the pH of sodium oxybate oral solutions. *See* Allphin 2012 at ¶ 9.

216. In another example, P. Nykanen et al., *Organic Acids as Excipients in Matrix Granule for Colon-Specific Drug Delivery*, 184 INT'L J. PHARMA. 251, 251 (1999) ("Nykanen 1999") teaches adding an organic acid to the formulation. The authors' subsequent publications in 2000s further discuss adding citric acid to the formulation. P. Nykanen et al., *Citric Acid as Excipient in Multiple-Unit Enteric-Coated Tablets for Targeting Drugs on the Colon*, 229 INT'L J. PHARMA. 155, 155 (2001) ("Nykanen 2001"); P. Nykanen et al., *Citric Acid as pH-Regulating Additive in Granules and the Tablet Matrix in Enteric-Coated Formulations for Colon-Specific Drug Delivery*, 59 PHARMAZIE 268, 268 (2004) ("Nykanen 2004").

217. A POSA would have been motivated, and would have a reasonable expectation of success, to use an acid as a pH-modifier in formulations with a modified release component, such as with sodium oxybate, for controlling the dissolution of the formulation. The prior art warns of the buffering effect of Na oxybate due to its large dosage and "strongly alkalinic" properties. For example, Liang 2006 teaches that (i) "[s]odium gamma-hydroxybutyrate is highly soluble, hygroscopic, and strongly alkaline," that this would be a problem because "penetrated/diffused sodium gamma-hydroxybutyrate may act as a strong base which reacts with pH sensitive coating polymers . . . weakening the coating layer and lowering the coating efficiency.," and (ii) "acidifiers" can "counteract the alkaline effect from any migrating gamma-hydroxybutyric acid salts." Liang 2006 at ¶¶ 5, 88. A POSA would have understood from Liang 2006's disclosure that one potential problem to formulating a modified release component of GHB would be that the strongly alkalinic Na GHB could have caused "migration" or premature release of the drug, and a potential solution would have been to add an acidifier to the formulation. *Id.* at ¶ 88.

218. A POSA would have been motivated to combine the prior art teachings of Liang 2006 with the general knowledge in the field to use an acid as a *separate* component for the purpose of adjusting the pH of the formulation.

ii. A POSA would have been motivated to add an acid separately from particles as a flavoring agent

219. It also would have been obvious to a POSA to add an acid as a separate particle for flavor modification purposes. Liang 2006 teaches the addition of taste-masking agents (i.e., flavoring agents). Liang 2006 at ¶ 53. Therefore, a POSA would have been motivated to add a flavoring agent to a GHB formulation in general. Likewise, Lebon 2013 also teaches the addition of flavoring agents. Lebon 2013 at Claims 6, 9. It further teaches that "an optional step of mixing with a lubricant and/or a flavoring and/or a sweetener and/or a colouring, which may or may not be in the form of granulate." *Id.* at col. 7, ll. 16-18. A POSA would have understood this teaching to disclose that a flavoring agent can be separate from the drug-containing particles.

220. It was well known in the prior art that acid could advantageously be used as a flavor modifier. *See* PHARMACEUTICAL DOSAGE FORMS 1996 at 168 (teaching that flavoring agents "enhance patient acceptance of the product" and is a necessity in suspensions intended for pediatric patients). Harmik Sohi et al., *Taste Masking Technologies in Oral Pharmaceuticals: Recent Developments and Approaches*, 30 DRUG DEV. & IND. PHARM. 429, 430 (1991) ("Sohi 1991") is a review article that discusses various methods of taste masking and teaches that citric acid can be used to mask the bitter taste commonly associated with many drugs. It also lists citric acid as a flavor modifying agent in at least three examples. *Id.* at 431. Sohi 1991 also discusses a formulation of an ibuprofen suspension that contains an acid for the dual purpose of buffering and taste masking. *Id.* at 433 ("The [ibuprofen suspension] composition is taste masked by primary taste-masking agents (sucrose/sorbitol/glycerin) and also contains a buffer acid (citric

acid/phosphoric acid) to adjust the pH of the suspension between 1.5 to 4.1."). Thus, a POSA would have been motivated to add an acid to the claimed formulation separately with a reasonable expectation of success that it would achieve flavor modification.

221. Jazz argues that "to the extent Lebon 2013 teaches that flavour-modifying acids may be 'added to the finished granulates' of its GHB formulations, that disclosure would have taught away from the claimed invention." Jazz's Final Validity Contentions at 201. I disagree with this argument. Given the aforementioned assumption that the '782 Patent has adequate written description and enablement for this claim limitation, the explicit disclosure in Lebon 2013 that the flavour-modifying acids can be separate from the GHB-containing particles, and the fact that there are only a handful of possibilities for formulating the acid as either together or separate with the immediate release and modified release particles (each of which would have been deemed obvious), a POSA would have been motivated to add an acid as a separate component and would have had a reasonable expectation of success in doing so.

222. Hence, a POSA would have been motivated to add acid separate from the immediate release particles and the modified release particles to, for example, modify the pH or the flavor.

2. Claim 2

a. "The formulation of claim 1, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof."

223. Claim 2 depends directly on claim 1 and further recites "wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium,

hydroxypropyl cellulose and mixtures thereof." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

224. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

225. A POSA would have found that prior art discloses the listed components as viscosity enhancing agents routinely used for formulations of oral suspension and also specifically for GHB. Liang 2006 discloses a GHB dosage form comprising such viscosity enhancing agents as xanthan gum, microcrystalline cellulose, hydroxypropylmethylcellulose, and hydroxypropyl cellulose. Liang 2006 at ¶¶ 53, 55. Another example is Gandhi 2011, which discloses examples of viscosity enhancing agents, including "xanthan gum," "hydroxy ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl- or ethylhydroxyethyl cellulose, carboxymethyl cellulose," and "microcrystalline cellulose." Gandhi 2011 at col. 10, ll. 21-27. It also discloses microcrystalline cellulose as a common viscosity enhancing agent. *See also* PHARMACEUTICAL SUSPENSIONS 2010 at 112 ("Generally used suspending agents in suspension include cellulosic derivatives (methylcellulose, carboxymethylcellulose, hydroxyethyl cellulose, and hydroxypropyl methylcellulose), synthetic polymers (carbomers, polyvinylpyrrolidone poloxamers, and polyvinyl alcohol), and polysaccharides and gums (alginates, xanthan, guar gum, etc.).").

226. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

3. Claim 3

a. "The formulation of claim 1, wherein the acid is selected from the group consisting of malic acid, citric acid,

tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid."

227. Claim 3 depends directly on claim 1 and further recites: "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

228. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

229. A POSA would have found that prior art discloses the listed components to be acids routinely used for formulations of oral suspension and also specifically used for GHB. Liang 2006 discloses adding an acid to a sodium oxybate formulation. Specifically, it claims a dosage form comprising "a neutralizing agent or agents selected from the group consisting of malic acid, citric acid, tartaric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, benzoic acid, a polyacid, and acidic ionic resins." Liang 2006 at Claim 3; *see also* Mehta 2014 at ¶ 106 (disclosing that "[t]he pH adjuster may be a buffering agent which may include one of the following or may be selected from the group consisting of one or more of a pharmaceutically acceptable acid selected from the group consisting of citric acid, ascorbic acid, acetic acid, tartartic acid, phosphoric acid"); PHARMACEUTICAL SUSPENSIONS 2010 at 86 (listing common acids used as a buffering agent, including boric acid, malic acid, citric acid, tartaric acid, and phosphoric acid, among others).

230. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

4. Claim 4

a. "The formulation of claim 1, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate."

231. Claim 4 depends directly on claim 1 and further recites: "wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

232. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

233. A POSA would have found that prior art discloses the list of lubricants in this claim for use in a GHB formulation. Liang 2006 discloses adding a lubricant to a sodium oxybate formulation. Specifically, it teaches that the lubricant may be "talc, sodium lauryl fumurate, fumed silicon dioxide, colloidal silica, titanium dioxide, kaolin, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, and sodium lauryl sulfate." Liang 2006 at ¶ 61.

234. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

5. Claim 5

a. "The formulation of claim 1, wherein the lubricant is magnesium stearate."

235. Claim 5 depends directly on claim 1 and further recites: "wherein the lubricant is magnesium stearate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

236. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. Liang 2006 expressly discloses the use of magnesium stearate as a lubricant. Liang 2006 at ¶ 61.

237. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

6. Claim 6

a. "The formulation of claim 1, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate."

238. Claim 6 depends directly on claim 1 and further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

239. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

240. A POSA would have found that the prior art discloses that the daily dose of Xyrem is 4.5 to 9 grams. Liang 2006 at ¶ 5; Lebon 2013 at col. 1, ll. 46-49. Further, the '782 Patent identifies no unique or unexpected properties associated with the recited range of oxybate amount, and a POSA would have arrived at the recited dosage ranges from the ranges disclosed in Liang 2006 as a result of routine optimization. Further still, the prior art taught that a single dose of GHB can have "a range of about 500 mg to about 12 g of drug." Allphin 2012 at ¶ 42. Thus, a POSA would have also been motivated to modify the amount of sodium oxybate in the single daily dose described in Liang 2006 to arrive at the claimed range of 4.0 g to 12.0 g of sodium oxybate.

241. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

7. Claim 7

a. "The formulation of claim 1, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium gamma-hydroxybutyrate."

242. Claim 7 depends directly on claim 1 and further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 4.0 g, about 6 g, about 7.5 g or about 9 g of sodium gamma-hydroxybutyrate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

243. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. Liang 2006 discloses that the daily dose of Xyrem is 4.5 to 9 grams. Liang 2006 at ¶ 5.

244. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

8. Claim 8

a. "The formulation of claim 1, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate."

245. Claim 8, which depends directly on claim 1 and further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

246. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. The prior art further discloses that the daily dose of Xyrem is 4.5 to 9 grams. Liang 2006 at ¶ 5; Lebon 2013 at col. 1, ll. 46-49.

247. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

9. Claim 9

a. "The formulation of claim 1, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate."

248. Claim 9 depends directly on claim 1 and further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-

hydroxybutyrate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

249. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. The prior art further discloses that the daily dose of Xyrem is 4.5 to 9 grams. Liang 2006 at ¶ 5; Lebon 2013 at col. 1, ll. 46-49.

250. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

10. Claim 10

a. "The formulation of claim 1, wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate."

251. Claim 10 depends directly on claim 1 and further recites: "wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

252. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. The prior art further discloses that the daily dose of Xyrem is 4.5 to 9 grams. Liang 2006 at ¶ 5; Lebon 2013 at col. 1, ll. 46-49.

253. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

11. Claim 11

a. "The formulation of claim 1, wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL."

254. Claim 11 depends directly on claim 1 and further recites: "wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL [i.e., 40,000 mg/L]." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

255. I have reviewed Jazz's Final Validity Contentions as to whether the "wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL" claim limitation has written description support in, and is enabled by, the '782 Patent specification. *See* Jazz's Final Validity Contentions at 210. Jazz contends that the written description legal requirement is satisfied because (i) "[t]he specification expressly teaches that it is an 'object of the invention' to 'maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours'" ('782 Patent at col. 4, ll. 5-7); (ii) "[s]uitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L [sic], maintained over a period of about 5-8 hours as described herein . . . " (*id.* at col. 22, ll. 26-32); and (iii) Example 3 stating that the formulations were "administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage." *See* Jazz's Final Validity Contentions at 210. "Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content." *Id.*

256. I have also reviewed Jazz's Final Validity Contentions concerning enablement of the Asserted Claims of the '782 Patent. *See* Jazz's Final Validity Contentions at 210. I understand

based on my review that Jazz asserts that the '782 Patent specification enables the full scope of the Asserted Claims the '782 Patent.

257. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, and is enabled by, the '782 Patent specification. Instead, for purposes of this report I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '782 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '782 Patent, and (b) the '782 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '782 Patent. I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

258. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '782 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to have a formulation of claim 1 wherein 8 h after administration of the formulation provides a blood concentration ranging from 10 mg/L to about 40 mg/mL, with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

259. A blood concentration of 40 mg/mL is equal to 40,000 mg/L. A POSA would thus have understood a concentration of 40 mg/mL of GHB as "probably hav[ing] proven fatal" to the human body. *See, e.g.*, A.W. Jones et al., *Concentration-Time Profiles of Gamma-Hydroxybutyrate in Blood After Recreational Doses Are Best Described by Zero-Order Rather Than First-Order Kinetics*, 33 J. ANAL. TOXICOL., 332, 332 (2009) ("Jones 2009") (describing

concentration in blood of even about 900 mg/L of GHB as "probably . . . fatal"). Thus, a POSA would have understood the claim limitation to include dangerous and even fatal blood levels.

260. This claim limitation is disclosed in Allphin 2012. Allphin 2012 teaches an embodiment for which "administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of plasma levels above 10 µg/mL." Allphin 2012 at ¶ 35. It further specifies that the controlled release form can "provid[e] GHB plasma concentrations of at least 10 µg/mL over . . . up to about 8 hours." *Id.* A POSA would thus have understood that the claimed range is disclosed in Allphin 2012. A POSA would further have been motivated to combine Liang 2006 with Allphin 2012 because they are both specifically directed to a formulation of sodium oxybate.

261. As discussed above, Jazz contends that written description is satisfied because "[t]he specification expressly teaches that it is an 'object of the invention' to 'maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours'" ('782 Patent at col. 4, ll. 5-7), "[s]uitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 mg/L [sic], maintained over a period of about 5-8 hours as described herein . . . " (*id.* at col. 22, ll. 26-32), and Example 3 stating that the formulations were "administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage." *See* Jazz's Final Validity Contentions at 210. "Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content." *Id.* The disclosure in Allphin 2012 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '782 Patent.

262. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and Allphin 2012 in view of the general knowledge in the field.

12. Claim 12

a. "The formulation of claim 1, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL."

263. Claim 12 depends directly on claim 1 and further recites: "wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL [i.e., 30,000 mg/L]." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

264. I have reviewed Jazz's Final Validity Contentions as to whether the "wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL" claim limitation has written description support in, and is enabled by, the '782 Patent specification. *See* Jazz's Final Validity Contentions at 210. Jazz contends that the written description legal requirement is satisfied because (i) "[t]he specification expressly teaches that it is an 'object of the invention' to 'maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours'" ('782 Patent at col. 4, ll. 5-7); (ii) "[s]uitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L [sic], maintained over a period of about 5-8 hours as described herein . . . " (*id.* at col. 22, ll. 26-32); and (iii) Example 3 stating that the formulations were "administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage." *See* Jazz's Final Validity Contentions at 210. "Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content." *Id.*

265. I have also reviewed Jazz's Final Validity Contentions concerning enablement of the Asserted Claims of the '782 Patent. *See* Jazz's Final Validity Contentions at 210. I understand based on my review that Jazz asserts that the '782 Patent specification enables the full scope of the Asserted Claims of the '782 Patent.

266. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, and is enabled by, the '782 Patent specification. Instead, for purposes of this report I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '782 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '782 Patent, and (b) the '782 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '782 Patent. I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

267. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '782 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to have a formulation of claim 1, wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL, with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

268. This claim limitation is disclosed in Allphin 2012. Allphin 2012 teaches an embodiment for which "administration of GHB using controlled release dosage forms as described herein can achieve a rapid rise in plasma concentrations of GHB, but with a prolonged duration of

plasma levels above 10 µg/mL." Allphin 2012 at ¶ 35. It further specifies that the controlled release form can "provid[e] GHB concentrations of at least 10 µg/mL over . . . up to about 8 hours." *Id.* A POSA would thus have understood that Allphin 2012 discloses concentrations within the range of claim 12.

269. Figures 12 and 14 in Allphin 2012 further disclose a blood concentration of GHB in µg/mL within the claimed range 8 hours after administration. Figure 12 depicts a graph illustrating the plasma concentration of sodium oxybate over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form (Treatment B) at a daily dose of 6 g. Allphin 2012 at ¶¶ 22, 99.

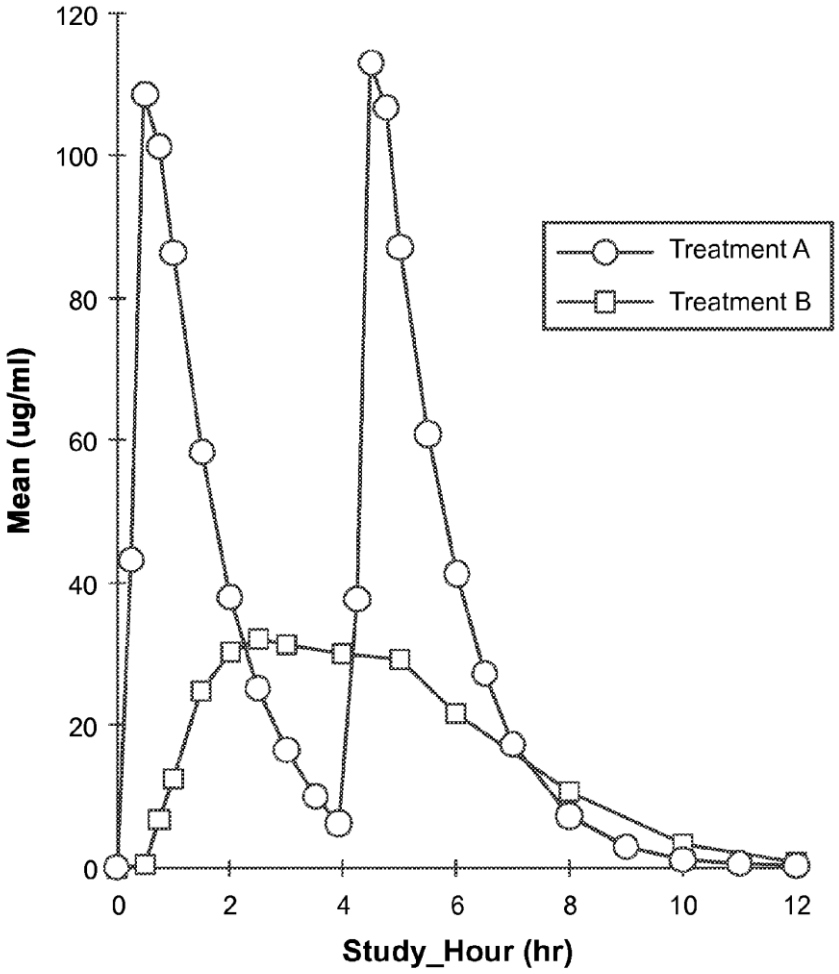


FIG. 12

270. Figure 14 depicts a graph illustrating the plasma concentration of GHB in µg/mL[1] over time provided by a sodium oxybate oral solution (Treatment A) and a sodium oxybate controlled release dosage form as described herein dosed at 4 g (Treatment D) and 8 g (Treatment E). *Id.* at ¶¶ 24, 99.

[1] A POSA would have recognized that the unit "ng/mL" [i.e., ***nano***grams/mL] in Fig. 14, making no sense, is a typo and should be "µg/mL" [i.e., ***micro***grams/mL] instead. Table 6, which contains a summary of pharmacokinetic data presented in Figure 14, shows all units in µg/mL.

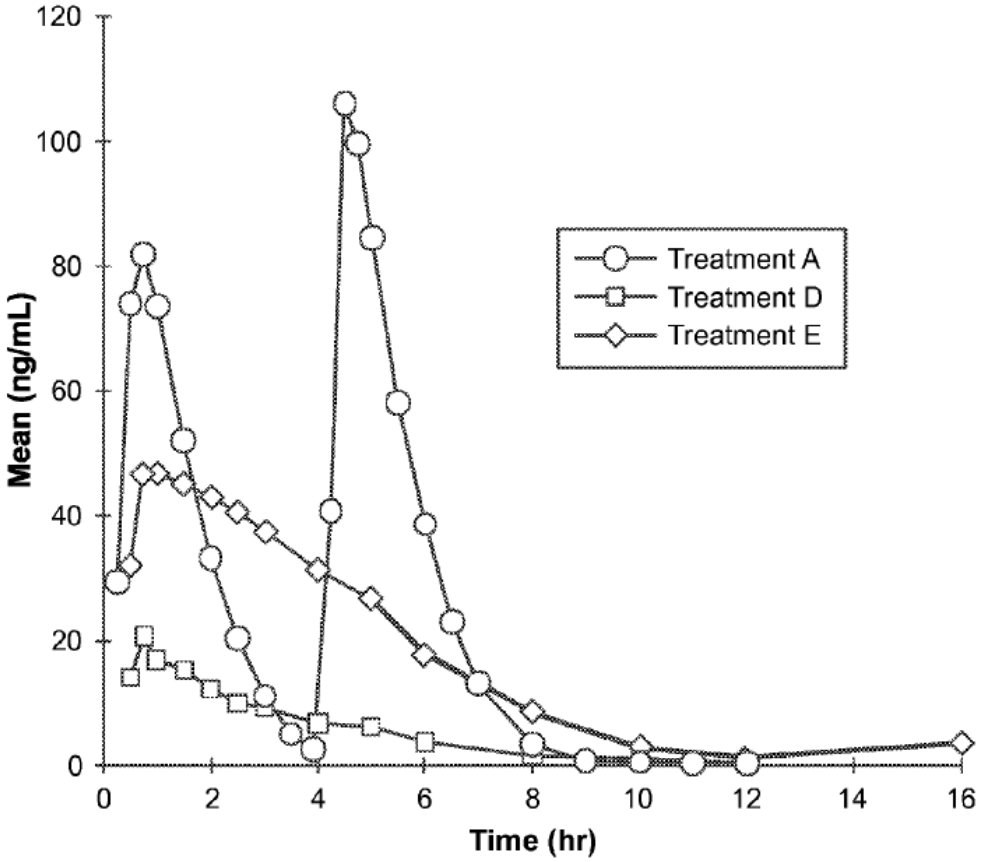


FIG. 14

271. Comparing Figure 12 and Figure 14 reveals that at least for Treatment E (treatment group with a daily dosage of 8 g), the plasma concentration of sodium oxybate 8 hours after administration is around 15 µg/mL, i.e., 15 mg/L. Thus, a POSA would have understood that the plasma concentrations within the range of claim 12 are disclosed in Allphin 2012. A POSA would further have been motivated to combine Liang 2006 with Allphin 2012 because they are both specifically directed to a formulation of sodium oxybate useful for the treatment of narcolepsy and trying to formulate a once-nightly formulation. Because Allphin 2012 alleges that it achieves this plasma concentration, a POSA would have understood that this plasma concentration could be

achieved using existing formulations under the assumption that this claim limitation is sufficiently described in, and enabled by, the '782 Patent specification.

272. As discussed above, Jazz contends that written description is satisfied because "[t]he specification expressly teaches that it is an 'object of the invention' to 'maintain the blood level of GHB from about 10 mg/L to about 20 mg/L for up to 8, 7, 6, or 5 hours'" ('782 Patent at col. 4, ll. 5-7), "[s]uitable blood levels of oxybate are at least about 10 mg/L, ranging up to about 70 m/L [sic], maintained over a period of about 5-8 hours as described herein . . . " (*id.* at col. 22, ll. 26-32), and Example 3 stating that the formulations were "administered to each of 6 beagle dogs, fasted and weighing approximately 10-12 kg, by oral gavage." *See* Jazz's Final Validity Contentions at 210. "Blood is sampled at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, and 10 h for determination of plasma GHB content." *Id.* The disclosure in Allphin 2012 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '782 Patent.

273. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and Allphin 2012 in view of the general knowledge in the field.

13. Claim 13

a. "The formulation of claim 1, wherein the formulation is a multiparticulate composition."

274. Claim 13 depends directly on claim 1 and further recites: "wherein the formulation is a multiparticulate composition." Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

275. It is my opinion that a POSA would have been motivated, and would have had a reasonable expectation of success, to obtain the recited subject matter in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

276. Liang 2006 further discloses that "the immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed/controlled release particles." *Id.* at ¶ 47. A POSA would have understood a multiparticulate dosage form refers to a dosage form comprising of multiple "granules, rounded granules of uniform size (often called pellets) and mini-tablets." WHO 2012 at 213. A POSA would thus have understood Liang 2006 to disclose a multiparticulate formulation.

277. Thus, a POSA would have found the additional subject matter of this claim – and the claimed subject matter as a whole – to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

14. Claim 14

278. Claim 14 is:

> 14. A unit dose comprising a formulation of gamma-hydroxybutyrate, wherein the formulation comprises:
>
> a plurality of immediate release particles comprising gamma-hydroxybutyrate;
>
> a plurality of modified release particles comprising gamma-hydroxybutyrate;
>
> a viscosity enhancing agent; and
>
> an acid;
>
> wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles.

279. Claim 14 is independent and identical to claim 1 other than the preamble, which is: "[a] unit dose comprising a formulation of gamma-hydroxybutyrate, wherein the formulation

comprises." A POSA would have understood the claim term "[a] unit dose" to refer to a dosage form that contains a fixed amount per administration. *See* Lebon 2013 at col. 5, ll. 55-57 (describing unit dose as dosage "per individual container containing the granulates.").

280. To the extent that this preamble is limiting (i.e., acts as a claim limitation), it is my opinion that this claim would have been obvious to a POSA over Liang 2006 in view of the general knowledge in the field. I note that Jazz does not challenge the obviousness of the claim preamble in its Final Validity Contentions. Jazz's Final Validity Contentions at 184-203.

281. The claim preamble is disclosed by Liang 2006. Liang 2006 discloses that "[c]ombining the immediate release component and one or more pH sensitive delayed/controlled release particles of the current invention can constitute a complete once-nightly or once-daily dose," and "combining" can mean "supplying and consuming all components . . . simultaneously in the same presentation or dosage form." Liang 2006 at ¶ 32.

282. Similarly, Lebon 2013 discloses that the granulates claimed can be formulated into a unit dose, and further explains that to mean the dose "per individual container containing the granulates." Lebon 2013 at col. 5, ll. 53-57.

283. Because the remaining limitations of claim 14 are identical to those of claim 1, it is my opinion that a POSA would have found this claim to be obvious over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field.

15. Claim 15

a. "The unit dose of claim 14, wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose,

carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof."

284. Claim 15 depends directly on claim 14 and further recites: "wherein the viscosity enhancing agent is selected from the group consisting of xanthan gum, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose sodium, hydroxypropyl cellulose and mixtures thereof." This claim limitation is also recited in claim 2. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

285. Therefore, this claim would have been obvious to a POSA over Liang 2006 in view of the general knowledge in the field for the same reasons as described above for claims 2 and 14.

16. Claim 16

a. "The unit dose of claim 14, wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid."

286. Claim 16 depends directly on claim 14 and further recites: "wherein the acid is selected from the group consisting of malic acid, citric acid, tartaric acid, boric acid, maleic acid, phosphoric acid, and benzoic acid." This claim limitation is also recited in claim 3. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

287. Therefore, this claim would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 3 and 14.

17. Claim 17

a. "The unit dose of claim 14, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium

stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate."

288. Claim 17 depends directly on claim 14 and further recites: "wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, stearic acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate." This claim limitation is also recited in claim 4. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

289. Therefore, this claim would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 4 and 14.

18. Claim 18

a. "The unit dose of claim 14, wherein the lubricant is magnesium stearate."

290. Claim 18 depends directly on claim 14 and further recites: "wherein the lubricant is magnesium stearate." This claim limitation is also recited in claim 5. Claim 18 is rendered obvious for the same reasons as claim 5. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

291. Therefore, this claim would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 5 and 14.

19. Claim 19

a. "The unit dose of claim 14, wherein the lubricant is magnesium stearate."

292. Claim 19 depends directly on claim 14 and further recites: "wherein 8 h after administration of the formulation provides a blood concentration ranging from 15 mg/L to about 30 mg/mL." This claim limitation is also recited in claim 12. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

293. Therefore, this claim would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 12 and 14.

20. Claim 20

a. "The unit dose of claim 14, wherein the unit dose comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate."

294. Claim 20 depends directly on claim 14 and further recites: "wherein the unit dose comprises an amount of gamma-hydroxybutyrate equivalent to from 4.0 g to 12.0 g of sodium gamma-hydroxybutyrate." This claim limitation is also recited in claim 6. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

295. Therefore, this claim would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 6 and 14.

21. Claim 21

a. "The unit dose of claim 14, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate."

296. Claim 21 depends directly on claim 14 and further recites: "wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 6 g of sodium gamma-hydroxybutyrate." This claim limitation is also recited in claim 8. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

297. Therefore, this claim would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 8 and 14.

22. Claim 22

a. "The unit dose of claim 14, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate."

298. Claim 22 depends directly on claim 14 and further recites: "wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 7.5 g of sodium gamma-hydroxybutyrate." This claim limitation is also recited in claim 9. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

299. Therefore, it would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 9 and 14.

23. Claim 23

a. "The unit dose of claim 14, wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate."

300. Claim 23 depends directly on claim 14 and further recites: "wherein unit dose contains an amount of gamma-hydroxybutyrate equivalent to about 9 g of sodium gamma-hydroxybutyrate." This claim limitation is also recited in claim 10. Jazz does not separately challenge the obviousness of this claim limitation. Jazz's Final Validity Contentions at 184-203.

301. Therefore, it would have been obvious to a POSA over Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field for the same reasons as described above for claims 10 and 14.

24. Claim 24

a. "The unit dose of claim 14, wherein the unit dose is a sachet."

302. Claim 24 depends directly on claim 14 and further recites: "wherein the unit dose is a sachet."

303. I have reviewed Jazz's Final Validity Contentions as to whether the "wherein unit dose is a sachet" claim limitation has written description support in, and is enabled by, the '079 Patent specification, which is the same as the specification of the '782 Patent. *See* Jazz's Final Validity Contentions at 205-06. Jazz contends that the written description legal requirement is satisfied because "[t]he specification of the ['782] Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10." *Id.* The corresponding disclosure in '782 Patent is at col. 6, ll. 5-11.

304. I have not been asked to consider whether this claim limitation indeed has adequate written description support in, or is enabled by, the '782 Patent specification. Instead, for purposes of this report I have been instructed by Counsel to take as true Jazz's contention that the specification satisfies the written description and enablement legal requirements based on the limited information from the '782 Patent specification identified by Jazz. In other words, I have been instructed by Counsel to assume that the language identified by Jazz is sufficient to demonstrate to a POSA that (a) the inventors had possession of all of the claimed subject matter of the Asserted Claims of the '782 Patent, and (b) the '782 Patent specification enables a POSA to practice the full scope of the Asserted Claims of the '782 Patent (including both resinate and non-resinate sachet formulations). Notably, I have been instructed by Counsel to make those assumptions for the sole purpose of the following analysis.

305. In view of these instructions, I have concluded that the subject matter of the Asserted Claims of the '782 Patent would have been obvious to a POSA as of the priority date, including that a POSA would have been motivated to achieve a sachet formulation as claimed with a reasonable expectation of success in light of Liang 2006 and/or Lebon 2013 in view of the general knowledge in the field. That analysis is set forth below.

306. Liang 2006 discloses "opening a sachet." In particular, Liang 2006 discloses that "[t]he dosage forms of the current invention comprise an immediate release component in the form of a solid, a semi-solid or a liquid. It can be a . . . sachet . . . or the like." Liang 2006 at ¶ 45. It would have been obvious to a POSA from its disclosures that a pre-mixed powder comprising both immediate release and controlled release component disclosed by Liang 2006 can be administered in a sachet. *Id.* at ¶ 47 ("[T]he immediate release component can be in the form of particles that are pre-mixed with the pH sensitive delayed/controlled release particles"); *id.* at ¶ 48 ("[T]he

immediate release component can be in the form of a powder that is pre-mixed with the pH sensitive delayed/controlled release particles prior to ingestion.").

307. As discussed above, Jazz contends that written description is satisfied because "[t]he specification of the ['782] Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10 ['782 patent at col. 6, ll. 5-11]." Jazz's Final Validity Contentions at 205-06. The disclosure in Liang 2006 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '782 Patent.

308. Lebon 2013 likewise discloses the use of a sachet to store the GHB formulation and indeed lists a sachet as very first among a handful of allowed choices. *Id.* at col. 5, ll. 49-51 ("The granulates according to the invention may be packaged in individual containers, for example in sachets, sticks, paper bags or bottles, and preferably in plastic ampoules.").

309. As discussed above, Jazz contends that written description is satisfied because "[t]he specification of the ['782] Patent expressly provides that 'it would be desirable to provide oxybate . . . in an extended release, oral liquid dosage form (including suspensions of oxybate containing particles as described herein, which in some embodiments can be supplied as a sachet which can be suspended in e.g., tap water by the end user).' *See* '079 Patent at 6:4-10 ['782 patent at col. 6, ll. 5-11]." Jazz's Final Validity Contentions at 205-06. The disclosure in Lebon 2013 is substantively identical to the disclosure that purportedly is sufficient to satisfy the written description requirement in the '782 Patent.

310. A POSA would have been motivated to arrive at a sachet dosage form because it is expressly taught by Liang 2006 and Lebon 2013 and because a POSA would have recognized that a sachet resolves various challenges associated with administrating a GHB formulation for narcolepsy, namely the high dose and the related challenge of swallowability. The benefits and methods of administrating a drug in a multiparticulate form as an oral suspension were well known in the art. It was known that treating narcolepsy using GHB requires a "high" dose. *See, e.g.*, Liang 2006 at ¶ 31 (disclosing that the dosage needed for oxybate is preferably "high"); Allphin 2012 at ¶ 29 (disclosing that Na GHB "requires a relatively high dose" and, therefore, "should be configured to deliver large doses of drug over a prolonged period of time, while being acceptably sized for oral administration"). For drugs at high doses, such dosage forms as tablets or capsules may not be appropriate, as they would be difficult for a patient to swallow. *See, e.g.*, Liang 2006 at ¶ 31 ("Preferably, due to the high dosage of GHB, the immediate release component is a liquid."). The advantages of administrating a multiparticulate drug as a powder for oral suspension stored in a sachet include increasing swallowability and reduce the challenges of food compatibility or choking. *See, e.g.*, Bowles 2013 at 64 ("By using a suspension form, we allow for swallowability and reduce the challenges of other multiparticulate administration methods such as food compatibility, choking or the use of expensive proprietary technologies."). Given the background knowledge of a POSA, it is thus my opinion that a POSA would have been motivated by Liang 2006 to use a sachet to facilitate administration of the large dose of GHB known to be needed in the art for the treatment of narcolepsy.

311. Further, a POSA would have been motivated to store a multiparticulate formulation of GHB in a sachet as directed by Liang 2006 and Lebon 2013 and because of the well-known advantages a sachet can provide, including a flexible method of drug administration. WHO 2012

teaches that "powders and multiparticulates [] provided in sachets" "possess great flexibility." *Id.* at 213. *See also* Bowles 2013 at 77 (explaining that liquid dosage forms require many different excipients and in higher levels compared to solid dosage form).

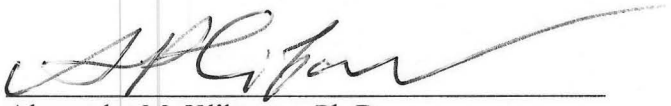
312. Finally, a POSA would have been motivated to use a sachet for use with the multiparticulate dosage form of the GHB formulation of Liang 2006 and/or Lebon 2013 in light of its teachings with a reasonable expectation of success because sachets were routinely used in the art for formulations at the priority date of the '782 Patent. For example, Balch 2012 discusses the administration of a powder for suspension dosage forms by opening a sachet. *Id.* at 195. *See also* Bowles 2013 at 57 ("It can be seen that commercially available multiparticulates are mainly supplied for administration in capsules, sachets, or multi-use containers."); WHO 2012 at 215 (describing sachets as a formulation dosage form for "sustained-release formulations"); Nexium 2014 Label at 6 (Nexium, a delayed-release formulation of esomeprazole magnesium, has a sachet dosage form).

313. Jazz states that "a POSA would have known that GHB is a hygroscopic drug product that would not have been well-suited to formulation in a sachet." Jazz's Final Validity Contentions at 145. I disagree with this conclusion. As of the time those references were published, GHB was known to be a hygroscopic drug. Liang 2006 at ¶ 5. But nonetheless both Liang 2006 and Lebon 2013 teach a sachet as a preferred dosage form. Given the aforementioned assumption that the '782 Patent has adequate written description and enablement for this claim limitation, as well as the explicit disclosure in both Liang 2006 and Lebon 2013 of formulating GHB in a sachet, a POSA would have been motivated to make a sachet formulation of GHB with a reasonable expectation of success.

314. Therefore, this claim would have been obvious to a POSA as discussed above.

315. Finally, with respect to any of the Asserted Claims of the Resinate Patents, I am aware of no objective indicia of non-obviousness to affect my foregoing obviousness conclusions.

Dated: January 17, 2023



Alexander M. Klibanov, Ph.D.

EXHIBIT 40

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW [redacted]
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1138-GBW
JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-1594-GBW

SUPPLEMENTAL EXPERT REPORT OF ALEXANDER M. KLIBANOV, PH.D.

1. I, Alexander M. Klibanov, Ph.D., previously submitted an opening expert report ("Opening Report") on January 17, 2023, on behalf of Defendant Avadel CNS Pharmaceuticals, LLC ("Avadel") in the above-captioned litigation against Plaintiffs Jazz Pharmaceuticals, Inc. and Jazz Pharmaceuticals Ireland Limited (together, "Jazz") as an expert witness regarding the validity of certain claims of U.S. Patent Nos. 11,077,079 (the "'079 Patent") and 11,147,782 (the "'782 Patent") (together, the "Resinate Patents"). My Opening Report is incorporated herein in its entirety.

2. Since submitting my Opening Report, Counsel for Avadel has asked me to review portions of the January 20, 2023, deposition testimony of Mr. Clark Allphin, a named inventor of the Resinate Patents (attached as Exhibit 4). This recent sworn testimony from Mr. Allphin provides additional support for my opinion that asserted claims 1-24 of the '782 Patent (the "Asserted Claims of the '782 Patent") would have been obvious in light of the prior art and the knowledge of a POSA.

3. In particular, Mr. Allphin testified regarding the following claim limitation in independent claim 1 of the '782 Patent: "wherein the viscosity enhancing agent and the acid are separate from the immediate release particles and the modified release particles." Ex. 4 at 383:21-384:2 (citing '782 Patent at claim 1). As noted in my Opening Report, this same limitation is also in independent claim 14 of the '782 Patent. Opening Rpt. at ¶¶ 278, 283.

4. With respect to the claim term "viscosity enhancing agent," Mr. Allphin testified that [redacted]

[redacted] Ex. 4 at 384:13-22. Mr. Allphin's testimony supports my opinion that a POSA would have been motivated to add a viscosity enhancing agent separately from the immediate release particles and the modified release particles with a reasonable expectation of success, including to hydrate the viscosity enhancing agent quickly so that it could efficiently suspend the particles after the patient adds the water, mixes the formulation, and then swallow the formulation. *See, e.g.*, Opening Rpt. at ¶ 198.

5. With respect to the claim term "acid," Mr. Allphin testified that [redacted] Ex. 4 at 384:23-385:5. Mr. Allphin's testimony supports my opinion that a POSA would have been motivated to add an acid separately from the immediate release particles and the modified release particles with a reasonable expectation of success, including to more quickly modify the pH surrounding the particles to counteract the strong alkalinity of sodium oxybate in the particles. *See, e.g.*, Opening Rpt. at ¶¶ 215-218.

6. Accordingly, Mr. Allphin's foregoing testimony supports my opinion expressed in my Opening Report that a POSA would have been motivated to add a viscosity enhancing agent and acid "separate from the immediate release particles and the modified release particles," and would have had a reasonable expectation of success in doing so.

Dated: January 27, 2023

Alexander M. Klibanov, Ph.D.

EXHIBIT 4

HIGHLY CONFIDENTIAL

Transcript of Clark Allphin, Corporate Designee, Volume 2

Date: January 20, 2023
Case: Jazz Pharmaceuticals, Inc., et al. -v- Avadel CNS Pharmaceuticals, LLC., et al.

Planet Depos
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302

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-691-MN

JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-1138-MN

JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-1594-MN

HIGHLY CONFIDENTIAL

Videotaped Deposition of JAZZ PHARMACEUTICALS
By and through its Designated Representative
CLARK ALLPHIN - VOLUME 2
New York, New York
Friday, January 20, 2023
8:53 a.m. EST

Job No.: 478324
Pages: 302 - 414
Reported by: Monique Vouthouris, CCR, RPR, CRR

303

Videotaped Deposition of CLARK ALLPHIN, held at the offices of:

QUINN, EMANUEL, URQUHART & SULLIVAN, LLP
51 Madison Avenue
New York, New York 10010
212.849.7000

Pursuant to notice, before Monique Vouthouris, Certified Court Reporter, Registered Professional Reporter, Certified Realtime Reporter, and Notary Public in and for the States of New York and New Jersey.

304

A P P E A R A N C E S

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305

ALSO PRESENT:
JAMES CEKOLA, Jazz Pharmaceuticals
CRAIG SIMAN, Avadel
ENRIQUE CASAS, Planet Depos Videographer

EXHIBIT 41

Transcript of Steven R. Little, Ph.D.

Date: April 13, 2023
Case: Jazz Pharmaceuticals, Inc., et al. -v- Avadel CNS Pharmaceuticals, LLC., et al.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-691-MN

JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-1138-MN

JAZZ PHARMACEUTICALS, INC., et al., Plaintiffs, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant. : C.A. No. 21-1594-MN

Videotaped Deposition of
STEVEN R. LITTLE, Ph.D.
Pittsburgh, Pennsylvania
Thursday, April 13, 2023
9:05 a.m.

Job No.: 488193
Pages: 1 - 143
Reported By: Brooklyn E. Schweitzer, RPR, CRR

Videotaped Deposition of STEVEN R. LITTLE, Ph.D., conducted at the offices of:

SAUL EWING ARNSTEIN & LEHR (Pittsburgh)
One PPG Place
Suite 3010
Pittsburgh, PA 15222

Pursuant to Notice, before Brooklyn E. Schweitzer, Registered Professional Reporter, Certified Realtime Reporter, and Notary Public in and for the Commonwealth of Pennsylvania.

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And

ON BEHALF OF DEFENDANT AVADEL:
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1271 Avenue of the Americas
New York, New York 10020

Also present: Jon Potler, Videographer
Jacob Balistreri, Videographer
Craig Siman

C O N T E N T S

E X H I B I T S

5

P R O C E E D I N G S
VIDEOGRAPHER: Here begins Media No. 1 in the deposition of Steven Little in the matter of Jazz Pharmaceuticals, Inc., et al., versus Avadel CNS Pharmaceuticals, LLC, et al., in the U.S. District Court for the District of Delaware.
Today's date is April 13th, 2023. The time is 9:05 a.m. The videographer today is Jon Potler here on behalf of Planet Depos. This deposition is taking place at One PPG Place, Suite 3010, Pittsburgh, Pennsylvania.
Would counsel please identify themselves and state whom they represent.
MS. DURIE: Daralyn Durie from Morrison Foerster, Avadel.
MS. WEIRES: Rebecca Weires from Morrison Foerster for Avadel.
MR. SIMAN: Craig Siman, Avadel.
MR. JONES: Andrew Jones, Morrison Foerster, for Avadel.
MR. SAWYER: Audra Sawyer, Latham & Watkins, for Avadel.
MR. CALVOSA: And Frank Calvosa and Gabe Brier from Quinn Emanuel on behalf of Plaintiffs and the witness.

6

VIDEOGRAPHER: The court reporter today is Brooklyn Schweitzer also here on behalf of Planet Depos. Would the court reporter please swear in the witness.
STEVEN R. LITTLE, Ph.D.,
was called, and having been duly sworn,
testified as follows:
DIRECT EXAMINATION
BY MS. DURIE:
Q Good morning.
A Good morning.
Q Can you please state your name for the record?
A It's Steven Ronald Little.
Q Professor Little -- is it okay if I call you Professor Little?
A Sure.
Q Okay. I'm going to hand you a piece of paper and a pen. If you could just take that.
Can you write down for me the chemical formula for gamma hydroxybutyric acid?
A Chemical formula? Okay.
Q And could you please write underneath that, label it gamma hydroxybutyric acid?
A (Witness complies.)

7

Q Now, underneath that, can you write for me the chemical formula for sodium gamma hydroxybutyrate?
A (Witness complies.)
Q And could you label that for me as well?
A What would you like me to label it as?
Q Sodium gamma hydroxybutyrate.
A (Witness complies.)
Q Thank you. Now, underneath that, could you write for me the chemical formula for gamma hydroxybutyrate?
MR. CALVOSA: Object to form.
THE WITNESS: What do you mean by the chemical formula of that molecule?
Q Well, do you have an understanding as to what gamma hydroxybutyrate refers to?
A I do, but if you write -- I'm wondering, do you want me to write the reaction product, or do you want me to write how it would actually exist in nature.
Q So is there, in your opinion, a chemical formula that is associated with the gamma hydroxybutyrate moiety?
A Yeah. It's -- so, for instance, it's here. In this case, it's associated with a

8

sodium. I could write it as if it's associated with water and the sodium ion and water in a solubilized form.
Q What if the -- what if gamma hydroxybutyrate is not associated with any other moiety?
A Then it would be unstable --
Q Okay.
A -- because there's a negative ion, and it can't exist without electroneutrality.
Q Okay. So I'd like for you to write me the chemical formula of gamma hydroxybutyrate even to the extent that it is existing in what you call an unstable form.
MR. CALVOSA: Object to form.
THE WITNESS: Okay.
Q And can you label that for me gamma hydroxybutyrate?
A (Witness complies.)
Q Can you hand me that piece of paper, please? Thank you.
MR. CALVOSA: And can I just see that?
MS. DURIE: Of course. And I would ask the court reporter to mark that as Exhibit 1.
(Exhibit 1 was marked for identification

9

and is attached to the transcript.)
Q Now, the molecule that you have labeled as gamma hydroxybutyrate, in your opinion, does that go by any other name?
MR. CALVOSA: And I'll just object to the form and to the characterization that he labeled it instead of you instructing him to label it as that.
MS. DURIE: No, he did label it as that.
MR. CALVOSA: You instructed him to label it as that.
BY MS. DURIE:
Q Well, let me ask you: The molecule that you labeled as gamma hydroxybutyrate, is that the chemical formula for that molecule?
A All three of those are the chemical formula for what's commonly called gamma hydroxybutyric.
Q With respect to the specific term gamma hydroxybutyric, is the chemical formula that you wrote that is associated with that a correct representation of its chemical formula?
A It depends on what you mean by chemical formula. So all three of those are the common usage of gamma hydroxybutyrate. The last one

10

would be a reaction -- I don't know. You could call it an intermediate, but it's a product, but it doesn't exist on its own. It can't because it's not electroneutral.
Q Is it your opinion that a person of skill in the art would use the term gamma hydroxybutyrate to refer to each of the three molecules that you have set forth in Exhibit 1?
A Yes, and Dr. Klibanov agrees with that.
Q If a person of skill in the art were to use the term gamma hydroxybutyric, how would one know which of those three chemical structures was being referred to?
A Well, it could be that you refer to it as gamma hydroxybutyric and a person in the skill with its common understanding could mean that it could be any of those forms. It could be that the context of the sentence or the context of the speech would confine it further, but it could mean all three.
Q Is there any way in your opinion to know, other than from context, which meaning to attribute to the term gamma hydroxybutyric in a given instance?
A Well, given that ultimately the active

11

pharmaceutical moiety is -- is present in all three, it would make sense that somebody would call all three gamma hydroxybutyric. So it's just the common usage of the term.
Q When you said the chemical moiety is present in all three, what chemical moiety are you referring to?
A Well, technically the -- the -- I mean, the problem is that you're having me draw this out of context. So, for instance, this guy here at the bottom is going to be in a hydrogen-bonded structure, and the ion is going to be here because it has to be in order to maintain neutrality. So this is dissolved.
So the ion's here, the ion's here, and the ion would be produced with dissolution.
Q Let me ask my question again. When you referred in your prior answer to the chemical moiety, what specifically were you referring to?
A The ion.
Q And when you say the ion, what chemical structure are you referring to?
A It's the ion form here. So it's the form that would need to exist with other things, but it's the form.

12

Q And that is the chemical formula that you wrote above the legend gamma hydroxybutyric; is that correct?
MR. CALVOSA: Object to form, and again to the characterization.
THE WITNESS: Well, all of these are gamma hydroxybutyric. You asked me to label it this (indicating).
BY MS. DURIE:
Q Correct. And so, again --
A But technically all of these would be GHB.
Q Okay.
A According to the common usage.
Q Okay. We'll get to that. But first, again, my question, when in your prior answer you referred to the chemical moiety that is present in all three, were you referring to the chemical structure that appears above the legend gamma hydroxybutyric in Exhibit 1?
A I'm referring to the one that's here, the one that's here, and the one that can be produced here by dissolving it.
Q Let me ask my question again. When you referred to the chemical moiety in your prior answer, is that chemical moiety the moiety that is

13

present above the legend gamma hydroxybutyric in Exhibit 1?
A Yeah. What I don't understand is you keep asking me about this moiety. This moiety right here does not exist on its own.
Q Okay. Not my --
A It has to be with other things.
Q Again, not my question. My question is not whether it exists alone. My question is whether in your answer when you referred to the chemical moiety, what you were referring to was the chemical moiety that is shown in Exhibit 1 above the legend gamma hydroxybutyric?
A It -- it's so the problem with this is that you're forcing a discussion of a thing that is not existing on its own. It has to be with other things, so it depends on what you mean.
Q In what way does it depend on what I mean?
A Because if you would like to talk about a portion of each of these molecules, we could, or we could talk about the portions that exist actually in nature.
Q Okay.
A How you would actually have them.
Q Okay. My question wasn't about what

14

exists in nature. It was endeavoring to understand your response to one of my questions. So in your answer, you had referred to a chemical moiety. Understanding your position that that chemical moiety may be present in each of the compositions that you have depicted, is that chemical moiety itself that you referred to the one that appears above the legend gamma hydroxybutyric?
A Technically, it's -- so in this case, it exists in a state with hydrogen bonds. In this state, it exists in electrostatic bond. In this state, it doesn't exist in a solid, but it could be produced by the dissolution. That's what I mean.
Q What is the this you refer to?
A The ion.
Q And when you say the ion, let me hand you a second piece of paper. And if you could write for me the chemical formula of the ion that you're referring to.
A There is no -- what do you mean by chemical formula?
Q Okay. You said you were referring to the ion.

15

A Mm-hmm.
Q Can you write down for me what you mean by the ion?
A It would be --
Q On the -- on this second piece of paper. Just write down --
A I would have to copy all of this again.
Q Okay. Again, just the ion. When you refer to the ion, can you write down for me just what you mean by the ion?
A No, I can't, because it would be existing with other things.
Q Okay. Again, my question isn't whether it exists with other things. Is there any way as a matter of chemical nomenclature to write down what you were referring to as the ion?
A Well, I could write it as a piece of a reaction. You know, I could do it that way.
Q Okay. So why don't you write it down as a piece of a reaction on that second piece of paper.
A (Witness complies.)
There'd be something here. Could draw it like this, and there'd be other stuff.
Q Okay. Now, when you said that ion is a piece of that reaction, can you draw a circle

16

around the ion in what you have depicted?
A I don't understand the question.
Q So you said that you could depict the ion as a piece of the reaction; isn't that right?
A Yes.
Q Is it your testimony that the ion is the entirety of the reaction that you have depicted?
MR. CALVOSA: Object to form. Sorry, object to form.
THE WITNESS: The entirety of the reaction? No. It's a product of a reaction.
BY MS. DURIE:
Q Okay. So can you circle for me that reaction product that constitutes the ion?
A No, because there'd be other things with it.
Q Okay. Again, not asking you about the other things. Just asking you about the ion itself. Is it possible for you to circle that?
A Ion itself? Okay. So this is what we're referring to with other stuff.
Q Very good. And can you please label that "ion," the thing that you have circled?
MR. CALVOSA: I'll just object to the instruction.

17

Q Is there any other nomenclature that you would use to describe the thing that you have circled?
A What do you mean by nomenclature?
Q As a chemist, is there any other way that you would refer to the thing that you've circled other than by calling it the ion?
A I haven't considered that.
Q Great. Can you please hand that to the court reporter, and I'll have that marked as Exhibit 2.
(Exhibit 2 was marked for identification and is attached to the transcript.)
Q Now, have you heard of gamma hydroxybutyrate referred to as an unbound anion?
A What do you mean by an unbound anion?
Q Well, that's a very good question. Does that phrase, an unbound anion, have any meaning to you as a chemist?
A Well, it -- in its form, you can consider it as being bound if there was an electrostatic bound, for instance. You could technically call it unbound if it was in a solution, but it would be in a hydrogen-bonded structure, and the other ion would be near it in order to maintain

18

electroneutrality.
So there would be association with those in solution as well. It just depends on what you mean.
Q Okay. As a chemist, if someone were to refer to -- were to refer to something as being an unbound anion, what would that mean to you?
A It could mean that it's in a solution in a hydrogen bonded network with its counterion within a certain length from it to maintain electroneutrality.
Q Okay. Now, does the phrase "the conjugate base" have a meaning to you as a chemist?
A It does.
Q What does that mean?
A A conjugate base is a -- it's a piece of a reaction where a proton was donated from an acid.
Q Now, I'm going to hand you another piece of paper. I think you've still got a pen there. Now, if you can hand me Exhibits 1 and 2 for the moment?
MR. CALVOSA: Can I just see --
MS. DURIE: Yeah, of course. Yeah, go ahead.
Q Okay. Now, with respect to the molecule

19

that you had labeled as gamma hydroxybutyric acid, I'm going to ask you to just write that down again. Write down the chemical formula for gamma hydroxybutyric acid.
A (Witness complies.)
Q Okay. Now, again, can you label it again for me, gamma hydroxybutyric acid?
A (Witness complies.)
Q Now, what is the charge that is associated with that molecule?
A The molecule is not charged.
Q Okay. So can you write down for me not charged next to that, underneath that? That's fine.
Now, could you draw for me again the chemical formula associated with sodium gamma hydroxybutyrate?
A (Witness complies.)
Q Now, could you label that sodium, and what is the charge associated with that molecule?
A The overall molecule is neutral.
Q Okay.
A Because of the electrostatic bond of positive and negative that maintains electroneutrality.

20

Q Very good. Now, I would like you to write down for me the chemical formula of the molecule that you wrote above the legend gamma hydroxybutyrate, and if you want to -- I don't want you to write on Exhibit 1. If you want to refer to Exhibit 1, you're welcome to do so, but the formula that you wrote above the legend gamma hydroxybutyrate.
A Okay.
Q And what is the charge that is -- actually, can I take a look at what you wrote?
A Mm-hmm.
Q Can you hand it to me?
So what you have written, is it your testimony that if I were to ask you to write gamma hydroxybutyrate, you would write the entirety of what you have just depicted?
MR. CALVOSA: Object -- I'm sorry. Objection to form.
THE WITNESS: If it's in a solution, that could be a form that it's in, yes.
BY MS. DURIE:
Q Okay. Is there any other form that gamma hydroxybutyrate could take?
MR. CALVOSA: Object to form.

21

THE WITNESS: It would either be in an electrostatic bond like I showed above. It could be the acid dissolved. So you referred to gamma hydroxybutyrate, actually, as the acid, but that's dissolved over on the right-hand side at the top of that figure.

Or if it's already dissolved, it would have to be in a structure like the one I drew at the bottom.

BY MS. DURIE:

Q Okay. Now, what is the electrostatic charge that is associated with the structure that you drew?

A Well, like the electrostatic bond in the middle, the whole thing would be neutral associated together, but there would be the ions in the overall complex that balance.

Q Okay. Now, I'm going to write down -- if we could have that marked as Exhibit 3, please.

(Exhibit 3 was marked for identification and is attached to the transcript.)

Q Now, I'm going to hand you a chemical formula that I have written on a piece of paper. That is what you originally wrote when I asked you to write down the chemical formula for gamma

22

hydroxybutyrate; right?

MR. CALVOSA: Object to form.

THE WITNESS: Well, I asked you what you meant by it, and I tried to do the best I could to refine it as we went through your questioning. So --

BY MS. DURIE:

Q Okay. But, again, when I first asked you to write the chemical formula for gamma hydroxybutyrate, what you wrote is the chemical formula that I just handed you; isn't that right?

MR. CALVOSA: Object to form.

THE WITNESS: Well, I didn't understand your question. I asked you what you were talking about. This is a piece of what would exist, but it's only a piece of what would exist.

BY MS. DURIE:

Q Let me ask my question again: When I asked you to write down the chemical formula for gamma hydroxybutyrate, what you initially wrote down is what I have just shown you; right?

MR. CALVOSA: Object to form. It mischaracterizes --

THE WITNESS: That's not --

MR. CALVOSA: -- the question, and I guess

23

the testimony.

THE WITNESS: That's not the way that I remember that. I remember you asking me a question. I asked you to refine your question, and then I explained that each of these structures that I drew would be referred to commonly as gamma hydroxybutyrate.

BY MS. DURIE:

Q At that point in time, is the chemical formula that you had written down underneath gamma hydroxybutyrate what I have just handed to you?

A I don't -- I don't understand what you're asking me.

Q Okay. At the point in time when on Exhibit 1 you wrote down GHB next to each of three formulas --

A Mm-hmm.

Q -- was the chemical formula shown at the bottom of the page above the legend gamma hydroxybutyrate what I have just handed to you?

A At the time that you were asking me what is referred to as GHB, I drew it for all three of these structures, and I explained that this would not exist on its own, it would be in another structure, and then I explained that all three of

24

them would be referred to as gamma hydroxybutyrate.

Q Okay. Now, with respect to the chemical formula that I have written down and handed to you, is there any name that you could associate with that chemical formula?

A It depends on what you mean. If what you mean is something that doesn't exist and it's as a reaction product, you could refer to this like you do the other ones as gamma hydroxybutyrate.

Q Okay. So if you were to write gamma hydroxybutyrate underneath the chemical formula that I have handed you, would that be accurate?

A It wouldn't be accurate from the standpoint of how it exists in reality, no.

Q Okay. My question is not about what exists in nature. My question is about what name you would put on the chemical formula that I have handed you.

So let me ask you this: I've given you a chemical formula. Write underneath that the name that you think -- well, first of all, let's let you sort your microphone. My questions have elicited many things over the course of my career, but a broken microphone is the first.

25

MR. CALVOSA: Powerful questioner.
VIDEOGRAPHER: Off the record at 9:30 a.m.
(A recess was taken.)
VIDEOGRAPHER: We are back on the record. The time is 9:31 a.m.
BY MS. DURIE:
Q So with respect to the chemical formula that I have handed you, without making any annotations to the chemical formula itself, could you write down underneath it whatever nomenclature you think most appropriately would describe that chemical formula?
A I could -- so I could write down here, like the others, gamma hydroxybutyrate. If I were to do so, it would be important to understand that a person of ordinary skill in the art would understand that this does not exist in the form that you wrote and can't exist in the form that you wrote.
Q Okay. So if gamma hydroxybutyrate is an important terminology for that molecule, please write that on that piece of paper underneath it.
A Well, I'm -- okay, but I'm saying that --
Q Okay. And hand that to the court reporter, let's have that marked as Exhibit 4.

26

(Exhibit 4 was marked for identification and is attached to the transcript.)
MR. CALVOSA: And if I could just see that after you get a chance --
MS. DURIE: Yeah, sure.
MR. CALVOSA: -- to take a look. Thank you.
BY MS. DURIE:
Q Now, I would like for you to write down again for me the chemical formula for sodium gamma hydroxybutyrate.
Now, do you understand sodium gamma hydroxybutyrate to include a gamma hydroxybutyrate moiety?
MR. CALVOSA: Objection to form.
THE WITNESS: What do you mean by moiety?
Q Well, I'm definitely not the chemist, so let me ask you: Does the term moiety have meaning to you as a chemist?
A Well, it could have meaning. I think it's important since here it seems like the phrases are important to understanding what a person of ordinary skill in the art would know exists. I need you to define for me what you mean by moiety, and then I can answer your question.

27

Q So what are -- what are the various things that moiety might mean to your understanding?
A Moiety can be this part (indicating). Moiety might be this part (indicating). Depends on what you mean.
Q Okay. So in terms of the definition of moiety in the context of chemistry, would it be fair to say, then, that a moiety is a part?
A Depends on what you mean.
Q Okay. What else might it mean? What is Part 1 for your definition of the word "moiety"?
A I think it depends on the context.
Q Okay, understood, but what are my options? If we're going to pick a definition of what moiety means --
A I haven't considered that.
Q So as a chemist, if you hear the word "moiety," what does that mean to you?
A It would depend on the context.
Q Again, what are the options? What might the term "moiety" mean to you as a chemist?
A I haven't considered that.
Q So is there any meaning that you could attribute to moiety as a chemist?
A Sure. I just drew it.

28

Q How about in words?
A I haven't considered that. Depends on what you mean by it.
Q Well, I understand it depends on what I mean, but I'm asking what the range of things are it might mean to you?
A I haven't considered that.
Q So as you sit here today as a chemist, if I were a student in your class, and let me actually back up. Do you teach classes?
A I do, yeah.
Q What classes are you teaching this semester?
A I'm not teaching a class this semester.
Q Okay. Let's say over the last five years or so, what classes have you taught?
A I've taught controlled drug delivery, transport phenomenon, masking, momentum transfer.
Q Is each of those a distinct class?
A In most cases, it is. At the University of Pittsburgh, we combine them into one very large what we call core, but in most programs, those are individual courses.
Q Okay. Do you teach graduate students as well as undergraduate students?

29

A I do.
Q Okay. What undergraduate -- let's say what undergraduate classes have you taught over the last five years?
A Well, the -- the transport phenomenon course is an undergraduate course. I've taught undergraduates biomaterials, drug delivery. I've taught graduate students bio delivery and materials as well.
Q So let's say I were an undergraduate in one of your classes, and I were to ask you as my chemistry professor, what does the word "moiety" mean in the context of chemistry, how would you answer that question?
A I'd say it depends on the context.
Q Okay. And what are the range of things it might mean?
A Well, in that case, we'd have some context. Here, we don't. So I'm asking you what you mean.
Q Again, not -- no context, just if I came up to you after class in general and I said, I'm studying chemistry, I keep seeing this word moiety, what does that mean? What would you say?
A I'd say it could mean different things in

30

different context.
Q And that's the best answer that you could give me to help me understand what moiety means in the context of chemistry?
A It'd be the most accurate answer I could give a student, yes.
Q Okay. So in the context of the chemical molecule that you have written down, that's sodium gamma hydroxybutyrate; right?
A This molecule is commonly referred to gamma hydroxybutyrate, GHB. It could also be referred to as sodium gamma hydroxybutyrate, but the most common usage of the term for this molecule is GHB.
Q Okay. But sodium gamma hydroxybutyrate, that is an accurate way to describe that molecule; right?
A I'd say gamma hydroxybutyrate is the common way to refer to this molecule. That would be accurate as well by the common usage.
Q Okay. Let me ask my question again. Is sodium gamma hydroxybutyrate an accurate way to describe the molecule of the chemical formula for which you've written down?
A You could call it sodium gamma

31

hydroxybutyrate, yes.
Q Okay. Now, with respect to that sodium gamma hydroxybutyrate molecule, are there any moieties included within it?
A It depends on what you mean by moiety.
Q In what way does it depend? What are the different definitions of moiety that could impact the answer to whether there are moieties included within the chemical structure that you have written down?
A I haven't considered that.
Q If I were to ask you to circle a gamma hydroxybutyrate moiety that is present within sodium gamma hydroxybutyrate, would you be able to do that?
A Well, as I said, this is commonly referred to as gamma hydroxybutyrate, so you could circle the whole molecule.
Q Okay. To your understanding, is there any form of gamma hydroxybutyrate that is present as a moiety within the sodium gamma hydroxybutyrate molecule?
A It depends on what you mean by moiety.
Q Is there any definition of moiety pursuant to which the answer to that question would be yes?

32

A I haven't considered that.
Q Okay. So as you sit here today, other than circling the entire molecule, is there any portion of the sodium gamma hydroxybutyrate molecule that you can circle that you would consider to be a gamma hydroxybutyrate -- gamma hydroxybutyrate moiety under any definition of moiety?
A As I said, it depends on what you mean by moiety.
Q I said under any definition of moiety.
A I haven't considered the different -- it depends on what you mean by moiety.
Q Okay. Again, I'm not -- I'm saying under any definition that as a chemist you would think was a plausible definition of moiety, under any definition, is there --
A Now --
Q Let me ask my question. Under any definition, is there any way for you to circle any portion of the sodium gamma hydroxybutyrate molecule and call it a gamma hydroxybutyrate moiety?
A I circled the whole thing. That's the way -- that's the common usage of the term. So --

33

Q Right.
A The whole thing.
Q And my question is, any sub portion of the molecule that you think also fairly could be called a gamma hydroxybutyrate moiety?
A It depends on what you mean by moiety.
Q Under any definition of moiety?
A I haven't considered the different definitions in the context of this. We have different things being thrown around in terms of definitions, and I want to be careful in regard to what I'm saying, and what's important is how a person who were in the skill were to understand the term, and I'm circling the whole thing. That's how a person would understand the term.
Q Okay. Now, I -- can you hand me -- let's first of all get that mark as Exhibit 5.
(Exhibit 5 was marked for identification and is attached to the transcript.)
Q Now, I am going to draw underneath that the same chemical formula that you wrote, and I'm going to circle a portion of it, and I'm going to hand it back to you.
MR. CALVOSA: Can I just --
MS. DURIE: You want to take a look?

34

MR. CALVOSA: Yeah.
MS. DURIE: Of course.
MR. CALVOSA: And then do you want to signify in any way what you drew versus what he drew, or no?
MS. DURIE: Sure. For the record, I will note that the witness drew what is depicted in the upper portion of Exhibit 5 next to the legend GHB, and I have -- I have written underneath that the same chemical formula, and I have put a box around a portion of it.
BY MS. DURIE:
Q Professor Little, you can take a look at Exhibit 5 as I have annotated it.
Now, do you see that underneath what you have wrote, I have written down the same chemical formula?
A You -- you have. You have a different -- you have different markings on it. Yes, you've written something that is similar.
Q In what way is what I wrote different from a chemistry perspective?
A Because you put a box --
Q Okay. Ignore the box. Ignore the box. I'm not asking about the box yet. Just with

35

respect to the chemical formula, do you agree that the chemical formula I wrote is the same chemical formula that you wrote?
A It is.
Q Okay. Now, with respect to the box, I put a box around a portion -- now, first of all, again, that chemical formula that I wrote could accurately be described as sodium gamma hydroxybutyrate; right?
A It could be described as gamma hydroxybutyrate, and you could describe it as sodium gamma hydroxybutyrate.
Q Okay. Now, the portion of the sodium gamma hydroxybutyrate that I've drawn a box around, is there any way to put a label to that portion?
A This is the same thing you asked me before. It -- this thing that you've circled without the sodium doesn't exist in nature.
Q Okay. Again, not my question, whether it exists in nature. My question is as a chemist, if I were to ask you is there a name that I could use to describe the thing that I've put a box around, what would your answer be?
A It would be the same as what I wrote right

36

there, because that's the same question that you asked me on Exhibit 4. It'd be what I wrote on Exhibit 4.
Q Well, what you said is it doesn't exist without other things. I understand that. But if I were an undergraduate student in one of your classes, and I were to say, as a matter of chemistry, are there words that I can use to describe the thing that I have put a box around, what would your answer be?
A It would be what I wrote on Exhibit 4.
Q So you would tell me it doesn't exist in nature?
A I would say that you could look at this, but it would be necessarily with other things in nature, and a person with ordinary skill in the art would understand that.
Q Right. But are there words that I could use to describe the thing that I have put a box around?
A Sure. I wrote it on Exhibit 4.
Q So if I were to say to you what are the words as a chemistry matter that describe the thing I've put a box around, you would say the chemistry way that a chemist would describe that

37

is to say that it doesn't exist in nature?
MR. CALVOSA: Object to form.
THE WITNESS: I would say that's fair, yeah. In chemistry, that does not exist in nature on its own. It has to be with other things in order to stabilize it.
BY MS. DURIE:
Q Not my question. As a chemist, is there any chemistry nomenclature that could be used to identify the thing I've put a box around?
A Well, again, I think it's important to recognize that what we're talking about here is what a person with ordinary skill in the art would understand, and a person with ordinary skill in the art would understand that what you've put a box around needs other things in order for it to exist.
So if you want to call it chemistry, you can, but chemistry is what I'm writing, too. So I disagree that what I'm talking about is not chemistry.
Q Okay. But, again, I'm not -- I'm not arguing about that. Just as a matter of chemistry nomenclature, in your opinion, is there any chemistry nomenclature that could be used to

38

specify the thing that I have put a box around on Exhibit 5?
A It's what I wrote on Exhibit 4.
Q Well, you didn't write -- what you said, to be clear, on Exhibit 4 is, POSA would know gamma hydroxybutyrate exists without other things.
So you would agree, that's not chemistry nomenclature; right?
A With other things.
Q Right.
A Yeah, not without.
Q Right, with other things. So let me ask you this: Is there any chemical formula in words that you could use to describe the thing inside the box?
A You could write that it's --
Q What did you write?
A Gamma hydroxybutyrate that a POSA understands does not exist in nature on its own.
Q Okay. Now, the thing that I put a box around, is there an electrostatic charge that is associated with that thing?
A Now, you only want me to look at what this is here?
Q Correct, the thing inside the box. Is

39

there an electrostatic charge associated with the thing inside the box?
A It has a local negative charge. In nature, it would be with other things that render it electroneutral.
Q Okay. Now, when you say it has a local negative charge, why does it have a local negative charge?
A It has a local negative charge because of the electron distribution in this area only, because you -- you have to ignore what's going on around it in order to say that. Yeah.
Q Why do you have to ignore what's going on around it in order to say that it has a local negative electrostatic charge?
A Well, what the actual electron distribution around this would be would always be dictated by what's around it.
Q Okay.
A So if you ignore everything else, then it would -- it's negative because it has an electron distribution that is associated with that oxygen.
Q Okay. Now, in the chemical formula for sodium gamma hydroxybutyrate, you wrote O negative.

40

A Mm-hmm.
Q Right? And then you wrote NA plus. And NA plus stands for sodium; right?
A NA plus stands for the sodium ion, yes.
Q Right. Now, why did you write a minus charge next to the O and a plus charge next to the sodium?
A Because in this situation, the sodium has donated an electron to the oxygen, but then you have to assume the sodium's not there at all. Right? I mean, you're -- the thing is -- I don't know how to answer your question because you told me not to assume the sodium's there.
Q Well, my question does not assume that the sodium is not there. My question is simply about the charge that is associated with the portion of the molecule that I drew a box around?
A But you can't do that without the sodium because the electron came from the sodium, so you can't just make the sodium disappear.
Q Again, I'm not trying to make the sodium disappear. But is it possible to think of there being a charge that is associated with the portion of the molecule that I drew a box around?
A You -- I don't understand your question.

41

So you're saying assume that the sodium is there, or the sodium is not there?
Q Is sodium is present in the molecule, but I am addressing the portion of the molecule around which I drew a box.
A Okay.
Q So my question is, in that context, is it possible to assign a charge to the portion of the molecule around which I drew a box?
A I think it's possible if the sodium is there, it's possible to draw it like this so this is negative and this is positive and this is an electrostatic bond.
Q Okay.
A But you have to assume the sodium's there.
Q Of course, of course. Now, with respect to that electrostatic bond, you talked about the fact that the sodium donates an electron --
A Mm-hmm.
Q -- I think you said to the oxygen. What do you mean by that?
A Well, this wants another electron. This doesn't want that outer valence electron. So it will move over here, and then what happens is you have an electrostatic force that holds these two

42

together.
Q Okay. Okay.
Now, you're familiar with the term anionic bond?
A Yes.
Q Okay. Would you call that bond that exists between the oxygen and the sodium anionic bond?
A Yes.
Q Okay. And what does the term anionic bond mean in chemistry?
A It's what I just described a few minutes --
Q It is a bond that is formed by this electron donation; is that fair?
A At least one, yes. In this case, it was one. Yes.
Q Okay. Now, when we look at the chemical formula for gamma hydroxybutyric acid, you drew that as -- I'm just going to show you. I don't want you to write on Exhibit 1, but I'm going to show you what's Exhibit 1. You see the chemical formula that you wrote above for gamma hydroxybutyric acid?
A Yes.

43

Q And on the right-hand side of that depiction, we see an OH; right?
A Well, it's a -- yes. It's a COOH.
Q Okay. And is there a bond between the oxygen and the H in the depiction of gamma hydroxybutyric acid?
A Yes.
Q What is that bond?
A It's a covalent bond.
Q What is a covalent bond?
A It's a bond where the two atoms share electrons.
Q And when you say the two atoms share electrons, can you explain what that means?
A Well, the number of electrons that are within the cloud associated with this is not enough to fill this valent shell and not enough to fill this valent shell, but together, they share. So as long as these two atoms stay within proximity, it's as if both of those shells are filled.
Q Okay. Now, in your view, is there a bright line between what constitutes a covalent bond and what constitutes an ionic bond?
A The most common understanding is that the

44

two are distinct.
Q Okay. Is it possible to have a bond that has some covalent characteristics and some ionic characteristics?
A That's not how a person with ordinary skill in the art would understand it. There are theories that you could consider that there's some blending between the two of them.
Q In what circumstance might there be some blending between the two of them?
A Well, if you -- if you want to say, for instance -- it's not how a person with ordinary skill in the art would understand the different bonds, but if you wanted to say, for instance, that there is --
Q And, again, don't write on Exhibit 1.
A Okay.
Q If you want to point to it, that's fine. Just don't write on it.
A Okay. If you wanted to consider that there is a -- there is an electronegativity here such that you would have electrons spending more time with the oxygen in the COO here versus the H, you could draw a line that would suggest that this isn't 100 percent equal sharing.

45

Q Mm-hmm.
A Likewise, it is possible to look at this and say -- again, it's not what a person with ordinary skill in the art would be thinking, but you could say that this isn't 100 percent here and 100 percent here.
And likewise in this case, because there's hydrogen bonds which are also associated with electronegativity, that the electrons would not spend all of their time here. They would spend their time in solvent and also with a -- what would be called a Debye or Bjerrum length away from this sodium ion in solution.
Q Okay. So if I understand you correctly, a covalent bond might have certain ionic features if the electron sharing is uneven; would that be fair?
A Yes. It doesn't say that it's not a covalent bond, but yes.
Q Okay. Is it also true that an ionic bond might have certain covalent features if the electron transfer is not 100 percent?
A I would say in that case it's less common that students would be talking about it that way.
Q Okay.

46

A I think it's probably the case that a -- you would be thinking of that as a -- as a true ionic bond, but it is possible that you could think about a theory where both in the case of the ionic bond and in the dissolved state, that the electrons are not 100 percent on the COO. Yeah.
Q Okay. So what you're saying is even where you have an ionic bond, it is possible that there is not a 100 percent donation of a particular electron; is that fair?
A No, that's not what I said. I said that it would be -- in a case -- any time you have electrostatic now, so in the case of an ionic bond or in a dissolved state, it would be the same thing, because in a dissolved state, the reason why you have hydrogen bonds is because these are partially positive, and this would be negative, and you would then therefore have -- if you want to think about it that way, you wouldn't have all the charge on it in either of these two instances.
Q Okay. So just to make sure that we're clear about what we're talking about, when we're talking about sodium gamma hydroxybutyrate, just as that molecule, is it possible that the electron donation from the sodium atom to the oxygen is not

47

100 percent?
A That's not the way a person with ordinary skill in the art would think about it, but it is possible both in the dissolved state, which is electrostatically driven complexation, and the electrostatic bond here that is electrostatically driven that it's not 100 percent on one side, but that's not how a person with ordinary skill in the art would think about it.
Q Now, when you say that's not how a person of ordinary skill in the art would think about it, what's your definition of the person of ordinary skill in the art?
A That's in my report. I would take you to it if you could give me my report.
MS. DURIE: Sure, could you get that? Let me have marked as Exhibit 6 a copy of the opening expert report of Steven Little.
(Exhibit 6 was marked for identification and is attached to the transcript.)
BY MS. DURIE:
Q Now, you said if you had a copy of your expert report you could point me to your definition of a person of ordinary skill in the art, so why don't you do that.

48

A I was referring to -- is this my claim --
Q No, this is your original opening report. Do you mean your claim construction declaration?
A Yes.
MS. DURIE: Okay. Let's get --
(Exhibit 7 was marked for identification and is attached to the transcript.)
Q So your definition of the person of ordinary skill in the art appears at Page 6 of Exhibit 7; is that right?
A Yes.
Q Okay. And so we're talking about someone who has at least a PhD in pharmaceutical sciences, chemistry, or chemical engineering, and two to four years of experience in the field of drug delivery technology or a similar technical field, or enough additional practical experience to have the same level of attainment; is that fair?
A I think I understand what you mean. I guess I prefer the way I wrote it.
Q What's wrong with what I said?
A Well, what do you mean by attainment?
Q Well, do you agree that the first sentence of your report, someone with at least a PhD and then two to four years of experience is the level

49

of expertise that you were using to define a person of ordinary skill in the art?
MR. CALVOSA: Just object to the form.
THE WITNESS: I think you could call it expertise.
Q Okay. Now, you were talking earlier in your testimony about theories around the extent to which ionic bonds might have a covalent character and covalent bonds might have an ionic character; is that fair?
A Yes.
Q And you said that was a theory, but not a way that a person of ordinary skill in the art would think about it; is that right?
A I think that they would maybe be aware of the theories. It's not the way that they would apply, and it's not the way that they would refer to it when they speak of it.
Q Okay. But you would agree that a person of ordinary skill in the art would be aware of the theories that you described about the ways in which ionic bonds might have some covalent character or covalent bonds might have some ionic character?
A I think they would be aware that you could

50

think about it that way. That's just not the way that they would be going about thinking about it, referring to it, drawing it, because like I said, it -- it makes it so that there's little to no distinction in any of the forms. So it's not the way they would be taught, and it's not the way they would refer to it.
Q Okay. Now, do you agree that for purposes of drug formulation, the distinction between an anion and a salt can be important?
A I don't know what you mean. I'm sorry. Could you ask your question again?
Q Sure. Do you agree that for purposes of drug formulation, the distinction between an anion and a salt could be important?
A I don't understand the question.
Q Well, let me ask it this way: You say that you teach classes in drug formulation; right?
A I do, yes.
Q Okay. And when you're thinking about formulating a drug and you're working with a particular API -- and let me just stop. Are you familiar with the term API?
A Yes.
Q Do you understand what that means?

51

A I do.
Q What --
A Active pharmaceutical ingredient.
Q Okay. So when you're engaged in drug formulation and you're working with a particular API, what props of that API are important in thinking about the drug formulation exercise?
MR. CALVOSA: Object to the form. Objection; outside of the scope.
THE WITNESS: It depends on the circumstance.
BY MS. DURIE:
Q Well, just give me, if I were in a drug formulation class -- I get it may be a long list, but what are some of the properties of an API that might be important in thinking about how you might go about formulating a drug?
MR. CALVOSA: Same objections.
THE WITNESS: Well, it could be how much of it you have. It could be its molecular weight. It could be any number of things.
BY MS. DURIE:
Q What -- what other things might be important in addition to how much of it you need to have and its molecular weight?

52

A It could be its purity.
Q What else?
MR. CALVOSA: Same objections. Can I just get a standing objection so I don't have to do it each time?
MS. DURIE: Yeah, sure.
MR. CALVOSA: Okay. Thank you.
THE WITNESS: It could be its amorphicity.
BY MS. DURIE:
Q Anything else?
A It could be its compatibility with other things.
Q Would you agree that if you're going to embark on drug formulation that, at least typically, the first choice of an API for a solid drug formulation would be the anhydrate of an active substance?
MR. CALVOSA: Object to form; objection to outside the scope. You can --
THE WITNESS: I don't have an opinion on that.
BY MS. DURIE:
Q Okay. That's not something you've ever taught in your class?
A I just don't have an opinion on it. I

53

haven't considered it.
Q You do consider yourself to be an expert in drug formulation; right?
A Yes.
Q Okay. And in the course of teaching classes on drug formulation, do you ever teach your students about how they should think about choosing particular form of the API if they want to formulate a solid drug formulation?
A That's awful specific. I don't think we get into that. It depends on the circumstance, how you would think about that problem.
Q Okay. How does it depend on the circumstance?
A It would just depend on the drug. It would depend on the dosage form.
Q Okay. If you're making a solid dosage form and you want to start with particular API, would it matter for purposes of drug formulation what the charge of that molecule is?
A I don't understand what you mean the charge of the molecule.
Q The charge of the API in question?
A The charge? Well, I mean, if you have an AP I, the molecule you'd be dealing with would

54

be -- I mean, in order for it to, for instance, be a solid, it would have to be neutral. If it was in a solution, it would be locally neutral, so I don't understand what you mean.
Q Well, let me ask this: Is it common in drug formulation to use a salt form of an API?
MR. CALVOSA: Objection; outside the scope and incomplete hypothetical.
THE WITNESS: Sometimes APIs that you would use would be salts.
BY MS. DURIE:
Q Okay. And why might one choose a salt form as an API for use in drug formulation?
MR. CALVOSA: Same objections.
THE WITNESS: Sometimes that's what's given to you. It could be that the salt form has -- it could be the salt form has different material properties.
BY MS. DURIE:
Q In what respect?
A Well, the salt would have different -- for instance, like a melting point. The salt would potentially have a different hardness, just for instance.
Q Do salt forms tend to be stable?

55

MR. CALVOSA: Objection; outside the scope --
THE WITNESS: Depends on the circumstance.
MR. CALVOSA: -- incomplete hypothetical. Just give me a second.
THE WITNESS: Sorry.
BY MS. DURIE:
Q Okay. Do salt forms tend to be soluble?
MR. CALVOSA: Same objections.
THE WITNESS: It, again, depends on the circumstance.
Q What's an example of a salt form that would be unstable?
MR. CALVOSA: Same objections, and I'll just note to the extent we're getting into validity, we had an agreement that we would keep on claim construction issues.
MS. DURIE: And I don't intend this to have anything to do with validity.
MR. CALVOSA: Only you're asking what's common and in the arts, so --
BY MS. DURIE:
Q Go ahead.
A Well, you could imagine a salt that's unstable. You could imagine a salt that you can't

56

put into solution because it would degrade, for instance.
Q Okay. Turning to -- back to Exhibit 1. And, again, I'm not asking you to write anything on it. But with respect to the three chemical formulas that you set forth on Exhibit 1, gamma hydroxybutyric acid, sodium gamma hydroxybutyrate, and the chemical structure that you wrote above the legend gamma hydroxybutyrate, would each of these three have different properties if they were included within a formulation?
MR. CALVOSA: And I'll just object to the form.
THE WITNESS: Each of those -- well, the first two could have different properties. The third one is in a solution. So it's all -- it's just the three different forms. So one of them is actually in the solution.
BY MS. DURIE:
Q Okay. So let's take the top one, gamma hydroxybutyric acid. What properties of gamma hydroxybutyric acid would you consider to be relevant in thinking about making a formulation from that chemical structure?
MR. CALVOSA: Objection; outside the

57

scope.
THE WITNESS: All of them.
Q Okay. So what would that be?
A I just went through them. It would be, like, the stability.
Q In terms of thinking about the differences between gamma hydroxybutyric acid and sodium gamma hydroxybutyrate, what differences between those two molecules would be relevant in thinking about making a formulation out of each of them?
MR. CALVOSA: Objection; outside the scope.
THE WITNESS: It'd be whatever the difference in the properties would be.
BY MS. DURIE:
Q Right. And --
A Between the two of them.
Q And do you have an understanding of what those differences are?
A Not off the top of my head. I don't have them memorized, no.
Q Okay. But even if it's not memorizing an exhaustive list, as you sit here, as someone who teaches development and formulation -- let me ask this question: I take it you thought about these

58

molecules in the context of forming your opinions in this case; right?
MR. CALVOSA: Objection, and I'll just caution the witness not to reveal any of the privileged information, but to the extent you want to ask him about his claim construction declaration, that's fine, but obviously there's undisclosed opinions, essentially.
MS. DURIE: I asked a very general question.
BY MS. DURIE:
Q In coming up with your opinions on your claim construction, you've thought about those molecules; right?
A I have. I just don't remember what the different physiochemical differences are sitting here. I can't remember.
Q As you sit here today, are there any physiochemical differences that you can identify for me between gamma hydroxybutyric acid and sodium gamma hydroxybutyrate that would be relevant to a formulator?
A I don't remember them, so I can't say. I don't have them memorized.
Q Regardless of memorizing them, just based

59

on your knowledge as a chemist, are there any differences that you can identify for me?
A From the physical properties, I don't remember them, so I can't say. I don't have them memorized.
Q And the fact that one is an acid and one is a salt, that wouldn't be any clue to you as to what any differences in their properties might be that would be relevant to a formulator; is that right?
A Like I said, it could be stability, for instance. It could be any number of things. I just don't have them memorized, so I don't remember.
Q Okay. And just based on your expert knowledge, that's not something you're able to determine from looking at the chemical formula?
A What the actual properties would be, you can't just look at a formula and just know what the properties are. There are computer programs that you can use to do that, but I said I don't have those memorized.
Q Okay.
MS. DURIE: Let me have marked as the next exhibit in order a copy of U.S. Patent 107,58,488.

60

(Exhibit 8 was marked for identification and is attached to the transcript.)
BY MS. DURIE:
Q Professor Little, have you read the '488 patent?
A Yes.
Q So I'm going to start by talking about Claim 1. If you could turn to Column 27.
So if we take a look at the preamble to Claim 1, it says, a formulation comprising immediate-release and sustained-release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma hydroxybutyrate and pharmaceutically acceptable salts of gamma hydroxybutyrate, and then it continues.
Do you see that?
A Yes.
Q Okay. Now, when the preamble to Claim 1 refers to pharmaceutically acceptable salts of gamma hydroxybutyrate, what does salts of gamma hydroxybutyrate mean in that phrase?
A It's -- it's the salts of the gamma hydroxybutyrate. It's that form. So it would be, for instance, like -- like sodium gamma

61

hydroxybutyrate.
Q Okay. And so if we take a look at Exhibit 1 -- and, again, not asking you to write on it -- but the second chemical formula that you wrote there about sodium gamma hydroxybutyrate, that would be an example of a pharmaceutically acceptable salt of gamma hydroxybutyrate; is that right?
A Yes.
Q Okay. Now, when the claim preamble says before that, immediately prior to that, gamma hydroxybutyrate, what do you understand that to refer to?
A Well, in this context, it would be the -- the butyric acid.
Q Okay. So it would be the chemical structure that you wrote at the top of Exhibit 1 above gamma hydroxybutyric acid; is that right?
A Yes.
Q Is there anything in your opinion that gamma hydroxybutyrate in the preamble to Claim 1 could refer to other than gamma hydroxybutyric acid?
MR. CALVOSA: Objection to form.
THE WITNESS: Well, in this context, it

62

would be any of the forms of gamma hydroxybutyrate that I drew and I discussed in my reports as what's being discussed in the whole preamble, but in the context of this sentence, it's gamma hydroxybutyric acid and pharmaceutically acceptable salts of gamma hydroxybutyric acid, because that's one of the common ways you could use gamma hydroxybutyrate.
BY MS. DURIE:
Q Okay. And I don't -- I don't want to limit your understanding here to what you think might be one common way to instantiate the claim. Okay? I want to direct your attention to what you understand the claim scope to be. Do you understand the difference?
A No.
Q Okay.
A I don't understand what you just said. I'm sorry.
Q Okay.
MR. CALVOSA: You're smarter than all of us. I don't known what instantiate means either.
Q Okay. So my questions are not directed for the moment to what examples of the claim might be. I want to focus your attention on what you

63

understand the complete scope of the claim to be. Do you understand that distinction?
MR. CALVOSA: Objection to form.
THE WITNESS: No.
Q Okay. So do you understand that the claim construction exercise is directed at understanding what the scope of a claim is?
A Well, I mean, it could be that the judge determines that.
Q Okay.
A Yeah.
Q Right. And in your claim construction declaration, you've offered your opinion as to the construction of certain claim terms; right?
A Yes.
Q And you understand that's an opinion about what the definition of those terms is in the context of the claim?
A Definition -- it's what a person of ordinary skill in the art would understand that it means when reading it.
Q Mm-hmm. Okay. And do you understand that in view of those definitions, a claim will have a particular scope?
A That may be the case, yes.

64

Q Okay. In fact, you submitted an expert report in this case I think that relates to infringement; right?
A Yes.
Q Okay. I'm not going to ask you about the details of your opinions, but in general, what you're doing is looking at the scope of a similar claim and rendering an opinion about whether some particular example falls within that scope; is that fair?
A I think that's -- I think that's fair.
Q Okay. So my questions are going to be directed to the scope of Claim 1 as you understand it. Does that make sense to you?
A I think I understand what you're saying.
Q Okay. Now, with respect specifically to the preamble, I want to focus your attention for right now just on the preamble and the scope that it defines. So when it says that each portion comprises at least one pharmaceutically active ingredient selected from gamma hydroxybutyrate and pharmaceutically acceptable salts of gamma hydroxybutyrate, I take it that your opinion is that could include sodium gamma hydroxybutyrate; right?

65

A Yes.
Q Okay. That could include, in your opinion, gamma hydroxybutyric acid; right?
A Yes.
Q Is there anything else in your opinion that could be included within the scope of a pharmaceutically active ingredient selected from gamma hydroxybutyrate and pharmaceutically acceptable salts of gamma hydroxybutyrate?
A It would be any of the pharmaceutically accepted salts.
Q Okay. Fair enough. Anything else?
A No.
Q Okay. Now, with respect to the meaning of the term gamma hydroxybutyrate as that term is used in the preamble, what do you understand that term to mean?
MR. CALVOSA: Objection to form.
THE WITNESS: Well, it's referring to what I just said. So this entire preamble is talking about what we just got done talking about.
BY MS. DURIE:
Q The question is not directed to the entire preamble. Specifically when it says a pharmaceutically active ingredient selected from

66

gamma hydroxybutyrate, in that phrase, what does the term gamma hydroxybutyrate refer to?
A It's referring to the acid form.
Q Okay. Is there anything other than the acid form that is encompassed within the term gamma hydroxybutyrate as it is used in that portion of the preamble?
A Well, given the whole sentence, I think that's what a person with ordinary skill in the art would understand this gamma hydroxybutyrate to be.
Q Okay. And is it your opinion that a person of skill in the art would understand that first reference to gamma hydroxybutyrate to exclude any other potential form of gamma hydroxybutyrate?
A Well, the other part of it includes the other forms. Is that answering your question or no?
Q So you're saying because the claim goes on to specify pharmaceutically acceptable salts of gamma hydroxybutyrate, that's why you would interpret the first reference to gamma hydroxybutyrate to be specific to the acid --
A Yes.

67

Q -- is that right? Okay. That understanding of gamma hydroxybutyrate as being specific to the acid, that's narrower than what you understand the ordinary meaning of that term to be; is that right?
A No, because the ordinary meaning could mean any of the forms. So that's one of the forms. So that's consistent with what the common usage would be.
Q Okay. But the common usage of the term gamma hydroxybutyrate to your understanding would encompass more than just the acid; right?
A It could.
Q Okay.
A But it depends on the sentence. It could encompass any of the forms.
Q Okay. And when you say any of the forms, what are all of the forms that you are referring to?
A It's -- I discussed that in my report. It's in Paragraph 20.
Q So in your report, you say the term gamma hydroxybutyrate would be understood to encompass the gamma hydroxybutyrate negative anion, gamma hydroxybutyric acid, and other forms of gamma

68

hydroxybutyrate such as salts; is that right?
A Yes.
Q And so those are three distinct things; right?
MR. CALVOSA: Object to form.
THE WITNESS: What do you mean by distinct?
Q Let me just say, you've identified three things: the anion, the acid, and the salt; right?
A And other forms of it such as salts, yes.
Q What else would be encompassed within other forms of gamma hydroxybutyrate other than salts?
A Well, altogether here, I think it's -- it's fair to characterize them as salts, and any time you would have an electrostatic bond, I think that would be included there as a salt.
Q Okay. So it's fair to say you're talking about three things: the anion, the acid, and the salt; right?
MR. CALVOSA: Objection to form.
THE WITNESS: Well, I mean, the anion is -- is with the salt, too. Right? I mean, the anion is in the salt. So it's not technically three separate things.

69

BY MS. DURIE:
Q Okay. Now, so you would understand if a person were to say gamma hydroxybutyrate, they, in your opinion, might be referring to the anion, might be referring to the acid, and might be referring to the salt; is that correct?
A Yeah, and they do in the prior art.
Q Okay. Now, returning to the preamble of Claim 1, in the preamble where it says gamma hydroxybutyrate, would a person of ordinary skill in the art understand that could be the acid?
MR. CALVOSA: Object to the form.
THE WITNESS: Yes.
Q Would a person of skill in the art understand that it could be salt?
A Well, it talks about the salts right after it.
Q I understand.
A So it wouldn't --
Q But, again, just taking the term gamma hydroxybutyrate in isolation, that term could mean the salt; right?
A Okay. We're talking about in isolation now, so not in the claim?
Q So, first of all, just in isolation, the

70

term gamma hydroxybutyrate could mean the salt; right?
A It could.
Q Okay. When you look at Claim 1 and you see the term gamma hydroxybutyrate, do you understand that term to exclude the salt?
MR. CALVOSA: Objection to form.
THE WITNESS: In the first instance of its usage, it would mean the acid and not the salt because what follows it is the salts.
BY MS. DURIE:
Q Okay. And that is, I take it, a usage that is narrower than what you understand the ordinary meaning to be; right?
A I -- I don't think I'd characterize it that way. I would characterize it as it is common to use it in this way. It is common to use it in any of the ways that we've discussed.
Q Okay. And so one way in which it was common to use the term gamma hydroxybutyrate is to refer to the negative anion; right?
MR. CALVOSA: Objection to form.
THE WITNESS: It would be the negative ion either in solution of other things or in a salt form or the ion that dissolved as a result of

71

adding the acid to a solution.
BY MS. DURIE:
Q In your expert report at Paragraph 22 on Page 7, you have drawn a chemical structure that is associated with -- or that represents the negatively charged gamma hydroxybutyrate anion; right?
A Yes.
Q Okay. And is that an accurate representation of the negatively charged gamma hydroxybutyrate -- strike that.
Is that an accurate representation in Paragraph 22 of the negatively charged gamma hydroxybutyrate anion?
A As I say in the footnote, as a reaction product, this in itself doesn't exist on its own, but yes.
Q Okay. And the term gamma hydroxybutyrate can be used to refer to that anion; right?
A With an understanding that it exists in the forms that we've discussed, yes.
Q Now, you say in the footnote a conjugate base is a reaction product that results when a hydrogen is donated from an acid.
So that chemical structure that you have

72

written down there, that is the chemical structure of the conjugate base; right?
A In the reaction that you would draw, yes, but the conjugate base in reality would be associated with other things as we've discussed.
Q The chemical structure that you have represented in Paragraph 22 of your declaration as being a conjugate base would have a charge of minus one; is that right?
A It would have this local charge that assumes that the other things around it are not there.
Q Okay. Let me ask my question again. Just looking at the chemical structure that you have drawn in Paragraph 22 of your declaration, what is the charge of that molecule?
A Assuming nothing else is around it, which wouldn't be the case in nature, it would be negative.
Q And would it be minus 1?
A No, because anything around it would necessarily draw an electron cloud away from it, and it can't exist on its own, so it would not.
Q Is there any way to represent what the -- what the charge associated with this molecule

73

would be just as a matter of chemistry? Is there any way to define that?
A I am describing it as chemistry. This -- you can't look at this on its own and say it's minus one. There's going to be other things around it. How a person in the skill and the art would understand it is it would be an electrostatic bond and it would be a minus one and plus one -- that's the common way to understand it -- or it would be in a hydrated form with hydrogen bonds and some other ion within some distance from it. Overall, it would be neutral, and you could say it's minus one. But if you start saying that electrostatic bonds aren't true and that it's not going to be exactly minus one, that would be true in every sense in every physical form, including dissolved.
Q Okay. Now, returning to the preamble to Claim 1. When it refers to a pharmaceutically active ingredient selected from gamma hydroxybutyrate and pharmaceutically acceptable salts of gamma hydroxybutyrate, is there any basis for your opinion -- strike that.
I take it your opinion is that the term gamma hydroxybutyrate does not, in that context,

74

refer to salt; right?
A Here because of the sentence, the first instance of it is referring to the acid --
Q Right.
A -- form.
Q And do you have any reason for your opinion that that first instance of gamma hydroxybutyrate is only referring to the acid other than the fact that it is followed by the phrase "pharmaceutically acceptable salts of gamma hydroxybutyrate"?
A Well, it's typically un -- it's typically used when you say a salt, you're talking about a salt of an acid. So in this sense, it makes sense that gamma hydroxybutyrate would be referring to one of the forms of it in the common usage, which is the acid form.
Q Okay. But is there -- do you have any reason for thinking that the meaning of gamma hydroxybutyrate in that first portion of the preamble is limited to the acid other than the fact that it's followed by the reference to the salt?
A The other reason would be that all of the forms that I describe in Paragraph 20 would be

75

included in this whole phrase. So that's why the instance of it being used here would be the acid.
Q You said that all of the forms would be included within the phrase. That would include the negative anion, the acid, and the salt; is that right?
A The negative ion within its form, the acid, and other forms of the gamma hydroxybutyrate such as salts.
Q Okay. And so when there's a reference to pharmaceutically acceptable salts of gamma hydroxybutyrate, does that phrase in your opinion include the gamma hydroxybutyrate negative anion?
A The negative ion would be -- it would be a part of the salt, which is why you refer to the salt also as gamma hydroxybutyrate.
Q Okay. And in your opinion, would the term gamma hydroxybutyrate also encompass the negative anion?
A I'm sorry. Could you repeat the question, please?
Q Sure. In your opinion, would the term gamma hydroxybutyrate also encompass the negative anion?
A In its forms, yes. The negative anion

76

would be in a form like a salt.
Q Not asking about the salt. I'm asking about the term gamma hydroxybutyrate as it appears in the preamble prior to the reference to pharmaceutically acceptable salts.
A Well --
Q In that -- do you understand what I'm referring to --
A No.
Q -- specifically?
A Because you keep trying to refer to this thing like it exists on its own in nature when it doesn't.
Q Okay. So let me do this. You have a copy of the patent in front of you, right, Exhibit 8?
A The '488 patent?
Q Yeah, exactly. Could you just hand that to me? Perfect. And I'm going to underline in Claim 1 the term gamma hydroxybutyrate as it appears in the preamble prior to the reference to pharmaceutically acceptable salts. Okay?
Now, my questions are just directed to what that underlined portion of the claim means. Are you with me?
A Yes.

77

Q Okay. So it's your testimony that that underlined portion of the claim refers to the acid; right?
A Yes.
Q Does that underlined portion of the claim also refer to the negatively charged anionic form?
A What do you mean by the negatively charged anionic form?
Q Fair enough. Let's take a look at Paragraph 20 of your declaration.
A Mm-hmm.
Q You say the term gamma hydroxybutyrate would be understood to encompass the gamma hydroxybutyrate negative anion; right?
A Yes.
Q Is the gamma hydroxybutyrate negative anion encompassed within the meaning of gamma hydroxybutyrate, specifically that phrase as I have underlined in it in preamble of Claim 1?
A This would be the acid form, so it would not -- the anion can be produced by dissolving the acid, but in this form, the anion isn't there.
Q Okay. Why in your opinion does the term gamma hydroxybutyrate, as it is used where I have underlined it in Claim 1, exclude the negative

78

anion?
A Because the salts are included afterwards, so the anion would be, in these salts -- like I said, you could dissolve the acid here and then the anion would be produced.
Q Let me ask my question again. Why is it your understanding that the term gamma hydroxybutyrate as I have underlined it excludes the negative anion?
A Well, because in this instance, it's referring to the acid.
Q Okay. And, again, my question is, why do you understand it to be referring only to the acid and not also to the negative anion?
A I already answered that question. Because when you read the whole thing, in context you see the salts follow it, and it says salts of gamma hydroxybutyrate. In this context, it's referring to the acid.
Q Okay. So the subsequent reference to salt is a reason in your opinion to exclude salts from the definition of the gamma hydroxybutyrate term that I've underlined; right?
A So I guess I wouldn't use the phrase "exclude," but I think in that instance of

79

it is just referring to the acid in this sentence.
Q Okay. So if I were asking for your definition of that term, gamma hydroxybutyrate, as it is used in the preamble, in that reference in the preamble, you would say that definition excludes the salt; right?
A I think in this instance, it's referring to the acid. So when you continue reading, it's pharmaceutically acceptable salts of the acid.
Q Okay. And only the acid?
A When you say only the acid, I don't understand what you mean.
Q That reference to gamma hydroxybutyrate where I've underlined it is only a reference to the acid?
A That's what they're referring to it as when they say it here. It could be -- you know, if you take it out of this context, GHB or gamma hydroxybutyrate could mean any of its forms. In this case, the form that they're referring to when they say gamma hydroxybutyrate is the acid form.
Q Okay. Now, is that usage of the term gamma hydroxybutyrate consistent throughout the '488 patent in your opinion?
A The way that I'm construing it here is

80

consistent throughout the patent, which means that in each instance, you have the freedom to be able to refer to it in any of its forms.
Q So it is your opinion that when the term gamma hydroxybutyrate is used throughout the '488 patent, it might refer to the acid, it might refer to the salt, and it might refer to the negative anion; is that right?
A Absolutely. That's the common usage of the term in the prior art, yes.
Q And so in the context of the '488 patent, the only way we would be able to know which of those three things was being referred to is from context; is that right?
A I think that's right. You would be able to infer it based on the context.
Q Okay.
MS. DURIE: Should we take a break?
MR. CALVOSA: Sure.
MS. DURIE: We've been going for over an hour.
VIDEOGRAPHER: We're going off the record. The time is 10:41 a.m.
(A recess was taken.)
VIDEOGRAPHER: This is the beginning of

81

Media No. 2. Going back on the record at 10:59 a.m.
BY MS. DURIE:
Q Professor Little, welcome back. I'm going to hand you another piece of paper. Could you write on that piece of paper for me the chemical structure for hydrogen?
A Okay.
Q And can you show me what you wrote?
A (Witness complies.)
Q Okay. And you wrote H2. And why did you write H2?
A Because H2 -- this exists in nature in a diatomic form.
Q Have you ever seen a reference in chemistry to an H?
A An H? You -- you see it sometimes in reactions with things moving around as intermediates, yes.
Q Okay. And an H in chemistry, what does that refer to?
A Well, it could be -- in the case I just referred to, it'd be a proton moving around.
Q Okay. And so if you were -- if you can write down H for me on that piece of paper.

82

A (Witness complies.)
Q So if you saw that H in chemistry and somebody asked you, what does that H stand for, what would you say?
A It depend on the context.
Q What are the things that that H might stand for?
A I haven't considered that.
Q Just as an expert in chemistry looking at an H, what might an H mean in chemistry?
A I haven't considered that sitting here today.
Q Can you think of anything that an H might be in chemistry?
A I just said one, which is a proton. It could be in a reaction process.
Q Okay. So why don't you write that, one thing it might mean is a proton; right?
A I guess it would be H plus, but okay.
Q Is that right? Are you happy with that, that if you saw an H in chemistry, one thing that might mean is a proton?
A I think it would depend on the context.
Q Again, I'm saying one thing it might mean, one possible thing it would mean?

83

A It's one possible thing it could mean depending on the context.
Q Okay. Fair enough. What other things might an H mean in chemistry depending on the context?
A I haven't considered that.
Q As you sit here today as an expert in chemistry, is there anything that you can think of that an H in chemistry might mean other than a proton?
A I haven't considered that for this. For this discussion, I haven't considered it.
Q Okay. Well, it's not really a question particularly specific to this discussion. I mean, you teach chemistry; right?
A I teach chemistry in my classes, but it's context-specific.
Q Okay. And do you teach H in your classes?
A No.
Q Okay. And so if I were one of your students and I came up to you and I said I've been reading this chemistry textbook, I keep seeing H, what is H, how would you answer?
MR. CALVOSA: Objection; outside of scope, incomplete hypothetical.

84

THE WITNESS: I would look at the context, so I'd look at the thing they're talking about.
BY MS. DURIE:
Q Okay. Is H ever used in chemistry to refer to hydrogen?
A It could be in a periodic table, yes.
Q Right. What is the chemical nomenclature associated with hydrogen in the periodic table?
A Well, each of the atoms in the periodic table is just listed with its one- or two-letter atomic abbreviation.
Q Mm-hmm. And what is the atomic abbreviation for hydrogen?
A It's H.
Q What's the atomic abbreviation for nitrogen in the periodic table?
A N.
Q What is -- is nitrogen something that is found in nature?
A Diatomic nitrogen is found in nature, N2, yes.
Q Okay. Is N found in nature?
MR. CALVOSA: Objection to form.
THE WITNESS: On its own, no. It might -- you know, you could draw it as a reaction moving

85

around.
BY MS. DURIE:
Q But if I were in your chemistry class and I saw an N, would it be reasonable for me to assume that the N referred to nitrogen?
MR. CALVOSA: Objection.
THE WITNESS: I think it --
MR. CALVOSA: Outside the scope and incomplete hypothetical. Sorry.
THE WITNESS: Depends on the context.
BY MS. DURIE:
Q Would that be a fair assumption in at least some contexts?
MR. CALVOSA: Objection; outside the scope, incomplete hypothetical, lacks foundation.
THE WITNESS: It could mean nitrogen depending on the context.
BY MS. DURIE:
Q I am handing you a molecule that I've written down, and I'm just going to ask you, do you recognize that molecule?
A No.
Q Do you know whether it has a name that is associated with it?
MR. CALVOSA: Before we go, can I just see

86

it?
MS. DURIE: Yeah, by all means. Yeah.
THE WITNESS: I don't recognize it.
BY MS. DURIE:
Q Do you know whether it has a name that is associated with it?
A I'm sure it has a name associated with it. I don't -- I don't recognize it.
Q Can you hand it back to me for a moment?
I'm handing it back to you, and I've labeled it.
MS. DURIE: Yeah, I'm sorry. Go ahead.
MR. CALVOSA: No, that's fine. I can see.
Q So do you know whether that molecule would be referred to as a cyclopentadienyl?
A I don't know. I'm not familiar with the molecule, so --
Q And do you know whether it exists in nature?
A What do you mean by exists in nature?
Q Well, you've been using that term a lot. What do you mean when you say something exists in nature?
A Well, if you're talking about in the context of a patent like this and you're talking

87

about, like, an actual drug, you would use it in a form that you would actually have available to you. It would not be like in the middle of a reaction product or something like that.
If it were in a solution, you know, you can have a cation or anion form locally, but it would be associated with a larger structure that would render it electroneutral.
Q Okay. Do you agree, though, that even chemical structures that are not found in nature according to that definition can have chemical nomenclatures associated with them?
MR. CALVOSA: Objection; outside the scope, incomplete hypothetical, lacks foundation.
THE WITNESS: I think it's common for a person of ordinary skill in the art to look at something like this and see nomenclature, but they would not then think that this nomenclature necessarily means this is how it would actually exist in nature.
BY MS. DURIE:
Q Right. The fact that something has a particular chemical nomenclature does not imply that the thing with that chemical nomenclature exists in nature; right?

88

A In the context that you're talking about, but in the context of a patent in suit, you would be thinking about how it actually exists in nature.
Q Okay. And that concept that you just articulated, that when reading the patent in suit you would be thinking about compounds that exist in nature, as you put it, that was one of the principles that you relied on in arriving at your understanding of what the claim terms mean; right?
A Could you repeat your question, please? Sorry.
Q Sure. That understanding that in interpreting the claim terms at issue you would take into consideration whether they were -- actually, strike that. That was terrible.
MS. DURIE: Could you read back the question?
(Pending question was read back by the court reporter.)
THE WITNESS: I think that's how a person of ordinary skill in the art understands phrases like the one that we're talking about as for them to be existing or usable in the context of the '488, they would be thinking about how they exist

89

in nature, yes.
BY MS. DURIE:
Q Okay. Great. And I'd ask the court reporter to mark as the next exhibit in order the two pages that we just marked.
(Exhibits 9 and 10 were marked for identification and are attached to the transcript.)
Q Let's go back to the '488 patent, and I want to return to Claim 1. So if we go a little bit further down Claim 1, in 1(c), it says, the formulation releases at least about 30 percent of its gamma hydroxybutyrate by one hour.
Do you see that?
A Yes.
Q What does gamma hydroxybutyrate mean in that context?
A It would mean the form of gamma hydroxybutyrate that you -- that you put into the dosage form.
Q And what could that be to your understanding?
A It could be gamma hydroxybutyrate and pharmaceutically acceptable salts of gamma hydroxybutyrate.

90

Q And so that -- in 1(c) where it says it releases about 30 percent of the gamma hydroxybutyrate by one hour, you understand gamma hydroxybutyrate there to encompass the acid; is that right?
A Well, that's what you put in. When the acid dissolved in this context, it would go into the form that we've been talking about that is in a dissolved state. So when you're releasing it, it's -- it's releasing it in a dissolved state or dissolved into a dissolved state.
Q But, again, I want to understand what this word "gamma hydroxybutyrate" means in the context of 1(c). So does that word "gamma hydroxybutyrate" in 1(c) encompass the acid?
A It did release -- so if you put in the acid, it did release the acid. It's just that the form of it in the dissolved state in this context is going to be not necessarily the dissolved acid because at the PKA that this would be dissolved at, it wouldn't be in an acid form.
Q Okay. But, again, I'm asking a question about what this word means when it's used here in 1(c) in the claim. So I'm not asking about what else may happen. I just want to understand what

91

you think this word means.
So as it is used in 1(c), does the word gamma hydroxybutyrate include the acid.
MR. CALVOSA: Objection; asked and answered.
THE WITNESS: If you put in the acid, that's what it's referring to, because that's what you put it in, and that's what it's releasing is what you put it in.
BY MS. DURIE:
Q Okay. So one thing that the word gamma hydroxybutyrate could be referring to in 1(c) is the acid; right?
A It's releasing the gamma hydroxybutyrate that was in the acid form that you put in, yes.
Q Well, hang on. I think you just said something different. You just said it's releasing the gamma hydroxybutyrate that was present in the acid form, and that's different, I think, from whether the term is referring to the acid itself. So I want to ask my question again.
The term gamma hydroxybutyrate in 1(c), does that term itself encompass the acid?
A I read it as it's gamma hydroxybutyrate, so it's the form of the hydroxybutyrate you put

92

in.
Q Okay. And so one thing that might refer to is the acid; right?
A If you put in the acid, then what it's releasing is the gamma hydroxybutyrate that was in the acid form that you put in.
Q Okay. So I just want to make sure that I'm clear: Is it your opinion that if the active ingredient that is referenced in the preamble is gamma hydroxybutyric acid, then gamma hydroxybutyrate in 1(c) refers to the acid?
A It's the gamma hydroxybutyrate that is being released that was in the acid form that you put in. That's why it says its gamma hydroxybutyrate.
Q Okay. But, again, I can't tell whether we're saying the same thing or whether we're saying different things. You said the gamma hydroxybutyrate that's being released from the acid?
A Well, it's the acid that you put in, so what is being released is necessarily the gamma hydroxybutyrate that was in the acid form.
Q Okay. And is the gamma hydroxybutyrate that is being released the acid itself or

93

something different?
A Well, ultimately when it's dissolved, the release form in this case -- like I said before -- at the pH would be in a dissociated state with hydrogen bonds and whatever else is in the solution to balance its neutrality, but now it's in dissolved form because it's released.
Q Okay. So ultimately we wind up with the anion; is that right?
MR. CALVOSA: Objection to form.
THE WITNESS: Well, again, the anion can't exist on its own. It's in a dissolved state. The cation that would be next to it would necessarily need to be there to maintain electroneutrality, and you'd have a hydrogen bonding network, but that's what it looks like when it's in a solution.
BY MS. DURIE:
Q Right. So at the end of the process that is spelled out -- strike that.
At the end of the process that you're discussing, your going to have both the anion and the cation present in solution; is that fair?
A Yes.
Q Okay. Now, I want to come back to my specific question, and I'm not asking you about

94

the overall process that's taking place. I'm asking you specifically about what the words gamma hydroxybutyrate in 1(c) mean.
Do the words gamma hydroxybutyrate in 1(c) mean the anion, or do they mean the acid, or do they mean both?
A It's what you put in at the beginning that was released.
Q So, again, let me ask my question: Does that word mean the acid, the anion, both, neither, or something else entirely?
A Well, it depends. If what you put in was the acid, it's releasing the gamma hydroxybutyrate that is in the form of the acid.
Q Okay. So if you put in the acid, gamma hydroxybutyrate refers to the acid. I understand that.
Now, what if what you put in is a salt? What does gamma hydroxybutyrate in 1(c) mean in that context?
A It's the gamma hydroxybutyrate that you put in that comes out.
Q And so in that context, gamma hydroxybutyrate in 1(c) refers to the salt; is that right?

95

A It would all be released together. Whatever you put in would all be released together.
Q I understand that, but I want to be clear about what we're talking about. One option for 1(c) is you put in the acid and gamma hydroxybutyrate in 1(c) refers to the acid; right?
A It's the gamma hydroxybutyrate that was in the acid form when you put it in.
Q Is that different from saying gamma hydroxybutyric acid?
A The difference is just that it's in a dissolved state because it's released.
Q Well, but --
A That's the only difference.
Q That is an important difference, and I want to --
A I disagree that's an important difference.
Q We can disagree about that, but I want to make sure that your testimony is precise.
So, again, returning to 1(c) and what gamma hydroxybutyrate means, can gamma hydroxybutyrate mean gamma hydroxybutyric acid?
A My answer's the same. If you put in the acid, it's releasing its gamma hydroxybutyrate

96

that was in the acid.
Q Is it releasing gamma hydroxybutyric acid, or is it releasing a gamma hydroxybutyrate anion that was, in your opinion, present in the acid?
A Well, the anion can be produced along with the complex in its dissolved state from the acid. Yes, it can. It's just that in -- when you -- when you talk about the acid form, if that's what you put in, it's releasing that, its gamma hydroxybutyrate.
Q When you say it's releasing that, is it releasing in that context gamma hydroxybutyric acid?
A It is releasing the acid. It's now in a dissolved state, though. So it would take the form of the dissolved state.
Q In the first instance, at the moment the release happens, is there a moment in time at which the acid is being released?
A Well, so I can only give you examples. So, for instance, if the acid was a solid, then that's what's released, but it just -- and now it's in a dissolved state.
Q So if the acid is a solid, the solid is released, and then it dissolves?

97

A Well, in order to release, it has to dissolve.
Q How do you know that to be true, that in order for the acid to be released from the dosage form, it must dissolve?
A Because how you detect release is in a dissolved state.
Q Is there a difference between being able to detect that a release has happened in the form of a molecule at the moment of release?
A They're the same thing, because when something releases, it's dissolved.
Q Okay. So let me go back to 1(c), and I think this is a yes or no question: Does the term gamma hydroxybutyrate in 1(c) include the acid itself in the form of the acid as distinct from its constituent parts?
A Well, if what you mean is if it was added as a solid, then it's in a dissolved state, but it's the same -- it's the same thing you added. So it's gamma hydroxybutyrate. That's what it's saying.
Q Okay. So just to be clear, the reference to its gamma hydroxybutyrate is a reference to whatever form of gamma hydroxybutyrate was present

98

in the immediate and sustained release portions?
A Yes. It's just in a dissolved state now.
Q Well, but -- you say except now it's in a dissolved state, and that's what I'm trying to understand, whether you're talking about it in the form in which it was present in the sustained release portion or its dissolved state. That's the difference I'm trying to understand.
So when it says in 1(c) that it releases 30 percent of its gamma hydroxybutyrate, is that a reference to the form of gamma hydroxybutyrate that was present in the sustained-released and immediate-release portions?
A It is. It's just that when you -- if you were talking about a situation where it was in a solid state, that's what is being used when you formulate it, and when you measure the release, it's in the dissolved state.
Q Okay. When you measure the release, it's in the dissolved state. So if I were to ask you in 1(c) in your own words, what is the definition of the words gamma hydroxybutyrate, what would you say the definition of those words is?
A I've already answered that question.
Q Well, I have not understood it, so I'd ask

99

you to answer the question. What is the definition of the words "gamma hydroxybutyrate" in 1(c)?
A It's the form of gamma hydroxybutyrate that you put in at the beginning.
Q Okay. And that could include the salt of gamma hydroxybutyrate; is that right?
A Yes.
Q Okay.
A It's just that it's in a dissolved state now.
Q Well, it is, but gamma hydroxybutyrate in 1(c) refers to the form in which you put in it, and one form you might have put it in is the salt; right?
A In the dissolved state now. There's water now because it's released. So a person of ordinary skill in the art would understand that it's the form you put in in a dissolved state now.
Q Okay. And so to be clear, then, your definition of gamma hydroxybutyrate in 1(c) is the form of gamma hydroxybutyrate that you started with, which might be the acid or might be the salt, in a dissolved state?
A Yes.

100

Q Okay. Now, let's go to Claim 12, and go to 12(c). Do you see where I am?
A Yes.
Q Okay. Now, 12(c) says, "The formulation releases at least about 30 percent of its gamma hydroxybutyrate or salt thereof."
Do you see that?
A Yes.
Q Okay. Now, when it says in Claim 1 "30 percent of its gamma hydroxybutyrate" and it says in Claim 12 "30 percent of its gamma hydroxybutyrate," do those two phrases mean the same thing in those two claims?
A Well, in the first instance, it's referring to any of the forms that you put in. Here, it just -- the way it's written is the acid or the salts of the acid. So together, they mean the same thing.
Q Okay. So your understanding is that the reference in 1(c) to 30 percent of its gamma hydroxybutyrate means the same thing as the reference in 12(c) to 30 percent of its gamma hydroxybutyrate or salt thereof?
A Could you repeat that question again, please?

101

Q Sure. It's your understanding that the reference to 30 percent of its gamma hydroxybutyrate in Claim 1 means the same thing as 30 percent of its gamma hydroxybutyrate or salt thereof in Claim 12?

A To the extent that what both mean is what you put in in the first place, then they mean the same thing, but it depends on what you put in in the first place as to what it actually would be meaning.

Q Okay. And that's true for both Claim 1 and Claim 12?

A Yes.

Q Right? But in terms of just what those words mean, it's your testimony that the words 30 percent of its gamma hydroxybutyrate in Claim 1 mean the same thing as the words 30 percent of its gamma hydroxybutyrate or salt thereof in Claim 12?

A Yeah. I think the way that I put it was the common usage of the term could mean the different forms that I describe. So here it could mean the different forms, and it depends on what form you put in, and here it's either the acid or the salts of the acid. So it's consistent throughout.

102

A person with ordinary skill in the art would understand in the context that you have the flexibility of any of the forms of gamma hydroxybutyrate may be included in that word when it's used.

Q Okay. So, again, I think I understand what you said, but just to be clear, in terms of thinking about, again, the question of claim scope, right, what is embraced within the claim, 30 percent of its gamma hydroxybutyrate in Claim 1 has the same scope in your opinion as 30 percent of its gamma hydroxybutyrate or salt thereof in Claim 12?

A I mean, again, I think I just -- I'd say it the way I said it before. Because the term has the flexibility of what it means, it means the form you put in in Claim 1, and it means the form you put it in Claim 12. That's the way I would say it.

Q Okay. Is there any difference in scope between those two phrases, in Claim 1 and in Claim 12?

A Well, I mean, I'm not an attorney. All I can do is say that when a person with ordinary skill in the art uses this phrase, it depends in the context how it would be read, and it's clear in the second case that it means the acid or the salt of the acid, and in the first case, it means any of the forms that are discussed in what you called the preamble.

103

Q Okay. Well, I want to -- let me back up. Is there any difference in the scope between the phrase in Claim 1 and the phrase in Claim 12?

A I mean, I -- I think the way I put it is what I just said. I mean, I'm -- I don't think I talk about scope in my report. I think that I answered your question, that --

Q Well, I don't think you did. And if you're talking about claim construction, you are talking about scope, because that's what we mean, is what these words mean and what they define.

So let me ask again. With respect to the phrase "30 percent of its gamma hydroxybutyrate" in Claim 1 and the phrase "30 percent of its gamma hydroxybutyrate or salt thereof" in Claim 12, in your opinion, is there any difference in scope between those two phrases?

MR. CALVOSA: And I'll just object as asked and answered. Object to form.

THE WITNESS: So what I -- I will add --

104

my answer's the same, but I'll add this: To the extent that you are implying that the scope is different depending on how it's used, I disagree, because what I'm saying is that a person with ordinary skill of the art understands that it could mean any of these things depending upon the context.

So there's not, in my opinion, a difference in scope in one usage versus the other usage. It's just that you have the freedom to refer to its form by using the frame gamma hydroxybutyrate.

BY MS. DURIE:

Q Okay. And specifically in the context of Claim 1, 30 percent of its gamma hydroxybutyrate could mean 30 percent of the gamma hydroxybutyrate that was present in the acid or in the salt; right?

A It's referring to what's in the preamble. It's what you put in, yes.

Q So acid or salt; right?

A It's the dissolved form of what you put in. Acid or salt could be included in the preamble, yes.

Q And that's also true in 12(c) when it

105

refers to 30 percent of its gamma hydroxybutyrate or salt? It's what you put in. It could be acid or salt; right?
A You could put in acid or salt in Claim 12, yes.
Q Right. Now, I want you to take a look at Claim 12 and imagine that you cross out the words "or salt thereof." Are you with me?
A Okay.
Q Okay. So if it's helpful for you to do that in your copy of the patent, you're welcome to, but just cross out or salt thereof.
A Okay.
Q Now, have we changed the scope of 12(c) in any way?
A I don't -- I think that both of them would be proper use, common use of the phrase.
Q Well, let me ask my question. Has the scope -- by crossing out "or salt thereof," have I changed the scope of 12(c)?
A Well, I think both are proper use of the phrase, so I don't think the terms, for instance -- I would disagree that the terms here mean that there's a problem with consistently the scope. It's just that -- the issue is that when a

106

person of ordinary skill in the art commonly uses this phrase, it could mean any of these.
So it's clear when you read it what it means, and whether you say "or salt thereof" or not, you could understand that as being any of the forms.
Q Okay. So if I cross out the words "or salt thereof," I take it, then, it's your opinion that has no effect on the scope of that claim; is that right?
A If now Claim 12 is different, and it didn't have "or salt thereof," I think that it's the gamma hydroxybutyrate that you put in in the first place that's being released.
Q And that could be the acid or the salt?
A Yes. It's -- in the preamble, it could be the acid or the salt.
Q And that means when I cross out the words "or salt thereof," I have not changed the scope of that claim?
A Yes. You're just using the phrase now in one of the common usages, which is that it means any of the forms of gamma hydroxybutyrate.
Q Okay. So in your opinion, there was no reason for the drafter of this claim to have

107

included the words "or salt thereof" in 12(c); right?
MR. CALVOSA: Objection; lacks foundation, outside the scope.
THE WITNESS: I don't have an opinion on that. I mean, you could have written it either way.
BY MS. DURIE:
Q You could write it either way and it would mean the same thing?
A I think that because the term, its common usage could mean any of its forms, you could write it either way.
Q And it would mean the same thing?
A I think in the context that we just discussed, I think that they would mean the same thing. It's just that the term can be used to represent any of the forms, and you understand what it means given the context.
Q Okay. Now --
MS. DURIE: Can I get the '079?
Q Sodium oxybate is something that is possible in principle to weigh; is that right?
A Yes.
Q Okay. The oxybate anion is not something

108

that it is possible in principle to weigh; right?
A Well, you could -- you could determine the weight that is contributed by the oxybate ion.
Q But you can't put it on a scale and weigh it; right?
A You can't have just solid anion. It would be unstable.
Q And so for that reason, it can't be weighed; right?
A If what you mean by weigh is physically putting it on a scale and only weighing the ion, no, but you could determine the weight contribution of the ion.
Q By doing a mathematical computation?
A Yes.
Q Okay. Do you agree that when in the form of gamma hydroxybutyric acid, the anion form does not exist?
A In the covalent bonded structure as a solid, it doesn't exist.
Q Does not exist?
A It's -- yeah. I'd say that the information for it is there. If you dissolve it, then it would be in the structures we've discussed. But as a covalent bond, a person of

109

ordinary skill in the skill and the art would not understand that as an ionic bond. They would understand that as a shared bond, a covalent bond.

Q Okay. And just to be clear, what that means is that, again, in the form of gamma hydroxybutyric acid -- strike that.

The anionic form does not exist in gamma hydroxybutyric acid?

MR. CALVOSA: Object to form.

THE WITNESS: A person of ordinary skill in the art would understand that is a covalent bond, not as an ionic bond.

BY MS. DURIE:

Q And that means that the anionic form does not exist in that structure?

A The ionic form wouldn't be understood to exist in the covalent bond.

MS. DURIE: Let me have marked as the next exhibit a copy of Dr. Klibanov's declaration.

(Exhibit 11 was marked for identification and is attached to the transcript.)

Q The court reporter has handed you what's been marked as Exhibit 11. It's a copy of Dr. Klibanov's declaration. I presume that you have read it?

110

A Yes.

Q Now, I want to direct your attention to Paragraph 13. And Dr. Klibanov says in the second sentence, in an ionic bond between the negatively charged gamma hydroxybutyrate ion and a positively charged sodium ion in solid form, the mutually donated electrons, the electron pairs are still shared, albeit unequally between the two molecular entities such that neither has a full pull, negative or positive, electrostatic charge, i.e., minus one or plus one respectively.

Do you disagree with that statement?

A Well, what I would say is that a person who were in the skill in the art would draw it as minus one and positive one and would think of it as positive one and minus one.

To the extent that you now want to start saying that it's not shared exactly equally, that's also true for any form of the anion. So any form of the anion would not be minus one then in any form, because it's got to be -- it's got to be with other things. So even a hydrogen bond, which is because of partial positive charges and negative charges, would be the same.

Q Okay. Is there anything about the

111

sentence that I read from Dr. Klibanov's declaration that you believe to be scientifically inaccurate?

A I would say that it's not how a person who were in the skill in the art thinks of it and what they understand commonly use. I think that you could think of it this way, but if you do think of it this way in the uncommon sense, there would be no instance where you would have minus one and plus one.

Q There would be no instance where you would have something that was minus one or plus one in nature; is that your argument?

A I prefer to say it the way that I did. There would be no instance where you would have minus one or plus one.

Q Now, to the extent that you have the anion and the cation present in a dissolved state, what would the charge on the cation be in that situation?

A In a dissolved state, a person who were in the skill in the art would understand it to be minus one or plus one, but according to Dr. Klibanov here, if you think about it this way, would be less than minus one and less than plus

112

one.

Q And why would it be less than one -- minus one or plus one in the dissolved state?

A Because the concept that he's advocating for as a way to look at this is that in a situation where you've got donation of electrons and you have electrostatic interactions, essentially the electron cloud would not be only located on the negative charge. There would be some distribution that would go outwards because of the presence of the sodium.

So when you have an electrostatic pairing, it's not 100 percent on one thing, but that would be true for any time you have something that it's associated with, like the partial positive charge of a hydrogen and a -- a hydrogen bond.

And, likewise, in a solution, you're not free of the cation. The cation has to be there. It's within a Debye or a Bjerrum length away. So you wouldn't have an absolute minus one or plus one anywhere.

MS. DURIE: Let me have marked as the next exhibit a copy of Patent 077,079.

(Exhibit 12 was marked for identification and is attached to the transcript.)

113

BY MS. DURIE:
Q Now, I've put in front of you a copy of the '079 patent. Have you read it?
A I have.
Q Okay. Now, in the context of the '079 patent, what do you understand the term gamma hydroxybutyrate to mean?
A I think I talk about that later in my report here.
Yeah. That's discussed in Column 3, and in my report, it starts on Page 13.
Q Okay. And so is it your understanding that in the context of the '079 patent, the term gamma hydroxybutyrate refers to the negatively charged or anionic form conjugate base of gamma hydroxybutyric acid?
A Yes.
Q Okay. Now, what is the charge that is associated with that molecule?
A It's anionic.
Q What is the numeric charge that is associated with that molecule?
A Well, if you think about ionic bonds and covalent bonds the way a person of ordinary skill in the art would, it would be minus one. If you

114

think about it the way Dr. Klibanov is advocating, in any form it would be less than minus one and in all forms minus one.
Q What does -- what do the words conjugate base mean in that definition?
A It's what we were talking about before that's earlier in my report.
Q Well, I -- I can read your report for myself, but I'd like to hear the words come out of your mouth.
A Okay.
Q So when you see the words conjugate base and the definition of gamma hydroxybutyrate in the '079 patent, what do those words conjugate base mean to you?
A A reaction product that results when a hydrogen is donated from an acid.
Q And it is that form of the molecule that the term gamma hydroxybutyrate means in the '079 patent; right?
A It's one of the forms of gamma hydroxybutyrate that includes the ion.
Q Are there any forms of gamma hydroxybutyrate that are included within the meaning of that term in the '079 patent other than

115

the conjugate base that you have just described?
A All of the forms would include the ion that I'm referring to here.
Q So --
A That is being described in the '079.
Q So let me ask my question again. When the term gamma hydroxybutyrate is used in the '079 patent, what does it refer to, if anything, other than the conjugate base?
A It refers to the forms that would include the ionic form, which they're referring to here as the conjugate base. Any of those forms would be included in the definition of the '079.
Q When you say any of those forms, what forms are you referring to?
A Well, it would be the salt form as a solid, or the dissolved form.
Q So I'm going to hand you a piece of paper, and I'd like you to write out for me the chemical structure associated with any and all of the forms that you believe are encompassed within the meaning of the term gamma hydroxybutyrate in the '079 patent.
A That would be -- I would need a lot more paper. It could be any salt of the --

116

Q Okay. Go ahead. So start writing. Start writing.
A (Witness complies.)
I'm going to do it this way. Cation from any pharmaceutically acceptable --
Q No. I want, like, actual chemical structure. I don't want words. I want chemical structures.
MR. CALVOSA: And I'll just object to the instruction. You can answer it any way you'd like.
Q Well, no. The question specifically is to draw for me the chemical structures that you understand to be encompassed within the term gamma hydroxybutyrate in the '079 patent.
A I consider this a chemical structure.
Q Okay. I'd like you to write it for me -- not with words, but with the type of chemical nomenclature -- what we see at the top of Exhibit 4.
MR. CALVOSA: Object to form.
THE WITNESS: In my opinion, this is the type of chemical nomenclature that --
Q Can you show it to me? Actually, can you hand it to me?

117

So I'd like you to give me some examples of structures that you believe are included within that definition. So, again, writing them out chemically, examples of structures that, in your mind, would be examples of gamma hydroxybutyrate as it is used in the '079 patent.

A Okay. You could do sodium; you could do calcium; you could do potassium.

Q Could you write out each of those for me, please?

A (Witness complies.)

Okay.

Q Okay. Now I'll hand this to the court reporter, and if you could please mark that as the next exhibit in order.

(Exhibit 13 was marked for identification and is attached to the transcript.)

MR. CALVOSA: And could I just see it?

MS. DURIE: You want to see it? Sure.

THE WITNESS: As examples.

BY MS. DURIE:

Q Okay. Now, if you could write at the top of Exhibit 13, please, '079 patent and examples of gamma hydroxybutyrate.

And so to be clear, each of the chemical

118

structures that you have written down is something that you would consider to be an example of gamma hydroxybutyrate as that term is defined in the '079 patent; is that right?

A Yes.

Q Okay. Can you hand that back to me for a moment?

And you have written the structure once next to sodium, once next to calcium with some other things. You have potassium. You don't have a recitation of the structure, but I assume that it is implied; is that right?

A What do you mean?

Q Well, let me ask you: With respect to the structure that we see here with potassium, are you suggesting that structure is gamma hydroxybutyrate?

A I'm just trying to draw examples of the salts there.

Q Okay. But I -- again, since we're talking about examples of the term gamma hydroxybutyrate in 079, don't you need to fill in something else here for this third example?

MR. CALVOSA: I can't --

THE WITNESS: I'm confused at your

119

question. So here I'm drawing the salt. Here I'm drawing a salt. Here I'm drawing a salt.

BY MS. DURIE:

Q Okay. The salt portion would have the gamma -- would have something else added to it in order to fall within the definition of gamma hydroxybutyrate; right?

A Well, it's -- so the negatively charged ionic form is here, and then you have a potassium here.

Q Actually, hang on. I misunderstood. I see what you've done. Fine. Great.

In your mind, is the definition of gamma hydroxybutyrate in the '079 patent different in scope from the definition of gamma hydroxybutyrate in the '488 patent?

MR. CALVOSA: Object to form.

THE WITNESS: Well, if what you mean by scope here is related to my discussion of whether the acid could be included, it's in my opinion that in the '079 the acid is not included in this explicit definition that's given.

BY MS. DURIE:

Q And why is it that you believe the acid is not included in the definition in the 079?

120

A Because the forms that it's discussing include the negatively charged or anionic form, and that form you would refer to overall as gamma hydroxybutyrate in the 079.

Q Is that negatively charged or anionic form present in gamma hydroxybutyric acid?

A We've already talked about this, and a person of ordinary skill in the art would not understand the covalent bond to have the negative and positive charge as an electrostatic bond.

Q Okay. Okay.

MS. DURIE: Okay. Let's take a break.

VIDEOGRAPHER: Off the record. The time is 11:56 a.m.

(A recess was taken.)

VIDEOGRAPHER: This is the beginning of Media No. 3. We are back on the record at 12:11 p.m.

BY MS. DURIE:

Q So I want to stick with the '079 patent for a moment, which I think you have in front of you in Column 3. We were discussing the definitional language there, and let me start by asking, do you agree that the language that appears in Column 3 at Lines 59 through 61 is

121

definitional?
A It is what the authors intended it to mean in this patent, because it says as used herein.
Q So would you agree that language is definitional for purposes of the '079 patent?
A It -- if by definitional you mean what I just said, then the answer is yes.
Q Do you agree that this language defines what the term gamma hydroxybutyrate means in the context of the '079 patent?
A I think it's what the authors intend it to mean in the context of this patent, yes.
Q I want to understand in your mind if there's a difference between what the authors intended it to mean and what it actually means.
A I don't understand the difference.
Q You said this term refers to what the authors intended the term to mean in the context of the patent. To your understanding, is this definition of what gamma hydroxybutyrate in fact means when used in the '079 patent?
A I don't -- what I understand is that when you see "as used herein," and then it defines a term, that that's what you would understand the term to mean in the '079 patent.

122

Q Right. And that's true each and every time that term is used; right?
A In the '079 patent, yes.
Q Okay. And the -- this definitional language in Column 3 refers to the term gamma hydroxybutyrate or oxybate; right?
A Yes. It's another way to say gamma hydroxybutyrate or GHB, yes.
Q And so the term gamma hydroxybutyrate and the term oxybate can be used interchangeably; is that right?
A Yes.
Q Now, the '079 patent also uses the term sodium oxybate; right?
A Yes.
Q Okay. Do oxybate and sodium oxybate mean the same thing?
A They -- they can, yes.
Q Okay. So is it your testimony that everywhere the patent says sodium oxybate, it could have been oxybate?
A No, not necessarily.
Q Okay. Is it your testimony that sodium oxybate is -- strike that.
That the meaning of oxybate encompasses

123

sodium oxybate; is that right?
A Sodium oxybate is one of the things that could be meant when oxybate or gamma hydroxybutyrate is used.
Q Okay. Now, is sodium oxybate negatively charged?
A The whole molecule is neutral, but it includes the anion in it.
Q Okay.
A An electrostatic bond.
Q Okay. Do this one more time. Why don't you write out sodium oxybate, the chemical formula for sodium oxybate.
A (Witness complies.)
Q And you say it includes the anion within it. Can you draw a box around what you consider to be the anion?
A Well, it's this -- it's how you drew the box up here. So it's this piece here, and it's an anionic bond, but that has to be here in order for you to do this, otherwise you can't draw it this way.
Q That has to be there in order for you to do this, otherwise you can't draw it this way. What does that mean?

124

A It's the conversation we had before. You can't just draw the negative charge here. It has to come from something. So you can't just exclude the sodium. The sodium has to be here for the anion to exist.
Q Okay. Now, you understand the term gamma hydroxybutyrate or oxybate to refer to the entirety of the molecule that you have drawn; is that right?
A When gamma hydroxybutyrate is used, it can refer to this entire molecule, yes.
Q Okay. And let's get that marked as the next exhibit in order, if you could hand it to the court reporter.
(Exhibit 14 was marked for identification and is attached to the transcript.)
Q So if you could put a circle around the entire molecule and label it gamma hydroxybutyrate.
A (Witness complies.)
Q You would consider that to be correct; right?
A Yes.
Q Okay. And you wrote the initials GHB, I see?

125

A Yes.
Q Would you also consider it correct to call that entire molecule gamma hydroxybutyrate?
A Yes.
Q Okay. So can you write out gamma hydroxybutyrate as well?
A (Witness complies.)
Q Now, the thing you put a box around, do you have a name for that?
A It's the ion in the form of sodium gamma hydroxybutyrate.
Q So why don't you label that box.
A (Witness complies.)
Q Now, you say it's the ion in the form of gamma hydroxybutyrate. What do you mean by in the form of?
A Well, the ion has to be in some form. It can't be on its own. So in this case, it's in the form of sodium gamma hydroxybutyrate.
Q Now, the thing that you have circled and labeled gamma hydroxybutyrate, is that the negatively charged or anionic form of gamma hydroxybutyric acid?
A Repeat your question again for me, please.
Q Sure. The entire thing that you've

126

circled --
A Okay.
Q -- and that you've labeled gamma hydroxybutyrate, is that the negatively charged or anionic form of gamma hydroxybutyric acid?
A A person who were in the skill in the art could say that, yes.
Q Okay. Why?
A Because the ion's in the form of sodium gamma hydroxybutyrate.
Q You say the ion's in the form of sodium gamma hydroxybutyrate. Sodium gamma hydroxybutyrate is not an ion, is it?
A Yes, it's ionic.
Q It has an ionic bond in it?
A Correct.
Q Right. You wouldn't refer to sodium gamma hydroxybutyrate as an ion, would you?
A I think a person of ordinary skill in the art would refer to it as an ion because there's an ion in the bond. It's an ionic compound.
Q Okay. And so it is your opinion as a person with skill in the art that the entire molecule, sodium gamma hydroxybutyrate, is correctly referred to as an ion?

127

A In the context of how gamma hydroxybutyrate is used in its common form, this whole thing is gamma hydroxybutyrate. It's ionic, yes.
Q Okay. And so -- now, you said it is appropriate also in your opinion to refer to that whole thing as the negatively charged or anionic form of gamma hydroxybutyric acid; is that right?
A This ionic form can be thought of as the ion as a result of the acid donating the proton. It's an ionic form, so as was done in the prior art, the whole thing is referred to as gamma hydroxybutyrate.
Q Okay. Let me ask my question again. Is it correct to refer to the whole thing, the gamma hydroxybutyrate -- strike that.
Is it appropriate in your mind to refer to the -- what you called the whole thing as the negatively charged or anionic form of gamma hydroxybutyric acid?
A The negatively charged anionic form of gamma hydroxybutyric acid is in this form.
Q That's not my question. I understand the distinction you're drawing, but that's not my question.

128

So I want to direct your attention -- what exhibit is that? Exhibit 14?
I want to direct your attention to Exhibit 14 to the thing you put a circle around and labeled gamma hydroxybutyrate. Is that whole thing that you put a circle around the negatively charged or anionic form of gamma hydroxybutyric acid?
A I'd say yes, and the reason why is that this can't exist without this. So if this wasn't here, you wouldn't have that either.
Q The entire thing that you drew a circle around is not negatively charged; correct?
A The entire thing is neutral because of the ionic bond, and the whole thing is necessary in order for this to have a negative charge.
Q The whole thing is necessary in order for the gamma hydroxybutyrate to have a negative charge?
A For the ion in the gamma hydroxybutyrate to have a negative charge, the whole thing has to be there.
Q And when you refer to the ion in the gamma hydroxybutyric, you are referring to the thing around which you drew the square; right?

129

A I am, but the ion can't exist on its own. That's why I drew this over, so that you realize that this sodium has got to be here in order for that to be an ion.
Q Okay. And the ion that you drew the rectangle around has a negative charge; right?
A Not on its own. It has to be associated with something else in order for it to have that negative charge.
Q Not my question. In the depiction that you have drawn, the ion that you drew the square box around has a negative charge?
MR. CALVOSA: Objection; asked and answered.
THE WITNESS: If you just look at the box, it doesn't have a negative charge because it can't exist like that, so no.
BY MS. DURIE:
Q In what you drew -- in the depiction that you drew, the thing that has the square box around it has a negative charge as you drew it; right?
A Not without the sodium it doesn't.
Q Didn't you draw the sodium?
A I did.
Q Right. So in the context of what you

130

drew, isn't it correct that the thing you put the box around has a negative charge?
A As associated with the sodium, yes.
Q Okay. Let's go back to Dr. Klibanov's declaration, which is Exhibit 11, and I want to direct your attention to Paragraph 8.
So in Paragraph 8, Dr. Klibanov writes, as a matter of naming convention as set forth in the nomenclature guide of the International Union of Pure and Applied Chemistry, the -ate suffix is used in chemistry to refer to anions, not acids.
Do you agree or disagree with that statement?
A That's not what it says.
Q Let me -- let me make sure that I've read it precisely. As a matter of naming convention as set forth in the nomenclature guide of the International Union of Pure and Applied Chemistry, IUPAC, the -ate suffix is used in chemistry in reference to anion, not acids.
Do you agree with that statement?
A I was reading, sorry, the actual phrase from the book, derived from acids.
Q No. So I was directing you to the sentence in Dr. Klibanov's declaration that I just

131

read to you. Do you disagree or agree with that sentence?
A I would prefer to say it the way that the reference he cites says it --
Q Okay, but --
A -- which says it's derived from the acids.
Q Okay, but I'm not asking what you would prefer. I want to know whether you think what he said is right or wrong or you don't know.
So with reference to what Dr. Klibanov wrote, the sentence beginning "as a matter of naming convention," do you think what he wrote was correct or incorrect or you don't know?
A I think that it could be considered to be correct as long as you understand that the acid is derived -- or the anion is derived from the acid and that the anion does not exist on its own as an unstable entity.
Q Okay. Do you agree that the ending -ate in chemistry is not a reference to an acid?
A I would say that it is a reference to something that comes from an acid and is associated with something else.
Q Okay. But it is -- it is -- the ending -ate is a reference to something that comes from

132

an acid but it is not a reference to an acid itself; right?
MR. CALVOSA: Just object to form to the extent it lacks foundation.
THE WITNESS: I think that what you're saying is partially correct. It just doesn't -- -ate does not mean that it's an anion on its own.
BY MS. DURIE:
Q And my question had nothing to do with anions on its own, so let me ask my question again.
Is it correct that in chemistry the ending -ate may refer to an anion that is derived from an acid but not to the acid itself?
MR. CALVOSA: I'll just object to the form, lacks foundation, incomplete hypothetical.
THE WITNESS: I think that's right, yes.
MS. DURIE: Okay. Let me have marked as the next exhibit a product specification.
(Exhibit 15 was marked for identification and is attached to the transcript.)
BY MS. DURIE:
Q I've handed you a product specification, and I just want you to take a look at the chemical representation that appears in the upper

133

right-hand side of the page. Do you see where I am?
A Yes.
Q The O and the NA that is shown there, do you have an understanding as to what that refers to?
A Yes. It's the O minus NA positive electrostatic bond.
Q Is it correct as a matter of chemical nomenclature to depict an ionic bond in that fashion?
A You could depict it in this way, but you would understand that there was an O minus NA plus plus there.
Q Now, you said a number of times that the anionic form of gamma hydroxybutyrate cannot exist in nature on its own; right?
A Yes.
Q Okay. Can the anionic form of gamma hydroxybutyrate be present as part of a solid dosage form?
A It could be present in one of its forms that we discussed, yes.
Q Okay. So when you say it could be present in one of its forms, are you referring to the salt

134

form or the acid form?
A Yes. The salt form and the acid form are commonly referred to as gamma hydroxybutyrate.
Q Could gamma hydroxybutyrate be present as an anion as part of a solid dosage form?
A On its own, it wouldn't be stable as a solid. So a person who were in the skill in the art wouldn't understand that phrase to be the ion on its own.
Q Okay. Can liquids form part of a solid dosage form?
A It's possible, but it depends.
Q Okay. Is it possible, for example, to have a gel as part of a solid dosage form?
A It's possible to have a gel, but it depends on what you mean.
Q In what way does it depend on what I mean?
A Well, for instance, if you're talking about the kind of gel that I believe Dr. Klibanov is talking about, that you could, like, grind, it's dehydrated, so it's not in a hydrated form. It's a salt because it's solid. It's dehydrated. Everything would then, as a solid, have to associate an electrostatic bond.
Q Would it be possible -- is it possible to

135

have a solid preparation that is in the form of a liquid gel?
A It is depending on the circumstance.
Q What is a liquid gel?
A It is a -- it's a capsule where you have a usually gelatin coating. Inside of it, you have a certain amount of liquids or suspensions or something along those lines.
Q Could you have gamma hydroxybutyrate present in a liquid gel formulation?
A It's possible that you could, yes.
Q If gamma hydroxybutyrate were present in a liquid gel formulation, would there be anions of gamma hydroxybutyrate present?
A Yes, in a dissolved structure with the salt and the hydrogen bonds. Yes.
Q When you say in a dissolved structure with the salt and the hydrogen bonds, there would be instances of the gamma hydroxybutyrate negatively charged anion present as such in the liquid gel; right?
MR. CALVOSA: Object to form.
THE WITNESS: In the same way that it would be present as a solid. It would be there with the other things, yes.

136

BY MS. DURIE:
Q Well, when you say the same way as it would be present as a solid, in a solid salt form, there would be an anionic bond between that negatively charged gamma hydroxybutyrate moiety and the salt; right?
A Yes.
Q In a liquid gel, that ionic bond would not be present; correct?
A You still have the ion associated with the complex. It's got to be there or you can't maintain electroneutrality. So it's just separated by a shell of water that's oriented towards the ions with the hydrogen bonding structure, and on the sodium, it's the opposite direction. So the oxygen is pointed towards the sodium. That whole thing is the dissolved form.
Q Do you have an ionic bond present in that form?
A Well, according to Dr. Klibanov, there's no difference between any of these bonds. I think a person who were in the skill and the art would understand that that's a dissolved form in a hydrated shell. Both ions are there, though.
Q So let me ask my question again. Would a

137

person of ordinary skill in the art understand that in that dissolved form there was some ionic bond between the gamma hydroxybutyrate cation and the salt?

A I think the common way to refer to it would be that it's not an ionic bond, but that doesn't mean that it's freestanding. It's there with other things in order to maintain electroneutrality.

Q In order to maintain electroneutrality of the entire composition?

A Even of the one molecule.

Q Is it your testimony that as a matter of scientific nomenclature when the gamma hydroxybutyrate cation is present in its dissolved state it forms part of a single molecule with a salt?

A You said cation. Did you mean to say cation?

Q No, I didn't. You're absolutely right. You're totally right. I apologize for that.

Is it your testimony that when the anionic form of gamma hydroxybutyrate is present in its dissolved form, it is part of a single molecule with a salt?

138

A It's part of a single complex overall that has both ions and water molecules that surround them in shells at a certain distance to keep them within a coulombic range while stabilizing them in a solution.

Q I understand that. But the anionic form of gamma hydroxybutyrate is not present as part of a single molecule with a salt when it is in its dissolved state; right?

A The molecule now becomes one entity with the complex. That whole complex would have to go together wherever that thing goes.

Q Okay. But there is a distinct gamma hydroxybutyrate molecule that is anion that is present within that larger complex that you have described when it is in its dissolved state?

MR. CALVOSA: Object to the form.

THE WITNESS: I just don't understand the distinction. So you're -- you're trying to make that somehow distinct. It's not distinct.

BY MS. DURIE:

Q I'm not asking whether that's distinct. I'm asking whether a matter of chemical terminology one could refer to that anion in its dissolved state as a molecule?

139

A I think a person who were in the skill in the art would think of it in terms of its overall association, is the way I think they would consider it.

Q And do you think it would be incorrect to refer to the gamma hydroxybutyrate anion that is present in the dissolved state as a molecule?

A I just don't think that's how a person who were in the skill in the art would be thinking about the term.

Q Do you think that would be incorrect as a matter of terminology?

A I mean, I -- you could -- I mean, you can call it what you want. You can imagine that perhaps there's some kind of definition that's given that you just gave, but it's not how a person who were in the skill in the art would think about the -- think about the molecules.

Q When you say it's not how a person of ordinary skill in the art would think of the molecules, what are the molecules that you're referring to?

A Gamma hydroxybutyrate.

Q Good. Thank you. I don't have any further questions.

140

MR. CALVOSA: I just have a couple.

CROSS-EXAMINATION

BY MR. CALVOSA:

Q Dr. Little, earlier the court reporter transcribed one of your answers as, well, again, the anion can exist on its own. It's in a dissolved state. The cation that would be next to it would be (sic) necessarily need to be there to maintain electroneutrality and would have -- and you'd have a hydrogen bonding network, but that's what it looks like when it's in a solution.

With respect to that first sentence, "well, again, the anion can exist on its own," is that what you meant to say?

A Can't exist on its own.

Q Okay. And following up where Ms. Durie left off about the liquid gel formulations, would a person of ordinary skill in the art put liquid gel formulations into a sachet?

A No.

Q Would a person of ordinary skill in the art put liquid gel formulations into a sachet, open that sachet, and then mix those liquid gel formulations with water?

(A discussion was held off the record.)

VIDEOGRAPHER: Off the record at 12:39.
(A discussion was held off the record.)
VIDEOGRAPHER: Back on the record now at 12:40 p.m.
BY MR. CALVOSA:
Q Would a person of ordinary skill in the art put liquid gel dosage forms into a sachet, open that sachet, and then mix those liquid gel dosage forms in with water?
A In my opinion, no.
Q Would a person of ordinary skill in the art consider liquid gel dosage forms to be micro particles?
A No.
MR. CALVOSA: I have no further questions.
MS. DURIE: Nothing further.
VIDEOGRAPHER: All right. This concludes today's deposition of Steven Little. We're going off the record at 12:41 p.m.
(Off the record at 12:41 p.m.)

ACKNOWLEDGMENT OF DEPONENT

I, STEVEN R. LITTLE, Ph.D., do hereby acknowledge that I have read and examined the foregoing testimony, and the same is a true, correct and complete transcription of the testimony given by me and any corrections appear on the attached errata sheet signed by me.

_____ _____
(DATE) (SIGNATURE)

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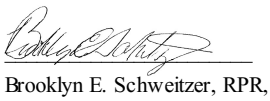
I, Brooklyn E. Schweitzer, the officer before whom the foregoing deposition was taken, do hereby certify that the foregoing transcript is a true and correct record of the testimony given; that said testimony was taken by me stenographically and thereafter reduced to typewriting under my direction; that reading and signing was requested; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 14th day of April, 2023. My commission expires: May 20th, 2026.



Brooklyn E. Schweitzer, RPR, CRR

April 14, 2023

Frank C. Calvosa, Esquire
Quinn, Emanuel, Urquhart & Sullivan, LLP - (NY)
51 Madison Avenue 22nd Floor
New York, NY 10010

Re: Deposition of **Steven R. Little, Ph.D.**
Date: 4/13/2023
Case: Jazz Pharmaceuticals, Inc., et al. -v- Avadel CNS Pharmaceuticals, LLC., et al.

Dear Sir/Madam,

Attached please find the above-referenced deposition transcript. If applicable, signature is required within 30 days from the date of this letter.

In accordance with the disposition of signature at the deposition or the pertinent jurisdictional rules, the deponent should follow these instructions to complete the Errata Sheet:

(1) Read the transcript and indicate any corrections or changes in ink on the enclosed Errata Sheet. Please include page and line numbers. If more space is needed for corrections, please use a blank sheet of paper. If no corrections or changes are necessary, please indicate "no corrections" or "no changes" on the Errata Sheet.

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Page	Line	Correction/Change and Reason
9	18	hydroxybutyric to "hydroxybutyrate" / mistranscription
10	15	hydroxybutyric to "hydroxybutyrate" / mistranscription
11	3	hydroxybutyric to "hydroxybutyrate" / mistranscription
12	7	hydroxybutyric to "hydroxybutyrate" / mistranscription
28	18	masking to "mass" / mistranscription
29	8	bio to "drug" / mistranscription
43	17&18	valent to "valence" / mistranscription
104	11	frame to "name" / mistranscription
111	6	understand commonly to "understand and commonly" / mistranscription
114	3	forms minus to "forms less than minus" / mistranscription
134	24	associate an to "associate as an" / mistranscription

4/18/23
(Date)

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ACKNOWLEDGMENT OF DEPONENT

I, Steven R. Little, Ph.D., do hereby acknowledge that I have read and examined the foregoing testimony, and the same is a true, correct and complete transcription of the testimony given by me and any corrections appear on the attached Errata sheet signed by me.

4/18/23 _____
(Date) (Signature)