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 2 OF 2: EXHIBITS A-O

Original Filing Date: April 26, 2023
Redacted Filing Date: May 4, 2023

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.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jeremy A. Tigan

Jack B. Blumenfeld (#1014)
Jeremy A. Tigan (#5239)
1201 North Market Street
P.O. Box 1347
Wilmington, DE 19899
(302) 658-9200
jblumenfeld@morrisnichols.com
jtigan@morrisnichols.com

F. Dominic Cerrito
Eric C. Stops
Evangeline Shih
Andrew S. Chalson
Gabriel P. Brier
Frank C. Calvosa
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010
(212) 849-7000
nickcerrito@quinnemanuel.com
ericstops@quinnemanuel.com
evangelineshih@quinnemanuel.com
andrewchalson@quinnemanuel.com
gabrielbrier@quinnemanuel.com
frankcalvosa@quinnemanuel.com

Attorneys for Plaintiffs
Jazz Pharmaceuticals, Inc. and
Jazz Pharmaceuticals Ireland Limited

MCCARTER & ENGLISH LLP

/s/ Daniel M. Silver

Daniel M. Silver (#4758)
Alexandra M. Joyce (#6423)
Renaissance Centre
405 N. King Street, 8th Floor
Wilmington, Delaware 19801
(302) 984-6300
dsilver@mccarter.com
ajoyce@mccarter.com

Kenneth G. Schuler
Marc N. Zubick
Alex Grabowski
Sarah W. Wang
LATHAM & WATKINS LLP
330 North Wabash Avenue, Suite 2800
Chicago, IL 60611
(312) 876-7700
kenneth.schuler@lw.com
marc.zubick@lw.com
alex.grabowski@lw.com
sarah.wang@lw.com

Herman Yue
LATHAM & WATKINS LLP
1271 Avenue of the Americas
New York, NY 10020
(212) 906-1200
Herman.Yue@lw.com

Audra M. Sawyer
LATHAM & WATKINS LLP
555 Eleventh Street, NW, Suite 1000
Washington, D.C. 20004
(202) 637-2200
Audra.sawyer@lw.com

Daralyn J. Durie
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, CA 94105
(415) 568-6034
ddurie@mofo.com

Kira A. Davis
Katherine E. McNutt
MORRISON & FOERSTER LLP
707 Wilshire Boulevard
Los Angeles, CA 90017
(213) 892-5200
kiradavis@mofo.com
kmcnutt@mofo.com

Counsel for Defendant
Avadel CNS Pharmaceuticals LLC

April 26, 2023

EXHIBIT A

From: Gabriel Brier <gabrielbrier@quinnemanuel.com>
Sent: Friday, March 17, 2023 11:07 AM
To: Yue, Herman (NY)
Cc: ajoyce@mccarter.com; dsilver@mccarter.com; MoFo-Avadel-Jazz@mofo.com; #C-M JAZZ PATENT LITIGATION - LW TEAM; Nick Cerrito; Eric Stops; Evangeline Shih; Andrew Chalson; Frank Calvosa; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel
Subject: RE: Jazz v. Avadel - Jazz's Proposed Claim Constructions

Counsel,

For clarification regarding Jazz's proposed constructions below, Jazz proposes that like the phrase "an amount of oxybate" in the '079 patent, the phrase "an amount of gamma-hydroxybutyrate" as used in the claims of the '782 patent should be construed as follows: "Plain and ordinary meaning, i.e., an amount of gamma-hydroxybutyrate without exclusion as to bound gamma-hydroxybutyrate (e.g., gamma-hydroxybutyrate salts or gamma-hydroxybutyrate resins)."

Regards,

Gabe

From: Gabriel Brier
Sent: Monday, March 13, 2023 2:00 PM
To: Herman.Yue@lw.com
Cc: ajoyce@mccarter.com; dsilver@mccarter.com; MoFo-Avadel-Jazz@mofo.com; jazzpatentlitigation.lwteam@lw.com; Nick Cerrito <nickcerrito@quinnemanuel.com>; Eric Stops <ericstops@quinnemanuel.com>; Evangeline Shih <evangelineshih@quinnemanuel.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; Frank Calvosa <frankcalvosa@quinnemanuel.com>; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel <jazzavadel@quinnemanuel.com>
Subject: Jazz v. Avadel - Jazz's Proposed Claim Constructions

Counsel,

Pursuant to the parties' agreement to exchange proposed claim constructions, below are Jazz's proposed constructions for the identified claim terms in the Sustained Release patents and the '079/'782 patents. We look forward to discussing this matter further with you tomorrow.

Regards,

Gabe

Sustained Release Patent Family

"the sustained release portion releases . . . its gamma-hydroxybutyrate"; "the formulation releases . . . its gamma-hydroxybutyrate"
"Plain and ordinary meaning, i.e., the [sustained release portion/formulation] releases . . . the gamma-hydroxybutyrate initially contained (i.e., selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate) within the [sustained release portion/formulation]"

'079/'782 Patent Family

"an amount of oxybate"
"Plain and ordinary meaning, i.e., an amount of oxybate without exclusion as to bound oxybate (e.g., oxybate salts or oxybate resins)"

"a solid oxybate formulation"; "the oxybate formulation"
"Plain and ordinary meaning, i.e., a [solid] formulation of oxybate without exclusion as to bound oxybate (e.g., oxybate salts or oxybate resins)"

"a formulation of gamma-hydroxybutyrate"
"Plain and ordinary meaning, i.e., a formulation of gamma-hydroxybutyrate without exclusion as to bound gamma-hydroxybutyrate (e.g., gamma-hydroxybutyrate salts or gamma-hydroxybutyrate resins)"

"particles comprising gamma-hydroxybutyrate"
"Plain and ordinary meaning, i.e., particles comprising gamma-hydroxybutyrate without exclusion as to bound gamma-hydroxybutyrate (e.g., gamma-hydroxybutyrate salts or gamma-hydroxybutyrate resins)"

EXHIBIT B

From: Gabriel Brier <gabrielbrier@quinnemanuel.com>
Sent: Wednesday, March 22, 2023 1:00 PM
To: Yue, Herman (NY)
Cc: ajoyce@mccarter.com; dsilver@mccarter.com; MoFo-Avadel-Jazz@mofo.com; #C-M JAZZ PATENT LITIGATION - LW TEAM; Nick Cerrito; Eric Stops; Evangeline Shih; Andrew Chalson; Frank Calvosa; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel
Subject: Jazz v. Avadel, Nos. 21-691, 21-1138, 21-1594

Counsel,

After further consideration, and given Avadel's confirmation on the parties' meet-and-confer that its proposal excludes sodium oxybate and Jazz's confirmation that its proposal has no similar exclusion, Jazz agrees that it would be more helpful to the Court if the parties present the same disputed term. Jazz's proposed constructions for the Sustained Release Patents and the '079/'782 Patents are below:

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

Regards,

Gabe

Gabe Brier | quinn emanuel urquhart & sullivan, llp
51 Madison Avenue, 22nd Floor, New York, NY 10010 | Office: (212) 849-7000 | Direct: (212) 849-7486 | Mobile: (917) 576-3454 | Fax: (212) 849-7100 | gabrielbrier@quinnemanuel.com

EXHIBIT C

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 ALEXANDER M. KLIBANOV, Ph.D., IN SUPPORT OF AVADEL'S RESPONSIVE SUPPLEMENTAL *MARKMAN* BRIEF

I, Dr. Alexander M. Klibanov, declare:

1. I am the same Alexander M. Klibanov who has submitted an opening expert report (my "Opening Invalidity Report") and a supplemental expert report in the above-captioned litigation on behalf of Avadel CNS Pharmaceuticals, LLC ("Avadel") on January 17 and 27, 2023, respectively. My professional background, qualifications, and experience are outlined in detail in my Opening Invalidity Report.

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. During more than half a century as a practicing chemist, I have extensively researched, published, taught, and lectured in many areas of chemistry, including biological, pharmaceutical formulation, general, and medicinal.

3. I have been asked by counsel for Avadel ("counsel") to provide opinions in support of Avadel's responsive supplemental *Markman* brief and in response to Dr. Steven R. Little's declaration ("Little Decl.") in support of Jazz's supplemental opening *Markman* brief. In particular, I have been asked by counsel to consider how a person of ordinary skill in the art (a "POSA") would have understood the claim terms "gamma-hydroxybutyrate" and "oxybate" as used in the claims of the patents-in-suit: 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") (collectively, the "Sustained Release patents") and U.S. Patent Nos. 10,077,079 ("'079 patent") and 11,147,782 ("'782 patent") (collectively, the "Resinate patents") (together, the "Asserted Patents").[1]

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, 2023, declaration ("Little Decl.") and accompanying Exhibits, and all of the Exhibits to this declaration cited herein. The opinions presented in this declaration 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 applicable legal principles explained to me by counsel and my review of the relevant materials.

[1] I understand that the parties dispute the proper priority dates for the Asserted Patents. However, my opinions expressed herein remain the same regardless of which of those priority dates is applied.

5. In my opinion, a POSA at the time of filing of the Sustained Release and 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 interdisciplinary 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.

6. I understand that Avadel and Jazz ("the parties") have proposed their respective constructions listed below for the claim terms "gamma-hydroxybutyrate" and "oxybate" (which two terms I will use interchangeably herein) in the Sustained Release and Resinate patents:

Claim Term	Jazz's Proposal	Avadel's Proposal
Gamma-hydroxybutyrate (Sustained Release patents)	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 (Resinate patents)	The negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid	The negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid

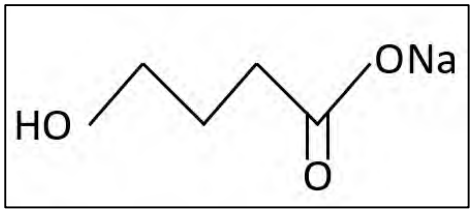
7. I understand that the parties dispute whether the definitions of "gamma-hydroxybutyrate/oxybate" cover the salts of gamma-hydroxybutyrate/oxybate. Dr. Little and Jazz contend that "bound forms of oxybate," such as pharmaceutically acceptable salts of gamma-

hydroxybutyrate, are encompassed in the definitions of the claim terms "gamma-hydroxybutyrate" and "oxybate" that Jazz proposes for both patent families. Jazz and Dr. Little also include gamma-hydroxybutyric acid in Jazz's proposed claim construction of "gamma-hydroxybutyrate," as used in the Sustained Release patents. Dr. Little does so based on his opinion that this is how a POSA ostensibly would have understood the claim term. As explained below, I disagree with Dr. Little that the plain and ordinary meaning of "gamma-hydroxybutyrate" to a POSA would have encompassed the salt forms of gamma-hydroxybutyric acid. *See, e.g.*, Little Decl. ¶ 19.

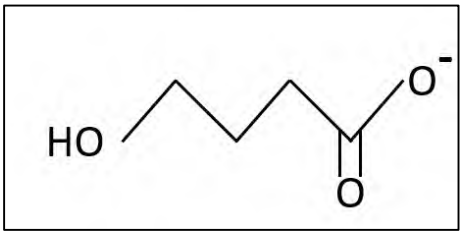
8. First, I disagree that the definition of the claim term "gamma-hydroxybutyrate" includes gamma-hydroxybutyric acid. While I recognize that in some instances the term "gamma-hydroxybutyrate" has been used, loosely and imprecisely I should say, to refer to gamma-hydroxybutyric acid, this usage is not scientifically accurate. 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. Ex. D (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) at 11 ("the endings 'ate' or 'ite' [are used] to name anions derived from acids."). Moreover, gamma-hydroxybutyrate and gamma-hydroxybutyric acid are distinct molecular entities, with different chemical formulas and different physical and chemical properties. Thus, I disagree that a POSA would have considered the claim term "gamma-hydroxybutyrate" to properly encompass gamma-hydroxybutyric acid. However, I understand from counsel that whether gamma-hydroxybutyric acid is encompassed by the definition of "gamma-hydroxybutyrate" is not material to the parties' current infringement dispute.

9. Second, as stated above, I do not agree with Dr. Little that the claim term "gamma-hydroxybutyrate" would have been understood by a POSA to encompass salts of gamma-hydroxybutyric acid.[2] *See, e.g.*, Little Decl. ¶ 19. In particular, I disagree that a POSA would have used the claim term "gamma-hydroxybutyrate" to refer to a salt of gamma-hydroxybutyrate or to a portion of a salt of gamma-hydroxybutyrate. Gamma-hydroxybutyrate and salts of gamma-hydroxybutyric acid (such as its sodium salt, also called sodium oxybate) are distinct molecular entities. Gamma-hydroxybutyrate is a negatively charged ion (also known as an "anion" and having an electrostatic charge of -1 (*i.e.*, minus one)) and, as Dr. Little himself correctly points out, it "cannot exist in solid form on its own." *Id.* ¶ 25. Salts of gamma-hydroxybutyric acid, by contrast, are electrostatically neutral molecules that can and do exist in solid forms.

10. I have depicted the chemical structures of sodium gamma-hydroxybutyrate and gamma-hydroxybutyrate, one underneath the other, below. As the images below demonstrate, these two molecular entities have different chemical structures:



Sodium gamma-hydroxybutyrate (sodium oxybate)



[2] The phrase "salts of gamma-hydroxybutyric acid" rather than "salts of gamma-hydroxybutyrate" is more appropriate scientifically, because a salt is formed when the hydrogen of an acid is replaced by a metal.

Gamma-hydroxybutyrate (oxybate)

11. Thus, a POSA would have known that it is scientifically wrong to refer to sodium oxybate (or another oxybate salt) as a "negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid." Indeed, a POSA would have understood that sodium oxybate is the sodium salt of gamma-hydroxybutyric acid, which is formed when the carboxylic hydrogen of the acid is replaced with a sodium (Na).

12. Dr. Little also contends that "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)." Little Decl. ¶ 24.

13. It would be oversimplistic and scientifically improper to view the gamma-hydroxybutyrate anion and the sodium cation in a sodium oxybate molecule as independent molecular entities. In an ionic bond between the negatively charged gamma-hydroxybutyrate ion and the positively charged sodium ion in solid form, the mutually donated electrons (the electron pair) are still shared, albeit unequally, between the two molecular entities, such that neither has a full (whole) negative or positive electrostatic charge (*i.e.*, -1 or +1, respectively). 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. Little Decl. ¶ 23. Ex. C-1 (Inorganic Chemistry: Principles of Structure and Reactivity by James E. Hueey, 4th Edn., 1993) at 92 ("there is no sharp boundary between ionic bonding and covalent bonding"). Thus, when sodium and oxybate ions are bound together in solid sodium oxybate, neither ion exists in the same form as it would when unbound and separate.

14. A POSA would not have characterized "gamma-hydroxybutyrate," defined as "the negatively charged or anionic form (conjugate base) of gamma-hydroxybutyric acid," to

encompass solid salts of gamma-hydroxybutyrate. Little Decl. ¶ 25. That is, a POSA would have understood that gamma-hydroxybutyrate and sodium gamma-hydroxybutyrate are distinct, non-overlapping entities. Nor would a POSA have considered the stand-alone gamma-hydroxybutyrate ion to be present in sodium gamma-hydroxybutyrate.

15. In his declaration, Dr. Little relies extensively on literature references that use the term "gamma-hydroxybutyrate." *See, e.g., id.* ¶ 26. I do not dispute that the terms "gamma-hydroxybutyrate" and its abbreviation "GHB" are sometimes used loosely and imprecisely in the literature. However, as described in greater detail below, the claim language of the Asserted Patents, as well as the lexicographic definition of gamma-hydroxybutyrate in the Resinate patents, would have clarified to a POSA any inconsistencies in the common usage of "gamma-hydroxybutyrate" and made clear that ***the claim term*** "gamma-hydroxybutyrate," as used in the Asserted Patents, neither includes nor encompasses gamma-hydroxybutyrate salts.

A. Sustained Release Patents

16. The claim language of the Sustained Release patents supports my opinion that the claim term "gamma-hydroxybutyrate," pursuant to the definitions that the parties have proposed (*see* my ¶ 6 above), does not include salts of gamma-hydroxybutyrate.

17. Independent claim 1 of the '488 patent is representative and reproduced below for easy reference (emphases added):

> 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.

18. The claims of the Sustained Release patents, as exemplified by claim 1 of the '488 patent in the preceding paragraph, begin by reciting (emphasis added) "[a] formulation comprising immediate and sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from ***gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate***." Likewise, the claim recites (emphasis added) a sustained release portion comprising "about 500 mg to 12 g of at least one pharmaceutically active ingredient selected from ***gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate***." Thus, a POSA would have recognized that the claims initially identify and differentiate between two types of "pharmaceutically active ingredient[s]" that may be used in the formulation: (1) "gamma-hydroxybutyrate" and (2) "pharmaceutically acceptable salts of gamma-hydroxybutyrate."

19. The claims of the Sustained Release patents then recite a sustained release portion that "releases greater than 40% of its gamma-hydroxybutyrate by about 4 to about 6 hours" and a

formulation that "releases at least about 30% of its gamma-hydroxybutyrate by one hour." *See, e.g.*, '488 patent, claim 1. These claim limitations refer to the release of one of the previously listed "pharmaceutically active ingredient[s]" (gamma-hydroxybutyrate), but not of the other (pharmaceutically acceptable salts of gamma-hydroxybutyrate). The requirement that, for example, "the sustained release portion releases . . . ***its*** gamma-hydroxybutyrate" would have indicated to a POSA that the gamma-hydroxybutyrate that is released from the formulation must be initially present in "the sustained release portion" of the formulation. Thus, a POSA would have understood the claims to require that the formulation and its sustained release portion both contain and release "gamma-hydroxybutyrate," but not "salts of gamma-hydroxybutyrate," which the claim delineates as a separate type of "pharmaceutically active ingredient." And for the reasons discussed earlier herein, I do not agree with Dr. Little's suggestion that the gamma-hydroxybutyrate anion that is released by the formulation is found in the salts of hydroxybutyric acids, such as sodium oxybate.

20. The effect of these claim limitations of the Sustained Release patents is that a formulation containing only a pharmaceutically acceptable salt of gamma-hydroxybutyrate, such as sodium gamma-hydroxybutyrate, would meet the claim preamble but not the "release" claim limitations, because what is released is not "gamma-hydroxybutyrate" but the corresponding gamma-hydroxybutyrate salt.

21. Independent claim 12 of the '488 patent further supports my opinion that a POSA would have understood the claims of the Sustained Release patents to clearly distinguish "gamma-hydroxybutyrate" from "pharmaceutically acceptable salts of gamma-hydroxybutyrate."

22. The preamble of claim 12 recites "[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." Claim 12 then recites a formulation that "releases at least about 30% of its gamma-hydroxybutyrate ***or salt thereof*** by one hour." Claim 1, by contrast, recites a formulation that "releases at least about 30% of ***its gamma-hydroxybutyrate***." This explicit difference in the description of what is released would have indicated to a POSA that when claim 1 recites "its gamma-hydroxybutyrate," that means something different than when claim 12 recites "its gamma-hydroxybutyrate or salt thereof."[3] Thus, when claim 1 refers to release of only "gamma-hydroxybutyrate," a POSA would have understood that it does ***not*** include the release of salts of gamma-hydroxybutyrate because, unlike claim 12, it does not say so.[4]

23. In other words, a POSA would have understood that if "salts of gamma-hydroxybutyrate" were included in the claim term "gamma-hydroxybutyrate," as Dr. Little repeatedly asserts, there would be no reason to add the "or salt thereof" language in some of the "release" portions of the claims of the Sustained Release patents, but not in others. And, if that were the case, the claim language would be grossly superfluous.

24. Consequently, I do not agree with Dr. Little's interpretation of the claims of the Sustained Release patents. He proposes that, although the claims refer separately to "gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate," the claim

[3] To be clear, a POSA would have understood that when a formulation releases a "salt[] of gamma-hydroxybutyrate," such as sodium gamma-hydroxybutyrate, the released sodium gamma-hydroxybutyrate dissolves in water and then dissociates, thereby resulting at that point in an aqueous solution containing a mixture of sodium cations and gamma-hydroxybutyrate anions.

[4] Likewise, parts c of independent claims 11 and 25 of the '956 patent (yet another member of the Sustained Release patent family) also both require that "the formulation releases [a certain percentage ('at least about 30%')] ***of its gamma-hydroxybutyrate or salt thereof*** [within a certain period of time ('by one hour')]" (emphasis and underlining added) and, therefore, further support my opinion that the claims of the Sustained Release patents differentiate between "gamma-hydroxybutyrate" and "salts of gamma-hydroxybutyrate."

limitations citing release of the sustained release portion's/formulation's gamma-hydroxybutyrate encompass release of both "gamma-hydroxybutyrate" alone and "pharmaceutically acceptable salts of gamma-hydroxybutyrate." Little Decl. ¶ 28 ("In my opinion, a POSA would understand 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.'"). In my opinion, that view is not consistent with how a POSA would have understood the claims. Rather, a POSA would have understood the claim term "gamma-hydroxybutyrate" in the "release" claim limitations to refer to the same claim term (and no more) as in the description of the formulation. Otherwise, certain claim terms (*e.g.*, "salts of gamma-hydroxybutyrate") would be unnecessary.

25. Dr. Little also argues that "a POSA would further recognize that 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." Little Decl. ¶ 30. I disagree with this argument, as explained below.

26. Claim 6 of the '488 patent depends from claim 1 and recites "the formulation of claim 1 comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof." Claim 7, which directly depends from claim 6 and indirectly from claim 1, further narrows the salt choice to only "a sodium salt of gamma-hydroxybutyrate."

27. First, that claims 6 and 7 of the '488 patent specify the particular "salts of gamma-hydroxybutyrate"[5] does not negate the clear language in claim 1 expressly distinguishing "gamma-hydroxybutyrate" from "pharmaceutically acceptable salts of gamma-hydroxybutyrate."

28. Second, claim 1 of the '488 patent, from which claims 6 and 7 depend, recites a formulation that can contain both (due to "at least one" of) gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate. Therefore, the claims can encompass a formulation that includes salts of gamma-hydroxybutyrate, including the specific salts recited in claims 6 and 7.[6] Accordingly, I do not agree with Dr. Little that claims 6 and 7 support his view that gamma-hydroxybutyrate encompasses salts of gamma-hydroxybutyrate.

29. Dr. Little relies extensively on references cited in the patent specification in his declaration. Little Decl. ¶ 26. However, the specification echoes the same distinction as the claim language between "gamma-hydroxybutyrate" and "salts of gamma-hydroxybutyrate." *See, e.g.*, '488 patent at 5:35-38 ("the drug incorporated in such compositions may be selected from GHB [*i.e.*, gamma-hydroxybutyrate] and pharmaceutically acceptable salts…of GHB"). Thus, imprecise or inconsistent usage of the terms in the cited references would not change a POSA's

[5] As alluded to above in footnote 2, it should be noted that this claim language is scientifically imprecise. Strictly speaking, there is no such thing as "a salt of gamma-hydroxybutyrate." Rather, a POSA would have understood that the salts in question are properly called as salts of gamma-hydroxybutyric acid. This is because a salt is formed when the hydrogen of an acid is replaced by a metal. To put it another way, a salt is formed when an acid reacts with a base. For example, upon the reaction of the acid gamma-hydroxybutyric acid with the base sodium hydroxide the salt sodium gamma-hydroxybutyrate is formed. *See, e.g.*, The Condensed Chemical Dictionary (ed. by Gessner G. Hawley, 10th Edn., 1981) at 907.

[6] As one example, claim 1 of the '488 patent could encompass a formulation with an immediate release portion that contains salts of gamma-hydroxybutyrate. Or, the claim could describe a formulation that includes both gamma-hydroxybutyrate and salts of gamma-hydroxybutyrate in either the immediate release or sustained release portion.

understanding of the terms as they are used in the patents. Based on the claims and specification, a POSA would not have considered "salts of gamma-hydroxybutyrate" to be included in the definition of "gamma-hydroxybutyrate."

B. Resinate Patents

30. I agree with Dr. Little that the specification of the Resinate patents provides a specific definition of the claim term "gamma-hydroxybutyrate/oxybate." Little Decl. ¶ 32; *see also* '079 patent at 3:59-61. As explained above, this express definition of gamma-hydroxybutyrate/oxybate does not include salts of gamma-hydroxybutyrate/oxybate. *See* ¶¶ 13, 15 above.

31. The claim language of the Resinate patents also supports my opinion that the definition of the claim term "gamma-hydroxybutyrate" proposed by both parties as their claim constructions does not include salts of gamma-hydroxybutyrate.

32. Independent claim 1 of the '079 patent is representative and reproduced below:

> 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.

33. Claim 1 and the other independent claim, claim 10, of the '079 patent clearly distinguish between the terms "oxybate" and "sodium oxybate." Specifically, claims 1 and 10 (and hence all of their dependent claims) recite "a single daily dose comprising an amount of ***oxybate*** equivalent to from 4.0 g to 12.0 g of ***sodium oxybate***" (emphases added). Due to this unambiguous difference between "oxybate" and "sodium oxybate" recited in the claims, a POSA would have understood that these two claim terms refer to two distinct entities.

34. In sum, the claims of the Sustained Release and Resinate patents, as well as the express definition of "gamma-hydroxybutyrate/oxybate" in the latter patent family's specification, would have led a POSA to conclude that the claim term "gamma-hydroxybutyrate" does ***not*** include salts of gamma-hydroxybutyrate, as Jazz and Dr. Little contend.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge.

Executed on April 4, 2023,

in Del Mar, California

Alexander M. Klibanov, Ph.D.

EXHIBIT C-1

Inorganic Chemistry

Principles of Structure and Reactivity

Fourth Edition

James E. Huheey
University of Maryland
Ellen A. Keiter
Eastern Illinois University
Richard L. Keiter
Eastern Illinois University

HarperCollins*CollegePublishers*

About the Cover
The crystal structure of *boggsite,* a recently discovered natural zeolite, is composed of sodium, calcium, aluminum, silicon, hydrogen, and oxygen. Its unique atomic structure of ten and twelve rings was determined by J. J. Pluth and J. V. Smith, geophysicists at the University of Chicago. Modeling tools used to construct the cover photograph are being developed in the Catalysis and Sorption Project of BIOSYM Technologies, Inc., San Diego, California. Structure of boggsite courtesy of Pluth, J. J.; Smith, J. V. *Am. Mineral.* **1990,** *75,* 501–507, and computer graphic by John M. Newsam, BIOSYM Technologies, Inc.

Sponsoring Editor: Jane Piro
Project Coordination: Elm Street Publishing Services, Inc.
Cover Design: Kay Fulton
Cover Photo: Professor John M. Newsam, BIOSYM Technologies, Inc.
Compositor: Better Graphics, Inc.
Printer and Binder: R. R. Donnelley & Sons Company
Cover Printer: Lehigh Press Lithographers

Inorganic Chemistry: Principles of Structure and Reactivity, Fourth Edition

Library of Congress Cataloging-in-Publication Data

Huheey, James E.
Inorganic chemistry: principles of structure and reactivity / James E. Huheey, Ellen A. Keiter, Richard L. Keiter.
p. cm.
Includes bibliographical references and index.
ISBN 0-06-042995-X
1. Chemistry, Inorganic. I. Keiter, Ellen A. II. Keiter, Richard L. III. Title.
QD151.2.H84 1993
546—dc20 92-36083

93 94 95 96 9 8 7 6 5 4 3 2 1

Chapter

4

Bonding Models in Inorganic Chemistry: 1. Ionic Compounds

Structure and bonding lie at the heart of modern inorganic chemistry. It is not too much to say that the renaissance of inorganic chemistry following World War II was concurrent with the development of a myriad of spectroscopic methods of structure determination. Methods of rationalizing and predicting structures soon followed. In this and following chapters we shall encounter methods of explaining and predicting the bonding in a variety of compounds.

The Ionic Bond

Although there is no sharp boundary between ionic bonding and covalent bonding, it is convenient to consider each of these as a separate entity before attempting to discuss molecules and lattices, in which *both* are important. Furthermore, because the purely ionic bond may be described with a simple electrostatic model, it is advantageous to discuss it first. The simplicity of the electrostatic model has caused chemists to think of many solids as systems of ions. We shall see that this view needs some modification, and there are, of course, many solids, ranging from diamond to metals, which require alternative theories of bonding.

Properties of Ionic Substances

Several properties distinguish ionic compounds from covalent compounds. These may be related rather simply to the crystal structure of ionic compounds, namely, a lattice composed of positive and negative ions in such a way that the attractive forces between oppositely charged ions are maximized and the repulsive forces between ions of the same charge are minimized. Before discussing some of the possible geometries, a few simple properties of ionic compounds may be mentioned:[1]

1. Ionic compounds tend to have very low electrical conductivities as solids but conduct electricity quite well when molten. This conductivity is attributed to the presence of *ions*, atoms charged either positively or negatively, which are free to move under the influence of an electric field. In the solid, the ions are

[1] Some very interesting ionic compounds prove to be exceptions to these rules. They are discussed in Chapter 7.

bound tightly in the lattice and are not free to migrate and carry electrical current. It should be noted that we have no absolute *proof* of the existence of ions in solid sodium chloride, for example, though our best evidence will be discussed later in this chapter (pages 111–113). The fact that ions are found when sodium chloride is melted or dissolved in water does not *prove* that they existed in the solid crystal. However, their existence in the solid is usually assumed, since the properties of these materials may readily be interpreted in terms of electrostatic attractions.

2. Ionic compounds tend to have high melting points. Ionic bonds usually are quite *strong* and they are *omnidirectional*. The second point is quite important, since ignoring it could lead one to conclude that ionic bonding was much stronger than covalent bonding—which is *not* the case. We shall see that substances containing strong, multidirectional covalent bonds, such as diamond, also have very high melting points. The high melting point of sodium chloride, for example, results from the strong electrostatic attractions between the sodium cations and the chloride anions, and from the lattice structure, in which each sodium ion attracts six chloride ions, each of which in turn attracts six sodium ions, etc., throughout the crystal. The relation between bonding, structure, and the physical properties of substances will be discussed at greater length in Chapter 8.

3. Ionic compounds usually are very hard but brittle substances. The hardness of ionic substances follows naturally from the argument presented above, except in this case we are relating the multivalent attractions between the ions with *mechanical* separation rather than separation through thermal energy. The tendency toward brittleness results from the nature of ionic bonding. If one can apply sufficient force to displace the ions slightly (e.g., the length of one-half of the unit cell in NaCl), the formerly attractive forces become repulsive as anion–anion and cation–cation contacts occur; hence the crystal flies apart. This accounts for the well-known cleavage properties of many minerals.

4. Ionic compounds are often soluble in polar solvents with high permittivities (dielectric constants). The energy of interaction of two charged particles is given by

$$E = \frac{q^+ q^-}{4\pi r \varepsilon} \tag{4.1}$$

where q^+ and q^- are the charges, r is the distance of separation, and ε is the permittivity of the medium. The permittivity of a vacuum, ε_0, is $8.85 \times 10^{-12}\ C^2\ m^{-1}\ J^{-1}$. For common polar solvents, however, the permittivity values are considerably higher. For example, the permittivity is $7.25 \times 10^{-10}\ C^2\ m^{-1}\ J^{-1}$ for water, $2.9 \times 10^{-10}\ C^2\ m^{-1}\ J^{-1}$ for acetonitrile, and $2.2 \times 10^{-10}\ C^2\ m^{-1}\ J^{-1}$ for ammonia, giving relative permittivities of $82\ \varepsilon_0$ (H_2O), $33\ \varepsilon_0$ (CH_3CN), and $25\ \varepsilon_0$ (NH_3). Since the permittivity of ammonia is 25 times that of a vacuum, the attraction between ions dissolved in ammonia, for example, is only 4% as great as in the absence of solvent. For solvents with higher permittivities the effect is even more pronounced.

Another way of looking at this phenomenon is to consider the interaction between the dipole moments of the polar solvent and the ions. Such solvation will provide considerable energy to offset the otherwise unfavorable energetics of breaking up the crystal lattice (see Chapter 8).

Occurrence of Ionic Bonding

Simple ionic compounds form only between very active metallic elements and very active nonmetals.[2] Two important requisites are that the ionization energy to form the cation, and the electron affinity to form the anion, must be energetically favorable. This does not mean that these two reactions must be exothermic (an impossibility—see Problem 4.13), but means, rather, that they must not cost too much energy. Thus the requirements for ionic bonding are (1) the atoms of one element must be able to lose one or two (rarely three) electrons without undue energy input and (2) the atoms of the other element must be able to accept one or two electrons (almost never three) without undue energy input. This restricts ionic bonding to compounds between the most active metals: Groups IA(1), IIA(2), part of IIIA(3) and some lower oxidation states of the transition metals (forming cations), and the most active nonmetals: Groups VIIA(17), VIA(16),[3] and nitrogen (forming anions).[4] All ionization energies are endothermic, but for the metals named above they are not prohibitively so. For these elements, electron affinities are exothermic only for the halogens, but they are not excessively endothermic for the chalcogens and nitrogen.

Structures of Crystal Lattices

Before discussing the energetics of lattice formation, it will be instructive to examine some of the most common arrangements of ions in crystals. Although only a few of the many possible arrangements are discussed, they indicate some of the possibilities available for the formation of lattices. We shall return to the subject of structure after some basic principles have been developed.

The first four structures described below contain equal numbers of cations and anions, that is, the 1:1 and 2:2 salts. Most simple ionic compounds with such formulations crystallize in one of these four structures. They differ principally in the coordination number, that is, the number of counterions grouped about a given ion, in these examples four, six, and eight.

The sodium chloride structure. Sodium chloride crystallizes in a face-centered cubic structure (Fig. 4.1a). To visualize the face-centered arrangement, consider *only* the sodium ions *or* the chloride ions (this will require extensions of the sketch of the lattice). Eight sodium ions form the corners of a cube and six more are centered on the faces of the cube. The chloride ions are similarly arranged, so that the sodium chloride lattice consists of two interpenetrating face-centered cubic lattices. The coordination number (C.N.) of both ions in the sodium chloride lattice is 6, that is, there are six chloride ions about each sodium ion and six sodium ions about each chloride ion.

Sodium chloride crystallizes in the cubic space group $Fm3m$ (see Table 3.7). that is, it is face-centered, has a three-fold axis, and has two mirror planes of different class. If there is one C_3 axis, however, three others must exist, and the

---

[2] It is true that ionic compounds such as $[NH_4]^+[B(C_6H_5)_4]^-$ are known in which there are no extremely active metals or nonmetals. Nevertheless, the above statement is for all practical purposes correct, and we can consider compounds such as ammonium tetraphenylborate to result from the particular covalent bonding properties of nitrogen and boron.

[3] Recall from the discussion in Chapter 2: Roman numerals are from the "American System" and Arabic numerals are from the "1–18 System" of labeling the periodic table.

[4] Since the transition between ionic bonding and covalent bonding is not a sharp one, it is impossible to define precisely the conditions under which it will occur. However, the generalization is helpful and does not rule out the possibility of unusual ionic bonds, for example, between two metals: Cs^+Au^-. See Chapter 12.

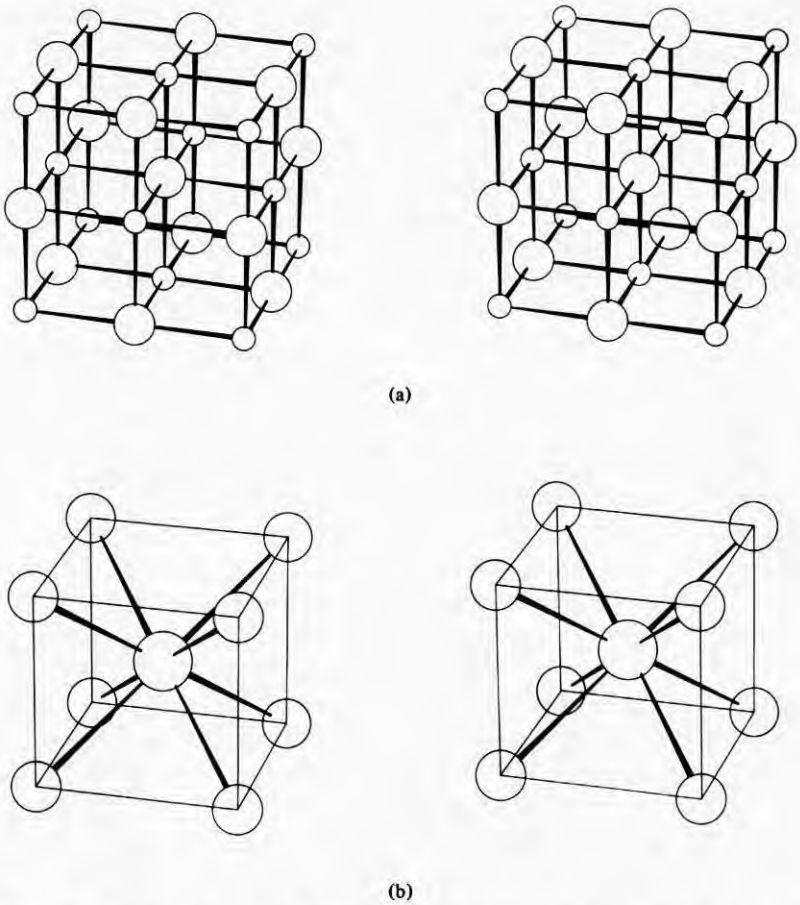


Fig. 4.1 Crystal structures of two 1:1 ionic compounds: (a) unit cell of sodium chloride, cubic, space group *Fm3m*; (b) unit cell of cesium chloride, cubic, space group *Pm3m*. [From Ladd, M. F. C. *Structure and Bonding in Solid State Chemistry*; Wiley: New York, 1979. Reproduced with permission.]

presence of two different mirror planes requires seven others. In fact, this compact symmetry label is enough to tell us that all elements of symmetry found in an octahedron are present. Thus, the Schoenflies equivalent of *Fm3m* is O_h.

The sodium chloride structure is adopted by most of the alkali metal halides: All of the lithium, sodium, potassium, and rubidium halides plus cesium fluoride. It is also found in the oxides of magnesium, calcium, strontium, barium, and cadmium.

The cesium chloride structure. Cesium chloride crystallizes in the cubic arrangement shown in Fig. 4.1b. The cesium or chloride ions occupy the eight corners of the cube and the counterion occupies the center of the cube.[5] Again,

[5] The structure of CsCl should not be referred to, incorrectly, as "body-centered cubic". True body-centered cubic lattices have the *same* species on the *corners* and the *center* of the unit cell, as in the alkali metals, for example.

we must consider a lattice composed either of the cesium ions or of the chloride ions, both of which have simple cubic symmetry. The coordination number of both ions in cesium chloride is 8; that is, there are eight anions about each cation and eight cations about each anion. The space group is $Pm3m$: The lattice is primitive, but otherwise the symmetry elements are the same as in NaCl.

Among the alkali halides, the cesium chloride structure is found only in CsCl, CsBr, and CsI at ordinary pressures, but all of the alkali halides except the salts of lithium can be forced into the CsCl structure at higher pressures. It is also adopted by the ammonium halides (except NH_4F), TlCl, TlBr, TlCN, CsCN, CsSH, CsSeH, and $CsNH_2$.

The zinc blende and wurtzite structures. Zinc sulfide crystallizes in two distinct lattices: hexagonal wurtzite (Fig. 4.2a) and cubic zinc blende (Fig. 4.2b). We shall not elaborate upon them now (see page 121), but simply note that in both the coordination number is 4 for both cations and anions. The space groups are $P6_3mc$ and $F\bar{4}3m$. Can you tell which is which?

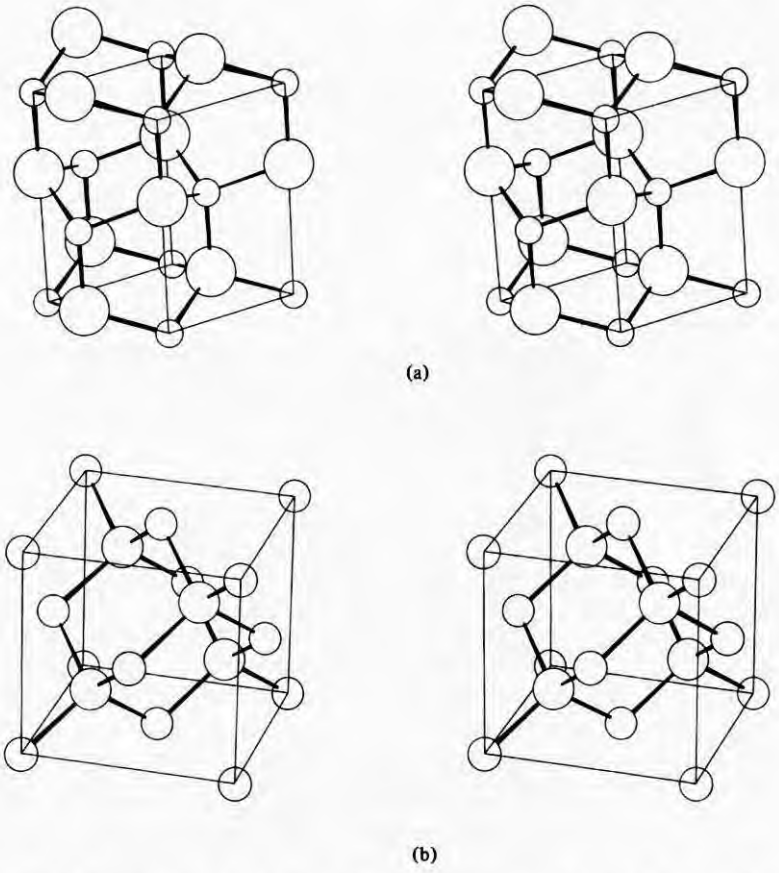


Fig. 4.2 Unit cells of two zinc sulfiide (2:2) structures; circles in order of decreasing size are S and Zn: (a) wurtzite, hexagonal, space group $P6_3mc$; (b) zinc blende, cubic, space group $F\bar{4}3m$. [From Ladd, M. F. C. *Structure and Bonding in Solid State Chemistry*; Wiley: New York, 1979. Reproduced with permission.]

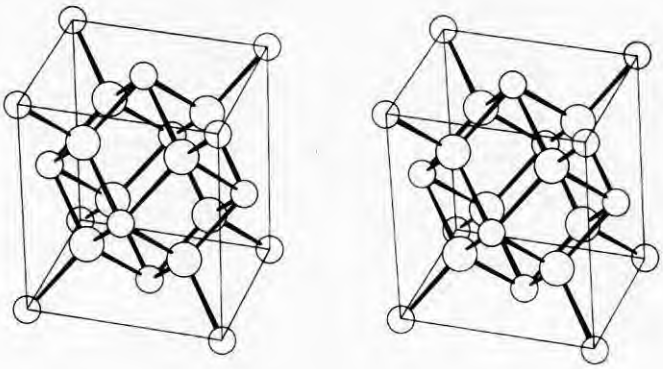


Fig. 4.3 Unit cell of the fluorite structure; smaller circle is Ca (not drawn to scale): cubic, space group *Fm*3*m*. [From Ladd, M. F. C. *Structure and Bonding in Solid State Chemistry*; Wiley: New York, 1979. Reproduced with permission.]

Many divalent metal oxides and sulfides such as BeO, ZnO, BeS, MnS, ZnS, CdS, and HgS adopt the zinc blende or wurtzite structures, or occasionally both. Other compounds with these structures include AgI, NH_4F, and SiC.

All the following structures have twice as many anions as cations (1:2 structures); thus the coordination number of the cation *must* be twice that of the anion: 8:4, 6:3, 4:2, etc. The inverse structures are also known where the cations outnumber the anions by two to one.

The fluorite structure. Calcium fluoride crystallizes in the fluorite structure, cubic *Fm*3*m* (Fig. 4.3). The coordination numbers are 8 for the cation (eight fluoride ions form a cube about each calcium ion) and 4 for the anion (four Ca^{2+} ions tetrahedrally arranged about each F^- ion).

Many difluorides and dioxides are found with the fluorite structure. Examples are the fluorides of Ca, Sr, Ba, Cd, Hg, and Pb, and the dioxides of Zr, Hf, and some lanthanides and actinides. If the numbers and positions of the cations and anions are reversed, one obtains the *antifluorite structure* which is adopted by the oxides and the sulfides of Li, Na, K, and Rb.

The rutile structure. Titanium dioxide crystallizes in three crystal forms at atmospheric pressure: anatase, brookite, and rutile (Fig. 4.4a). Only the last (tetragonal $P4_2/mnm$) will be considered here. The coordination numbers are 6 for the cation (six oxide anions arranged approximately octahedrally about the titanium ions) and 3 for the anion (three titanium ions trigonally about the oxide ions). The rutile structure is also found in the dioxides of Cr, Mn, Ge, Ru, Rh, Sn, Os, Ir, Pt, and Pb.

The β-cristobalite structure. Silicon dioxide crystallizes in several forms (some of which are stabilized by foreign atoms). One is β-cristobalite (Fig. 4.4b), which is related to zinc blende (Fig. 4.2b) having a silicon atom where every zinc *and* sulfur atom is in zinc blende, and with oxygen atoms between the silicon atoms.[6] Other compounds adopting the β-cristobalite structure are BeF_2, $ZnCl_2$, SiS_2 at high pressures, and $Be(OH)_2$ and $Zn(OH)_2$, although the latter are distorted by hydrogen bonding. Another form of SiO_2, tridymite, is related to the

[6] The structure of β-cristobalite has been determined several times over the past 60 years, but crystal disorder has led to uncertainty in the space group assignment (Hyde, B. G.; Andersson, S. *Inorganic Crystal Structures*; Wiley: New York, 1989; pp 393–395.

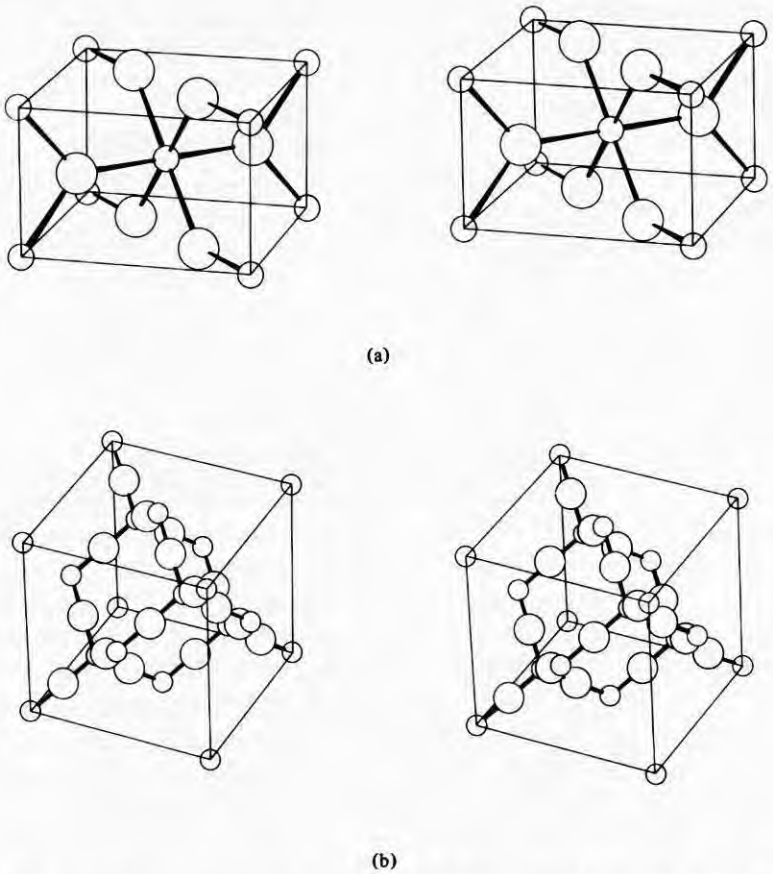


Fig. 4.4 Crystal structures of two more 1:2 compounds; oxygen is the larger circle in both: (a) unit cell of rutile, TiO_2, tetragonal, space group $P4_2/mnm$; (b) unit cell of β-cristobalite, SiO_2. [From Ladd, M. F. C. *Structure and Bonding in Solid State Chemistry*; Wiley: New York, 1979. Reproduced with permission.]

wurtzite structure in the same way that β-cristobalite is related to zinc blende. The coordination numbers in β-cristobalite and tridymite are 4 for silicon and 2 for oxygen.

The calcite and aragonite structures. Almost all of the discussion in this chapter is of compounds containing simple cations and anions. Nevertheless, most of the principles developed here are applicable to crystals containing polyatomic cations or anions, though often the situation is more complicated. Examples of two structures containing the carbonate ion, CO_3^{2-}, are *calcite* (Fig. 4.5a) and *aragonite* (Fig. 4.5b). Both are calcium carbonate. In addition $MgCO_3$, $FeCO_3$, $LiNO_3$, $NaNO_3$, $InBO_3$, and YBO_3 have the calcite structure (rhombohedral $R\bar{3}c$). The coordination number of the metal ion is 6. Larger metal ions adopt the aragonite structure (orthorhombic *Pcmn*) with nine oxygen atoms about the metal ion. Examples are, in addition to calcium carbonate, $SrCO_3$, KNO_3, and $LaBO_3$.

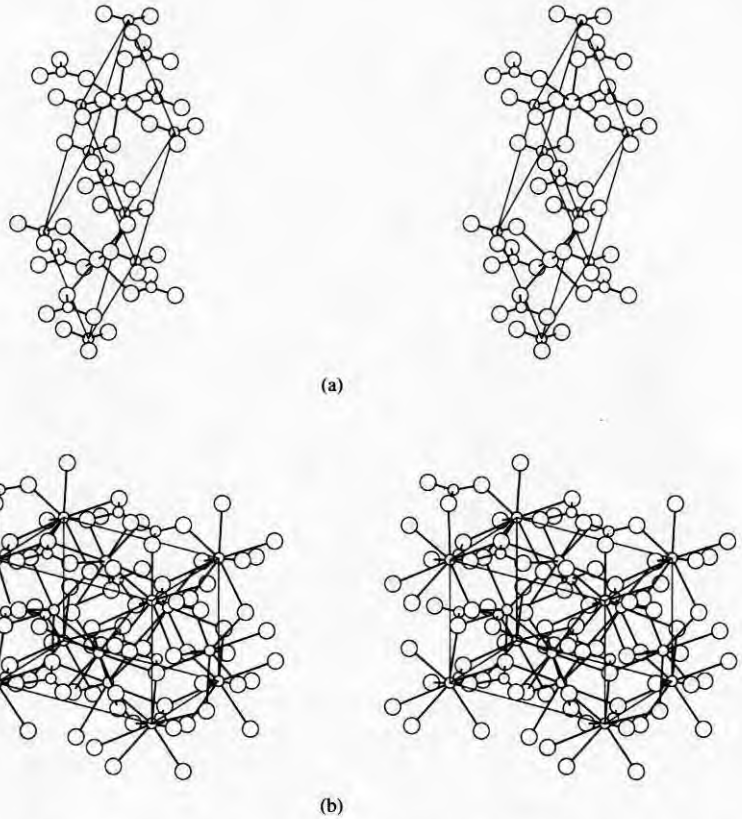


Fig. 4.5 Crystal structures of two forms of calcium carbonate: (a) unit cell of calcite, rhombohedral, space group $R\bar{3}c$; (b) unit cell of aragonite, orthorhombic, space group *Pcmn*. Circles in decreasing order of size are oxygen, calcium, and carbon. [From Ladd, M. F. C. *Structure and Bonding in Solid State Chemistry*; Wiley: New York, 1979. Reproduced with permission.]

Lattice Energy

The energy of the crystal lattice of an ionic compound is the energy released when ions come together from infinite separation to form a crystal:

$$M^{+}_{(g)} + X^{-}_{(g)} \longrightarrow MX_{(s)} \qquad (4.2)$$

It may be treated adequately by a simple electrostatic model. Although we shall include nonelectrostatic energies, such as the repulsions of closed shells, and more sophisticated treatments include such factors as dispersion forces and zero-point energy, simple electrostatics accounts for about 90% of the bonding energies. The theoretical treatment of the ionic lattice energy was initiated by Born and Landé, and a simple equation for predicting lattice energies bears their names. The derivation follows.

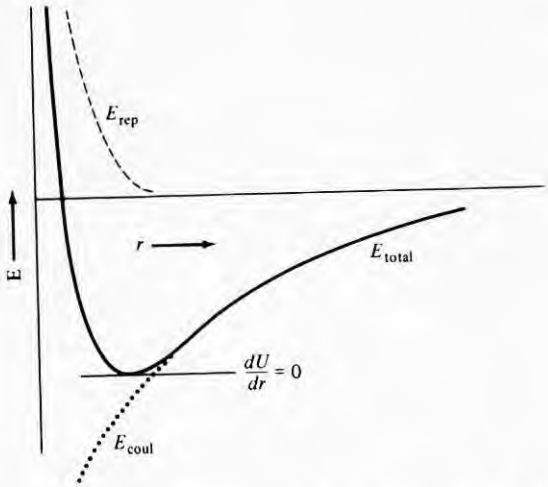


Fig. 4.6 Energy curves for an ion pair.

Consider the energy of an ion pair, M^+, X^-, separated by a distance r. The electrostatic energy of attraction is obtained from Coulomb's law.[7]

$$E_C = \frac{Z^+ Z^-}{4\pi\varepsilon_0 r} \tag{4.3}$$

Since one of the charges is negative, the energy is negative (with respect to the energy at infinite separation) and becomes increasingly so as the interionic distance decreases. Figure 4.6 shows the coulombic energy of an ion pair (dotted line). Because it is common to express Z^+ and Z^- as multiples of the electronic charge, $e = 1.6 \times 10^{-19}$ coulomb, we may write:

$$E_C = \frac{Z^+ Z^- e^2}{4\pi\varepsilon_0 r} \tag{4.4}$$

Now in the crystal lattice there will be more interactions than the simple one in an ion pair. In the sodium chloride lattice, for example, there are attractions to the six nearest neighbors of opposite charge, repulsions by the twelve next nearest neighbors of like charge, etc. The summation of all of these geometrical interactions is known as the *Madelung constant*, A. The energy of a pair of ions in the crystal is then:

$$E_C = \frac{AZ^+ Z^- e^2}{4\pi\varepsilon_0 r} \tag{4.5}$$

The evaluation of the Madelung constant for a particular lattice is straightforward. Consider the sodium ion (⊗) at the center of the cube in Fig. 4.7. Its nearest neighbors are the six face-centered chloride ions (●), each at a characteristic distance determined by the size of the ions involved. The next nearest neighbors are the twelve sodium ions (⊙) centered on the edges of that unit cell (cf. Fig. 4.1a inverted). The distance of these repelling ions can be related to the first distance by simple geometry, as can the distance of eight chloride ions in the next shell (those at the corners of the cube). If this process is followed until every ion in the crystal is included, the

[7] Note that these are *ionic charges* and not nuclear charges for which Z is also used.

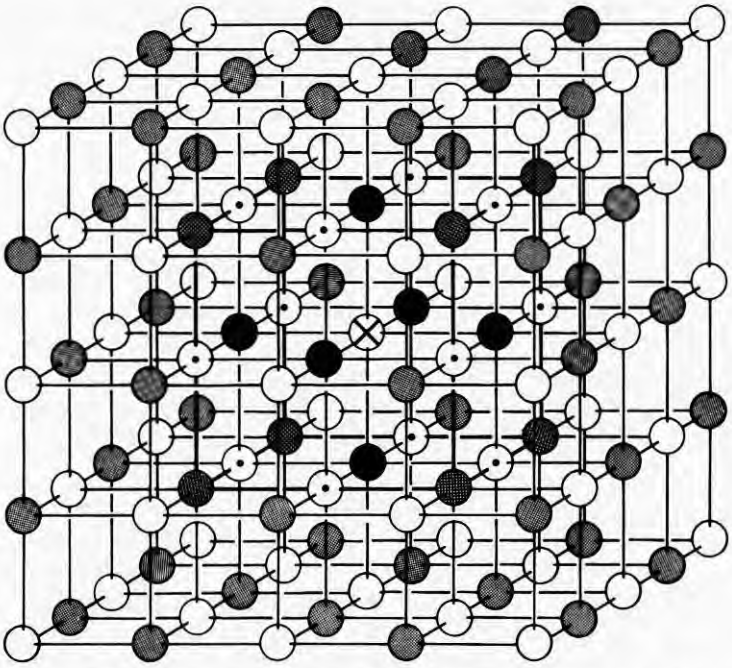


Fig. 4.7 An extended lattice of sodium chloride. Starting with the sodium ion marked ⊗, there are six nearest neighbors (●), twelve next nearest neighbors (⊙), eight next, next nearest neighbors (darkly shaded), and so on.

Madelung constant, A, may be obtained from the summation of all interactions. The first three terms for the interactions described above are

$$A = 6 - \frac{12}{\sqrt{2}} + \frac{8}{\sqrt{3}} \cdots \tag{4.6}$$

Fortunately, the Madelung constant may be obtained mathematically from a converging series, and there are computer programs that converge rapidly. However, we need not delve into these procedures, but may simply employ the values obtained by other workers (Table 4.1). The value of the Madelung constant is determined

Table 4.1
Madelung constants of some common crystal lattices

Structure	Coordination number	Geometrical factor, A	Conventional factor, A[a]
Sodium chloride	6:6	1.74756	1.74756
Cesium chloride	8:8	1.76267	1.76267
Zinc blende	4:4	1.63806	1.63806
Wurtzite	4:4	1.64132	1.64132
Fluorite	8:4	2.51939	5.03878
Rutile	6:3	2.408[b]	4.816[b]
β-Cristobalite	4:2	2.298	4.597
Corundum	6:4	4.1719[b]	25.0312[b]

[a] Use $Z_{\pm}$ = highest common factor.

[b] Exact values depend upon details of structure.

only by the geometry of the lattice and is independent of ionic radius and charge. Unfortunately, previous workers have often incorporated ionic charge into the value which they used for the Madelung constant. The practice appears to have arisen from a desire to consider the energy of a "molecule" such as MX_2:

$$E = \frac{-AZ_{\pm}^2 e^2}{4\pi\varepsilon_0 r} \tag{4.7}$$

where $A = 2A$ and $Z_{\pm}^2$ is the highest common factor of Z^+ and Z^- (1 for NaCl, CaF_2, and Al_2O_3; 2 for MgO, TiO_2, and ReO_3; etc.). We could ignore this confusing practice and use the geometric Madelung constant, A, only, except that values reported in the literature are almost invariably given in terms of Eq. 4.7. Values for both A and A are given in Table 4.1, and the reader may readily confirm that use of either Eq. 4.5 or 4.7 yields identical results.[8]

Returning to Eq. 4.5 we see that unless there is a repulsion energy to balance the attractive coulombic energy, no stable lattice can result. The attractive energy becomes infinite at infinitesimally small distances. Ions are, of course, not point charges but consist of electron clouds which repel each other at very close distances. This repulsion is shown by the dashed line in Fig. 4.6. It is negligible at large distances but increases very rapidly as the ions approach each other *closely*.

Born suggested that this repulsive energy could be expressed by

$$E_R = \frac{B}{r^n} \tag{4.8}$$

where B is a constant. Experimentally, information on the Born exponent, n, may be obtained from compressibility data, because the latter measure the resistance which the ions exhibit when forced to approach each other more closely. The total energy for a mole of the crystal lattice containing an Avogadro's number, N, of units is

$$U = E_C + E_R = \frac{ANZ^+Z^-e^2}{4\pi\varepsilon_0 r} + \frac{NB}{r^n} \tag{4.9}$$

The total lattice energy is shown by the solid line in Fig. 4.6. The minimum in the curve, corresponding to the equilibrium situation, may be found readily:

$$\frac{dU}{dr} = 0 = -\frac{ANZ^+Z^-e^2}{4\pi\varepsilon_0 r^2} - \frac{nNB}{r^{n+1}} \tag{4.10}$$

Physically this corresponds to equating the *force* of electrostatic attraction with the repulsive forces between the ions. It is now possible to evaluate the constant B and remove it from Eq. 4.9. Since we have fixed the energy at the minimum, we shall use

[8] For further discussion of the problem of defining Madelung constants, see Quane, D. *J. Chem. Educ.* **1970**, *47*, 396.

Table 4.2
Values of the Born exponent, *n*

Ion configuration	*n*
He	5
Ne	7
Ar, Cu^+	9
Kr, Ag^+	10
Xe, Au^+	12

U_0 and r_0 to represent this energy and the equilibrium distance. From Eq. 4.10:

$$B = \frac{-AZ^+Z^-e^2r^{n-1}}{4\pi\varepsilon_0 n} \tag{4.11}$$

$$U_0 = \frac{AZ^+Z^-Ne^2}{4\pi\varepsilon_0 r_0} - \frac{ANZ^+Z^-e^2}{4\pi\varepsilon_0 r_0 n} \tag{4.12}$$

$$U_0 = \frac{ANZ^+Z^-e^2}{4\pi\varepsilon_0 r_0}\left(1 - \frac{1}{n}\right) \tag{4.13}$$

This is the Born–Landé equation for the lattice energy of an ionic compound. As we shall see, it is quite successful in predicting accurate values, although it omits certain energy factors to be discussed below. It requires only a knowledge of the crystal structure (in order to choose the correct value for A) and the interionic distance, r_0, both of which are readily available from X-ray diffraction studies.

The Born exponent depends upon the type of ion involved, with larger ions having relatively higher electron densities and hence larger values of n. For most calculations the generalized values suggested by Pauling (see Table 4.2) are sufficiently accurate for ions with the electron configurations shown.

The use of Eq. 4.13 to predict the lattice energy of an ionic compound may be illustrated as follows. For sodium chloride the various factors are

$A = 1.74756$ (Table 4.1)

$N = 6.022 \times 10^{23}$ ion pairs mol^{-1}, Avogadro's number

$Z^+ = +1$, the charge of the Na^+ ion

$Z^- = -1$, the charge of the Cl^- ion

$e = 1.60210 \times 10^{-19}$ C, the charge on the electron (Appendix B)

$\pi = 3.14159$

$\varepsilon_0 = 8.854185 \times 10^{-12}\ C^2\ J^{-1}\ m^{-1}$ (Appendix B)

$r_0 = 2.814 \times 10^{-10}$ m, the experimental value. If this is not available, it may be estimated as 2.83×10^{-10} m, the sum of radii of Na^+ and Cl^- (Table 4.4).

$n = 8$, the average of the values for Na^+ and Cl^- (Table 4.2).

Performing the arithmetic, we obtain $U_0 = -755$ kJ mol^{-1}, which may be compared with the best experimental value (Table 4.3) of -770 kJ mol^{-1}. We may feel confident using values predicted by the Born–Landé equation where we have no experimental values.

As long as we do not neglect to understand each of the factors in the Born–Landé equation (4.13), we can simplify the calculations. It should be realized that the only variables in the Born–Landé equation are the charges on the ions, the internuclear distance, the Madelung constant, and the value of n. Equation 4.13 may thus be simplified with no loss of accuracy by grouping the constants to give:

$$U_0 = 1.39 \times 10^5 \text{ kJ mol}^{-1} \text{ pm} \left(\frac{Z^+ Z^- A}{r_0}\right)\left(1 - \frac{1}{n}\right) \tag{4.14}$$

Note that the internuclear distance should have the units of picometers, as given in Table 4.4. If working with angstrom units and kcal mol^{-1}, the value of the grouped constants is 332 kcal mol^{-1} Å.

Equation 4.13 accounts for about 98% of the total energy of the lattice. For more precise work several other functions have been suggested to replace the one given above for the repulsion energy. In addition, there are three other energy terms which affect the result by a dozen or so kJ mol^{-1}: van der Waals or London forces (see Chapter 8), zero-point energy, and correction for heat capacity. The latter arises because we are usually interested in applying the results to calculations at temperatures higher than absolute zero, in which case we must add a quantity:

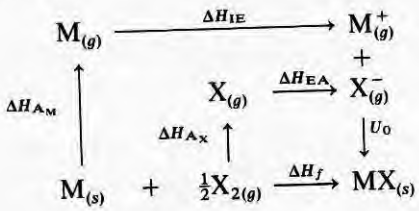
$$\Delta E = \int_0^T (C_{v(\text{MX})} - C_{v(\text{M}^+)} - C_{v(\text{X}^-)})\, dT \tag{4.15}$$

where the C_v terms are the heat capacities of the species involved.[9]

The best calculated values, taking into account these factors, increase the accuracy somewhat: $U_0 = -778$, overestimating the experimental value by slightly less than 1%. Unless one is interested in extreme accuracy, Eq. 4.13 is quite adequate.

The Born–Haber Cycle

Hess's law states that the enthalpy of a reaction is the same whether the reaction takes place in one or several steps; it is a necessary consequence of the first law of thermodynamics concerning the conservation of energy. If this were not true, one could "manufacture" energy by an appropriate cyclic process. Born and Haber[10] applied Hess's law to the enthalpy of formation of an ionic solid. For the formation of an ionic crystal from the elements, the Born–Haber cycle may most simply be depicted as



It is necessary that

$$\Delta H_f = \Delta H_{\text{A}_\text{M}} + \Delta H_{\text{A}_\text{X}} + \Delta H_{1\text{E}} + \Delta H_{\text{EA}} + U_0 \tag{4.16}$$

The terms $\Delta H_{\text{A}_\text{M}}$ and $\Delta H_{\text{A}_\text{X}}$ are the enthalpies of atomization of the metal and the nonmetal, respectively. For gaseous diatomic nonmetals, ΔH_A is the enthalpy of dissociation (bond energy plus RT) of the diatomic molecule. For metals which vaporize to form monatomic gases, ΔH_A is identical to the enthalpy of sublimation. If sublimation occurs to a diatomic molecule, M_2, then the dissociation enthalpy of the reaction must also be included:

---

[9] It is commonly assumed that the independent cations and anions will behave as ideal monatomic gases with heat capacities (at constant volume) of $\frac{3}{2}R$.

[10] Born, M. *Verhandl. Deut. Physik. Ges.* **1919**, *21*, 13; Haber, F.; *Ibid.* **1919**, *21*, 750.

$$M_2 \longrightarrow 2M \tag{4.17}$$

Values for the ionization energy, IE, and the electron affinity, EA, may be obtained from Tables 2.3 and 2.5. Bond dissociation energies for many molecules are given in Appendix E. A useful source of many data of use to the inorganic chemist has been written by Ball and Norbury.[11]

Uses of Born–Haber-Type Calculations

The enthalpy of formation of an ionic compound can be calculated with an accuracy of a few percent by means of the Born–Landé equation (Eq. 4.13) and the Born–Haber cycle. Consider NaCl, for example. We have seen that by using the predicted internuclear distance of 283 pm (or the experimental value of 281.4 pm), the Madelung constant of 1.748, the Born exponent, n, and various constants, a value of -755 kJ mol^{-1} could be calculated for the lattice energy. The heat capacity correction is 2.1 kJ mol^{-1}, which yields $U_0^{298} = -757$ kJ mol^{-1}. The Born–Haber summation is then

$$\begin{aligned} U_0^{298} &= -757 \text{ kJ mol}^{-1} \\ \Delta_{DE} &= +496 \text{ kJ mol}^{-1} \\ \Delta H_{IE} &= -349 \text{ kJ mol}^{-1} \\ \Delta H_{A_{Cl}} &= +121 \text{ kJ mol}^{-1} \\ \Delta H_{A_{Na}} &= +108 \text{ kJ mol}^{-1} \\ \hline \sum &= -381 \text{ kJ mol}^{-1} \end{aligned}$$

This can be compared with an experimental value for the enthalpy of formation, $\Delta H_f^{298} = -411$ kJ mol^{-1}

Separation of the energy terms in the Born–Haber cycle gives us some insight into their relative importance in chemical bonding. For example, the ΔH_A terms are always positive, but are usually of relatively small size compared with the other terms and do not vary greatly from compound to compound.[12] The ionization energies are always greatly endothermic. Electron affinities for the halogens are exothermic, but for the chalcogens they are endothermic as a result of forcing the second electron into the negatively charged X^- ion. In either case, the summation of ionization energy and electron affinity is *always* endothermic, and it is only the overwhelming exothermicity of the attraction of the ions for each other that makes ionic compounds stable with respect to dissociation into the elements. At room temperature this energy appears as the lattice energy. It should not be supposed, however, that at temperatures above the boiling point of the compound (1413 °C for NaCl, for example) no reaction would occur between an active metal and nonmetal. Even in the gas phase there will be electrostatic stabilization of the ions through the formation of ion pairs, M^+X^-. The latter should be added to the Born–Haber cycle, and to clarify the nature of the energy relationships, it is best to draw it in more explicit form as in Fig. 4.8. In such a diagram the individual enthalpies can be portrayed and related to the original enthalpy of the starting materials.[13]

---

[11] Ball, M. C.; Norbury, A. H. *Physical Data for Inorganic Chemists*; Longman: London, 1974.

[12] This statement is strictly true only for the halogens. The dissociation energies of O_2 and N_2 are considerably larger.

[13] For a discussion of this point as well as several others concerning Born–Haber–type cycles, see Haight, G. P., Jr. *J. Chem. Educ.* **1968**, *45*, 420.

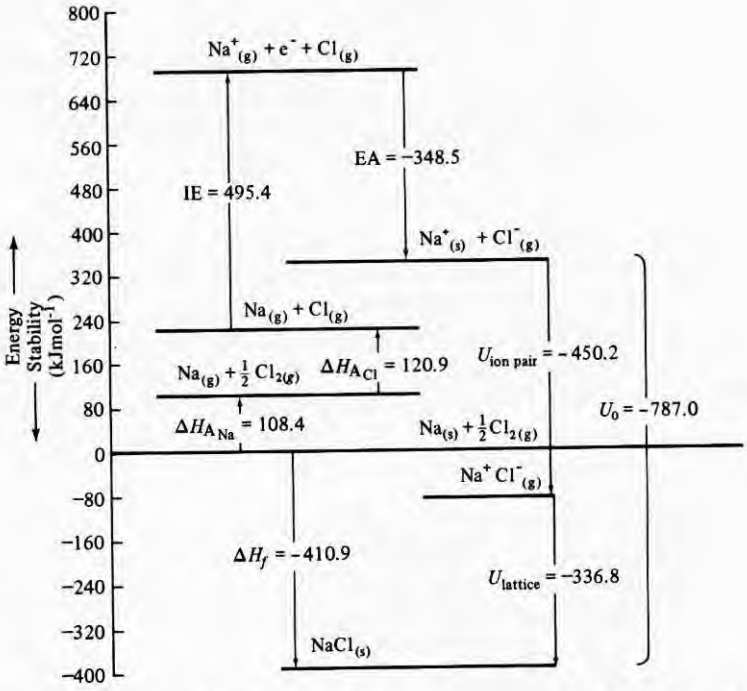


Fig. 4.8 Born–Haber diagram showing relative magnitudes of various terms for sodium chloride. [Adapted from Haight, G. P., Jr. *J. Chem. Educ.* **1968**, *45*, 420–422. Reproduced with permission.]

Most of the enthalpies associated with steps in the cycle can be estimated, to a greater or less accuracy, by experimental methods. The lattice energy, however, is almost always obtained theoretically rather than from experimental measurement. It might be supposed that the "enthalpy of dissociation" of a lattice could be measured in the same way as the enthalpy of atomization of the metal and nonmetal, that is, by heating the crystal and determining how much energy is necessary to dissociate it into ions. Unfortunately, this is experimentally very difficult. When a crystal sublimes (ΔH_S), the result is not isolated gaseous ions but ion pairs and other clusters. For this reason it is necessary to use Eq. 4.13 or some more accurate version of it. We can then use the Born–Haber cycle to check the accuracy of our predictions if we can obtain accurate data on every other step in the cycle. Values computed from the Born–Haber cycle are compared with those predicted by Eq. 4.13 and its modifications in Table 4.3.

Once we have convinced ourselves that we are justified in using theoretical values for U_0, we can use the cycle to help obtain information on any other step in the cycle which is experimentally difficult to measure. For many years electron affinities were obtained almost exclusively by this method since accurate estimates were difficult to obtain by direct experiment.

Finally, it is possible to predict the heat of formation of a new and previously unknown compound. Reasonably good estimates of enthalpies of atomization, ionization energies, and electron affinities are now available for most elements. It is

Table 4.3

Experimental and calculated lattice energies ($-U_0$) of alkali halides (kJ mol^{-1})

Salt	Experimental (Born–Haber cycle)	Simple model (Eq. 4.13)	"Best values"[a]	Kapustinskii approximation[b]
LiF	1034	1008	1033	952.7
LiCl	840.1	811.3	845.2	803.7
LiBr	781.2	766.1	797.9	792.9
LiI	718.4	708.4	739.7	713.0
NaF	914.2	902.0	915.0	884.9
NaCl	770.3	755.2	777.8	752.9
NaBr	728.4	718.8	739.3	713.4
NaI	680.7	663.2	692.0	673.6
KF	812.1	797.5	813.4	788.7
KCl	701.2	687.4	708.8	680.7
KBr	671.1	659.8	679.5	674.9
KI	632.2	623.0	640.2	613.8
RbF	780.3	761.1	777.8	760.2
RbCl	682.4	661.5	686.2	661.9
RbBr	654.0	636.4	659.0	626.3
RbI	616.7	602.5	622.2	589.9
CsF	743.9	723.0	747.7	713.0
CsCl	629.7	622.6	652.3	625.1
CsBr	612.5	599.6	632.2	602.1
CsI	584.5	568.2	601.2	563.6

[a] Calculated using a modified Born equation with corrections for polarization effects, repulsion between nearest and next nearest neighbors, and zero-point energy (Cubicciotti, D. *J. Chem. Phys.* **1959**, *31*, 1646–1651; *ibid.*, **1961**, *34*, 2189).

[b] See Eq. 4.20.

then necessary to make some good guesses as to the most probable lattice structure, including internuclear distances and geometry. The internuclear distance can be estimated with the aid of tables of ionic radii. Sometimes it is also possible to predict the geometry (in order to know the correct Madelung constant) from a knowledge of these radii (see next section). In such a case it is possible to predict the lattice energy and the enthalpy of formation (the latter almost as accurately as it could be measured if the compound were available). Examples of calculations on hypothetical compounds are given below, and a final example utilizing several methods associated with ionic compounds is given on page 127.

Consideration of the terms in a Born–Haber cycle helps rationalize the existence of certain compounds and the nonexistence of others. For example, consider the hypothetical sodium dichloride, Na^{2+}, $2Cl^-$. Because of the $+2$ charge on the sodium ion, we might expect the lattice energy to be considerably larger than that of NaCl, adding to the stability of the compound. But if all the terms are evaluated, it is found that the increased energy necessary to ionize sodium to Na^{2+} is more than that which is returned by the increased lattice energy. We can make a very rough calculation assuming that the internuclear distance in $NaCl_2$ is the same as in NaCl[14] and that

[14] We shall see that this overestimates the distance, but for the present approximation it should be adequate.

it would crystallize in the fluorite structure with a Madelung constant of $A = 2.52$. The lattice energy is then $U_0 = -2180$ kJ mol^{-1}. The summation of Born–Haber terms is

$$\begin{aligned} U_0 &= -2180 \\ \Delta H_{A_{Na}} &= +108 \\ \Delta H_{IE_1} &= +496 \\ \Delta H_{IE_2} &= +4562 \\ 2\Delta H_{EA} &= -698 \\ \Delta H_{A_{Cl}} &= +242 \\ \hline \Delta H_f &= +2530 \text{ kJ mol}^{-1} \end{aligned}$$

Although the estimation of U_0 by our crude approximation may be off by 10–20%, it cannot be in error by over 100%, or 2500 kJ mol^{-1}. Hence we can see why $NaCl_2$ does not exist: *The extra stabilization of the lattice is insufficient to compensate for the very large second ionization energy.*

A slightly different problem arises when we consider the *lower* oxidation states of metals. We know that CaF_2 is stable. Why not CaF as well? Assuming that CaF would crystallize in the same geometry as KF and that the internuclear distance would be about the same, we can calculate a lattice energy for CaF, $U_0 = -795$ kJ mol^{-1}. The terms in the Born–Haber cycle are

$$\begin{aligned} U_0 &= -795 \\ \Delta H_{A_{Ca}} &= +178 \\ \Delta H_{IE} &= +590 \\ \Delta H_{EA} &= -328 \\ \Delta H_{A_F} &= +79 \\ \hline \Delta H_f &= -276 \text{ kJ mol}^{-1} \end{aligned}$$

An enthalpy of formation of -276 kJ mol^{-1}, though not large, is perfectly acceptable because it is about the same as that of LiI, for example. Why then does CaF not exist? Because if one *were* able to prepare it, it would spontaneously disproportionate into CaF_2 and Ca exothermically.[15]

$$\begin{array}{lllll} 2\text{CaF} & \longrightarrow & \text{CaF}_2 + \text{Ca} & & \\ 2\Delta H_f = -550 & & \Delta H_f = -1220 & \Delta H_f = 0 & \Delta H_r = -670 \text{ kJ mol}^{-1} \end{array} \qquad (4.18)$$

An examination of the ionic compounds of the main group elements would show that all of the ions present have electronic configurations that are isoelectronic with noble gases; hence the supposed "stability of noble gas configurations". But what type of stability? It is true that the halogens are from 295 to 350 kJ mol^{-1} lower in energy as halide ions than as free atoms. But the formation of the O^{2-}, S^{2-}, N^{3-}, Li^+, Na^+, Mg^{2+}, and Ca^{2+} ions is *endothermic* by 250 to 2200 kJ mol^{-1}. Even though these ions possess noble gas configurations, they represent *higher* energy states than the free atoms. The "stability" of noble gas configurations is meaningless unless one considers the stabilization of the ionic lattice. For the main group elements the

[15] The direction of chemical reaction will be determined by the *free energy*, ΔG, not the enthalpy, ΔH. However, in the present reaction the *entropy* term, ΔS, is apt to be comparatively small and since $\Delta G = \Delta H - T\Delta S$, the free energy will be dominated by the enthalpy at moderate temperatures.

noble gas configuration is that which maximizes the gain from high charges (and large lattice energies) while holding the cost (in terms of ionization potential–electron affinity energies) as low as possible. This is shown graphically in Fig. 4.9. Although the second ionization energy for a metal is always larger than the first, and the third larger than the second, the increase is moderate except when a noble gas configuration is broken. Then the ionization energy increases markedly because the electron is being removed from the $n - 1$ shell. Below this limit the lattice energy increases faster with oxidation state than does the ionization energy, so that the most stable oxidation state is the one that maximizes the charge without breaking the noble gas configuration. This is why aluminum always exists as Al^{3+} when in ionic crystals despite the fact that it costs 5140 kJ mol^{-1} to remove three electrons from the atom!

For transition metals, all electrons lost on ionization are either *ns* or $(n - 1)d$ electrons which, as we have seen, are very similar in energy. Hence there are no abrupt increases in ionization energy, only the more gradual change accumulating from loss of electrons to form higher Z^{n+}, and these will be compensated by higher lattice energies. Consider, for example, CuCl and $CuCl_2$. We may calculate (cf. Prob-

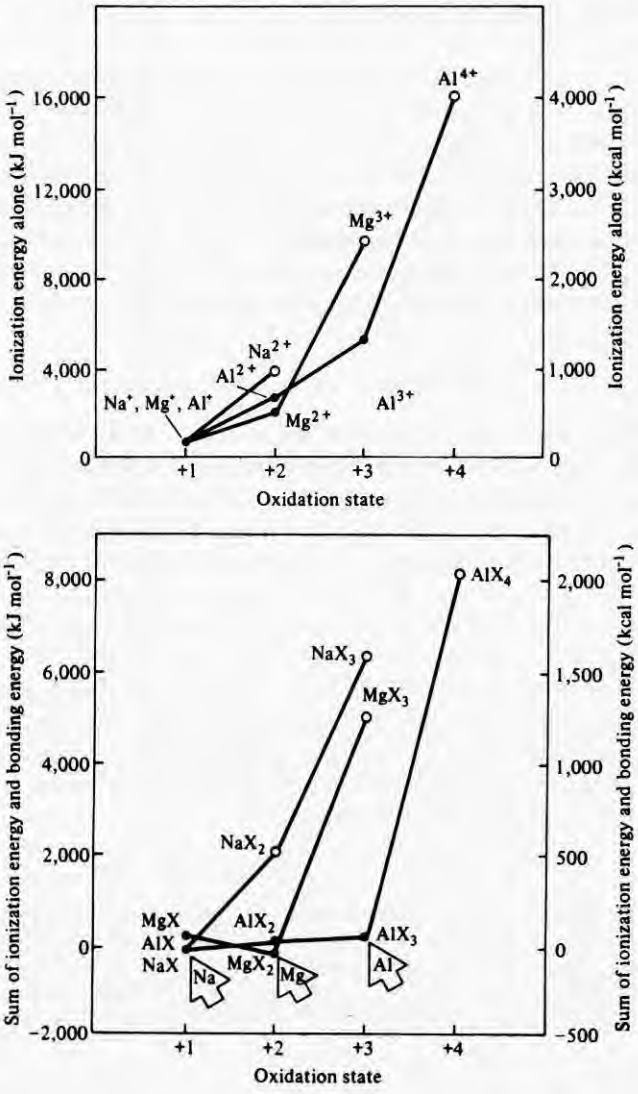


Fig. 4.9 Energies of free cations and of ionic compounds as a function of the oxidation state of the cation. *Top:* Lines represent the ionization energy necessary to form the +1, +2, +3, and +4 cations of sodium, magnesium, and aluminum. Note that although the ionization energy increases most sharply when a noble gas configuration is "broken," *isolated cations are always less stable in higher oxidation states. Bottom:* Lines represent the sum of ionization energy and ionic bonding energy for hypothetical molecules MX, MX_2, MX_3, and MX_4 in which the interatomic distance, r_0, has been arbitrarily set at 200 pm. Note that the most stable compounds (identified by arrows) are NaX, MgX_2, and AlX_3. (All of these molecules will be stabilized additionally to a small extent by the electron affinity of X.)

lem 4.25) the enthalpies of formation as follows (kJ mol^{-1}):

Term	*CuCl*	*$CuCl_2$*
$\Delta H_{A_{Cu}}$	+338	+338
ΔH_{IE_1}	+746	+746
ΔH_{IE_2}		+1958
$\Delta H_{A_{Cl_2}}$	+121	+242
ΔH_{EA}	−349	−698
U_0	−973	−2772
ΔH_f	−117	−186

The enthalpy of atomization of copper does not differ at all for the two compounds, and the atomization of chlorine adds only a small difference for the second mole of chlorine. The major energy cost for $CuCl_2$ is the second ionization energy of copper which is compensated by the electron affinity to form the second chloride ion and especially the lattice energy. Since the electron ionized to form Cu^{2+} is a *d* electron and does not break a noble gas structure, IE_2 is not excessive, and both CuCl and $CuCl_2$ are stable compounds.

Some Simplifications and "Rules of Thumb"

In the same way that Fig. 4.9 was sketched with "average" values to illustrate the stability of compounds with noble gas configurations, we can simplify Eq. 4.14 further by inserting some "average" values. It must be clearly understood that this is merely clearing away some of the numerical shrubbery to lay out the picture of the chemical forest in clearer detail. Let us assume that we are studying compounds M^+X^- with an internuclear distance of about 200 pm. Of course, $Z^+ = -Z^- = 1$. To be as general as possible, let's use an average value of $A = 2$, which is not too inaccurate for present purposes (about 20% error) for NaCl, CsCl, CaF_2, TiO_2, and both ZnS structures. Equation 4.14 reduces to

$$U_0 \approx -1400 \text{ kJ mol}^{-1} \approx -330 \text{ kcal mol}^{-1} \approx -14 \text{ eV} \qquad \textbf{(4.19)}$$

This approximation is somewhat high for most compounds chiefly because an internuclear distance of 200 pm is too small for most compounds. But it has the useful asset of requiring that only the coefficients of Eq. 4.14 be remembered. Furthermore, it allows some simple predictions to be made without involving the detailed calculation of the above examples. For example, can we make a "rule of thumb" to predict when a compound M^+X^- will be readily oxidized to $M^{2+}2X^-$? Using Eq. 4.14, we predict that the lattice energy will double, or increase by one to one-and-a-half MJ mol^{-1}, upon conversion to MX_2. By far the major energy that has to be paid to accomplish this change is IE_2 of the metal. While a thorough examination of *all* of the energy terms is necessary for a *careful* analysis of the situation, we are led to believe that if the additional cost of ionization is less than about 1.3–1.5 MJ mol^{-1} (13–15 eV) for the higher oxidation state, it may well be stable, too. In the case of copper, given above, we have

$$IE_1 = 0.75 \text{ MJ mol}^{-1} \qquad IE_2 = 2.0 \text{ MJ mol}^{-1} \qquad IE_3 = 3.5 \text{ MJ mol}^{-1}$$

Our rule of thumb follows the more careful calculations above and predicts that both Cu(I) and Cu(II) compounds will be stable and, furthermore, it also works where data are not available for a more careful analysis: Cu(III) compounds are predicted to be unstable or marginally stable (Chapter 14).

On the other hand, if the succeeding ionization energies are too near each other, as was the case for IE_1 and IE_2 of calcium above:

$$IE_1 = 0.6 \text{ MJ mol}^{-1} \qquad IE_2 = 1.1 \text{ MJ mol}^{-1} \qquad IE_3 = 4.9 \text{ MJ mol}^{-1}$$

then the lower oxidation state (Ca^+) is unstable because it is *too* readily oxidized to Ca^{2+}. Of course, Ca^{3+} is unavailable because it is too prohibitively expensive.

Ahrens,[16] who was the first to point out this rule of thumb, contrasted the behavior of titanium:

$$IE_1 = 0.66 \text{ MJ mol}^{-1} \qquad IE_2 = 1.3 \text{ MJ mol}^{-1}$$
$$IE_3 = 2.6 \text{ MJ mol}^{-1} \qquad IE_4 = 4.2 \text{ MJ mol}^{-1}$$

with that of zirconium:

$$IE_1 = 0.66 \text{ MJ mol}^{-1} \qquad IE_2 = 1.3 \text{ MJ mol}^{-1}$$
$$IE_3 = 2.2 \text{ MJ mol}^{-1} \qquad IE_4 = 3.3 \text{ MJ mol}^{-1}$$

The differences between the successive oxidation states for titanium are just sufficient to allow marginally stable Ti(II) and Ti(III) oxidation states in addition to Ti(IV). The corresponding lower oxidation states are uncommon for zirconium whose chemistry is dominated by Zr(IV).

Of intermediate accuracy between the rough rule of thumb given above and the precise Born–Landé equation is a suggestion made by Kapustinskii.[17] He noted that the Madelung constant, the internuclear distance, and the empirical formula of a compound are all interrelated.[18] He has suggested that in the absence of knowledge of crystal structure (and hence of the appropriate Madelung constant) a reasonable estimation of the lattice energy can be obtained from the equation:

$$U_0 = \frac{120{,}200\nu Z^+ Z^-}{r_0}\left(1 - \frac{34.5}{r_0}\right) \text{ (kJ mol}^{-1}\text{)} \qquad \textbf{(4.20)}$$

where ν is the number of ions per "molecule" of the compound and r_0 is estimated as the sum of the ionic radii (Table 4.4), $r_+ + r_-$ (pm). For the sodium chloride example given previously, $\nu = 2$ and $r_0 = 281$ pm, yielding a lattice energy of -750 kJ mol^{-1}, or about 98% of the experimental value, comparing favorably with that obtained from Eq. 4.13. Of course, the usefulness of Eq. 4.20 lies not in its prediction of the

---

[16] Ahrens, L. H. *Geochim. Cosmochim. Acta* **1953**, *3*, 1. Ahrens values, 8–10 eV, seem low in the light of subsequent experience. A careful analysis has suggested that differences of 13–15 eV (1.3–1.5 MJ mol^{-1}) between successive ionization energies will lead to multiple, stable oxidation states (Porterfield, W. W. *Inorganic Chemistry: A Unified Approach*; Addison-Wesley: Reading, MA, 1984; pp 416–420).

[17] Kapustinskii, A. F. *Z. Phys. Chem. (Leipzig)* **1933**, *B22*, 257; *Zh. Fiz. Khim.* **1943**, *5*, 59; *Quart. Rev. Chem. Soc.* **1956**, *10*, 283.

[18] This follows from the fact that, given a certain number of ions of certain sizes, the number of ways of packing them efficiently is severely limited. Simple cases of this are discussed in the sections entitled "Efficiency of Packing and Crystal Lattices" and "Radius Ratio". For more thorough discussions of Kapustinskii's work, see Waddington, T. C. *Adv. Inorg. Chem. Radiochem.* **1959**, *1*, 157; or Dasent, W. E. *Inorganic Energetics*, 2nd ed.; Cambridge University: Cambridge, 1982; pp 76–79.

lattice energy of sodium chloride, which is well known and provides a check on its accuracy, but in giving reasonably accurate estimates for compounds that are not well known (see Problem 4.24).

In summary, in addition to allowing simple calculations of the energetics of ionic compounds, the Born–Haber cycle provides insight into the energetic factors operating. Furthermore, it is an excellent example of the application of thermodynamic methods to inorganic chemistry and serves as a model for other, similar calculations not only for solids, but also for reactions in solution and in the gas phase.

Size Effects

Ionic Radii

The determination of the sizes of ions has been a fundamental problem in inorganic chemistry for many years. Many indirect methods have been suggested for apportioning the internuclear distance between two ions, relatively easy to obtain, into cationic and anionic radii. Although these have been ingenious and provide insight into atomic properties, they are no longer necessary.

When an X-ray crystallographer determines the structure of a compound such as NaCl (Fig. 4.1a), usually only the *spacing* of ions is determined, because the repeated spacings of the atoms diffract the X rays as the grooves on a phonograph record diffract visible light. However, if very careful measurements are made, accurate maps of electron density can be constructed since, after all, it is the electrons of the in-

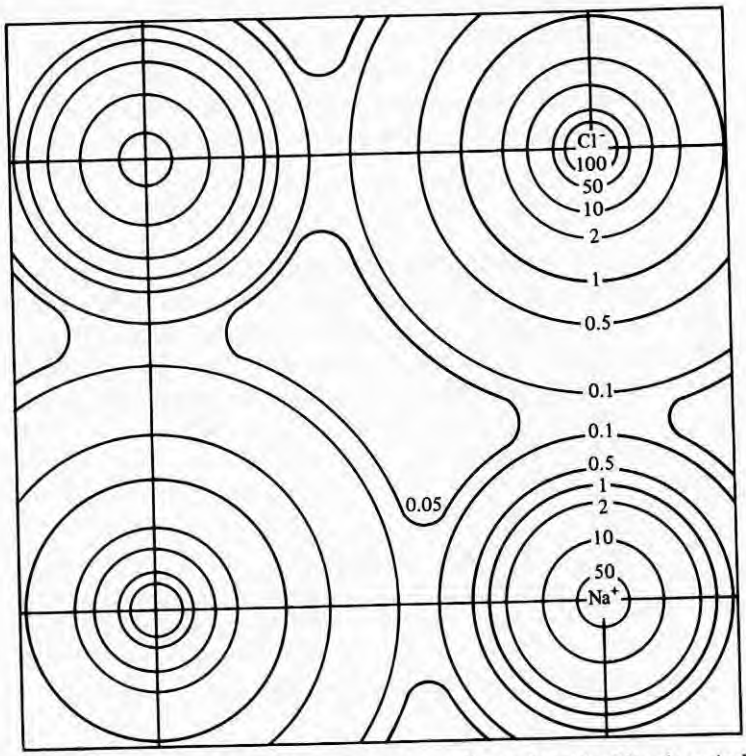


Fig. 4.10 Electron density contours in sodium chloride. Numbers indicate the electron density (electrons $Å^{-3} = 10^{-6}$ electrons pm^{-3}) along each contour line. The "boundary" of each ion is defined as the minimum in electron density between the ions. The internuclear distance is 281 pm (= 2.81 Å). [Modified from Schoknecht, G. *Z. Naturforsch.* **1957**, *12A*, 983. Reproduced with permission.]

dividual atoms that scatter the X rays. The result is Fig. 4.10. One may now apportion the interatomic distance in NaCl, 281 pm, using the minimum in electron density as the operational definition of "where one ion stops and the other starts".

Although not many simple ionic compounds have been studied with the requisite accuracy to provide data on ionic radii, there are enough to provide a basis for a complete set of ionic radii. Such a set has been provided in the crystal radii of Shannon and Prewitt.[19] Values of these radii are given in Table 4.4.

Factors Affecting the Radii of Ions

A comparison of the values given in Table 4.4 allows one to make some conclusions regarding the various factors that affect ionic size. We have already seen that progressing to the right in a periodic series should cause a decrease in size. If the ionic charge remains constant, as in the +3 lanthanide cations, the decrease is smooth and moderate. Progressing across the main group metals, however, the ionic charge is increasing as well, which causes a precipitous drop in cationic radii: Na^+ (116 pm), Mg^{2+} (86 pm), Al^{3+} (67.5 pm). In the same way, for a given metal, increasing oxidation state causes a shrinkage in size, not only because the ion becomes smaller as it loses electron density, but also because the increasing cationic charge pulls the anions in closer. This change can be illustrated by comparing the bond lengths in the complex anions $FeCl_4^{2-}$ and $FeCl_4^-$. The Fe(III)—Cl bond length is 11 pm shorter than the Fe(II)—Cl bond length.[20]

For transition metals the multiplicity of the spin state affects the way in which the anions can approach the cation; this alters the effective radius. Although this is an important factor in determining cationic radii, it is beyond the scope of the present chapter and will be deferred to Chapter 11.

For both cations and anions *the crystal radius increases with the increase in coordination number*. As the coordination number increases, the repulsions among the coordinating counterions become greater and cause them to "back off" a bit. Alternatively, one can view a *lower* coordination number as allowing the counter-ions to compress the central ion and reduce its crystal radius.

As we shall see over and over again, the simple picture of billiard-ball-like ions of invariant radius is easy to describe but generally unrealistic. The fluorides and oxides come closest to this picture, and so the values in Table 4.4 work best with them. Larger, softer anions in general will present more problems. Little work has been done in this area, but Shannon[21] has presented a table, analogous to Table 4.4, for sulfides.

Radii of Polyatomic Ions

The sizes of polyatomic ions such as NH_4^+ and SO_4^{2-} are of interest for the understanding of the properties of ionic compounds such as $(NH_4)_2SO_4$, but the experimental difficulties attending their determination exceed those of simple ions. In addition, the problem of constancy of size from one compound to the next—always a problem

---

[19] Shannon, R.; Prewitt, C. T. *Acta Crystallogr.* **1969**, *B25*, 925; Shannon, R. D. *ibid.* **1976**, *A32*, 751. Most inorganic books in the past, including the first edition of the present one, have given some set of "traditional" ionic radii based on indirect estimates. The Shannon and Prewitt *crystal radii* given in Table 4.4 are about 14 pm larger for cations and 14 pm smaller for anions than the best set of traditional radii.

[20] Lauher, J. W.; Ibers, J. A. *Inorg. Chem.* **1975**, *14*, 348.

[21] Shannon, R. D. In *Structure and Bonding in Crystals*; O'Keefe, M.; Navrotsky, A., Eds.; Academic: New York, 1981, Vol. II, Chapter 16.

Table 4.4

Effective ionic radii of the elements[a]

Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm
Ac^{3+}	6	126		6	59	Cl^{7+}	4	22
Ag^{1+}	2	81	Bi^{3+}	5	110		6	41
	4	114		6	117	Cm^{3+}	6	111
	4 SQ	116		8	131	Cm^{4+}	6	99
	5	123	Bi^{5+}	6	90		8	109
	6	129	Bk^{3+}	6	110	Co^{2+}	4 HS[b]	72
	7	136	Bk^{4+}	6	97		5	81
	8	142		8	107		6 LS[c]	79
Ag^{2+}	4 SQ	93	Br^{1-}	6	182		HS	88.5
	6	108	Br^{3+}	4 SQ	73		8	104
Ag^{3+}	4 SQ	81	Br^{5+}	3 PY	45	Co^{3+}	6 LS	68.5
	6	89	Br^{7+}	4	39		HS	75
Al^{3+}	4	53		6	53	Co^{4+}	4	54
	5	62	C^{4+}	3	6		6 HS	67
	6	67.5		4	29	Cr^{2+}	6 LS	87
Am^{2+}	7	135		6	30		HS	94
	8	140	Ca^{2+}	6	114	Cr^{3+}	6	75.5
	9	145		7	120	Cr^{4+}	4	55
Am^{3+}	6	111.5		8	126		6	69
	8	123		9	132	Cr^{5+}	4	48.5
Am^{4+}	6	99		10	137		6	63
	8	109		12	148		8	71
As^{3-}	6	210[d]	Cd^{2+}	4	92	Cr^{6+}	4	40
As^{3+}	6	72		5	101		6	58
As^{5+}	4	47.5		6	109	Cs^{1+}	6	181
	6	60		7	117		8	188
At^{7+}	6	76		8	124		9	192
Au^{1+}	6	151		12	145		10	195
Au^{3+}	4 SQ	82	Ce^{3+}	6	115		11	199
	6	99		7	121		12	202
Au^{5+}	6	71		8	128.3	Cs^{1-}	10	348[c]
B^{3+}	3	15		9	133.6	Cu^{1+}	2	60
	4	25		10	139		4	74
	6	41		12	148		6	91
Ba^{2+}	6	149	Ce^{4+}	6	101	Cu^{2+}	4	71
	7	152		8	111		4 SQ	71
	8	156		10	121		5	79
	9	161		12	128		6	87
	10	166	Cf^{3+}	6	109	Cu^{3+}	6 LS	68
	11	171	Cf^{4+}	6	96.1	D^{1+}	2	4
	12	175		8	106	Dy^{2+}	6	121
Be^{2+}	3	30	Cl^{1-}	6	167		7	127
	4	41	Cl^{5+}	3 PY	26		8	133
Dy^{3+}	6	105.2		8	97		7 HS	104
	7	111	Hg^{1+}	3	111		8	110
	8	116.7		6	133	Mn^{3+}	5	72
	9	122.3	Hg^{2+}	2	83		6 LS	72
Er^{3+}	6	103		4	110		HS	78.5
	7	108.5		6	116	Mn^{4+}	4	53

Continued

Table 4.4 (*Continued*)
Effective ionic radii of the elements[a]

Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm
	8	114.4		8	128		6	67
	9	120.2	Ho^{3+}	6	104.1	Mn^{5+}	4	47
Eu^{2+}	6	131		8	115.5	Mn^{6+}	4	39.5
	7	134		9	121.2	Mn^{7+}	4	39
	8	139		10	126		6	60
	9	144	I^{1-}	6	206	Mo^{3+}	6	83
	10	149	I^{5+}	3 PY	58	Mo^{4+}	6	79
Eu^{3+}	6	108.7		6	109	Mo^{5+}	4	60
	7	115	I^{7+}	4	56		6	75
	8	120.6		6	67	Mo^{6+}	4	55
	9	126	In^{3+}	4	76		5	64
F^{1-}	2	114.5		6	94		6	73
	3	116		8	106		7	87
	4	117	Ir^{3+}	6	82	N^{3-}	4	132
	6	119	Ir^{4+}	6	76.5	N^{3+}	6	30
F^{7+}	6	22	Ir^{5+}	6	71	N^{5+}	3	4.4
Fe^{2+}	4 HS	77	K^{1-}	—	313[c]		6	27
	4 SQ HS	78	K^{1+}	4	151	Na^{1-}	—	276[c]
	6 LS	75		6	152	Na^{1+}	4	113
	HS	92		7	160		5	114
	8 HS	106		8	165		6	116
Fe^{3+}	4 HS	63		9	169		7	126
	5	72		10	173		8	132
	6 LS	69		12	178		9	138
	HS	78.5	La^{3+}	6	117.2		12	153
	8 HS	92		7	124	Nb^{3+}	6	86
Fe^{4+}	6	72.5		8	130	Nb^{4+}	6	82
Fe^{6+}	4	39		9	135.6		8	93
Fr^{1+}	6	194		10	141	Nb^{5+}	4	62
Ga^{3+}	4	61		12	150		6	78
	5	69	Li^{1+}	4	73		7	83
	6	76		6	90		8	88
Gd^{3+}	6	107.8		8	106	Nd^{2+}	8	143
	7	114	Lu^{3+}	6	100.1		9	149
	8	119.3		8	111.7	Nd^{3+}	6	112.3
	9	124.7		9	117.2		8	124.9
Ge^{2+}	6	87	Mg^{2+}	4	71		9	130.3
Ge^{4+}	4	53		5	80		12	141
	6	67		6	86	Ni^{2+}	4	69
H^{1+}	1	−24		8	103		4 SQ	63
	2	−4	Mn^{2+}	4 HS	80		5	77
Hf^{4+}	4	72		5 HS	89		6	83
	6	85		6 LS	81	Ni^{3+}	6 LS	70
	7	90		HS	97		HS	74
Ni^{4+}	6 LS	62	Pd^{3+}	6	90	Sb^{3+}	4 PY	90
No^{2+}	6	124	Pd^{4+}	6	75.5		5	94
Np^{2+}	6	124	Pm^{3+}	6	111		6	90
Np^{3+}	6	115		8	123.3	Sb^{5+}	6	74

Continued

Table 4.4 (*Continued*)
Effective ionic radii of the elements[a]

Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm
Np^{4+}	6	101		9	128.4	Sc^{3+}	6	88.5
	8	112	Po^{4+}	6	108		8	101
Np^{5+}	6	89		8	122	Se^{2-}	6	184
Np^{6+}	6	86	Po^{6+}	6	81	Se^{4+}	6	64
Np^{7+}	6	85	Pr^{3+}	6	113	Se^{6+}	4	42
O^{2-}	2	121		8	126.6		6	56
	3	122		9	131.9	Si^{4+}	4	40
	4	124	Pt^{4+}	6	99		6	54
	6	126		8	110	Sm^{2+}	7	136
	8	128	Pt^{2+}	4 SQ	74		8	141
OH^{1-}	2	118		6	94		9	146
	3	120	Pt^{4+}	6	76.5	Sm^{3+}	6	109.8
	4	121	Pt^{5+}	6	71		7	116
	6	123	Pu^{3+}	6	114		8	121.9
Os^{4+}	6	77	Pu^{4+}	6	100		9	127.2
Os^{5+}	6	71.5		8	110		12	138
Os^{6+}	5	63	Pu^{5+}	6	88	Sn^{4+}	4	69
	6	68.5	Pu^{6+}	6	85		5	76
Os^{7+}	6	66.5	Ra^{2+}	8	162		6	83
Os^{8+}	4	53		12	184		7	89
P^{3-}	6	200[d]	Rb^{1-}	—	317[c]		8	95
P^{3+}	6	58	Rb^{1+}	6	166	Sr^{2+}	6	132
P^{5+}	4	31		7	170		7	135
	5	43		8	175		8	140
	6	52		9	177		9	145
Pa^{3+}	6	118		10	180		10	150
Pa^{4+}	6	104		11	183		12	158
	8	115		12	186	Ta^{3+}	6	86
Pa^{5+}	6	92		14	197	Ta^{4+}	6	82
	8	105	Re^{4+}	6	77	Ta^{5+}	6	78
	9	109	Re^{5+}	6	72		7	83
Pb^{2+}	4 PY	112	Re^{6+}	6	69		8	88
	6	133	Re^{7+}	4	52	Tb^{3+}	6	106.3
	7	137		6	67		7	112
	8	143	Rh^{3+}	6	80.5		8	118
	9	149	Rh^{4+}	6	74		9	123.5
	10	154	Rh^{5+}	6	69	Tb^{4+}	6	90
	11	159	Ru^{3+}	6	82		8	102
	12	163	Ru^{4+}	6	76	Tc^{4+}	6	78.5
Pb^{4+}	4	79	Ru^{5+}	6	70.5	Tc^{5+}	6	74
	5	87	Ru^{7+}	4	52	Tc^{7+}	4	51
	6	91.5	Ru^{8+}	4	50		6	70
	8	108	S^{2-}	6	170	Te^{2-}	6	207
Pd^{1+}	2	73	S^{4+}	6	51	Te^{4+}	3	66
Pd^{2+}	4 SQ	78	S^{6+}	4	26		4	80
	6	100		6	43		6	111
Te^{6+}	4	57	U^{3+}	6	116.5		6	74
	6	70	U^{4+}	6	103	Xe^{8+}	4	54

Continued

Table 4.4 (*Continued*)
Effective ionic radii of the elements[a]

Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm	Ion	Coordination number[b]	pm
Th^{4+}	6	108		7	109		6	62
	8	119		8	114	Y^{3+}	6	104
	9	123		9	119		7	110
	10	127		12	131		8	115.9
	11	132	U^{5+}	6	90		9	121.5
	12	135		7	98	Yb^{2+}	6	116
Ti^{2+}	6	100	U^{6+}	2	59		7	122
Ti^{3+}	6	81		4	66		8	128
Ti^{4+}	4	56		6	87	Yb^{3+}	6	100.8
	5	65		7	95		7	106.5
	6	74.5		8	100		8	112.5
	8	88	V^{2+}	6	93		9	118.2
Tl^{1+}	6	164	V^{3+}	6	78	Zn^{2+}	4	74
	8	173	V^{4+}	5	67		5	82
	12	184		6	72		6	88
Tl^{3+}	4	89		8	86		8	104
	6	102.5	V^{5+}	4	49.5	Zr^{4+}	4	73
	8	112		5	60		5	80
Tm^{2+}	6	117		6	68		6	86
	7	123	W^{4+}	6	80		7	92
Tm^{3+}	6	102	W^{5+}	6	76		8	98
	8	113.4	W^{6+}	4	56		9	103
	9	119.2		5	65			

[a] Values of crystal radii from Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751–767.

[b] SQ = square planar; PY = pyramidal; HS = high spin; LS = low spin.

[c] Huang, R. H.; Ward, D. L.; Dye, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 5707–5708.

[d] Modified from Pauling, L. *Nature of the Chemical Bond*, 3rd ed.; Cornell University: Ithaca, NY, 1960. These values are only approximate.

even in simple ions—often becomes much worse. For example, one set of data indicates that the radius of the ammonium ion is consistently 175 pm, but a different set indicates that it is the same size as Rb^+, 166 ppm.[22] This is not a serious discrepancy, but it is a disturbing one since its source is not obvious.

Yatsimirskii[23] has provided an ingenious method for estimating the radii of polyatomic ions. A Born–Haber calculation utilizing the enthalpy of formation and related data can provide an estimate of the lattice energy. It is then possible to find what value of the radius of the ion in question is consistent with this lattice energy. These values are thus termed *thermochemical radii*. The most recent set of such values is given in Table 4.5. In many cases the fact that the ions (such as CO_3^{2-}, CNS^-, CH_3COO^-) are markedly nonspherical limits the use of these radii. Obviously they

[22] Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

[23] Yatsimirskii, K. B. *Izv. Akad. Nauk SSSR, Otdel, Khim. Nauk* **1947**, 453; **1948**, 398. See also Mingos, D. M. P.; Rolf, A. L. *Inorg. Chem.* **1991**, *30*, 3769–3771, where the shape of the ion is taken into consideration as well as its size (see Problem 4.42).

Table 4.5
Thermochemical radii of polyatomic ions[a]

Ion	pm	Ion	pm	Ion	pm	Ion	pm
Cations		**Anions**		**Anions**		**Anions**	
NH_4^+	151	CoF_6^{2-}	230	$MnCl_6^{2-}$	308	PtF_6^{2-}	282
Me_4N^+	215	CrF_6^{2-}	238	MnF_6^{2-}	242	PtI_6^{2-}	328
PH_4^+	171	CrO_4^{2-}	242	MnO_4^-	215	$SbCl_6^-$	337
Anions		$CuCl_4^{2-}$	307	N_3^-	181	SeO_3^{2-}	225
$AlCl_4^-$	281	$FeCl_4^-$	344	NCO^-	189	SeO_4^{2-}	235
BCl_4^-	296	$GaCl_4^-$	275	$NH_2CH_2CO_2^-$	176	SiF_6^{2-}	245
BF_4^-	218	$GeCl_6^{2-}$	314	NO_2^-	178	$SnBr_6^{2-}$	349
BH_4^-	179	GeF_6^{2-}	252	NO_3^-	165	$SnCl_6^{2-}$	335
BrO_3^-	140	HCl_2^-	187	O_2^-	144	SnI_6^{2-}	382
CH_3COO^-	148	HCO_2^-	155	O_2^{2-}	159	SO_4^{2-}	244
ClO_3^-	157	HCO_3^-	142	OH^-	119	$TiBr_6^{2-}$	338
ClO_4^-	226	HF_2^-	158	$PbCl_6^{2-}$	334	$TiCl_6^{2-}$	317
CN^-	177	HS^-	193	$PdCl_6^{2-}$	305	TiF_6^{2-}	275
CNS^-	199	HSe^-	191	$PtBr_6^{2-}$	328	VO_3^-	168
CO_3^{2-}	164	IO_3^-	108	$PtCl_4^{2-}$	279	VO_4^{3-}	246
$CoCl_4^{2-}$	305	$IO_2F_2^-$	163	$PtCl_6^{2-}$	299	$ZnBr_4^{2-}$	285
		$IrCl_6^{2-}$	221			$ZnCl_4^{2-}$	272
						ZnI_4^{2-}	309

[a] Data from Jenkins, H. D. B.; Thakur, K. P. *J. Chem. Educ.* **1979**, *56*, 576–577, adjusted to be compatible with Shannon–Prewitt crystal radii. Used with permission.

can be reinserted into further thermochemical calculations and thus provide such data as the anticipated lattice energy of a new (sometimes hypothetical) compound.

In the case of tetrahedral and especially octahedral ions, the symmetry is sufficiently high that the ions may be considered pseudospherical, and so the values more closely represent the physical picture that we have of ionic radii.

Efficiency of Packing and Crystal Lattices

If we consider atoms and ions to be hard spheres, we find that there are certain geometric arrangements for packing them which are more efficient than others. This can be confirmed readily in two dimensions with a handful of coins. For example, if a set of coins of the same size (dimes, for example) is arranged, it will be found that six of them fit perfectly around another (i.e., touching each other and the central dime), giving a coordination number of 6. However, only five quarters or four silver dollars will fit around a dime,[24] illustrating the importance of size in determining the optimum coordination number. The effect of charge can also be illustrated. If all of the atoms are the same, the most efficient two-dimensional lattice is the closest packed, six-coordinate arrangement. If they are of the same size but opposite charge, the six-coordinate structure is not stable since it will have too many repulsions of like-charge ions. This can also be readily shown with coins (using heads and tails to

[24] The fit is not exact in the latter two cases.

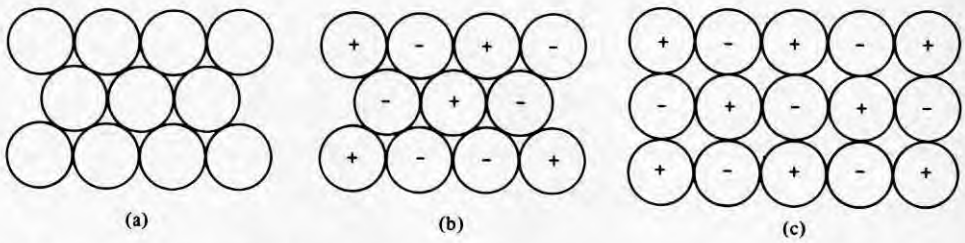


Fig. 4.11 Two-dimensional lattices: (a) stable, six-coordinate, closest packed lattice of uncharged atoms; (b) unstable, six-coordinate lattice of charged ions; (c) stable, four-coordinate lattice of charged ions.

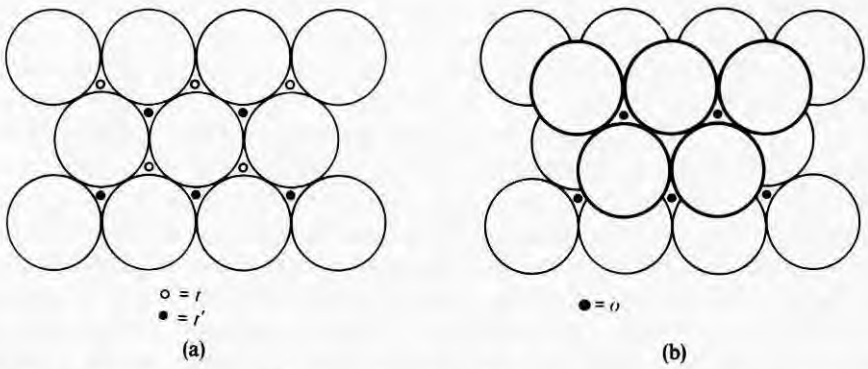


Fig. 4.12 (a) Sites created by layer 1 and available to accept atoms in layer 2. (b) Covering all t sites by atoms in the second layer, making the t' sites (relabeled o) unavailable for occupancy by close-packed atoms.

represent charge), and it can be seen that the most stable arrangement is a square lattice of alternating charge (Fig. 4.11c).

The same principles hold for three-dimensional lattices. Consider first a lattice composed only of uncharged atoms as in a metal or a crystal of noble gas atoms. The first layer will consist of a two-dimensional, closest packed layer (Fig. 4.11a). The second layer will be of the same type but centered over the "depressions" that exist where three atoms in the first layer come in contact (Fig. 4.12a).[25] A layer containing n atoms will have $2n$ such sites capable of accepting atoms (marked t and t'), but once an atom has been placed in either of the two equivalent sets (t and t') the remainder of that layer must continue to utilize that type of site (Fig. 4.12b), and the remaining n sites (labeled o) are not utilized by the packing atoms.

The third layer again has a choice of n sites out of a possible $2n$ available (t and t' types again). One alternative places the atoms of the third layer over those of the first; the other places the atoms of the third layer over the o sites of the first layer. In

[25] The reader is strongly urged to build these structures using Styrofoam spheres and to consult texts on structural chemistry such as Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; 1984; *The Third Dimension in Chemistry*; Clarendon: Oxford, 1956. The present discussion merely presents the more salient features of the subject.

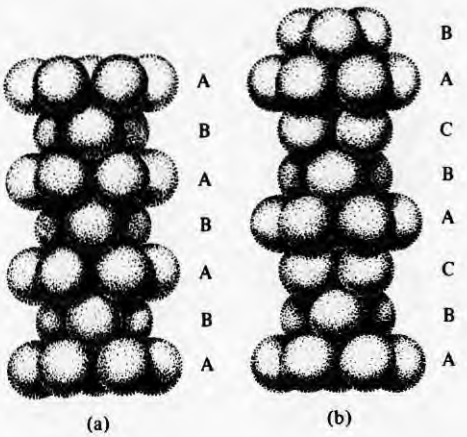


Fig. 4.13 Arrangement of layers in hexagonal closest packed (a) and cubic closest packed (b) structures. These are "side views" compared with the "top views" shown in the preceding figures.

the first type the layers alternate ABABAB and the lattice is known as the hexagonal closest packed (*hcp*) system. Alternatively, the cubic closest packed (*ccp*) system has three different layers, ABCABC. Both lattices provide a coordination number of 12 and are equally efficient at packing atoms into a volume.

It is easy to see the unit cell and the origin of the term *hexagonal closest packed*. In Fig. 4.13a the unit cell can be constructed by drawing a hexagon through the nuclei of the six outer atoms in layer A and a parallel hexagon in the next A layer above, and then connecting the corresponding vertices of the hexagons with perpendicular lines to form a hexagonal prism (Fig. 4.13a).

One could follow a similar practice and construct a similar hexagonal "sandwich" with two layers (B, C) of "filler," but a cubic cell of higher symmetry can be constructed; the second system is thus characterized as *cubic closest packed*. The relation between the cubic unit cell (which is identical to the face-centered cubic cell we have already seen) is not easy to visualize unless one is quite familiar with this system. The easiest way is to take a face-centered cubic array (Fig. 4.14c), and by removing

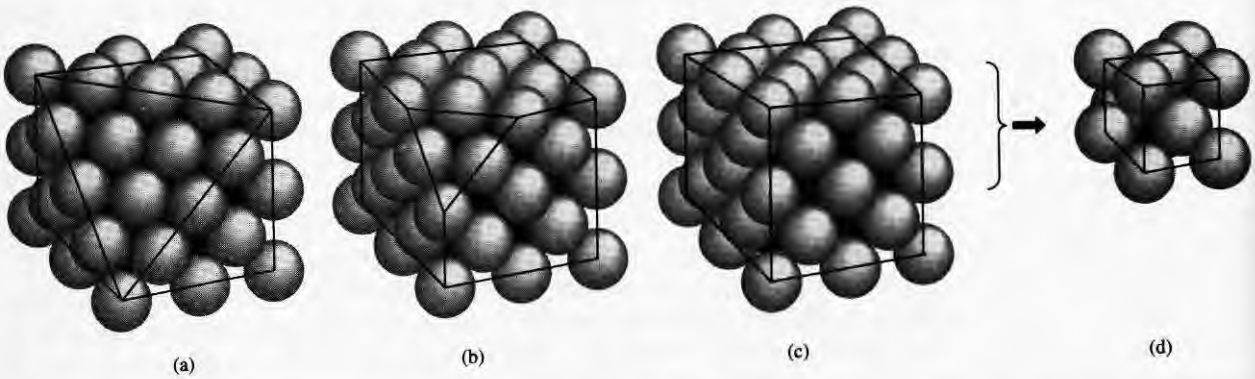


Fig. 4.14 Unit cells in the cubic closest packed systems. (a) A face-centered array of atoms. Note that the exposed layer consists of a closest packed array of fifteen atoms. Consider this the "A layer". (b) A closest packed layer of six atoms placed on (a). Consider this the "B layer". (c) The final atom, a member of the "C layer," is added to complete the cube. The *fcc* unit cell is redrawn in (d). Note that the single atom that composes the "C layer" does not lie above any atom in the "A layer" (as it would if this were *hcp*).

an atom (Fig. 4.14b), then a few more (Fig. 4.14a), reveal the closest packed layers corresponding to A, B, and C in Fig. 4.13b.

The noble gases and most metals crystallize in either the *hcp* or the *ccp* structure as would be expected for neutral atoms. The alkali metals, barium, and a few transition metals crystallize in the *body-centered cubic* system, though the reasons for this choice are unknown.

If all the packing atoms are no longer neutral (e.g., half are cations and half are anions), the closest packed structures are no longer the most stable, as can be seen from the similar two-dimensional case (see above). However, these structures may still be useful when considered as limiting cases for certain ionic crystals. Consider lithium iodide, in which the iodide anions are so much larger than the lithium cations that they may be assumed to touch or nearly touch. They can be considered to provide the framework for the crystal. The much smaller lithium ions can then fit into the small interstices between the anions. If they expand the lattice slightly to remove the anion–anion contact, the anionic repulsion will be reduced and the crystal stabilized, but the simple model based on a closest packed system of anions may still be taken as the limiting case and a useful approximation.

Where the lithium ions fit best will be determined by their size relative to the iodide ions. Note from above that there are two types of interstices in a closest packed structure. These represent tetrahedral (*t*) and octahedral (*o*) holes because the coordination of a small ion fitted into them is either tetrahedral or octahedral (see Fig. 4.12). The octahedral holes are considerably larger than the tetrahedral holes and can accommodate larger cations without severe distortion of the structure. In lithium iodide the lithium ions fit into the octahedral holes in a cubic closest packed lattice of iodide ions. The resulting structure is the same as found in sodium chloride and is face-centered (note that face-centered cubic and cubic closest packed describe the same lattice).

Consider a closest packed lattice of sulfide ions. Zinc ions tend to occupy tetrahedral holes in such a framework since they are quite small (74 pm) compared with the larger sulfide ions (170 pm). If the sulfide ions form a *ccp* array, the resulting structure is zinc blende; if they form an *hcp* array, the resulting structure is wurtzite. See Fig. 4.15.

Although in the present discussion size is the only parameter considered in determining the choice of octahedral versus tetrahedral sites, the presence of covalent bonding (d^2sp^3 versus sp^3 hybridization, see Chapter 5) and/or ligand field stabilization (see Chapter 11) can affect the stability of ions in particular sites. Size will usually be the determining factor when these additional factors are of small importance—for example, when considering alkali and alkaline earth ions. The concept of closest packing of anions is also very useful in considering polar covalent macromolecules such as the silicates and iso- and heteropolyanions.[26]

If the cations and anions are of approximately the same size, the limiting case of the framework being determined by the larger ion is inappropriate, and we simply determine the most efficient lattice for oppositely charged ions of equal size. This turns out to be the CsCl lattice, which maximizes cation–anion interaction (C.N. = 8) and is the most stable structure when the sizes of the cation and anion are comparable.

---

[26] Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; Clarendon: Oxford, 1984. For a comprehensive and detailed discussion of the broad usefulness of classifying structures in terms of closest-packed structures, see Douglas, B. E.; McDaniel, D. H.; Alexander, J. J. *Concepts and Models of Inorganic Chemistry*, 2nd ed.; Wiley: New York, 1983; pp 198–208.

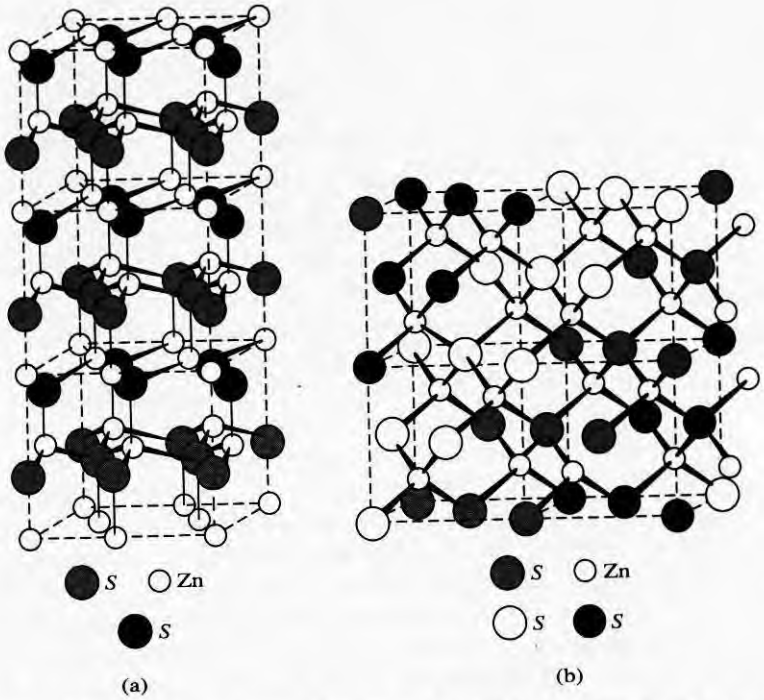


Fig. 4.15 (a) The structure of wurtzite. The sulfide ions form an *hcp* array with A (gray) and B (black) alternating layers (Cf. Fig. 4.13a). (b) The structure of zinc blende. The sulfide ions form a *ccp* array with A (white), B (black), and C (gray) layers. (Cf. Figs. 4.13b and 4.14.) Note that in both structures the zinc atoms (*small* white circles) occupy tetrahedral holes.

Radius Ratio

It is not difficult to calculate the size of the octahedral hole in a lattice of closest packed anions. Figure 4.16 illustrates the geometric arrangement resulting from six anions in contact with each other and with a cation in the octahedral hole. Simple geometry allows us to fix the diagonal of the square as $2r_- + 2r_+$. The angle formed by the diagonal in the corner must be 45°, so we can say:

$$\frac{2r_-}{2r_- + 2r_+} = \cos 45° = 0.707 \tag{4.21}$$

$$r_- = 0.707r_- + 0.707r_+ \tag{4.22}$$

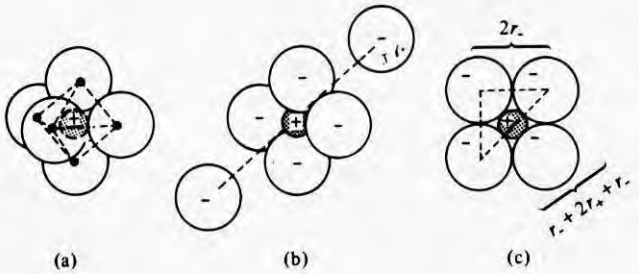


Fig. 4.16 (a) Small cation (dashed line) in octahedral hole formed by six anions. (b) Dissection of octahedron to illustrate geometric relationships shown in (c).

Table 4.6
Radius ratio and coordination number

Coordination number	Geometry	Limiting radius ratio[a]	Possible lattice structures
4	Tetrahedral	0.414; 2.42	Wurtzite, zinc blende
6	Octahedral	0.732; 1.37	NaCl, rutile
8	Cubic	1.000	CsCl, fluorite
12	Cuboctohedral[b]		[c]

[a] The second ratio is merely the reciprocal of the first. It is often convenient to have both values.

[b] The atoms in the top three layers of Fig. 4.13b form a cuboctohedron.

[c] Coordination number 12 is not found in simple ionic crystals. It occurs in complex metal oxides and in closest packed lattices of atoms.

$$0.293r_- = 0.707r_+ \tag{4.23}$$

$$\frac{r_+}{r_-} = \frac{0.293}{0.707} = 0.414 \tag{4.24}$$

This will be the limiting ratio since a cation will be stable in an octahedral hole only if it is at least large enough to keep the anions from touching, that is, $r_+/r_- > 0.414$. Smaller cations will preferentially fit into tetrahedral holes in the lattice. By a similar geometric calculation it is possible to determine that the lower limit for tetrahedral coordination is $r_+/r_- = 0.225$. For radius ratios ranging from 0.225 to 0.414, tetrahedral sites will be preferred. Above 0.414, octahedral coordination is favored. By similar calculations it is possible to find the ratio when one cation can accommodate eight anions (0.732) or twelve anions (1.000). A partial list of limiting radius ratio values is given in Table 4.6.

The use of radius ratios to rationalize structures and to predict coordination numbers may be illustrated as follows.[27] Consider beryllium sulfide, in which $r_{Be^{2+}}/r_{S^{2-}} = 59$ pm/170 pm = 0.35. We should thus expect a coordination number of 4 as the Be^{2+} ion fits most readily into the *tetrahedral* holes of the closest packed lattice, and indeed this is found experimentally: BeS adopts a wurtzite structure.

In the same way we can predict that sodium ions will prefer *octahedral* holes in a closest packed lattice of chloride ions ($r_{Na^+}/r_{Cl^-} = 116$ pm/167 pm = 0.69), forming the well-known sodium chloride lattice with a coordination number of 6 (Fig. 4.1a).

With larger cations, such as cesium, the radius ratio ($r_{Cs^+}/r_{Cl^-} = 181$ pm/167 pm = 1.08) increases beyond the acceptable limit for a coordination number of 6; the coordination number of the cations (and anions) increases to 8, and the cesium chloride lattice (Fig. 4.1b) results. As we have seen, although this is an efficient structure for cations and anions of about the same size, it cannot be directly related to a closest packed structure of anions.

Table 4.6 indicates that a coordination number of 12 should be possible when the radius ratio is 1.00. Geometrically it is possible to fit 12 atoms about a central

[27] Since crystal radii vary slightly with coordination number, values from Table 4.4 were taken for C.N. = 6 as "average" values.

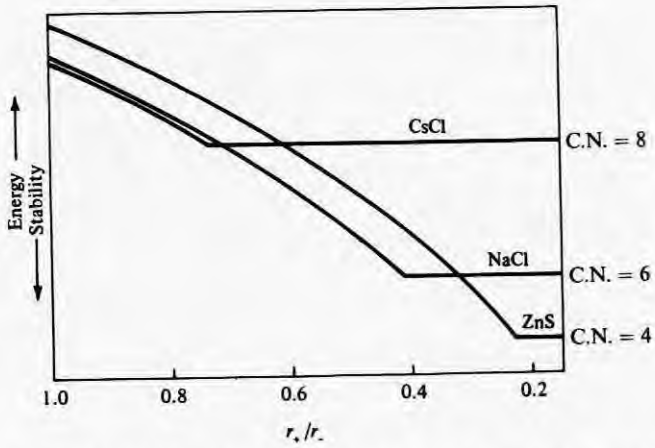


Fig. 4.17 The total energy of a cubic lattice of rigid anions and cations as a function of r_+ with r_- fixed, for different coordination configurations. When the anions come into mutual contact as a result of decreasing r_+ their repulsion determines the lattice constant and the cohesive energy becomes constant when expressed in terms of r_-. Thus near the values of r_+/r_- at which anion–anion contact takes place, the radius ratio model predicts phase transitions to structures of successively lower coordination numbers. Note that the "breaks" in the curves correspond to the values listed in Table 4.6. [From *Treatise on Solid State Chemistry*; Hannay, N. B., Ed.; Plenum: New York, 1973.]

atom (see the discussion of closest packing in metals, page 119), but it is impossible to obtain mutual twelve-coordination of cations and anions because of the limitations of geometry. Twelve-coordination does occur in complex crystal structures of mixed metal oxides in which one metal acts as one of the closest packing atoms and others fit into octahedral holes, but a complete discussion of such structures is more appropriate in a book devoted to the structures of solids.[28]

The change in coordination number as a result of the ratio of ionic radii is shown graphically in Fig. 4.17. In general, as the cation decreases in size the lattice is stabilized (lattice energy becomes more negative) until anion–anion contact occurs. Further shrinkage of the lattice is impossible without a reduction in coordination number; therefore, zinc sulfide adopts the wurtzite or the zinc blende structure, gaining additional energy over what would be possible in a structure with a higher coordination number. Note that although there is a significant difference in energy between structures having coordination numbers 4 and 6, there is little difference between 6 and 8 (the two lines almost coincide in Fig. 4.17 on the left). The difference in energy between six- and eight-coordinate structures is less than 1% based on electrostatics.

In a 1:1 or 2:2 salt, the appropriate radius ratio is obviously the ratio of the smaller ion (usually the cation) to the larger to determine how many of the latter will fit around the smaller ion. In compounds containing different numbers of cations and anions (e.g., SrF_2, TiO_2, Li_2O, Rb_2S) it may not be immediately obvious how to apply the ratio. In such cases it is usually best to perform two calculations. For

[28] See Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; Clarendon: Oxford, 1984; pp 480–589.

example, consider SrF_2:

$$\frac{r_{Sr^{2+}}}{r_{F^-}} = \frac{132}{119} = 1.11 \quad \text{maximum C.N. of } Sr^{2+} = 8$$

$$\frac{r_{F^-}}{r_{Sr^{2+}}} = \frac{119}{132} = 0.90 \quad \text{maximum C.N. of } F^- = 8$$

Now there must be twice as many fluoride ions as strontium ions, so the coordination number of the strontium ion must be twice as large as that of fluoride. Coordination numbers of 8 (Sr^{2+}) and 4 (F^-) are compatible with the maximum allowable coordination numbers and with the stoichiometry of the crystal. Strontium fluoride crystallizes in the fluorite lattice (Fig. 4.3).

A second example is SnO_2:

$$\frac{r_{Sn^{4+}}}{r_{O^{2-}}} = \frac{83}{126} = 0.66 \quad \text{maximum C.N. of } Sn^{4+} = 6$$

$$\frac{r_{O^{2-}}}{r_{Sn^{4+}}} = \frac{126}{83} = 1.52 \quad \text{maximum C.N. of } O^{2-} = 6$$

Considering the stoichiometry of the salt, the only feasible arrangement is with $C.N._{O^{2-}} = 3$, $C.N._{Sn^{4+}} = 6$; tin dioxide assumes the TiO_2 or rutile structure of Fig. 4.4. Note that the radius ratio would allow three more tin(IV) ions in the coordination sphere of the oxide ion, but the stoichiometry forbids it.

One final example is K_2O:

$$\frac{r_{K^+}}{r_{O^{2-}}} = \frac{152}{126} = 1.21 \quad \text{maximum C.N. of } K^+ = 8$$

$$\frac{r_{O^{2-}}}{r_{K^+}} = \frac{126}{152} = 0.83 \quad \text{maximum C.N. of } O^{2-} = 8$$

Considering the stoichiometry of the salt, the structure must be antifluorite (Fig. 4.3, reversed) with $C.N._{O^{2-}} = 8$, $C.N._{K^+} = 4$.

The radius ratio quite often predicts the correct coordination numbers of ions in crystal lattices. It must be used with caution, however, when covalent bonding becomes important. The reader may have been puzzled as to why beryllium sulfide was chosen to illustrate the radius ratio rule for coordination number 4 (page 123) instead of zinc sulfide, which was used repeatedly earlier in this chapter to illustrate four-coordinate structures such as wurtzite and zinc blende. The reason is simple. If ZnS had been used, it would have caused more confusion than enlightenment: It violates the radius ratio rule! Proceeding as above, we have $r_+/r_- = 88$ pm/170 pm = 0.52, indicating a coordination number of 6, yet both forms of ZnS, wurtzite and zinc blende, have a C.N. of 4, for both cations and anions. If one argues that 0.52 does not differ greatly from 0.41, the point is well taken, but there exist more vexing cases. The radius ratio for mercury(II) sulfide, HgS, is 0.68, yet it crystallizes in the zinc blende structure. In both of these examples the sp^3 hybridized *covalent* bonding seems to be the dominant factor. Both ZnS and especially HgS are better regarded as infinite covalent lattices (see Chapter 7) than as ionic lattices.

It should be kept clearly in mind that the radius ratio rules apply strictly only to the packing of hard spheres of known size. As this is seldom the case, it is surprising that the rules work as well as they do. Anions are not "hard" like billiard balls, but polarizable under the influence of cations. To whatever extent such polarization or covalency occurs, errors are apt to result from application of the radius ratio rules. Covalent bonds are directed in space unlike electrostatic attractions, and so certain orientations are preferred.

There are, however, other exceptions that are difficult to attribute to directional covalent bonds. The heavier lithium halides only marginally obey the rule, and perhaps a case could be made for C.N. = 4 for LiI (Fig. 4.18). Much more serious, however, is the problem of coordination number 6 versus 8. The relative lack of eight-coordinate structures—CsCl, CsBr, and CsI being the only known alkali metal examples—is commonly found, if hard to explain. There are no eight-coordinate

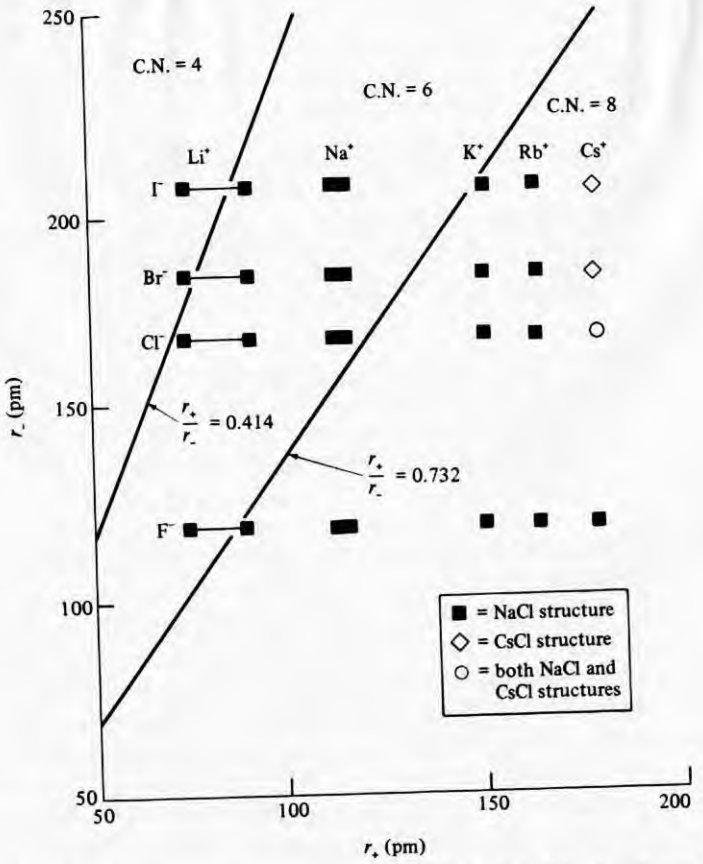


Fig. 4.18 Actual crystal structures of the alkali halides (as shown by the symbols) contrasted with the predictions of the radius ratio rule. The figure is divided into three regions by the lines $r_+/r_- = 0.414$ and $r_+/r_- = 0.732$, predicting coordination number 4 (wurtzite or zinc blende, upper left), coordination number 6 (rock salt, NaCl, middle), and coordination number 8 (CsCl, lower right). The crystal radius of lithium, and to a lesser extent that of sodium, changes with coordination number, so both the radii with C.N. = 4 (left) and C.N. = 6 (right) have been plotted.

oxides, MO, even though the larger divalent metal ions, such as Sr^{2+}, Ba^{2+}, and Pb^{2+}, are large enough that the radius ratio rule would predict the CsCl structure. There is no simple explanation for these observations. We have seen that the Madelung constant for C.N. = 8 is only marginally larger than that for C.N. = 6. Thus small energies coming from other sources can tip the balance.

The radius ratio is a useful, though imperfect, tool in our arsenal for predicting and understanding the behavior of ionic compounds.[29] From a theoretical point of view it rationalizes the choice of lattice for various ionic or partially ionic compounds. Its failings call our attention to forces in solids other than purely electrostatic ones acting on billiard-ball-like ions. We shall encounter modifications and improvements of the model in Chapter 7.

The Predictive Power of Thermochemical Calculations on Ionic Compounds

The following example will illustrate the way in which the previously discussed parameters, such as ionic radii and ionization energies, can be used advantageously to explore the possible existence of an unknown compound. Suppose one were interested in dioxygenyl tetrafluoroborate, $[O_2]^+[BF_4]^-$. At first thought it might seem an unlikely candidate for existence since oxygen tends to gain electrons rather than lose them. However, the ionization energy of molecular oxygen is not excessively high (1165 kJ mol^{-1}; cf. Hg, 1009 kJ mol^{-1}), so some trial calculations might be made as follows.

The first values necessary are some estimates of the ionic radii of O_2^+ and BF_4^-. For the latter we may use the value obtained thermochemically by Yatsimirskii, 218 pm. An educated guess has to be made for O_2^+, since if we are attempting to make it for the first time (as was assumed above), we will not have any experimental data available for this species. However, we note that the CN^- ion, a diatomic ion which should be similar in size, has a thermochemical radius of 177 ppm. Furthermore, an estimate based on covalent and van der Waals radii (see Chapter 8) gives a similar value. Because O_2^+ has lost one electron and is positively charged, it will probably be somewhat smaller than this. We can thus take 177 pm as a conservative estimate; if the cation is smaller than this, the compound will be more stable than our prediction and even more likely to exist. Adding the radii we obtain an estimate of 395 pm for the interionic distance.

Next the lattice energy can be calculated. One method would be to assume that we know nothing about the probable structure and use the Kapustinskii equation (Eq. 4.20) and $r_0 = 395$ pm. The resulting lattice energy is calculated to be -555 kJ mol^{-1}.

Alternatively, we might examine the radius ratio of $O_2^+BF_4^-$ and get a crude estimate of $\frac{177}{218} = 0.8$. The accuracy of our values does not permit us to choose between coordination number 6 and 8, but since the value of the Madelung constant does not differ appreciably between the sodium chloride and cesium chloride structures, a value of 1.75 may be taken which will suffice for our present rough calculations. We may then use the Born–Landé equation (Eq. 4.13), which provides an estimate of -616 kJ mol^{-1} for the attractive energy, which will be decreased by about 10% (if

[29] An analysis of 227 compounds indicated that the radius ratio rule worked about two-thirds of the time. Particularly troublesome were Group IB (11) and IIB (12) chalcogenides like HgS. Nathan, L. C. *J. Chem. Educ.* **1985**, *62*, 215–218.

$n = 10$) to 20% (if $n = 5$). The two calculations thus agree that the lattice energy will probably be in the range -480 to -560 kJ mol^{-1} (-115 to -134 kcal mol^{-1}). This is a quite stable lattice and might be sufficient to stabilize the compound.

Next we might investigate the possible ways of producing the desired compound. Because the oxidation of oxygen is expected to be difficult to accomplish we might choose vigorous oxidizing conditions, such as the use of elemental fluorine:

$$O_2 + \tfrac{1}{2}F_2 + BF_3 \longrightarrow [O_2]^+[BF_4]^- \qquad \textbf{(4.25)}$$

It is possible to evaluate each term in a Born–Haber cycle based on Eq. 4.25.

The usual terms we have encountered in previous Born–Haber cycles may be evaluated readily:

Ionization energy of $O_2 = 1165$ kJ mol^{-1}

Dissociation of $\frac{1}{2}F_2 = 79$ kJ mol^{-1}

Electron affinity of $F = -328$ kJ mol^{-1}

One additional term occurs in this Born–Haber cycle: the formation of the tetrafluoroborate ion in the gas phase:

$$BF_{3(g)} + F^-_{(g)} \longrightarrow BF^-_{4(g)} \qquad \textbf{(4.26)}$$

Fortunately, the enthalpy of this reaction has been experimentally measured[30] to be -423 kJ mol^{-1}. Adding in the value of -500 ± 20 kJ mol^{-1} for the lattice energy provides an estimate of the heat of the reaction in Eq. 4.25 that is essentially zero. This is somewhat discouraging, since if Eq. 4.25 is not exothermic, entropy will drive the reaction to the left because all of those species are gases, and dioxygenyl tetrafluoroborate would not be expected to be stable. Recall, however, that our estimates were on the conservative side. We would therefore expect that dioxygenyl tetrafluoroborate is either energetically unfavorable or may form with a relatively low stability. It certainly is worth an attempt at synthesis.

In fact, dioxygenyl tetrafluoroborate *has* been synthesized by a reaction similar to Eq. 4.25, although in two steps: the formation of intermediate oxygen fluorides and then combination with boron trifluoride.[31] It is a white crystalline solid that slowly decomposes at room temperature. Energy calculations of this type are exceedingly useful in guiding research on the synthesis of new compounds. Usually it is not necessary to start with the complete absence of knowledge assumed in the present example. Often one or more factors can be evaluated from similar compounds. It was the observation of the formation of dioxygenyl hexafluoroplatinate(V) and similar calculations that led Bartlett to perform his first experiment in an attempt to synthesize compounds of xenon. This successful synthesis overturned prior chemical dogma (see Chapter 17).

Now that we have seen that dioxygenyl compounds can be prepared, we might be interested in preparing the exotic and intriguing compound dioxygenyl superoxide, $O_2^+O_2^-$. Using methods similar to those discussed above, we can set up a

---

[30] Srivastava, R. D.; Uy, O. M.; Farber, M. *J. Chem. Soc., Faraday Trans. 1* **1974**, *70*, 1033.

[31] Keith, J. N.; Solomon, I. J.; Sheft, I.; Hyman, H. H. *Inorg. Chem.* **1968**, *7*, 230–234. Goetschel, C. T.; Campanile, V. A.; Wagner, C. D.; Wilson, J. N. *J. Am. Chem. Soc.* **1969**, *91*, 4702–4707

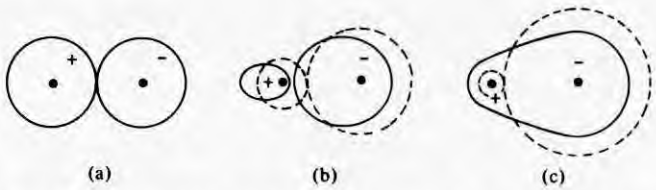


Fig. 4.19 Polarization effects: (a) idealized ion pair with no polarization, (b) mutually polarized ion pair, (c) polarization sufficient to form covalent bond. Dashed lines represent hypothetical unpolarized ions.

Born–Haber cycle and evaluate the following terms.

$O_2 \longrightarrow O_2^+ + e^-$	$\Delta H = 1165\ \text{kJ mol}^{-1}$
$O_2 + e^- \longrightarrow O_2^-$	$\Delta H = -42\ \text{kJ mol}^{-1}$
Lattice energy	$\Delta H \approx -500\ \text{kJ mol}^{-1}$
	$\Delta H_f \approx +623\ \text{kJ mol}^{-1}$

The calculations support our intuitive feelings about this compound. If it were somehow possible to make an ionic compound $O_2^+O_2^-$, it would decompose with the release of a large amount of energy:

$$O_2^+O_2^- \longrightarrow 2O_2 \qquad \Delta H \approx -623\ \text{kJ mol}^{-1}$$

Dioxygenyl superoxide is not a likely candidate for successful synthesis.

Covalent Character in Predominantly Ionic Bonds

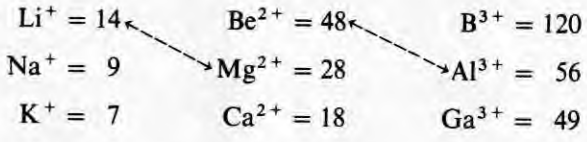
It is probable that every heteronuclear bond the chemist has to deal with contains a mixture of covalent and ionic character. Ordinarily we speak glibly of an ionic compound or a covalent compound as long as the compound in question is predominantly one or the other. In many cases, however, it is convenient to be able to say something about intermediate situations. In general, there are two ways of treating ionic–covalent bonding. The method that has proved most successful is to consider the bond to be covalent and then consider the effect of increasing charge displacement from one atom toward another. This method will be discussed in the next chapter. Another method is to consider the bond to be ionic and then allow for a certain amount of covalency to occur. The second method was championed by Kasimir Fajans[32] in his quanticule theory. The latter theory has found no place in the repertoire of the theoretical chemist largely because it has not proved amenable to the quantitative calculations which other theories have developed. Nevertheless, the qualitative ideas embodied in "Fajans' rules" offer simple if inexact approaches to the problem of partial covalent character in ionic compounds.

Fajans considered the effect which a small, highly charged cation would have on an anion. If the anion were large and "soft" enough, the cation should be capable of polarizing it, and the extreme of this situation would be the cation actually penetrating the anionic electron cloud giving a covalent (shared electron) bond (Fig. 4.19).

[32] Fajans, K. *Naturwissenschaften* **1923**, *11*, 165. For a more recent discussion of the same subject, see Fajans, K. *Struct. Bonding Berlin* **1967**, *3*, 88–105. For an interesting short sketch on the theory and the man, see Hurwic, J. *J. Chem. Educ.* **1987**, *64*, 122.

Fajans suggested the following rules to estimate the extent to which a cation could polarize an anion and thus induce covalent character. Polarization will be increased by:

1. *High charge and small size of the cation.* Small, highly charged cations will exert a greater effect in polarizing anions than large and/or singly charged cations. This is often expressed by the *ionic potential*[33] of the cation: $\phi = Z^+/r$. For some simple ions, ionic potentials are as follows (r in nm):



Obviously there is no compelling reason for choosing Z/r instead of Z/r^2 or several other functions that could be suggested, and the values above are meant merely to be suggestive. Nevertheless, polarization does follow some charge-to-size relationship, and those cations with large ionic potentials are those which have a tendency to combine with polarizable anions to yield partially covalent compounds. The ionic potentials listed also rationalize an interesting empirical observation indicated by the dashed arrows: The first element in any given family of the periodic chart tends to resemble the second element in the family to the right. Thus lithium and magnesium have much in common (the best known examples are the organometallic compounds of these elements) and the chemistry of beryllium and aluminum is surprisingly similar despite the difference in preferred oxidation state.[34] This relationship extends across the periodic chart; for example, phosphorus and carbon resemble each other in their electronegativities (see Chapter 18).

A word should be said here concerning unusually high ionic charges often found in charts of ionic radii. Ionic radii are often listed for Si^{4+}, P^{5+}, and even Cl^{7+}. Although at one time it was popular, especially among geochemists, to discuss silicates, phosphates, and chlorates as though they contained these highly charged ions, no one today believes that such highly charged ions have any physical reality. The only possible meaning such radii can have is to indicate that if an ion such as P^{5+} or Cl^{7+} could exist, its high charge combined with small size would cause it immediately to polarize some adjacent anion and form a covalent bond.

2. *High charge and large size of the anion.* The polarizability of the anion will be related to its "softness," that is, to the deformability of its electron cloud. Both increasing charge and increasing size will cause this cloud to be less under the influence of the nuclear charge of the anion and more easily influenced by the charge on the cation. Thus large anions such as I^-, Se^{2-}, and

---

[33] Cartledge, G. H. *J. Am. Chem. Soc.* **1928**, *50*, 2855, 2863; *ibid.* **1930**, *52*, 3076.

[34] It is true that the value of the ionic potential of Li^+ is closer to that of Ca^{2+} than to that of Mg^{2+}, and a strong argument has been made that Li^+ resembles Ca^{2+} more than Mg^{2+} [Hanusa, T. P. *J. Chem. Educ.* **1987**, *64*, 686.] The strength of the Fajans approach and the related idea of diagonal resemblance rests on its *qualitative* success. The diagonal rule and the ionic potential should be used as *guides* rather than as substitutes for close inspection of each individual situation.

Te^{2-} and highly charged ones such as As^{3-} and P^{3-} are especially prone to polarization and covalent character.

A question naturally occurs: What about the polarization of a large cation by a small anion? Although this occurs, the results are not apt to be so spectacular as in the reverse situation. Even though large, a cation is not likely to be particularly "soft" because the cationic charge will tend to hold on to the electrons. Likewise, a small anion can tend to polarize a cation, that is, repel the outside electrons and thus make it possible to "see" the nuclear charge better, but this is not going to lead to covalent bond formation. No convincing examples of reverse polarization have been suggested.

3. *Electron configuration of the cation.* The simple form of the ionic potential considers only the net ionic charge of the ion with respect to its size. Actually an anion or polarizable molecule will feel a potential resulting from the total positive charge minus whatever shielding the electrons provide. To use the ionic charge is to assume implicitly that the shielding of the remaining electrons is perfect, that is, 100% effective. The most serious problems with this assumption occur with the transition metal ions since they have one or more *d* electrons which shield the nucleus poorly. Thus for two ions of the same size and charge, one with an $(n-1)d^x ns^0$ electronic configuration (typical of the transition elements) will be more polarizing than a cation with a noble gas configuration $(n-1)s^2$ $(n-1)p^6 ns^0$ (alkali and alkaline earth metals, for example). As an example, Hg^{2+} has an ionic radius (C.N. = 6) of 116 pm, yet it is considerably more polarizing and its compounds are considerably more covalent than those of Ca^{2+} with almost identical size (114 pm) and the same charge.

Results of Polarization

One of the most common examples of covalency resulting from polarization can be seen in the melting and boiling points of compounds of various metals.[35] Comparing the melting points of compounds having the same anion, but cations of different size, we have $BeCl_2$ = 405 °C, $CaCl_2$ = 782 °C; for cations of different charge, we have NaBr = 747 °C, $MgBr_2$ = 700 °C, $AlBr_3$ = 97.5 °C; for a constant cation, but anions of different sizes, we have LiF = 845 °C, LiCl = 605 °C, LiBr = 550 °C, LiI = 449 °C; and for ions having the same size and charge, the effect of electron configuration can be seen from $CaCl_2$ = 782 °C, $HgCl_2$ = 276 °C. Care must be taken not to interpret melting points and boiling points too literally as indicators of the degree of covalent bonding; there are many effects operative in addition to covalency and these will be discussed at some length in Chapter 8.

A second area in which polarization effects show up is the solubility of salts in polar solvents such as water. For example, consider the silver halides, in which we have a polarizing cation and increasingly polarizable anions. Silver fluoride, which is quite ionic, is soluble in water, but the less ionic silver chloride is soluble only with the inducement of complexing ammonia. Silver bromide is only slightly soluble and silver iodide is insoluble even with the addition of ammonia. Increasing covalency from fluoride to iodide is expected and decreased solubility in water is observed.

[35] One learns in general chemistry courses that ionic compounds have high melting points and covalent ones have low melting points. Although this oversimplification can be misleading, it may be applied to the present discussion. A more thorough discussion of the factors involved in melting and boiling points will be found in Chapter 8.

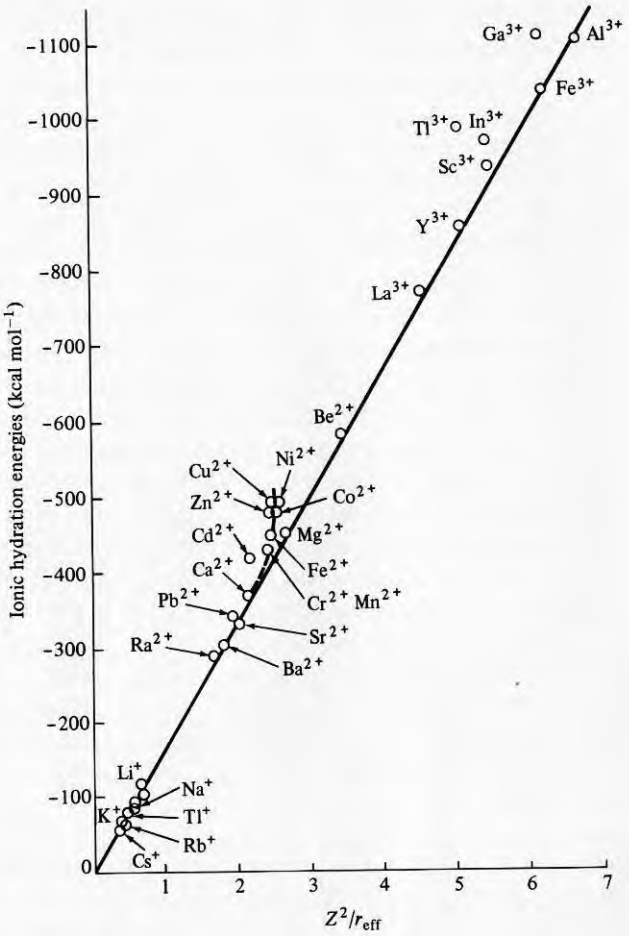


Fig. 4.20 Hydration energies as a function of size and charge of cations. [From Philips, C. S. G.; Williams, R. J. P. *Inorganic Chemistry*; Clarendon: Oxford, 1965. Reproduced with permission.]

Silver nalide	K_{sp}
Silver fluoride	Soluble
Silver chloride	2×10^{-10}
Silver bromide	5×10^{-13}
Silver iodide	8×10^{-17}

As in the case of melting points, solubility is a complex process, and there are many factors involved in addition to covalency.

Closely related to solubility are the hydration enthalpies of ions. It has been found[36] that it is possible to correlate the hydration enthalpies of cations with their "effective ionic radii" by the expression (see Fig. 4.20)

$$\Delta H = -69{,}500(Z^2/r_{eff}) \text{ kJ mol}^{-1} \quad (r_{eff} \text{ in pm}) \tag{4.27}$$

[36] Latimer, W. M.; Pitzer, K. S.; Slansky, C. M. *J. Chem. Phys.* **1939**, *7*, 108–111.

In this case the reason for the correlation is fairly obvious. The parameter r_{eff} is equal to the ionic radius plus a constant, 85 pm, the radius of the oxygen atom in water. Therefore, r_{eff} is effectively the interatomic distance in the hydrate, and the Born–Landé equation (Eq. 4.13) can be applied.

A third, and perhaps the most fundamental, aspect of polarization can be seen in the bond lengths of silver halides. If we predict these distances using the ionic radii of Table 4.4, our accuracy decreases markedly in the direction AgF > AgCl > AgBr > AgI:

Compound	$r^+ + r^-$	r_{exp}	Δ
AgF	248	246	−2
AgCl	296	277	−19
AgBr	311	289	−22
AgI	320	281	−39

The Shannon–Prewitt ionic radii ($r^+ + r^-$) are based on the most ionic compounds, the fluorides and oxides for the radii of the metal cations, and the alkali halides for the radii of the anions of the remaining halides. The shortening of silver halide bond lengths is attributable to polarization and covalency.

The basis for other correlations between size, charge, and chemical properties is not so clearcut. Chemical reactions can often be rationalized in terms of the polarizing power of a particular cation. In the alkaline earth carbonates, for example, there is a tendency toward decomposition with the evolution of carbon dioxide:

$$MCO_3 \longrightarrow MO + CO_2 \qquad \textbf{(4.28)}$$

The ease with which this reaction proceeds (as indicated by the temperature necessary to induce it) decreases with increasing cation size: $BeCO_3$, unstable; $MgCO_3$, 350 °C; $CaCO_3$, 900 °C; $SrCO_3$, 1290 °C; $BaCO_3$, 1360 °C. The effect of *d* electrons is also clear: Both $CdCO_3$ and $PbCO_3$ decompose at approximately 350 °C despite the fact that Cd^{2+} and Pb^{2+} are approximately the same size as Ca^{2+}. The decomposition of these carbonates occurs as the cation polarizes the carbonate ion, splitting it into an O^{2-} ion and CO_2.

Stern[37] has extended the qualitative argument on decomposition by showing that the enthalpies of decomposition of carbonates, sulfates, nitrates, and phosphates are linearly related to a charge/size function, in this case $r^{1/2}/Z^*$ (see Fig. 4.21). Although the exact theoretical basis of this correlation is not clear, it provides another interesting example of the general principle that size and charge are the important factors that govern the polarizing power of ions and, consequently, many of their chemical properties.

From the preceding, it might be supposed that covalent character in predominantly ionic compounds always destabilizes the compound. This is not so. Instability results from polarization of the anion causing it to split into a more stable compound (in the above cases the oxides) with the release of gaseous acidic anhydrides. As will be seen in Chapter 16, many very stable, very hard minerals have covalent–ionic bonding.

[37] Stern, K. H. *J. Chem. Educ.* **1969**, *46*, 645.

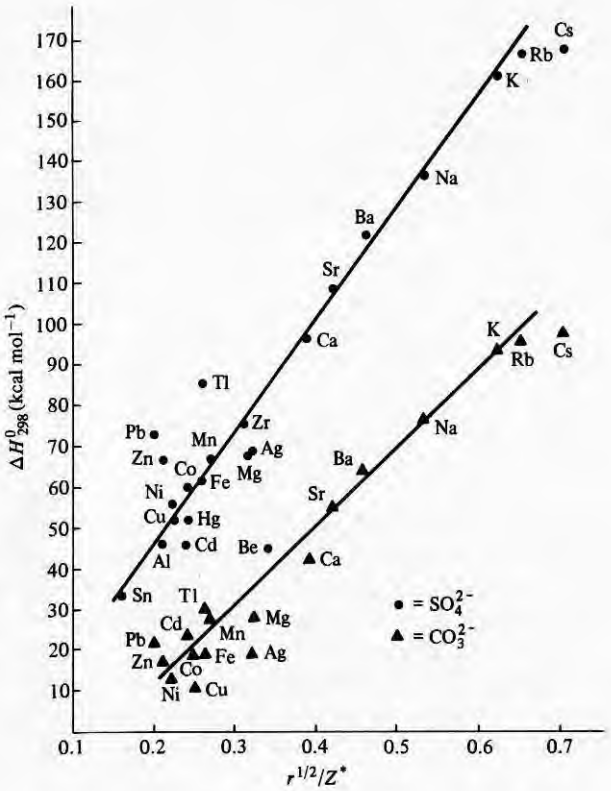


Fig. 4.21 Enthalpy of decomposition of sulfates and carbonates as a function of size and charge of the metal cation. [From Stern, K. H. *J. Chem. Educ.* **1969**, *46*, 645–649. Reproduced with permission.]

Conclusion

Ionic crystals may be viewed quite simply in terms of an electrostatic model of lattices of hard-sphere ions of opposing charges. Although conceptually simple, this model is not completely adequate, and we have seen that modifications must be made in it. First, the bonding is not completely ionic with compounds ranging from the alkali halides, for which complete ionicity is a very good approximation, to compounds for which the assumption of the presence of ions is rather poor. Secondly, the assumption of a perfect, infinite mathematical lattice with no defects is an oversimplification. As with all models, the use of the ionic model does not necessarily imply that it is "true", merely that it is convenient and useful, and if proper caution is taken and adjustments are made, it proves to be a fruitful approach.

Problems

4.1 Both CsCl and CaF_2 exhibit a coordination number of 8 for the cations. What is the structural relationship between these two lattices?

4.2 The contents of the unit cell of any compound must contain an integral number of formula units. (Why?) Note that unit cell boundaries "slice" atoms into fragments: An atom on a face will be split in *half* between *two* cells; one on an *edge* will be split into *quarters* among *four* cells, etc. Identify the number of Na^+ and Cl^- ions in the unit cell of sodium chloride illustrated in Fig. 4.1a and state how many formula units of NaCl the unit cell contains. Give a complete analysis.

4.3 The measured density of sodium chloride is 2.167 g cm^{-3}. From your answer to Problem 4.2 and your knowledge of the relationships among density, volume, Avogadro's

number, and formula weight, calculate the volume of the unit cell and thence the length of the edge of the cell. Calculate the length $r_+ + r_-$. Check your answer, $r_+ + r_-$, against values from Table 4.4.

4.4 Study Figs. 4.1–4.3 and convince yourself of the structural relatedness of all of the cubic structures and of all of the hexagonal structures.

4.5 The structure of diamond, a covalent crystal, is shown in Fig. 7.1. How is it related to some of the structures of ionic compounds discussed in this chapter?

4.6 What simple mathematical relationship exists between the empirical formula, numbers of cations and anions in the unit cell, and the coordination numbers of the cations and anions in a binary metal halide, M_aX_b?

4.7 If you did not do Problem 2.21 when you read Chapter 2, do so now.

4.8 One generalization of the descriptive chemistry of the transition metals is that the heavier congeners (e.g., Mo, W) more readily show the highest oxidation state than does the lightest congener (e.g., Cr). Discuss this in terms of ionization energies.

4.9 Show your understanding of the Born–Haber cycle by calculating the heat of formation of potassium fluoride analogous to the one in the text for sodium chloride.

4.10 Using any necessary data from appropriate sources, predict the enthalpy of formation of KCl by means of a Born–Haber cycle. You can check your lattice energy against Table 4.3.

4.11 Using any necessary data from appropriate sources, predict the enthalpy of formation of CaS by means of a Born–Haber cycle.

4.12 Show your understanding of the meaning of the Madelung constant by calculating A for the isolated $F^-Be^{2+}F^-$ fragment considered as a purely ionic species.

4.13 The ionic bond is often described as "the metal wants to lose an electron and the nonmetal wants to accept an electron, so the two react with each other." Criticize this statement quantitatively using appropriate thermodynamic quantities.

4.14 Why is the thermite reaction:

$$2Al + M_2O_3 = 2M + Al_2O_3 \quad (M = Fe, Cr, etc.) \tag{4.29}$$

so violently exothermic? (The ingredients start at room temperature and the metallic product, iron, etc., is *molten* at the end of the reaction.)

4.15 We have seen, in Chapter 2, that platinum hexafluoride has an electron affinity more than twice as great as fluorine. Yet when lithium metal reacts with platinum hexafluoride, the crystalline product is Li^+F^-, not $Li^+PtF_6^-$. Explain.

4.16 To ionize Mg to Mg^{2+} costs *two* times as much energy as to form Mg^+. The formation of O^{2-} is *endothermic* rather than exothermic as for O^-. Nevertheless, magnesium oxide is always formulated as $Mg^{2+}O^{2-}$ rather than as Mg^+O^-.

a. What theoretical reason can be given for the $Mg^{2+}O^{2-}$ formulation?

b. What simple experiment could be performed to prove that magnesium oxide was not Mg^+O^-?

4.17 Some experimental values of the Born exponent are: LiF, 5.9; LiCl, 8.0; LiBr, 8.7; NaCl, 9.1; NaBr, 9.5. What is the percent error incurred in the calculation of lattice energies by Eq. 4.13 when Pauling's generalization (He = 5, Ne = 7, etc.) is used instead of the experimental value of n?

4.18 Using Fig. 4.7 generate the first five terms of the series for the Madelung constant for NaCl. How close is the summation of these terms to the limiting value given in Table 4.1?

4.19 The enthalpy of formation of sodium fluoride is -571 kJ mol^{-1}. Estimate the electron affinity of fluorine. Compare your value with that given in Table 2.5.

4.20 Calculate the proton affinities of the halide ions. The enthalpies in question are those of the type:

$$X^- + H^+ \longrightarrow HX$$

Compare your values with those given in Table 9.5.

4.21 Perform radius ratio calculations to show which alkali halides violate the radius ratio rule.

4.22 Even if there are exceptions to the radius ratio rule, or if exact data are hard to come by, it is still a valid guiding principle. Cite three independent examples of pairs of compounds illustrating structural differences resulting from differences in ionic radii.

4.23 Berkelium is currently available in microgram quantities—sufficient to determine structural parameters but not enough for thermochemical measurements.

a. Using the tabulated ionic radii and the radius ratio rule, estimate the lattice energy of berkelium dioxide, BkO_2.

b. Assume that the radius ratio rule is violated (it is!). How much difference does this make in your answer?

4.24 The crystal structure of LaF_3 is different from those discussed. Assume it is unknown. Using the equation of Kapustinskii, estimate the lattice energy.

4.25 Copper(I) halides crystallize in a zinc blende structure. Copper(II) fluoride crystallizes in a distorted rutile structure (for the purposes of this problem assume there is no distortion). Calculate the enthalpies of formation of CuF and CuF_2. Discuss. (All of the necessary data should be readily available, but if you have difficulty finding a quantity, see how much of an argument you can make without it.)

4.26 Thallium has two stable oxidation states, +1 and +3. Use the Kapustinskii equation to predict the lattice energies of TlF and TlF_3. Predict the enthalpies of formation of these compounds. Discuss.

4.27 Plot the radii of the lanthanide(III) (Ln^{3+}) ions from Table 4.4 versus atomic number. Discuss.

4.28 All of the alkaline earth oxides, MO, except one crystallize in the rock salt (NaCl) structure. What is the exception and what is the likely structure for it? (Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; Oxford University: Oxford, 1984.)

4.29 It is not difficult to show mathematically that with the hard sphere model, anion–anion contact occurs at $r^+/r^- = 0.414$ for C.N. = 6. Yet Wells (*Structural Inorganic Chemistry*, 5th ed.; Oxford University: Oxford, 1984) states that even with the hard sphere model, we should not expect the change to take place until $r_+/r_- \simeq 0.35$. Rationalize this apparent contradiction. (Hint: Cf. Fig. 4.17.)

4.30 There exists the possibility that a certain circularity may develop in the radius ratio arguments on page 125. By assuming a coordination number of 6 were the calculations biased? Discuss.

4.31 Perform a calculation similar to that on page 127 for the formation of dioxygenyl hexafluoroplatinate(V):

$$O_2 + PtF_6 \longrightarrow O_2^+PtF_6^- \qquad (4.30)$$

All data (or approximations, if necessary) may be obtained from Chapters 2 and 4. Predict the enthalpy of reaction for this equation. Carefully note any assumptions you must make.

4.32 Repeat the calculation in Problem 4.31, but for the reaction:

$$Xe + PtF_6 \longrightarrow Xe^+PtF_6^- \qquad (4.31)$$

Should xenon react with platinum hexafluoride?

4.33 Suppose that someone argues with you that your answer to Problem 4.32 is invalid, and that any prediction that Neil Bartlett might have made on the basis of similar reasoning (see Chapter 17) is equally invalid—he was just lucky—the reaction product of Eq. 4.31 is not a simple ionic compound, $Xe^+PtF_6^-$, but a mixture of compounds, and apparently the xenon is *covalently* bound. What is your reply?

4.34 Calculate the enthalpy of the reaction $CuI_2 \rightarrow CuI + \frac{1}{2}I_2$. Carefully list any assumptions.

4.35 Which of the following will exhibit the greater polarizing power?

a. K^+ or Ag^+ **b.** K^+ or Li^+ **c.** Li^+ or Be^{2+}

d. Cu^{2+} or Ca^{2+} **e.** Ti^{2+} or Ti^{4+}

4.36 As one progresses across a transition series (e.g., Sc to Zn) the polarizing power of M^{2+} ions increases perceptibly. In contrast, in the lanthanides, the change in polarizing power of M^{3+} changes much more slowly. Suggest two reasons for this difference.

4.37 Some general chemistry textbooks say that if a fluorine atom, Z = 9, gains an electron, it will become a fluoride ion with ten electrons that cannot be bound as tightly (because of electron–electron repulsion) as the nine of the neutral atom, so the radius of the fluoride ion (119 pm) is much greater than the radius of the neutral fluorine atom (71 pm). Discuss and criticize.

4.38 If the addition of an electron $F + e^- \rightarrow F^-$ causes a great increase in size, why does not the addition of *two* electrons to form the oxide ion ($r_- = 126$ pm) cause it to be much larger than the fluoride ion ($r_- = 119$ pm)?

4.39 A single crystal of sodium chloride for an X-ray structure determination is a cube 0.3 mm on a side.

a. Using data from Table 4.4, calculate how many unit cells are contained in this crystal.

b. Compute the density of NaCl. Compare your value with that in a handbook.

4.40 There has been a recent flurry of interest in the possibility of "cold fusion" of hydrogen atoms (the deuterium isotope) in metallic palladium.[38] The original idea came from the enormous solubility of hydrogen gas in palladium. Palladium metal has an *fcc* lattice. Hydrogen atoms occupy the octahedral holes. If 70% of the octahedral holes are filled by hydrogen atoms and the lattice does not expand upon hydrogenation, how many grams of hydrogen will be contained in one cubic centimeter of the palladium hydride? Compare this to the density of liquid hydrogen in $g\,cm^{-3}$. Comment. (Rieck, D. F. *J. Chem. Educ.* **1989**, *66*, 1034.)

4.41 Mingos and Rolf[39] have discussed the packing of molecular ions in terms of their shape as well as size. Three indices, each ranging in value from 0.00 to 1.00, are used to describe the shape of an ion: the *spherical index*, F_s; the *cylindrical index*, F_c; and the *discoidal index*, F_d. Consider the following index values and try to correlate them with what you know of the shapes of the ions. If you are uncertain as to the shapes, refer to Chapters 6 and 12.

a. NH_4^+, NMe_4^+, BF_4^-, ClO_4^- (T_d), PF_6^-, and $OsCl_6^{3-}$ (O_h) all have values $F_s = 1.00$, $F_c = 0.00$, $F_d = 0.00$.

b. $Au(CN)_2^-$ and I_3^- ($D_{\infty h}$) have values $F_s = 0.00$, $F_c = 1.00$, $F_d = 1.00$.

c. $AuBr_4^-$, $PtCl_4^{2-}$ (D_{4h}) both have values $F_s = 0.00$, $F_c = 0.50$, $F_d = 1.00$, and $Ni(CN)_4^{2-}$ has values $F_s = 0.00$, $F_c = 0.54$, $F_d = 1.00$.

d. When it is trigonal bipyramidal (D_{3h}), $Ni(CN)_5^{3-}$ has values $F_s = 0.75$, $F_c = 0.25$, $F_d = 0.14$ but when it is square pyramidal (C_{4v}), the values are $F_s = 0.68$, $F_c = 0.16$, $F_d = 0.32$.

---

[38] Fleischmann, M.; Pons, S. *J. Electroanal. Chem.* **1989**, *261*, 301–308.

[39] Mingos, D. M. P.; Rolf, A. L. *Inorg. Chem.* **1991**, *30*, 3769–3771; *J. Chem. Soc. Dalton* **1991**, 3419–3425.

EXHIBIT D

International Union of Pure and Applied Chemistry

Division VIII Chemical Nomenclature and Structure Representation Division

Nomenclature of Organic Chemistry. IUPAC Recommendations and Preferred Names 2013.

Prepared for publication by Henri A. Favre and Warren H. Powell, Royal Society of Chemistry, ISBN 978-0-85404-182-4

Chapter P-7 RADICALS, IONS, AND RELATED SPECIES

P-70 INTRODUCTION

P-70.1 GENERAL METHODOLOGY.

The nomenclature for radicals, ions and related species is described in this Chapter. Its rules are based on the same principles as those of organic compounds defined in the Chapters P-1 to P-6. The nomenclature was revised in 1993 (ref. 3). For definitions, symbols and conventions, see ref. 14; see also ref. 28. In the 1979 recommendations (ref. 1), radicals were called 'free radicals' to distinguish them from substituent prefixes which were also called radicals. That distinction was dropped in the 1993 publications (refs. 2, 3).

P-70.2 SENIORITY OF RADICALS AND IONS

As classes, radicals and ions are senior to acids and other classes in the following order:

(1) radicals;
(2) anions;
(3) cations.

P-70.3 NAME FORMATION

Substitutive names and functional class names denote radicals and ions and related compounds. Parent hydrides and parent compounds are selected and modified by use of specific suffixes (called cumulative suffixes) and prefixes; traditional endings are used to describe anions derived from acids and related compounds (see P-72.2.2.2). The nomenclature of di- and trivalent radicals does not indicate nor imply an electronic structure or spin multiplicity.

P-70.3.1 Suffixes, prefixes, and endings for radicals and ions in substitutive nomenclature are listed in Table 7.1. They are also described in Table 3.4.

Table 7.1 Suffixes or Endings and Prefixes for Radicals and Ions in Substitutive Nomenclature

Operation	Suffix or Ending	Prefix
Radicals formed by		
loss of H•	yl	ylo
loss of 2 H•		
from one atom	ylidene	
from different atoms	diyl	
loss of 3 H•		
from one atom	ylidyne	
from different atoms	triyl or ylylidene	
addition of H•	hydryl	
Anions formed by		
loss of H^+	ide	
	ate, ite (endings)	
addition of H^-	uide	
addition of an electron	elide [1]	
Cations formed by		
loss of H^-	ylium	
addition of H^+	ium	
loss of an electron	elium [1]	

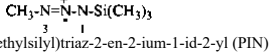
[1] The suffixes 'elide' and 'elium' are recommended to denote modification of a parent hydride by the addition or the subtraction of one electron, respectively.

P-70.3.2 Basic multiplying prefixes are used to denote multiplicity of the suffixes 'yl', 'ylidene', 'ylidyne', 'ide', 'uide', 'ium' and the prefix 'ylo'. Multiplying prefixes 'bis', 'tris', etc., are used before the suffix 'ylium' and before compound suffixes, such as 'aminium', 'olate', etc.

P-70.3.3 In names, suffixes and endings are cited in a specific order as described below.

P-70.3.3.1 When two or more cumulative suffixes are present in a name, the order of citation is the reverse of the order of seniority for radicals and ions as given in P-70.2, i.e.,'ium', 'ylium', 'ide', 'uide', 'yl', 'ylidene', 'ylidyne'.

Example:

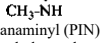


3-methyl-1-(trimethylsilyl)triaz-2-en-2-ium-1-id-2-yl (PIN)

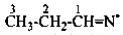
P-70.3.3.2 When functional and cumulative suffixes are present, the order of citation is prescribed by specific rules.

P-70.3.3.2.1 A cumulative suffix may be added to a functional suffix to form a defined compound suffix (see P-71.3.2).

Examples:



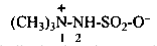
methanaminyl (PIN)
methylazanyl
(traditional name: methylamino)



propan-1-iminyl (PIN)
propylideneazanyl

P-70.3.3.2.2 In zwitterionic compounds, cumulative suffixes precede functional suffixes and have seniority for lowest locants:

Example:



1,1,1-trimethylhydrazin-1-ium-2-sulfonate (PIN)

P-70.4 GENERAL RULES FOR THE SELECTION OF PREFERRED NAMES

The concept of preferred IUPAC names as applied to radicals and ions is based on the following principles.

(1) substitutive nomenclature based on carbane and heterane nomenclatures and a set of suffixes and prefixes designed to express the formal operations needed to generate radicals and ions systematically are used to generate preferred IUPAC names; accordingly, the preferred IUPAC name for a radical may not be the same as the preferred prefix.

(2) some names are retained as preferred IUPAC names, notably contracted names such as methoxide, ethoxide, etc., and methoxyl, ethoxyl, etc. related to the substitutive prefixes derived from alcohols and related hydroxy compounds.

(3) some names are retained only for use in general nomenclature, for example the 'onium cations' such as ammonium and sulfonium, carbene, $CH_2^{2\bullet}$; amide, NH_2^-; and $CH_3\text{-}C(O)^-$, acetyl anion.

(4) functional class names using class names such as cation, anion, etc. can be used in general nomenclature, but systematically constructed names or retained names are preferred IUPAC names, for example, 'methylium' not 'methyl cation', for CH_3^+; 'acetylium' not 'acetyl cation' for $CH_3\text{-}C(O)^+$; 'ethanide' not 'ethyl anion' for $CH_3\text{-}CH_2^-$; and 'methaniumyl' not 'methyl radical cation', for $CH_4^{\bullet+}$.

P-71 RADICALS

P-71.1 GENERAL METHODOLOGY

Radicals are named by modifying a parent hydride name to signal the subtraction or addition of one or more hydrogen atoms, H•. The modification to signal the addition of a single hydrogen atom is recommended for the first time. These two operations are expressed by suffixes.

The suffixes 'yl' (–H•), 'ylidene' (–2H•), 'ylidyne' (–3H•) denote the removal of hydrogen atoms, a subtractive operation.

The suffix 'hydryl' denotes the additive operation, i.e., the addition of a single hydrogen atom.

The prefix 'ylo' is used to indicate the removal of 'H•' from a substituent group, a subtractive operation.

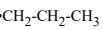
P-71.2 RADICALS DERIVED FROM PARENT HYDRIDES

P-71.2.1 Monovalent radicals.

P-71.2.1.1 A radical formally derived by the removal of one hydrogen atom from a mononuclear parent hydride of an element of Group 14, from a terminal atom of an unbranched acyclic hydrocarbon, or from any position of a monocyclic saturated hydrocarbon ring is named by replacing the 'ane' ending of the systematic name of the parent hydride by 'yl'.

Examples:

methyl (PIN)



propyl (PIN)

germyl (preselected name)

cyclobutyl (PIN)

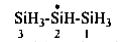
P-71.2.1.2 A radical formally derived by the removal of one hydrogen atom from any position of a parent hydride, or a modified parent hydride other than those described by P-71.2.1.1, above, is named by adding the suffix 'yl' to the name of the parent hydride, eliding the final letter 'e' of the name of the parent hydride, if any. As an exception, the IUPAC preferred name for HO• is 'hydroxyl', a retained name for the systematic name 'oxidanyl' (see ref. 12, IR-6.4.7); and the IUPAC preferred name for HOO• is 'hydroperoxyl', a retained name for the systematic name 'dioxidanyl'. These retained names must not be used when substituted, for example, $CH_3\text{-}O\bullet$ is named 'methoxyl' or 'methyloxidanyl', and not 'methylhydroxyl' (see P-71.3.4).

Examples:

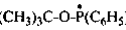
sulfanyl (preselected name)

azanyl (preselected name)
aminyl (traditional name: amino)

boranyl (preselected name)
(not boryl)

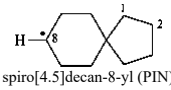


trisilan-2-yl (preselected name)



tert-butoxytri(phenyl)-λ^5-phosphanyl (PIN)
[(2-methylpropan-2-yl)oxy]tri(phenyl)-λ^5-phosphanyl
(1,1-dimethylethoxy)tri(phenyl)-λ^5-phosphanyl

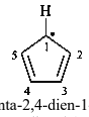
bicyclo[2.2.1]heptan-2-yl (PIN)



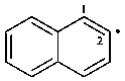
spiro[4.5]decan-8-yl (PIN)

propan-2-yl (PIN)
1-methylethyl
isopropyl

2-methylpropan-2-yl (PIN)
1,1-dimethylethyl
tert-butyl [see P-70.4 (1)]



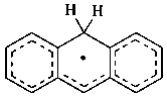
cyclopenta-2,4-dien-1-yl (PIN)
cyclopentadienyl (see P-76)



naphthalen-2-yl (PIN)

P-71.2.1.3 A radical created by the addition of a single hydrogen atom, H•, may be indicated by suffix 'hydryl' when the position of the hydrogen atom must be specified:

Example:



anthracene-9-hydryl (PIN)
anthracen-9-iumelide (see P-70.3.1)
anthracen-9-eliumuide (see P-70.3.1)
2,9-dihydroanthracen-2-yl

P-71.2.2 Divalent and trivalent radicals.

The names of divalent and trivalent radicals are formed substitutively using the suffixes 'ylidene' and 'ylidyne' in two ways:

(1) replacing the ending 'ane' of a mononuclear parent hydride of an element of Group 14, or from a terminal atom of an unbranched acyclic hydrocarbon, or from any position of a monocyclic saturated hydrocarbon ring by the appropriate suffix (corresponds to P-71.2.1.1)

(2) adding the appropriate suffix to the name of a parent hydride, other than those described by P-71.2.1.1, at any position eliding the final letter 'e' of the name of the parent hydride, if any (corresponds to P-71.2.1.2).

These systematic names are preferred to retained names which may be used in general nomenclature.

P-71.2.2.1 Specific method and retained names

A radical formally derived by the removal of two hydrogen atom from one skeletal atom of a mononuclear parent hydride of an element of Group 14, or from one terminal skeletal atom of an unbranched acyclic hydrocarbon, or from one skeletal atom of a monocyclic saturated hydrocarbon ring is named by replacing the 'ane' ending of the systematic name of the parent hydride by the suffix '-ylidene' or '-diyl'. The suffix '-ylidyne' or '-triyl' is used to name radicals formally derived by the removal of three hydrogen atoms from a mononuclear parent hydride of an element of Group 14 or from a terminal atom of an unbranched acyclic hydrocarbon.

Systematic names are the preferred IUPAC names. The retained names carbene or methylene, nitrene or aminylene and carbyne, can be used in general nomenclature, with full substitution. The use of the systematic or retained names does not imply a specific electronic configuration. If needed, such a distinction would be made by using a separate word such as singlet or triplet, or a descriptive phrase. The disposition of the two unpaired electrons in the structures is equivalent to that given in the Red Book as $CH_2^{2\bullet}$ (see ref. 12, IR-6.4.7).

Examples:

methylidene (PIN)
carbene
methylene

silylidene (preselected name)
silanediyl
(not silylene)

methylidyne (PIN)
methanetriyl
carbyne

diphenylmethylidene (PIN)
diphenylmethanediyl
diphenylcarbene
diphenylmethylene

benzylsilylidene (PIN)
benzylsilanediyl

cyclohexylidene (PIN)
cyclohexane-1,1-diyl

ethylidyne (PIN)
ethane-1,1,1-triyl
(not methylcarbyne)

P-71.2.2.2 General method

With the exception of the radicals named in P-71.2.2.1, the names of divalent and trivalent radicals derived by the removal of two or three hydrogen atoms from one position of a parent hydride are formed by adding the suffixes '-ylidene' or '-diyl' and '-ylidyne' or '-triyl', respectively, to the name of the parent hydride, with elision of the final letter 'e', if present. The name azanylidene is the preselected name for $HN^{2\bullet}$; nitrene or aminylidene are retained names for use in general nomenclature.

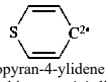
Examples:

$HN^{2\bullet}$
azanylidene (preselected name)
azanediyl
aminylidene
aminylene
nitrene

$H_2P^{3\bullet}$
λ^5-phosphanylidyne (preselected name)
λ^5-phosphanetriyl
phosphoranylidyne
phosphoranetriyl

$H_2N\text{-}N^{2\bullet}$
hydrazinylidene (preselected name)
diazanylidene
hydrazine-1,1-diyl
diazane-1,1-diyl
(traditional name: hydrazono)
(not aminonitrene)

$H_2P\text{-}P^{2\bullet}$
diphosphanylidene (preselected name)
diphosphane-1,1-diyl



4*H*-thiopyran-4-ylidene (PIN)
4*H*-thiopyran-4,4-diyl

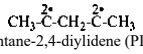
P-71.2.3 Multiple radical centers (polyradicals)

Polyradicals containing two or more radicals centers, formally derived by the removal of two or more hydrogen atoms from each of two or more different skeletal atoms of a parent hydride, are named by adding to the name of the parent hydride combinations of the suffix 'yl' for a monovalent radical center, 'ylidene' for a divalent radical center, and 'ylidyne' for a trivalent radical center, together with the appropriate numerical prefixes indicating the number of each kind of radical center. The final letter 'e' of the name of the parent hydride, if present, is elided when followed by 'y'. All substituents, including characteristic groups, when present, are cited as prefixes. Preferred IUPAC names result from the application of this rule.

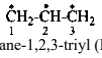
Examples:

ethane-1,2-diyl (PIN)
(traditional name: ethylene)

hydrazine-1,2-diyl (preselected name)
diazane-1,2-diyl

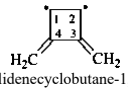


pentane-2,4-diylidene (PIN)

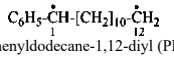


propane-1,2,3-triyl (PIN)

benzene-1,4-diyl (PIN)
{traditional names: *p*-phenylene;
1,4-phenylene [see P-70.4 (1)]}



3,4-dimethylidenecyclobutane-1,2-diyl (PIN)



1-phenyldodecane-1,12-diyl (PIN)

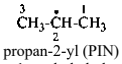
P-71.2.4 Acyclic radicals derived by the removal of one or more hydrogen atoms from nonterminal chain positions are named in two ways:

(1) by citing the locant of the nonterminal position of the chain

(2) by substituting a parent radical that has the free valence(s) at the end of a chain.

Method (1) generates preferred IUPAC names. The principal chain is chosen, if necessary, by the method indicated in Section P-46 for substituent groups.

Example:



propan-2-yl (PIN)
1-methylethyl

P-71.2.5 The λ-convention

Divalent and trivalent radical centers in a parent hydride formally derived by the removal of two or three hydrogen atoms from the same skeletal atom in its standard valence state may be described by the λ-convention (see P-14.1). Locants for the radical centers are followed by the symbol λ^n, where '*n*' is the bonding number of the skeletal atom (see P-14.1). This method is only for general nomenclature.

Examples:

$Cl_2C^{2\bullet}$
dichloro-λ^2-methane
dichloromethylidene (PIN)
dichloromethanediyl

$FC^{3\bullet}$
fluoro-λ^1-methane
fluoromethylidyne (PIN)
fluoromethanetriyl

$C_6H_5\text{-}N^{2\bullet}$
phenyl-λ^1-azane
benzenaminylidene (PIN)
phenylazanediyl

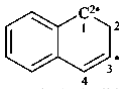
P-71.2.6 'Added indicated hydrogen' for radicals of mancude ring systems

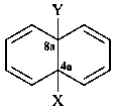
A radical center at a position in a mancude parent hydride where there is an insufficient number of hydrogen atoms to apply directly the recommendations for the use of 'yl' or 'ylidene' given in P-71.2.1 and P-71.2.2 is derived formally from a dihydro derivative of the cyclic parent hydride. Such a radical can also be described by applying the principle of 'added indicated hydrogen' (see P-14.7 and P-58.2). In this method the 'hydro' derivative is described by specifying the hydrogen atom of a dihydro pair that remains after the radical center is created, by citing in italic capital *H* and the locant of the skeletal atom to which the hydrogen atom resides, both enclosed in a set of parentheses and inserted into the name of the corresponding parent hydride immediately after the locant for the radical center.

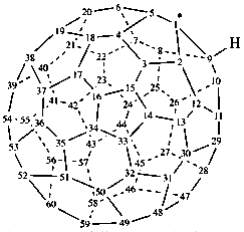
Names formed by the 'added indicated hydrogen' method are preferred to names using 'hydro' prefixes (see P-58.2.5).

Examples:


1,3-thiazol-3(2*H*)-yl (PIN)
2,3-dihydro-1,3-thiazol-3-yl
(nondetachable hydro prefixes, see P-58.2.5)


naphthalen-3-yl-1(2*H*)-ylidene (PIN)
1,2-dihydronaphthalen-3-yl-1-ylidene
(nondetachable hydro prefixes; see P-58.2.5)


X = •; Y = H
naphthalen-4a(8a*H*)-yl (PIN)
4a,8a-dihydronaphthalen-4a-yl
(nondetachable hydro prefixes, see P-58.2.5)
X = •; Y = •
naphthalene-4a,8a-diyl (PIN)
4a,8a-dihydronaphthalene-4a,8a-diyl
(nondetachable hydro prefixes, see P-58.2.5)


(C_{60}-I_h)[5,6]fulleren-1(9*H*)-yl (PIN)
1,9-dihydro(C_{60}-I_h)[5,6]fulleren-1-yl
(nondetachable hydro prefixes, see P-58.2.5)

P-71.3 RADICAL CENTERS ON CHARACTERISTIC GROUPS

P-71.3.1 Acyl radicals

Acyl radicals, i.e., radicals with at least one chalcogen or nitrogen atom attached to a radical center by a (formal) double bond, which may be considered to be formally derived by the removal of a hydroxy group from acid characteristic groups, are named by replacing the 'ic acid' or 'carboxylic acid' ending of the name of the acid with 'oyl' or 'yl', or 'carbonyl', according to the method for forming names of acyl groups (see P-65.1.7). Substituent groups denoted by prefixes such as 'oxo', 'thioxo', 'sulfanylidene', etc., may be used in general nomenclature.

Compound acyl radicals formed from acyclic parent hydrocarbons and substituent prefixes such as 'oxo', 'thioxo', 'sulfanylidene', and 'imino' can be used in general nomenclature; they are used in CAS index nomenclature.

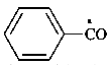
Examples:

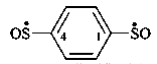
$CH_3\text{-}[CH_2]_4\text{-}\dot{C}O$
hexanoyl (PIN)
1-oxohexyl

$(CH_3)_2\dot{P}O$
dimethylphosphinoyl (PIN)
dimethyl(oxo)-λ^5-phosphanyl

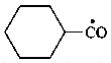
$CH_3\text{-}\dot{C}S$
ethanethioyl (PIN)
1-sulfanylideneethyl
1-thioxoethyl

$CH_3\text{-}CH_2\text{-}CH_2\text{-}\dot{C}(=NH)$
butanimidoyl (PIN)
1-iminobutyl

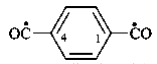

benzoyl (PIN)
benzenecarbonyl



benzene-1,4-disulfinyl (PIN)
(1,4-phenylene)bis(oxo-λ^4-sulfanyl)



cyclohexanecarbonyl (PIN)
cyclohexyl(oxo)methyl



benzene-1,4-dicarbonyl (PIN)
terephthaloyl
(1,4-phenylene)bis(oxomethyl)

P-71.3.2 A radical derived formally by the removal of hydrogen atoms from an amine, imine, or amide characteristic group is named by adding the appropriate cumulative suffix '-yl' or '-ylidene' to the basic suffix as shown here. This method is preferred to that using parent such as 'azanyl', and 'nitrene', or the functional modifier 'imidyl' in functional class nomenclature.

Table 7.2 Suffixes for Radicals of Amines, Imines and Amides

$-NH_2$	amine (preselected suffix)	$-\dot{N}H$	aminyl (preselected suffix)
		$-N^{2\bullet}$	aminylidene (preselected suffix)
=NH	imine (preselected suffix)	=N•	iminyl (preselected suffix)
$-(C)O-NH_2$	amide (preferred suffix)	$-(C)O-\dot{N}H$	amidyl (preferred suffix)
		$-(C)O-N^{2\bullet}$	amidylidene (preferred suffix)
$-CO-NH_2$	carboxamide (preferred suffix)	$-CO-\dot{N}H$	carboxamidyl (preferred suffix)
		$-CO-N^{2\bullet}$	carboxamidylidene (preferred suffix)

Examples:

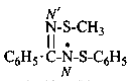
$CH_3-\dot{N}H$
methanaminyl (PIN)
methylazanyl
methylaminyl
(traditionally: methylamino)

$\overset{3}{C}H_3-\overset{2}{C}H_2-\overset{1}{C}H=N^{\bullet}$
propan-1-iminyl (PIN)
propylideneazanyl

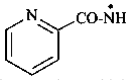
$C_6H_5-\dot{N}H$
benzenaminyl (PIN)
phenylaminyl
phenylazanyl
(traditionally: phenylamino)
(not anilino)

$(CH_3)_3P=N^{\bullet}$
trimethyl-λ^5-phosphaniminyl (PIN)
trimethylphosphane imidyl

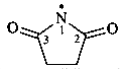
$H\dot{C}O-NH$
formamidyl (PIN)
formylazanyl
formylaminyl



N′-(methylsulfanyl)-*N*-(phenylsulfanyl)benzenecarboximidamidyl (PIN)



pyridine-2-carboxamidyl (PIN)



2,5-dioxopyrrolidin-1-yl (PIN)
succinimidyl

$C_6H_5-N^{2\bullet}$
benzenaminylidene (PIN)
phenylnitrene
phenylaminylene

$CH_3-CO-N^{2\bullet}$
acetamidylidene (PIN)
acetylnitrene
acetylaminylene

P-71.3.3 Polyamine, polyimine and polyamide radicals

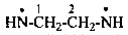
Polyradicals with radical centres identically derived but located on two or more amine, imine, or amide characteristic groups are named in two ways:

(1) by using suffixes (see P-71.3.2) denoting the removal of one hydrogen atom from each characteristic group and the multiplying prefixes 'bis-', 'tris-', etc.;

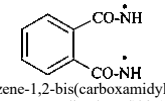
(2) by multiplicative nomenclature based on the parent radicals 'azanyl' and 'azanylidene'.

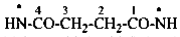
In order to avoid any confusion, the name 'aminyl' is reserved for denoting the suffix in substitutive nomenclature; the parent radical 'azanyl' (not 'aminyl') is used in multiplicative nomenclature. Method (1) leads to preferred IUPAC names when a suffix described in P-71.3.2 is available.

Examples:


(1) (ethane-1,2-diyl)bis(aminyl) (PIN)
(2) ethane-1,2-diylbis(azanyl)

(1) methanebis(iminyl) (PIN)
(2) methanediylidenebis(azanyl)


(1) benzene-1,2-bis(carboxamidyl) (PIN)
(2) (benzene-1,2-dicarbonyl)bis(azanyl)


(1) butanebis(amidyl) (PIN)
(2) butanedioylbis(azanyl)

(1) hexanebis(amidylidene) (PIN)
(2) hexanedioylbis(azanylidene)
hexanedioylbis(aminylidene)
hexanedioylbis(nitrene)

P-71.3.4 A radical derived formally by the removal of the hydrogen atom of a hydroxy group (or chalcogen analogue) of an acid or hydroxy characteristic group is named in two ways:

(1) additively, using the term 'oxyl' or 'peroxyl' derived from the terms 'oxy' or 'peroxy' (not dioxy);

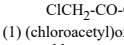
(2) by substituting the parent radicals 'oxidanyl' (preselected name), for HO•, or 'dioxidanyl' (preselected name), for HOO•, by the appropriate substituent groups.

The names methoxyl, ethoxyl, propoxyl, butoxyl, *tert*-butoxyl, phenoxyl, and aminoxyl, which may be considered as contractions of the systematically formed names, such as methanyloxyl or methyloxyl, are retained and are preferred IUPAC names (see P-63.2.2.2 for names such as methoxy, ethoxy, etc.).

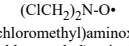
Method (1) generates preferred IUPAC names.

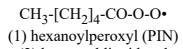
Examples:

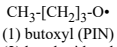

(1) methoxyl (PIN)
(2) methyloxidanyl

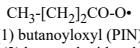

(1) (chloroacetyl)oxyl (PIN)
chloroacetoxyl
(2) (chloroacetyl)oxidanyl


aminoxyl (preselected name;
a contraction of aminooxyl)


(1) bis(chloromethyl)aminoxyl (PIN)
(2) [bis(chloromethyl)amino]oxidanyl


(1) hexanoylperoxyl (PIN)
(2) hexanoyldioxidanyl


(1) butoxyl (PIN)
(2) butyloxidanyl

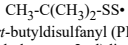

(1) butanoyloxyl (PIN)
(2) butanoyloxidanyl

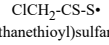
Chalcogen analogues are named on the basis of preselected parent radical names, such as 'sulfanyl', 'selanyl', 'disulfanyl', etc.

Examples:


phenylsulfanyl (PIN)
(not benzenesulfenyl;
sulfenic acids are no longer recognized; see P-56.2)


methylselanyl (PIN)

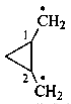

tert-butyldisulfanyl (PIN)
(2-methylpropan-2-yl)disulfanyl

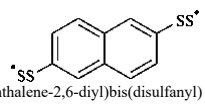

(chloroethanethioyl)sulfanyl (PIN)

P-71.4 ASSEMBLIES OF PARENT RADICALS

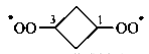
Polyradicals with radical centers identically derived from the same parent hydride or the same characteristic group (except for polyacyl or polyamide radicals described in P-71.3.1 and P-71.3.3, respectively) but located in different parts of the structure are named, if possible, according to the principles for nomenclature of assemblies of identical units linked by multivalent substituents (see P-15.3).

Examples:


(cyclopropane-1,2-diyl)dimethyl (PIN)


(naphthalene-2,6-diyl)bis(disulfanyl) (PIN)

•O-C(CH_3)$_2$-CH_2-C(CH_3)$_2$-O•
(1) (2,4-dimethylpentane-2,4-diyl)bis(oxyl) (PIN)
(1,1,3,3-tetramethylpropane-1,3-diyl)bis(oxyl)
(2) (2,4-dimethylpentane-2,4-diyl)bis(oxidanyl)



(1) (cyclobutane-1,3-diyl)bis(peroxyl) (PIN)
(2) (cyclobutane-1,3-diyl)bis(dioxidanyl)

P-71.5 PREFIXES DENOTING RADICALS

The presence of a radical center in a substituent that is to be cited as a prefix is expressed in two ways:

(1) by using the prefix 'ylo' that indicates the subtraction of a hydrogen atom from a substituent group, for example '–ylomethyl' for –CH_2•;

(2) by concatenation of prefixes, for example 'oxylcarbonyl' for –CO-O•.

This prefix is a nondetachable prefix, attached to the parent substituent prefix, which is formed by usual methods. The presence of two or more radical centers in a substituent cited as a prefix or the removal of two or more hydrogen atoms from a substituent cited as prefix is indicated by the appropriate multiplying prefix, 'di', 'tri', etc.

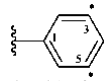
Examples:

ylomethyl (preferred prefix)

ylooxidanyl (preselected prefix)
ylooxy
(not ylohydroxy)

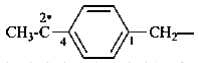
yloformyl (preferred prefix)

oxylcarbonyl (preferred prefix)
(ylooxidanyl)formyl



3,5-diylophenyl (preferred prefix)

yloamino (preselected prefix)
yloazanyl



[4-(1,1-diyloethyl)phenyl]methyl (preferred prefix)

P-71.6 ORDER OF CITATION AND SENIORITY OF SUFFIXES 'YL', 'YLIDENE', AND 'YLIDYNE'

The suffixes 'yl', 'ylidene', and 'ylidyne' are cited in that order in a name, if applicable; lowest locants are assigned to radicals as a set, then in the order 'yl', 'ylidene' and 'ylidyne'. The order of citation is identical to that used for naming substituent groups (see P-29.3.2.2).

Example:

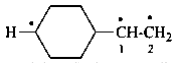
•CH_2-$CH^{2•}$
ethan-1-yl-2-ylidene (PIN)

P-71.7 CHOICE OF PARENT RADICAL

When a choice of a parent radical is necessary, the following criteria are applied, in the order given, until a decision is reached.

(a) Parent with the maximum number of radical centers of any kind in a single parent structure:

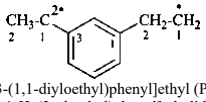
Example:



1-(4-ylocyclohexyl)ethane-1,2-diyl (PIN)
[not 4-(1,2-diyloethyl)cyclohexyl;
ethane has two radical centres, cyclohexane only has one]

(b) Parent with the maximum number of '-yl' radical centers, then -ylidene radical centers;

Example:



2-[3-(1,1-diyloethyl)phenyl]ethyl (PIN)
{not 1-[3-(2-yloethyl)phenyl]ethylidene;
ethyl is senior to ethylidene}

(c) Parent with the maximum number of radical centers at the skeletal atom first cited in the seniority order of classes: N > P > As > Sb > Bi > Si > Ge > Sn > Pb > B > Al > Ga > In > Tl > O > S > Se > Te > C (see P-44.1.2)

The seniority order for radicals is now the order of seniority of classes rather than the order of skeletal replacement ('a') prefixes as used in RC-81.3.3.2, ref. 3.

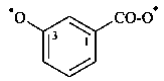
Example:

•CH_2-C(CH_3)$_2$-O•
(2-methyl-1-ylopropan-2-yl)oxyl (PIN)
(1,1-dimethyl-2-yloethyl)oxidanyl
(not 2-methyl-2-ylooxidanylpropyl;
oxyl is senior to propyl)

(d) Further choice, if necessary, is made by giving priority to the corresponding suffixes (see Table 4.4) and by using the general seniority order of classes (see P-41) and parent structures (see P-44).

(1) maximum number of radical centers according to the order of suffixes (see P-33).

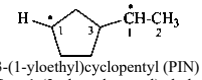
Example:



[3-(ylooxidanyl)benzoyl]oxyl (PIN)
[3-(ylooxidanyl)benzoyl]oxidanyl
{not 3-[(ylooxidanyl)carbonyl]phenoxyl;
ylooxidanyl is senior to phenoxyl}

(2) rings are senior to chains

Example:



3-(1-yloethyl)cyclopentyl (PIN)
[not 1-(3-ylocyclopentyl)ethyl;
cyclopentyl is senior to ethyl]

P-72 ANIONS

P-72.1 GENERAL METHODOLOGY

Anions are named in two ways:

(1) by using suffixes and endings;

(2) by functional class nomenclature.

Method (1) leads to preferred IUPAC names. Some names and some contracted names are retained as preferred IUPAC names and for use in general nomenclature.

The following suffixes are used:

‘ide’ (preferred suffix; corresponding to removal of a hydron, H^+),

‘uide’ (preferred suffix; corresponding to the addition of a hydride ion, H^-),

‘elide’ (preferred suffix; corresponding to the addition of an electron)

The endings ‘ate’ and ‘ite’ are used to indicate removal of a hydron from the –OH group of acids and hydroxy compounds.

Functional class nomenclature is based on the class name ‘anion’ in association with the name of the corresponding radical (not necessarily the name of the corresponding substituent group).

P-72.2 ANIONS FORMED BY REMOVAL OF HYDRONS

P-72.2.1 Functional class nomenclature

Functional class nomenclature can be used, in general nomenclature, to describe anionic compounds. An anion that can be considered as derived formally by adding an electron to a radical may also be named by adding the class name ‘anion’ as a separate word to the name of the substituent group. The names are formed by using the names of corresponding radicals (not necessarily the name of substitutent groups) and the class name ‘anion’ as a separate word. The multiplying prefixes ‘di’, ‘tri’, etc., are added to the class name to denote multiple anions. This type of nomenclature is limited to anions having anionic centers in the same structure. Systematic names (see P-72.2.2) are preferred IUPAC names.

Examples:

H_3C^- methyl anion
methanide (PIN)

acetyl anion
1-oxoethan-1-ide (PIN)

benzenesulfinyl anion
oxo(phenyl)-λ^4-sulfanide (PIN)

CH_3-NH^-
methanaminyl anion
methanaminide (PIN)

$(C_6H_5)_2C^{2-}$
diphenylmethylidene dianion
diphenylmethanediide (PIN)

phenyl anion
benzenide (PIN)

cyclopenta-2,4-dien-1-yl anion
cyclopenta-2,4-dien-1-ide (PIN)
cyclopentadienide (see P-76)

P-72.2.2 Systematic nomenclature

P-72.2.2.1 Anions derived from parent hydrides and their derivatives

An anion derived formally by the removal of one or more hydrons from any position of a neutral parent hydride is preferably named by using the suffix '-ide', with elision of the final letter 'e' of the parent hydride, if any. Numerical prefixes 'di', 'tri', etc. are used to denote multiplicity; locants identify positions of the negative charges.

The name 'acetylide', for $^{-}C{\equiv}C^{-}$, is retained for general use only.

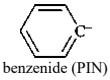
Examples:

$(NC)_3C^-$
tricyanomethanide (PIN)

$(C_6H_5)_2C^{2-}$
diphenylmethanediide (PIN)

$(CH_3)_2P^-$
dimethylphosphanide (PIN)
dimethylphosphinide

$HC{\equiv}Si^-$
methylidynesilanide (PIN)


benzenide (PIN)


cyclopenta-2,4-dien-1-ide (PIN)
cyclopentadienide (see P-76)

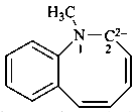
$^{-}C{\equiv}C^{-}$
ethynediide (PIN)
acetylide

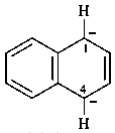
P-72.2.2.1.1 'Added indicated hydrogen' for anions of mancude ring systems

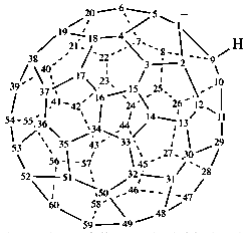
An anionic center at a position in a mancude parent hydride where there is an insufficient number of hydrogen atoms to apply directly recommendations for the use of 'ide' given in P-72.2.2.1 is derived formally from a dihydro derivative of the cyclic parent hydride. Such an anion can also be described by applying the principle of 'added indicated hydrogen' (see P-14.7). In this method the 'hydro' derivative is described by specifying the hydrogen atom of a dihydro pair that remains after the anionic center is created by citing in italic capital *H* and the locant of the skeletal atom at which the hydrogen atom resides, both enclosed in a set of parentheses and inserted into the name of the corresponding parent hydride immediately after the locant for the anionic center. Names formed by the 'added indicated hydrogen' method are preferred IUPAC names (see P-58.2).

Examples:


pyridin-1(2*H*)-ide (PIN)
1,2-dihydropyridine-1-ide


1-methyl-1-benzazocine-2,2(1*H*)-diide (PIN)
1-methyl-1,2-dihydro-1-benzazocine-2,2-diide


1,4-dihydronaphthalene-1,4-diide (PIN)


(C_{60}-I_h)[5,6]fulleren-1(9*H*)-ide (PIN)
1,9-dihydro(C_{60}-I_h)[5,6]fulleren-1-ide

P-72.2.2.2 Anions derived from characteristic groups are assigned IUPAC preferred names that are retained names or derived as follows:

(1) for acids, alcohols and amines by modifying the normally used in substitutive nomenclature:

(a) the endings 'ate' or 'ite' to name anions derived from acids;

(b) the ending 'ate' to name anions derived from alcohols,

(c) the suffix 'aminide' (formed by adding 'ide' to the suffix of the corresponding amine with elision of the final 'e' of 'amine', i.e., 'amin(e) + ide') to name anions derived from amines where the negative charge is on the nitrogen atom;

(2) by the appropriate preselected anionic parent names in the case of other characteristic groups, such as 'azanide' for NH_2^-, 'azanediide' for NH^{2-}, 'oxidanide' for HO^-.

(3) amides, hydrazides and imides are not named directly by method (1), as are amines and imines; the reason being that there could be real ambiguity to have the suffix 'ide' used at the end of names such as amide, hydrazides, etc.

Method (2) generates preferred names. Also, the name 'amide', which may be used in general nomenclature to designate the parent anion NH_2^-, would result in a certain degree of ambiguity. However, the use of parents 'azanide' and 'azanediide' eliminates all possible ambiguity.

P-72.2.2.2.1 Anions derived from acids
P-72.2.2.2.2 Anions derived from hydroxy compounds

P-72.2.2.2.1 Anions derived from acids

P-72.2.2.2.1.1 The preferred IUPAC name of anions formed by the removal of a hydron from the chalcogen atom (O, S, Se, and Te) of an acid or peroxyacid characteristic group or functional parent compound is formed by replacing the 'ic acid' or 'ous acid' ending of the acid name by 'ate' or 'ite', respectively. Names of acids are described in Sections P-65 and P-67.

This is a change from recommendation RC-83.1.6 (ref. 3) in which peroxyacids and their chalcogen analogues modified by functional replacement were named on the basis of an anionic parent hydride.

Examples:

$CH_3CO\text{-}O^-$
acetate (PIN)

$CH_3\text{-}CH_2\text{-}CO\text{-}O\text{-}O^-$
propaneperoxoate (PIN)

$CH_3\text{-}CS\text{-}O\text{-}O^-$
ethaneperoxothioate (PIN)
(ethanethioyl)dioxidanide
(thioacetyl)dioxidanide

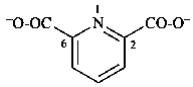
$CH_3\text{-}CO\text{-}O\text{-}S^-$
ethane(*OS*-thioperoxoate) (PIN)
(acetyloxy)sulfanide
(not acetoxysulfanide)

$CH_3\text{-}CH_2\text{-}CO\text{-}S^- \leftrightarrow CH_3\text{-}CH_2\text{-}CS\text{-}O^-$
propanethioate (PIN)

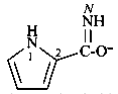
$CH_3\text{-}CO\text{-}S^- \leftrightarrow CH_3\text{-}CS\text{-}O^-$
ethanethioate (PIN)

$C_6H_5\text{-}SO_2\text{-}O^-$
benzenesulfonate (PIN)

$(C_6H_5\text{-}CH_2)_2P\text{-}O^-$
dibenzylphosphinite (PIN)



pyridine-2,6-dicarboxylate (PIN)



1*H*-pyrrole-2-carboximidate (PIN)

P-72.2.2.2.1.2 Acid esters of organic acids

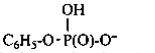
Preferred IUPAC names of acid esters of 'organic acids' as discussed in P-65 are formed substitutively (see P-65.6.3.3.5) rather than by the method of 'hydrogen salts'. Preferred IUPAC names of acid esters of inorganic acids as discussed in P-67.1.3.2 are formed by the method of 'hydrogen salts'; see P-65.6.2.3 and P-65.6.3.3.5.

Examples:

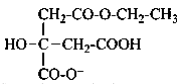
$HOOC\text{-}[CH_2]_4\text{-}CO\text{-}O^-$
5-carboxypentanoate (PIN)
hydrogen hexanedioate

$C_6H_5\text{-}P(O)(OH)\text{-}O^-$
hydrogen phenylphosphonate (PIN)
[not hydroxy(phenyl)phosphinate;
phosphonic acid is senior to phosphinic acid]

$CH_3\text{-}CH_2\text{-}O\text{-}CO\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}O^-$
4-ethoxy-4-oxobutanoate (PIN)
ethyl butanedioate
ethyl succinate



phenyl hydrogen phosphate (PIN)



2-(carboxymethyl)-4-ethoxy-2-hydroxy-4-oxobutanoate (PIN)
4-ethyl 2-(carboxymethyl)-2-hydroxybutanedioate
3-ethyl 1-hydrogen citrate
4-hydrogen 2-(2-ethoxy-2-oxoethyl)-2-hydroxybutanedioate

P-72.2.2.2.2 Anions derived from hydroxy compounds

An anion formed by subtracting a hydron from the chalcogen atom of a hydroxy characteristic group, or a chalcogen analogue, that can be expressed by a suffix such as 'ol', 'thiol', 'peroxol', etc., is preferably named by using suffixes 'olate', 'thiolate', 'peroxolate', etc., formed by addition of the ending 'ate' to the suffixes 'ol', 'thiol', 'peroxol', etc. The multiplying prefixes 'bis', 'tris', etc. are used before these suffixes, to avoid any ambiguity.

The retained names hydroxide, for HO^-, and hydroperoxide, for HOO^-, are preseleted names but cannot be substituted; thus, for $CH_3\text{-}O^-$ and $CH_3\text{-}OO^-$ the names are methoxide or methanolate or methyloxidanide, and methaneperoxolate or methyldioxidanide, respectively.

The traditional names methoxide, ethoxide, propoxide, butoxide, *tert*-butoxide, phenoxide (but not isopropoxide), and aminoxide, for $CH_3\text{-}O^-$, $C_2H_5\text{-}O^-$, $C_3H_7\text{-}O^-$, $C_4H_9\text{-}O^-$, $(CH_3)_3C\text{-}O^-$, $C_6H_5\text{-}O^-$, and $H_2N\text{-}O^-$, are retained as preferred IUPAC names or preselected name. *tert*-Butoxide cannot be substituted. Isopropoxide, $(CH_3)_2CH\text{-}O$–, is retained for general nomenclature but cannot be substituted.

Examples:

$CH_3\text{-}O^-$
methoxide (PIN)
methanolate

EXHIBIT E

US 20180021284A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2018/0021284 A1**

(43) **Pub. Date: Jan. 25, 2018**

Mégret et al.

(54) **MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS**

(71) Applicant: **Flamel Ireland Limited**, Dublin (IE)

(72) Inventors: **Claire Mégret**, Lyon (FR); **Hervé Guillard**, Villeurbanne (FR); **Jean-François DUBUISSON**, Lyon (FR)

(21) Appl. No.: **15/655,924**

(22) Filed: **Jul. 21, 2017**

Related U.S. Application Data

(60) Provisional application No. 62/365,812, filed on Jul. 22, 2016, provisional application No. 62/399,413, filed on Sep. 25, 2016, provisional application No. 62/474,330, filed on Mar. 21, 2017.

Publication Classification

(51) **Int. Cl.**

A61K 31/22	(2006.01)
A61K 9/14	(2006.01)
A61K 9/50	(2006.01)

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

CPC ***A61K 31/22*** (2013.01); ***A61K 9/5026*** (2013.01); ***A61K 9/5015*** (2013.01); ***A61K 9/14*** (2013.01)

(57) **ABSTRACT**

Modified release formulations of gamma-hydroxybutyrate having improved dissolution and pharmacokinetic properties are provided, and therapeutic uses thereof.

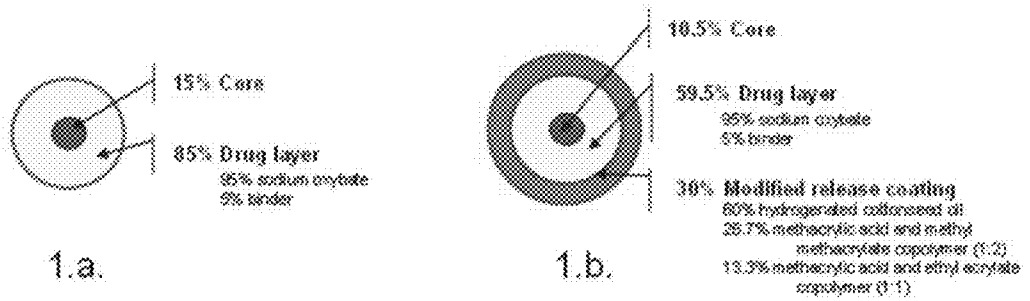


Figure 1

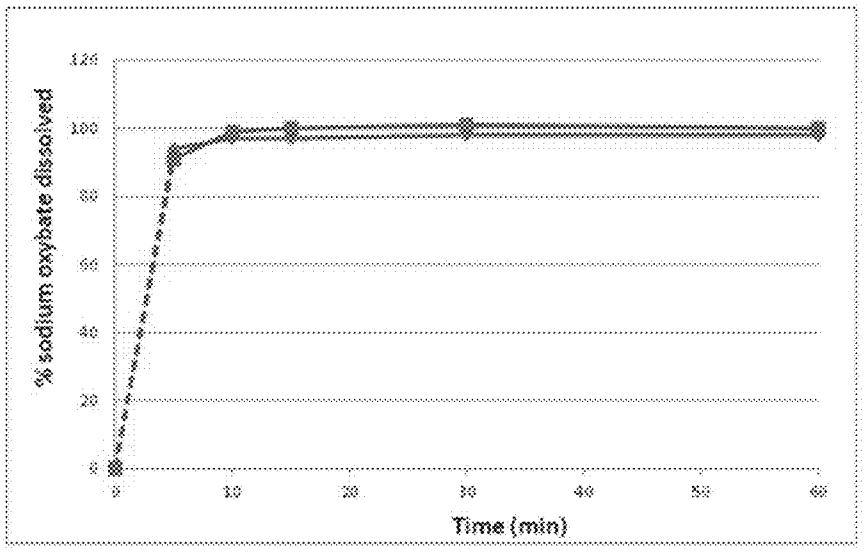


Figure 2

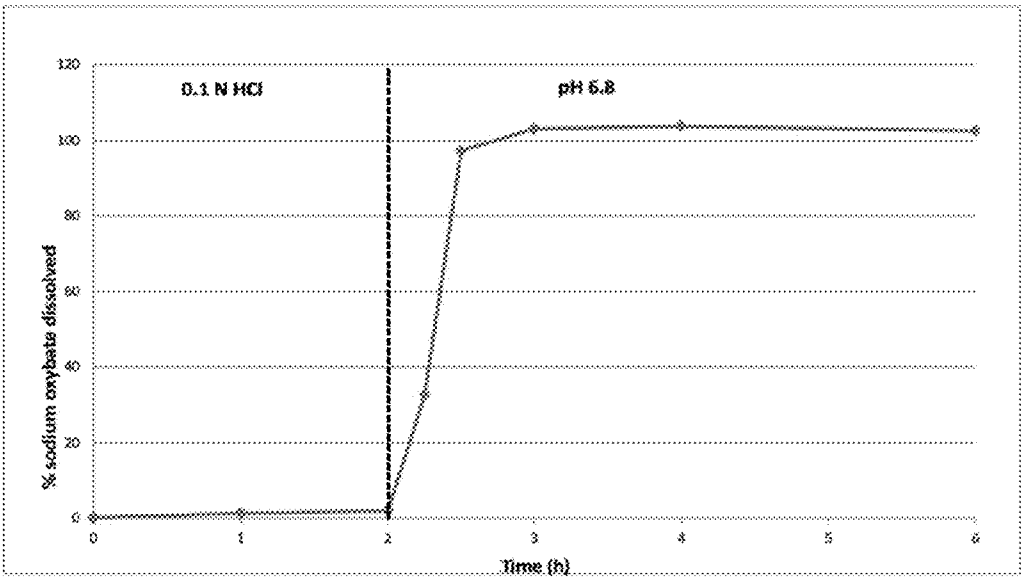


Figure 3

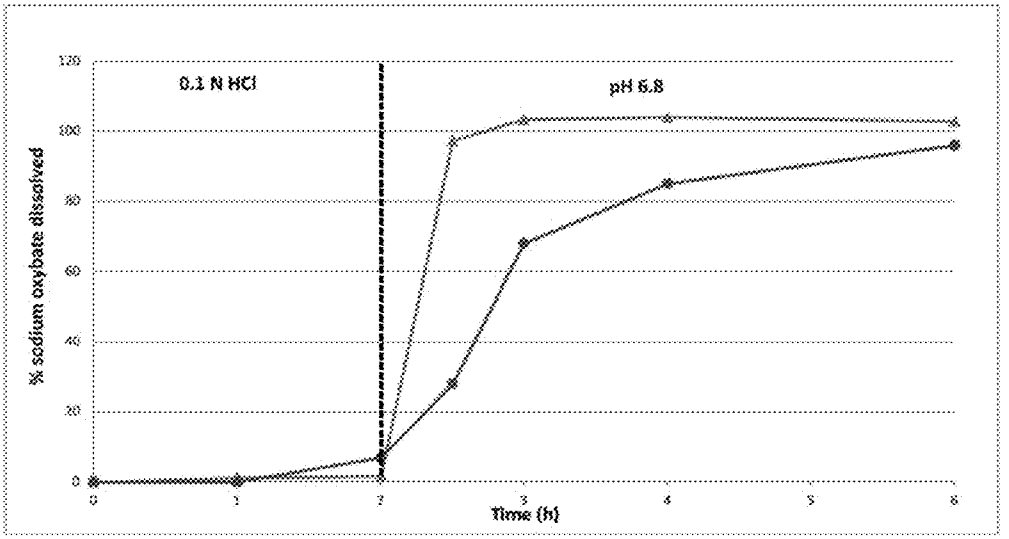


Figure 4

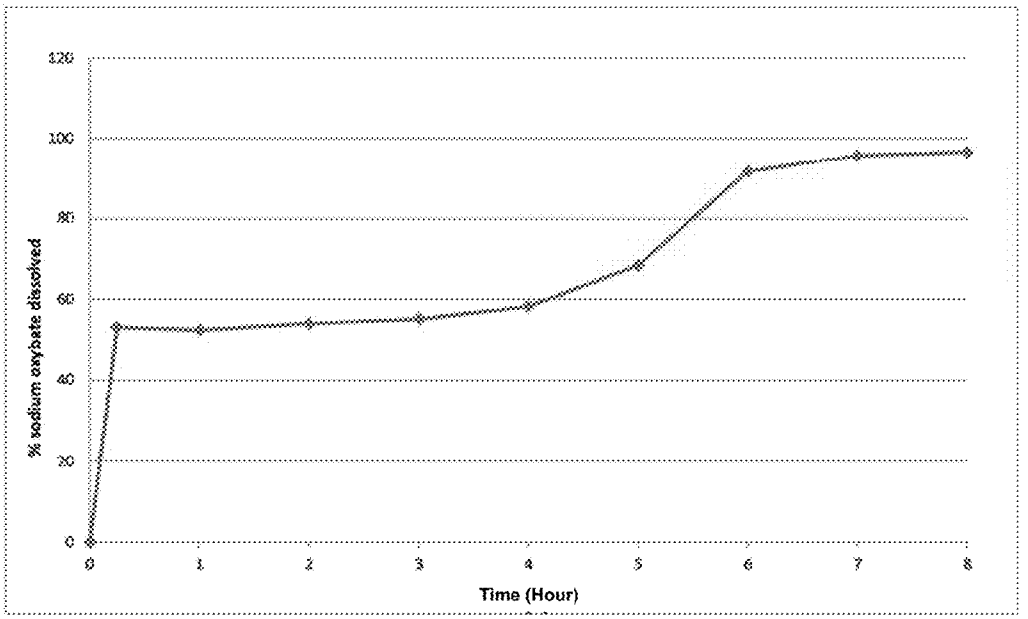


Figure 5

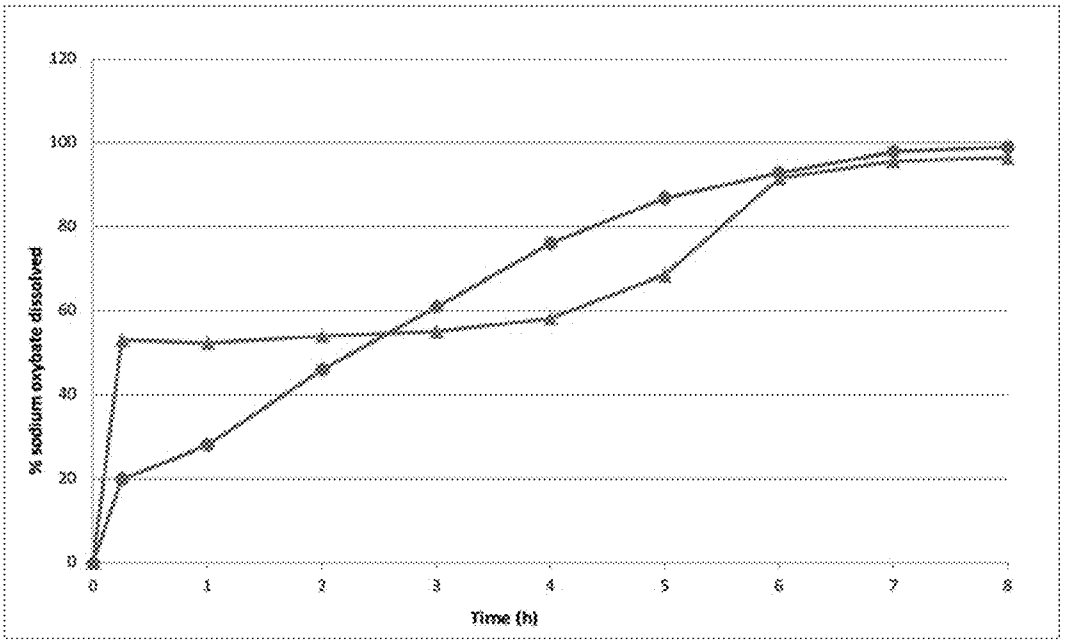


Figure 6

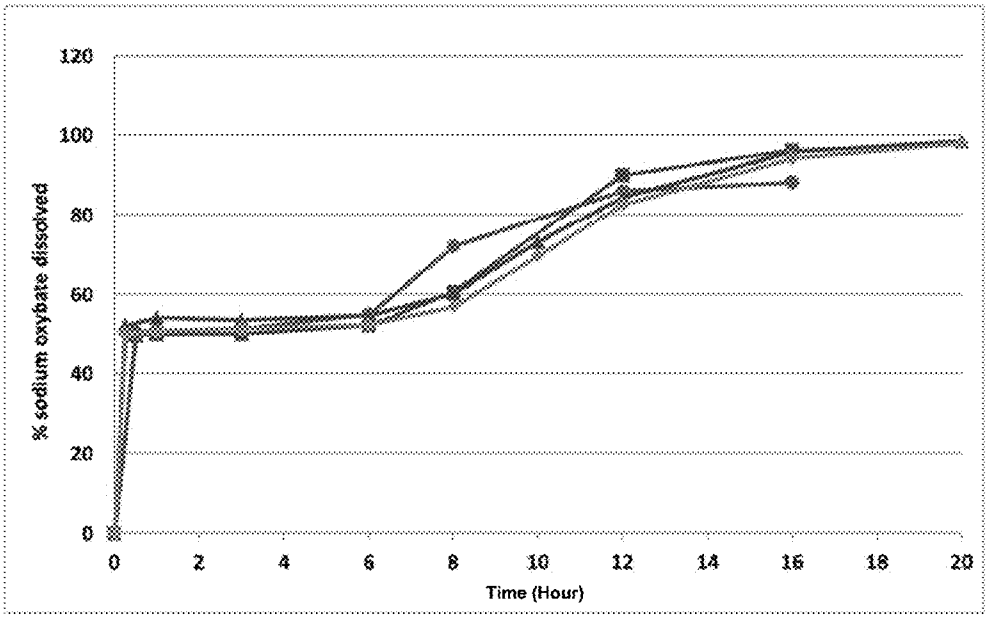


Figure 7

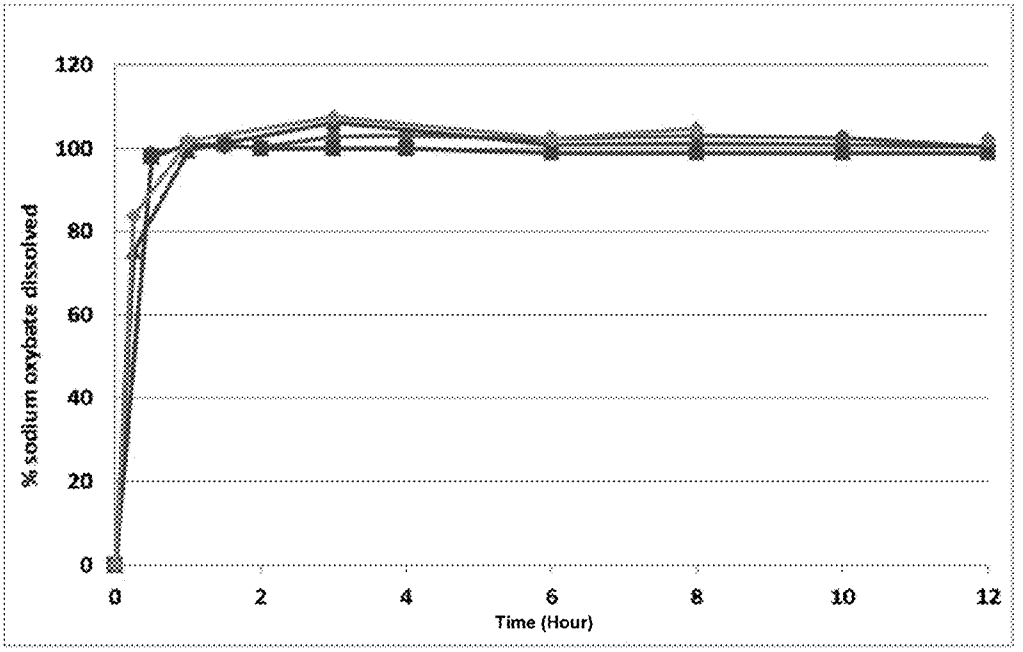


Figure 8

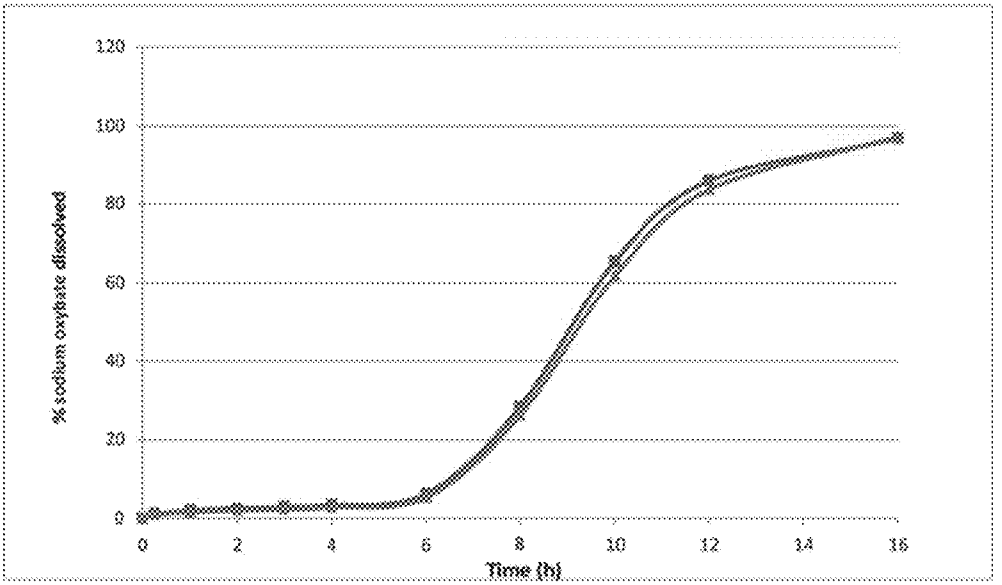


Figure 9

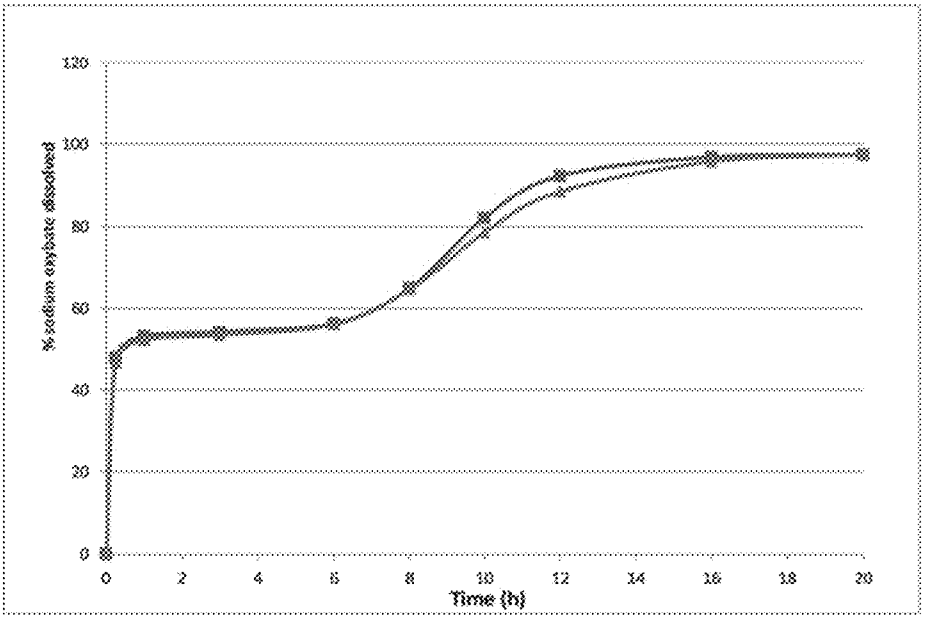


Figure 10

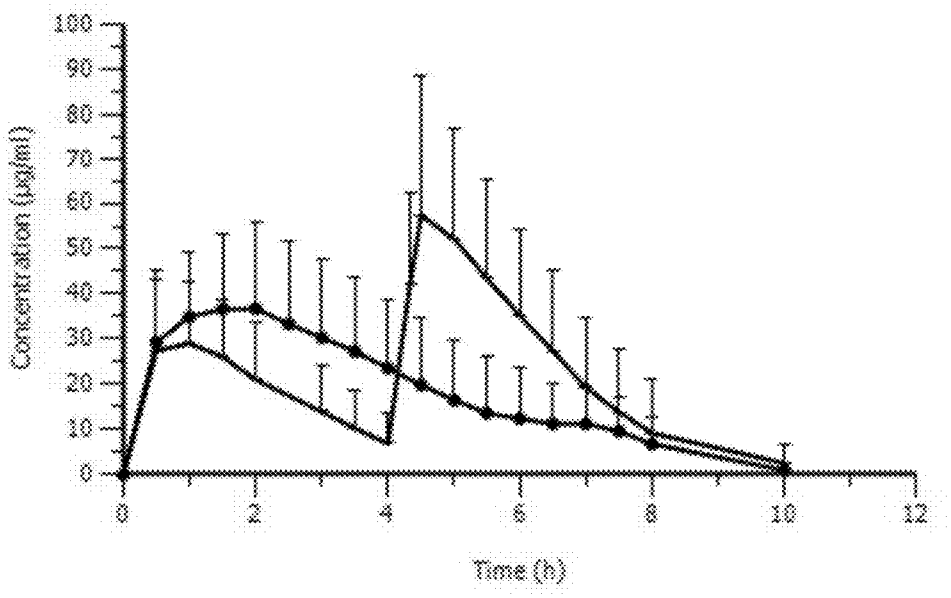


Figure 11

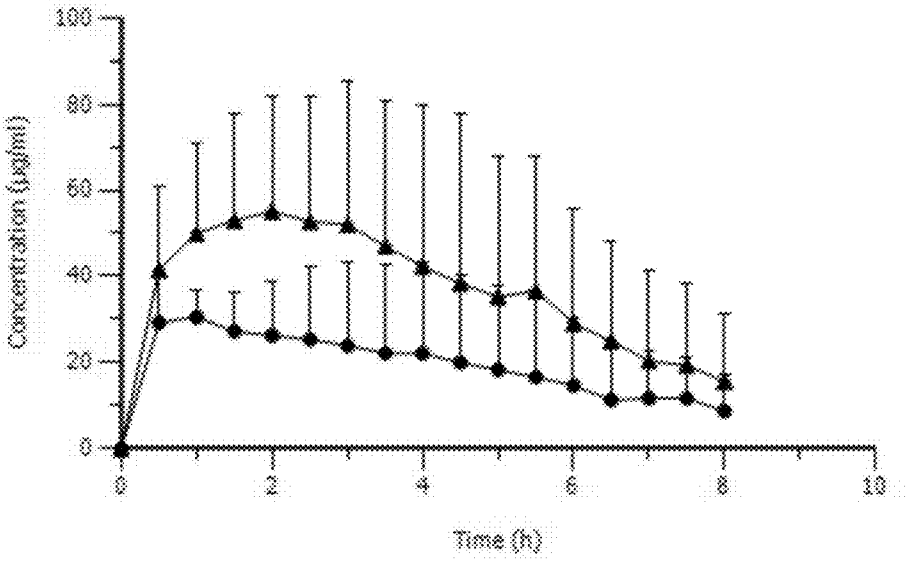


Figure 12

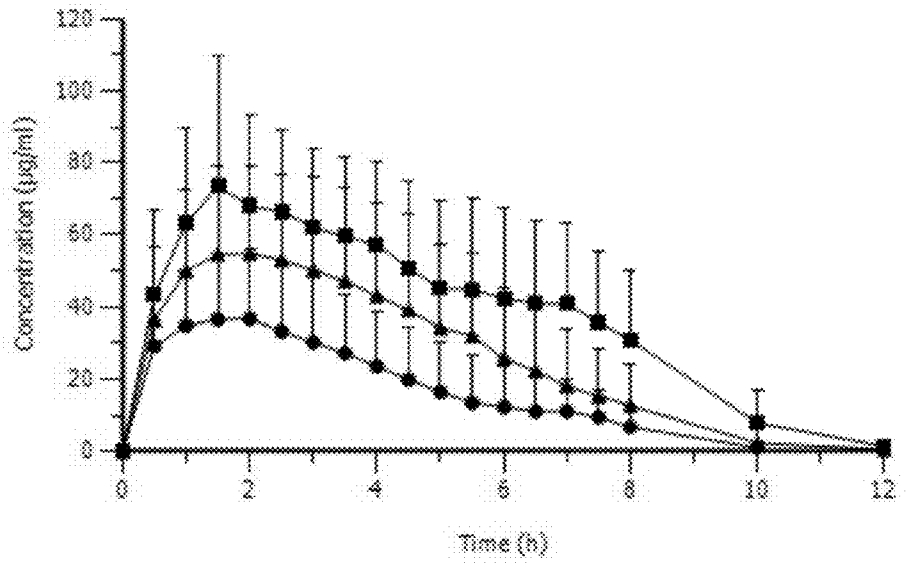


Figure 13

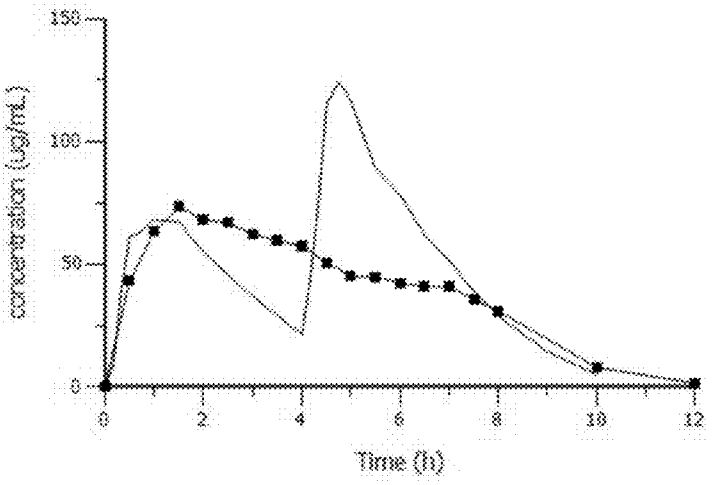


Figure 14

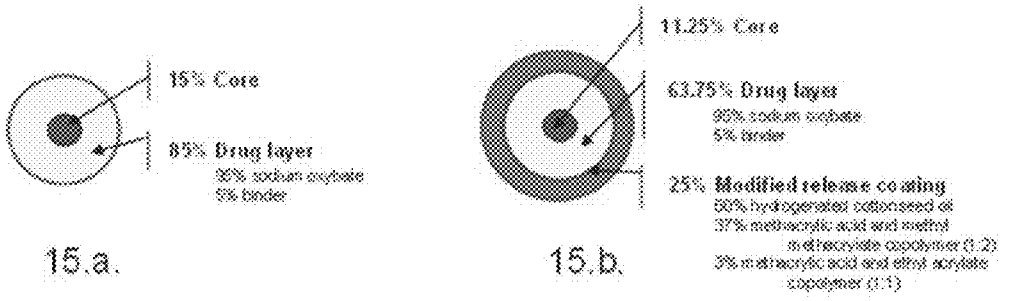


Figure 15

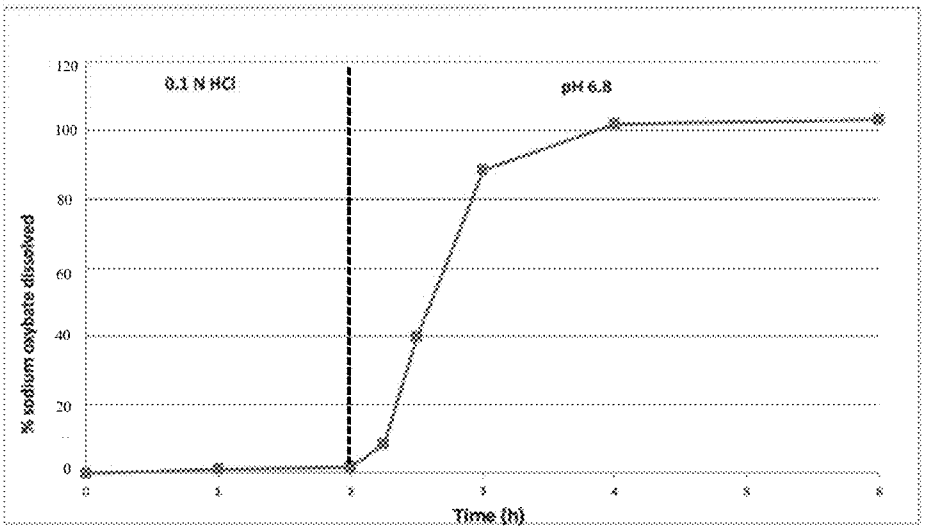


Figure 16

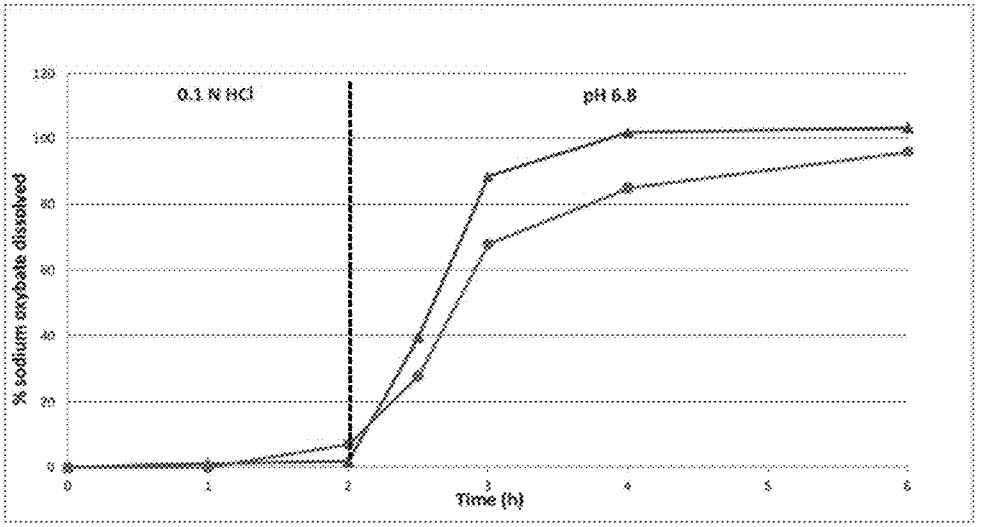


Figure 17

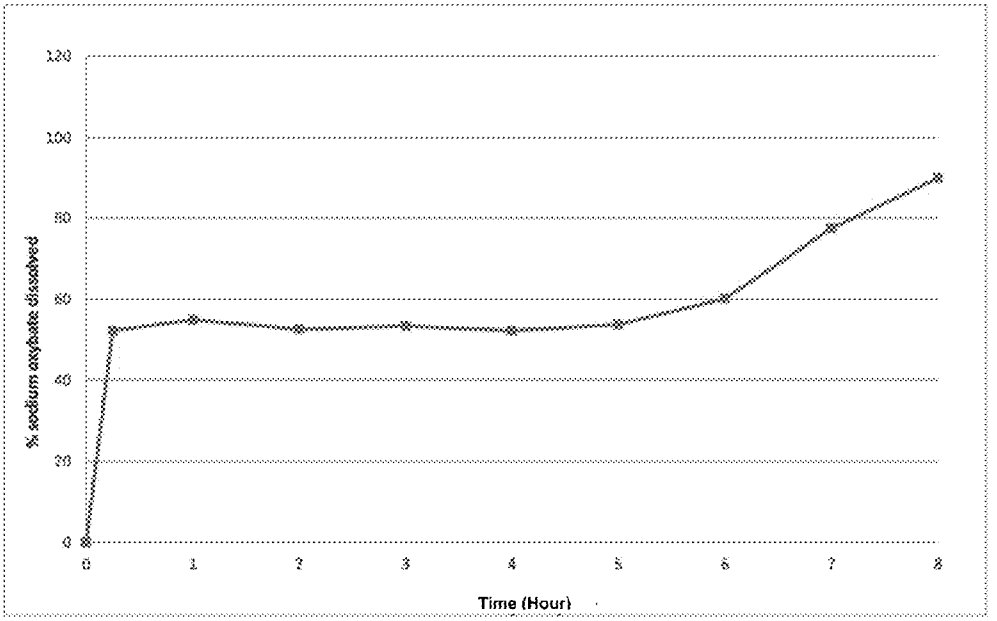


Figure 18

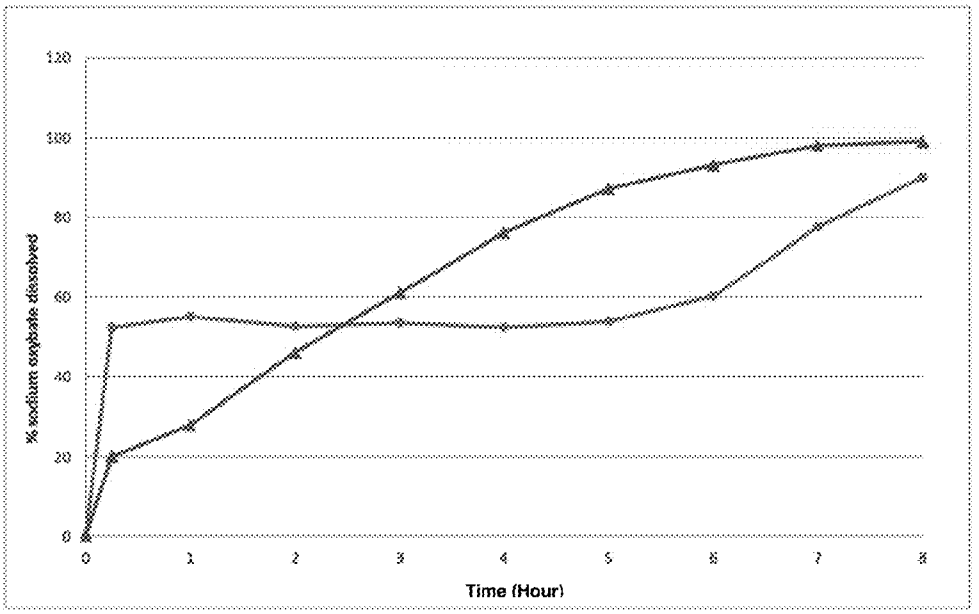


Figure 19

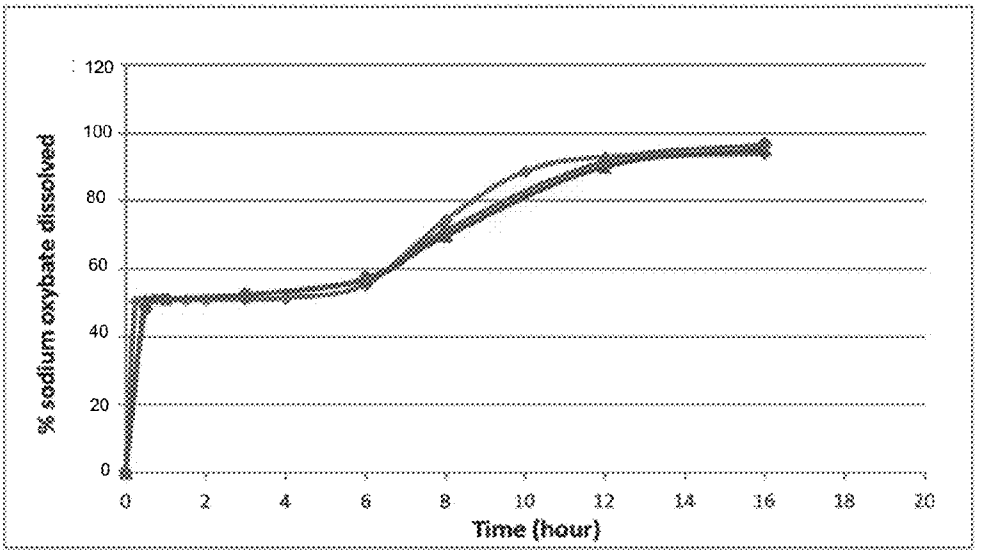


Figure 20

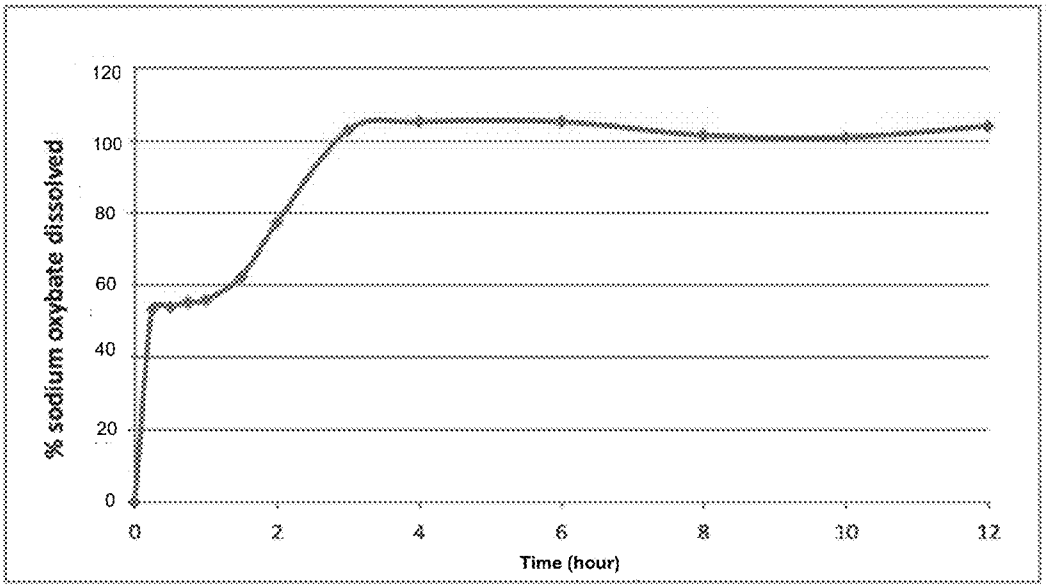


Figure 21

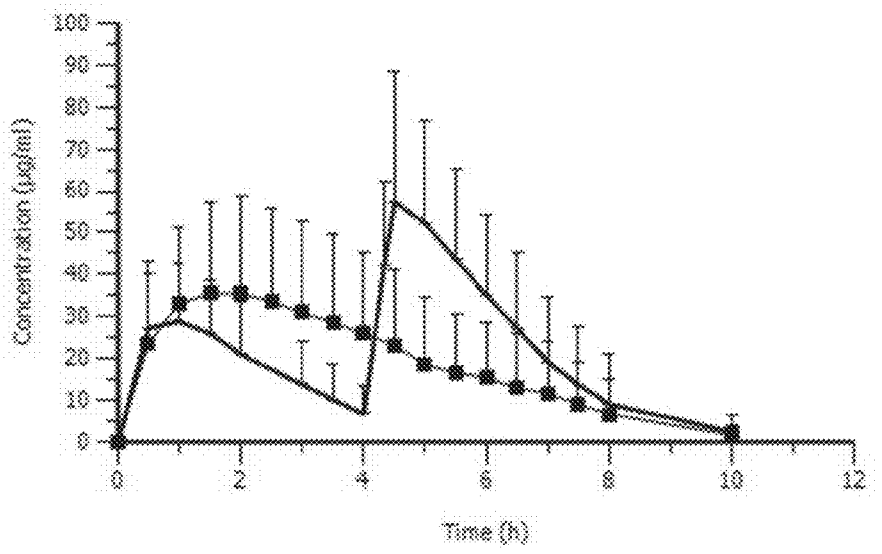


Figure 22

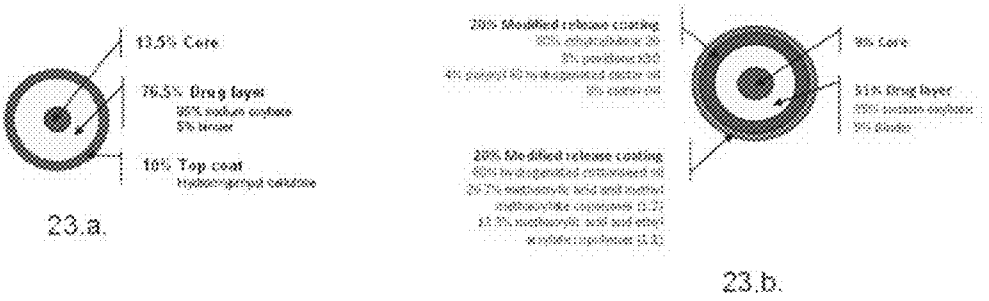


Figure 23

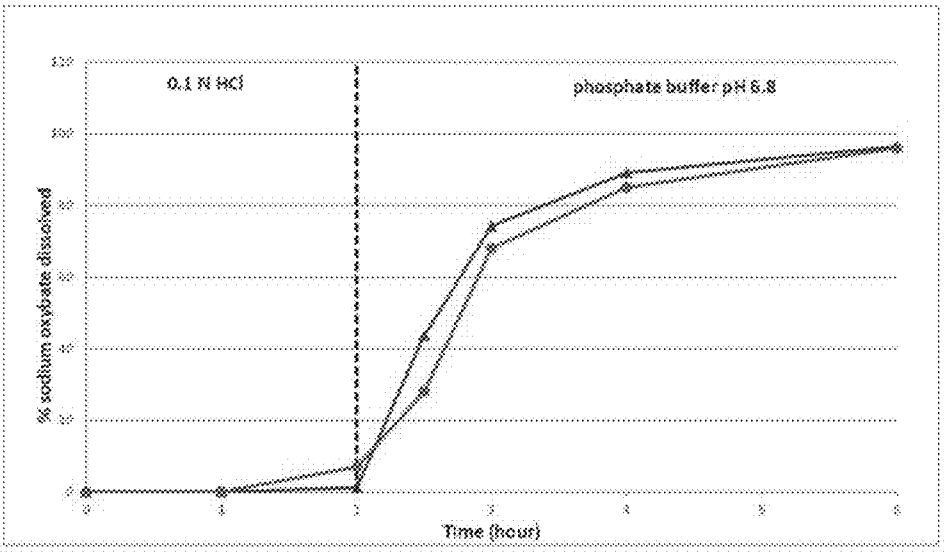


Figure 24

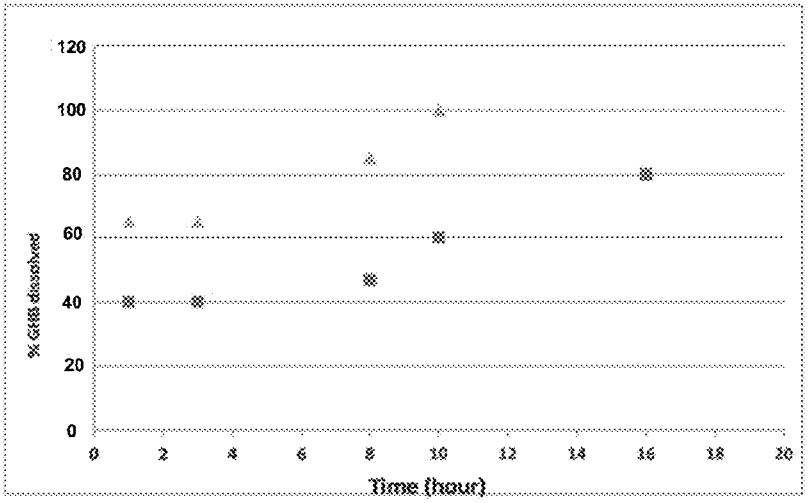


Figure 25

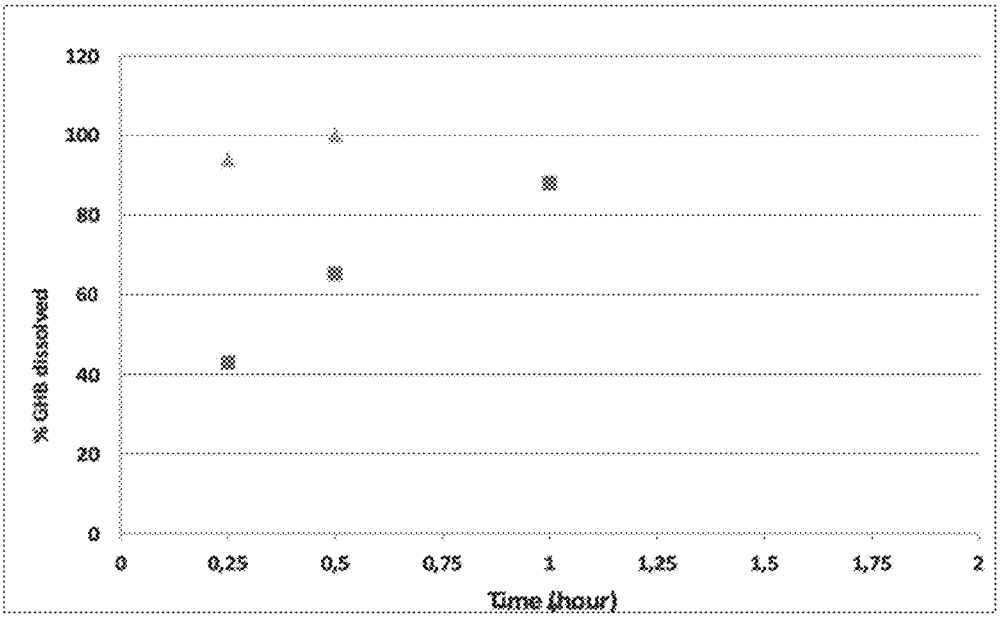


Figure 26

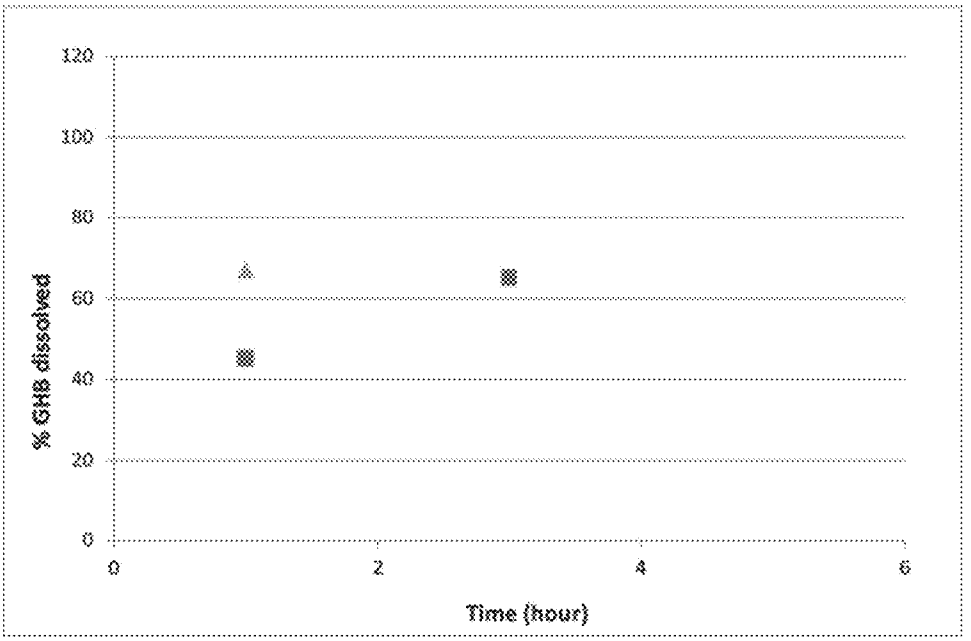


Figure 27

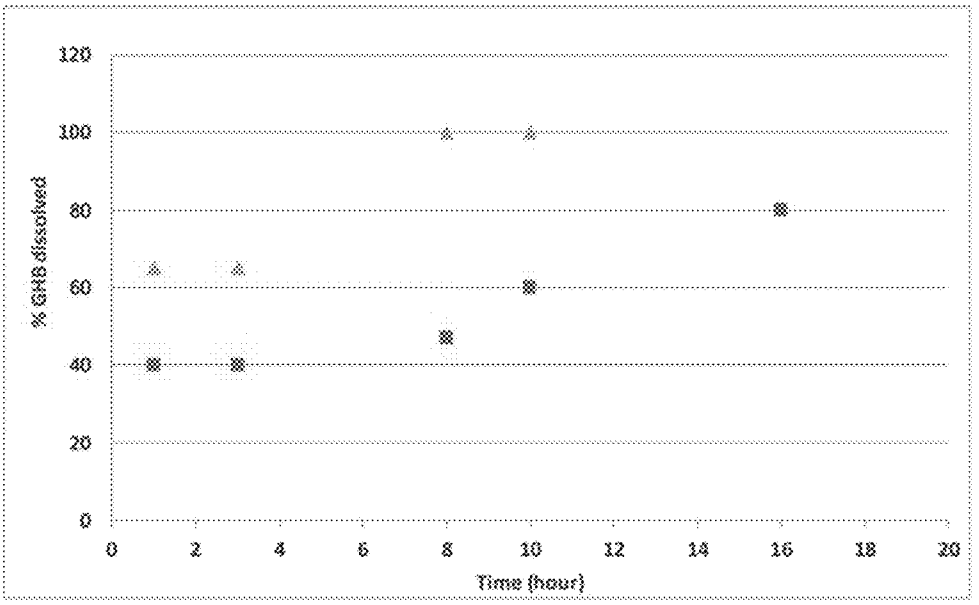


Figure 28

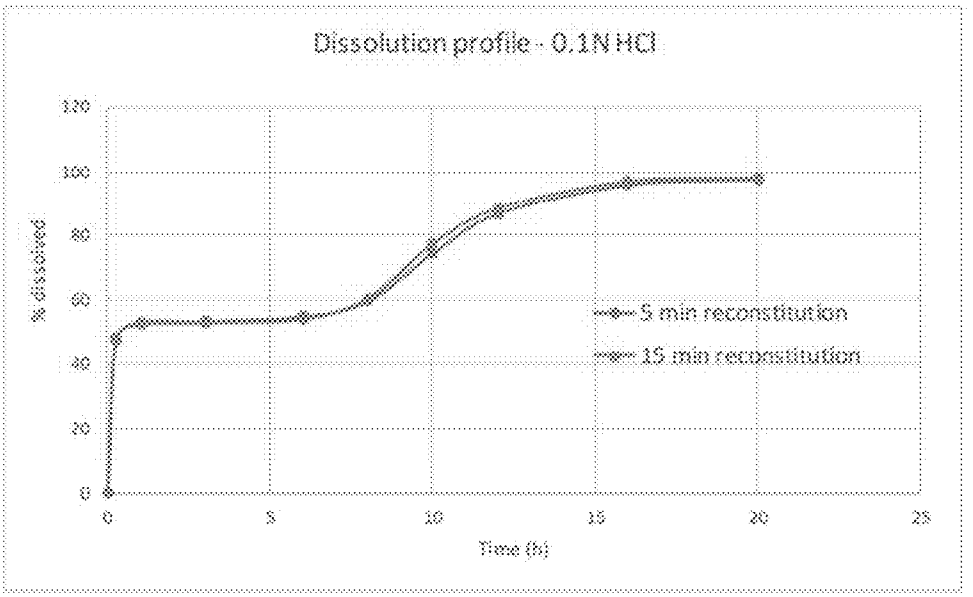


Figure 29

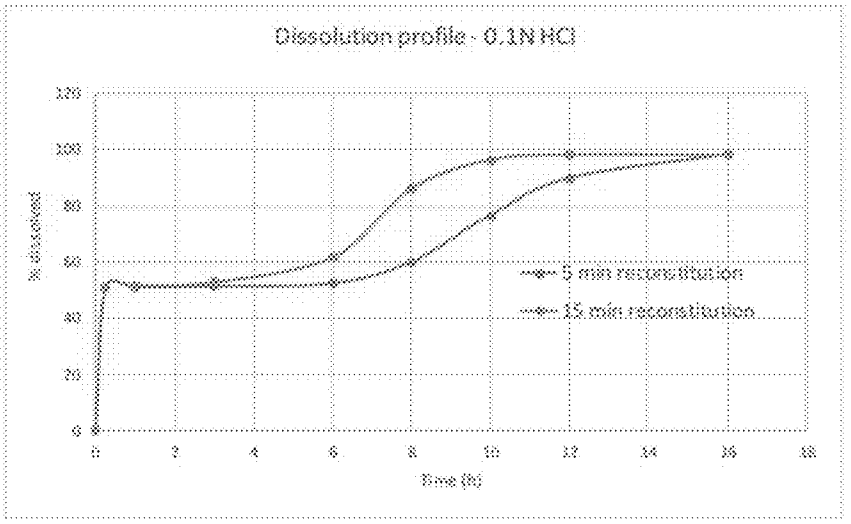


Figure 30

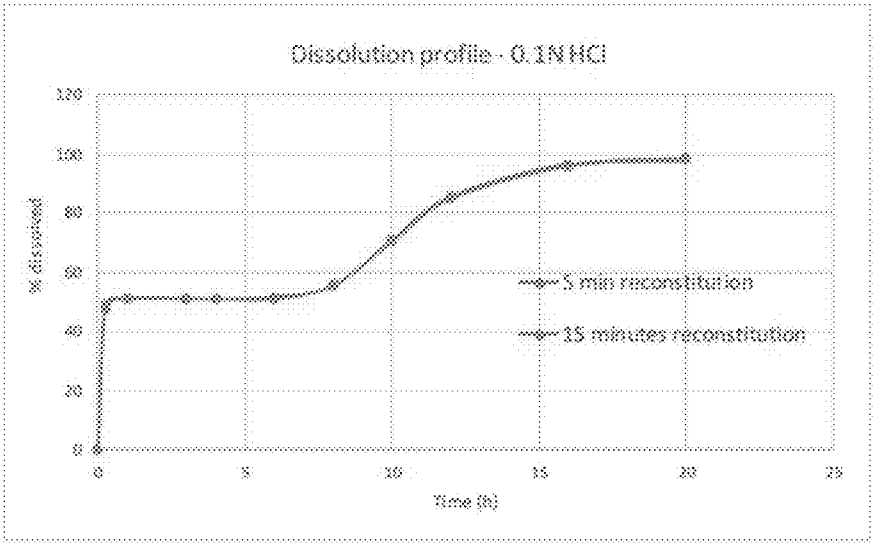


Figure 31

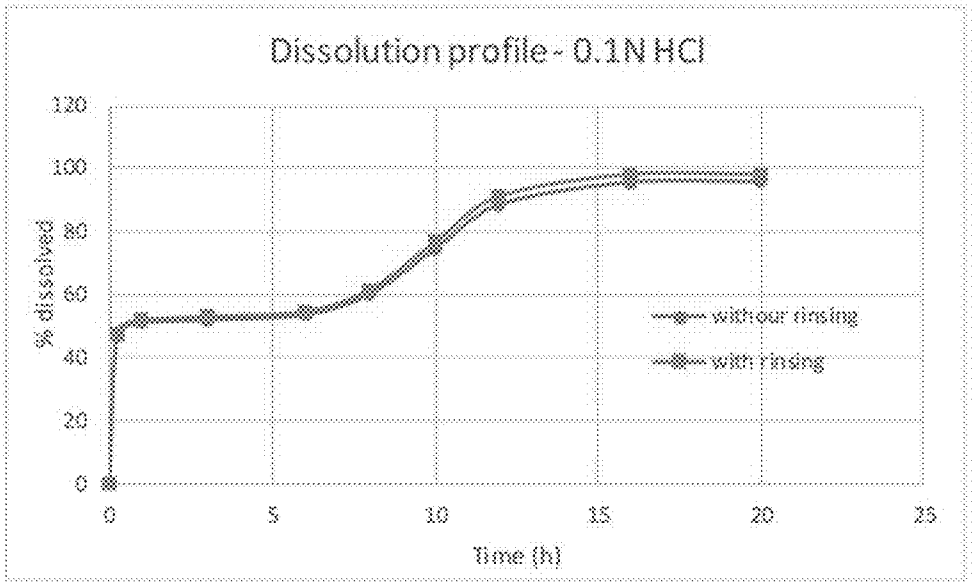


Figure 32

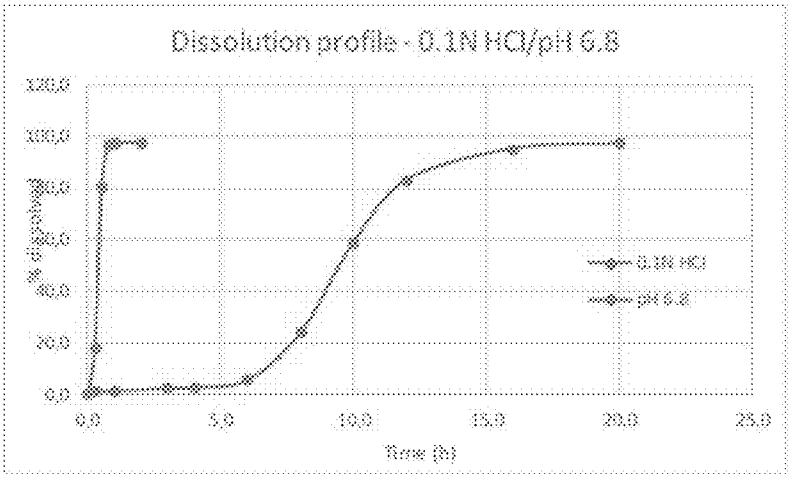


Figure 33

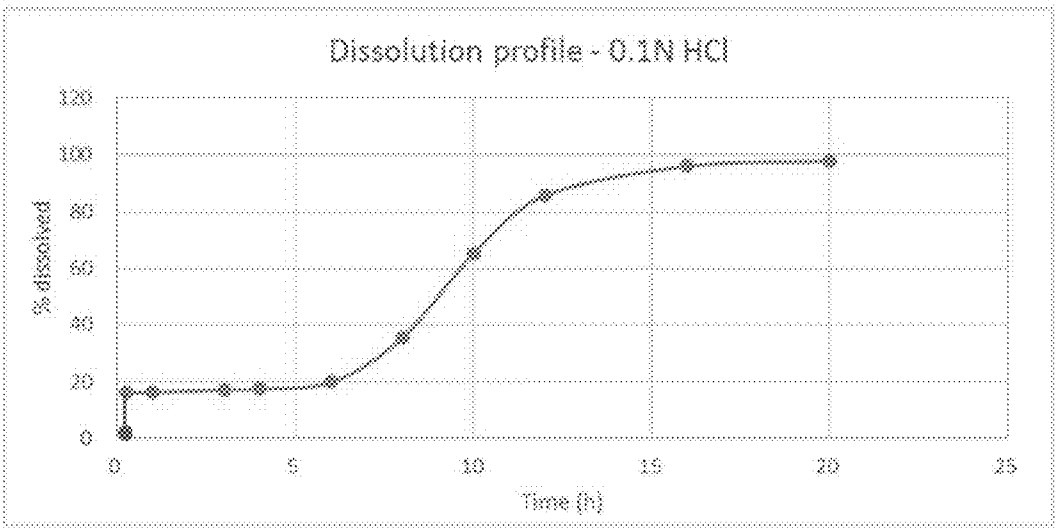


Figure 34

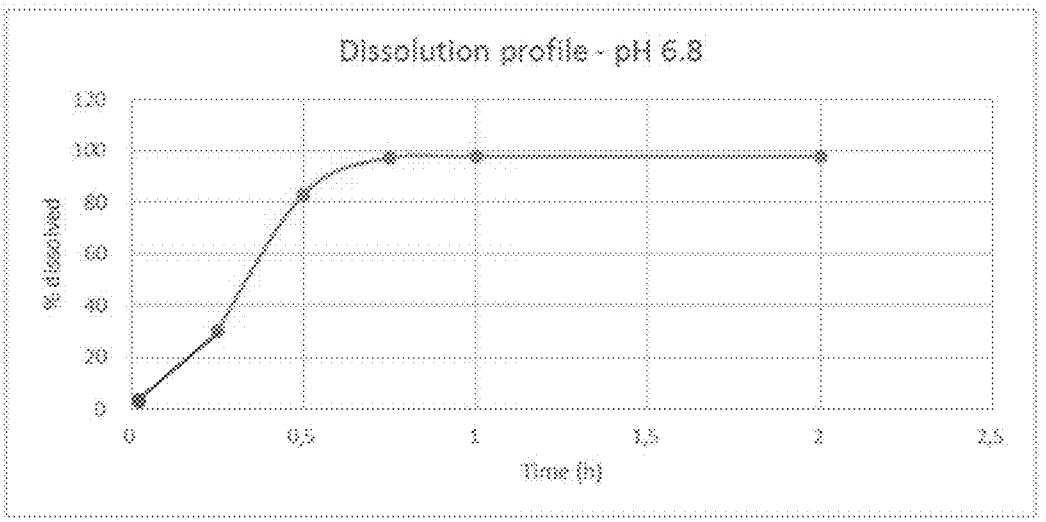


Figure 35

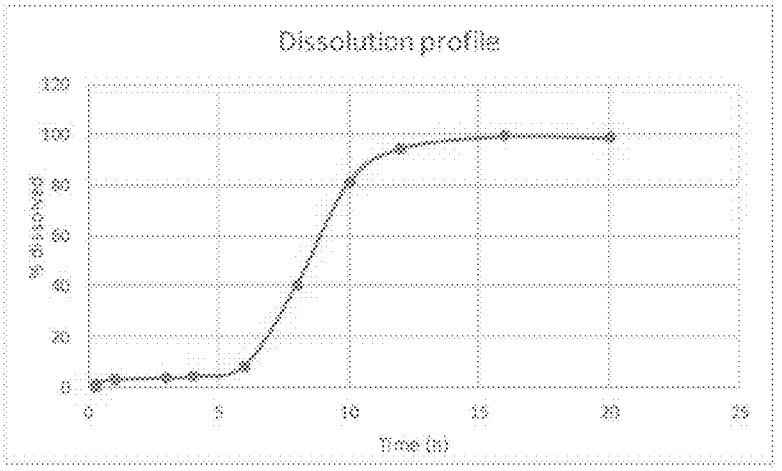


Figure 36

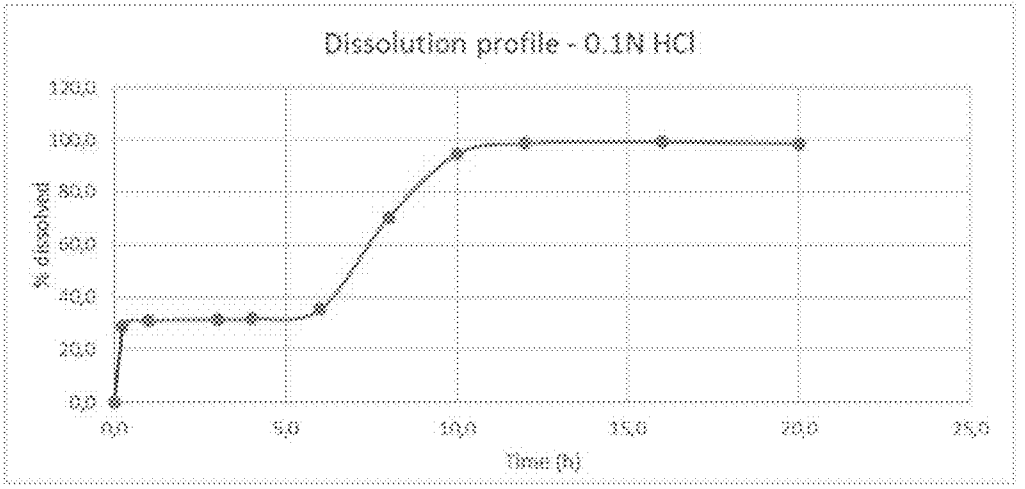


Figure 37

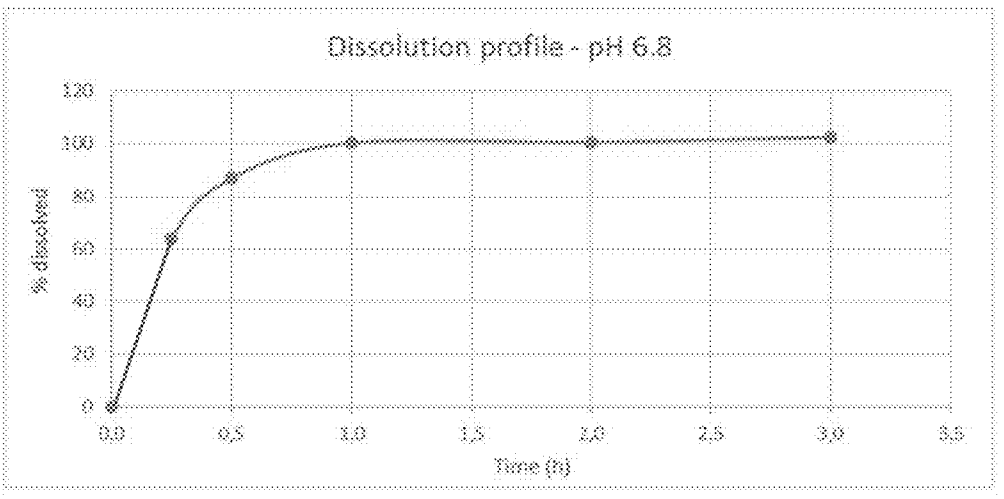


Figure 38

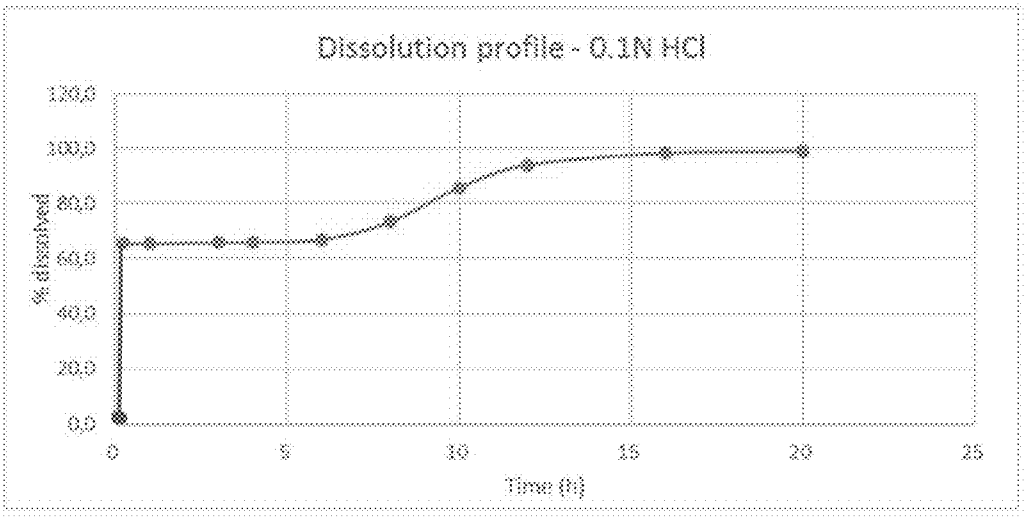


Figure 39

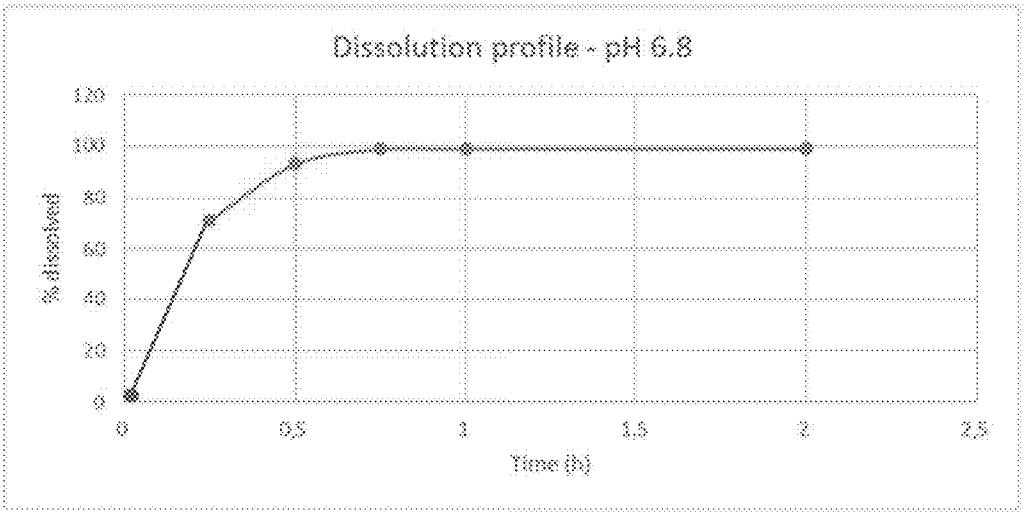


Figure 40

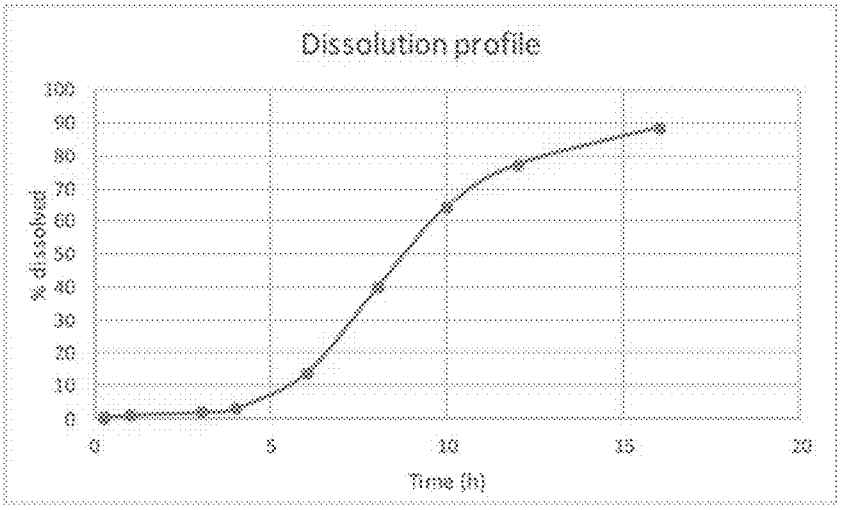


Figure 41

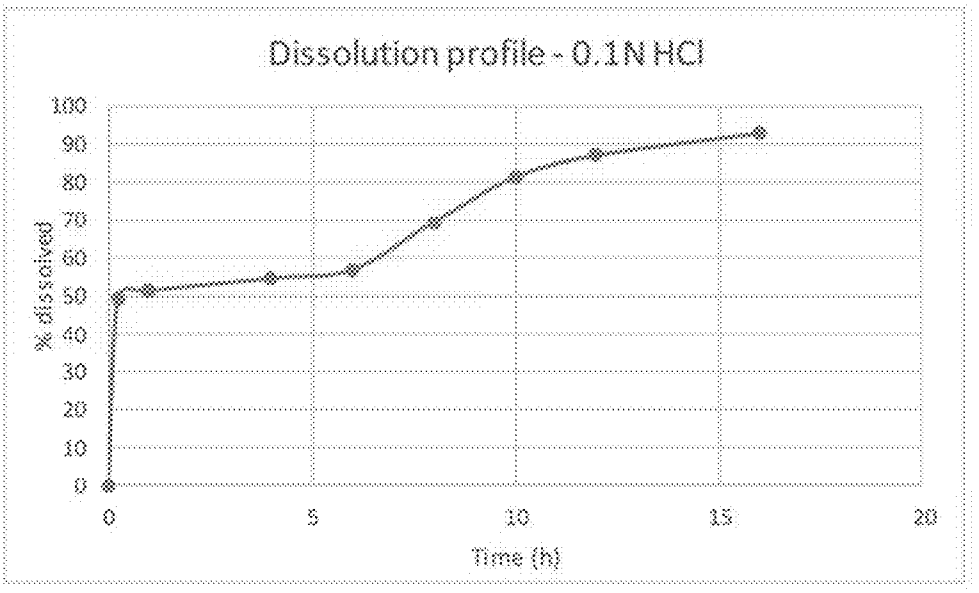


Figure 42

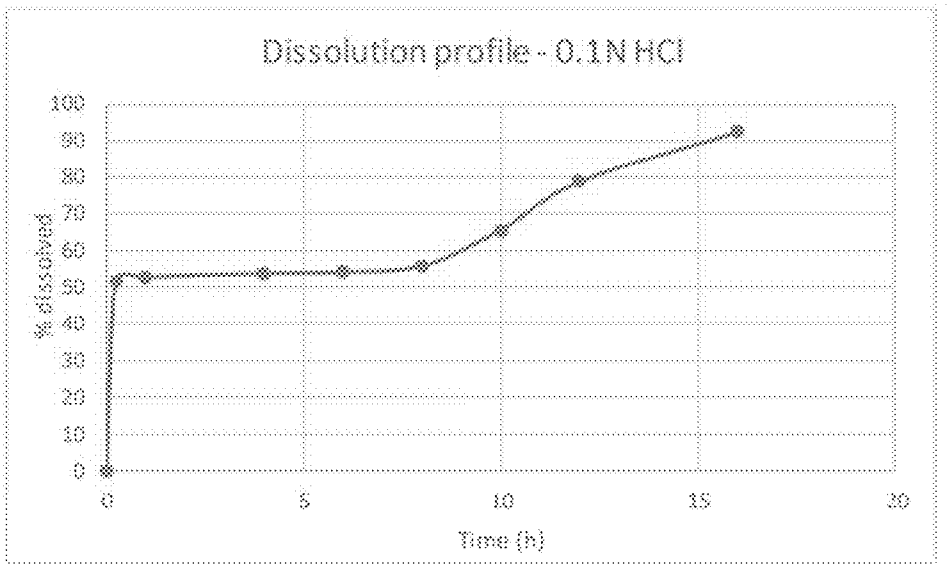


Figure 43

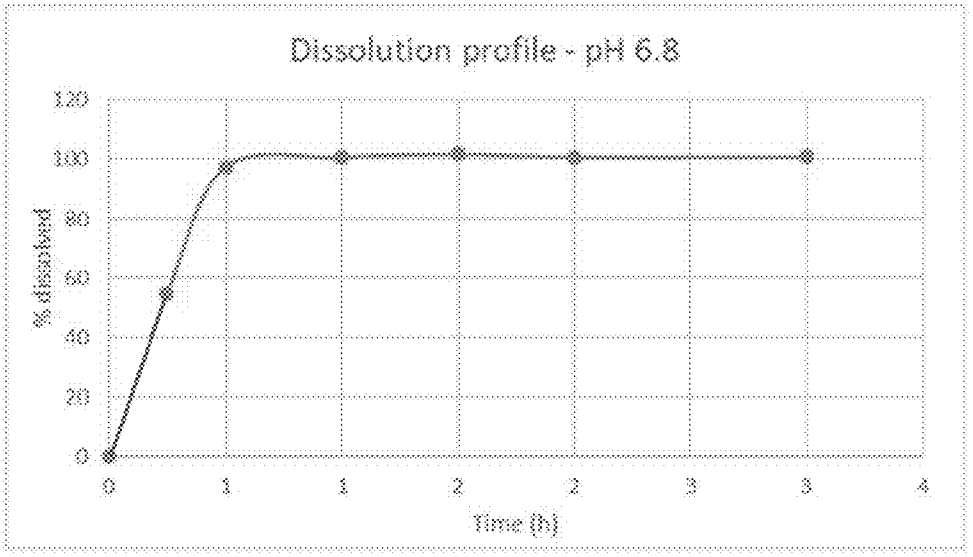


Figure 44

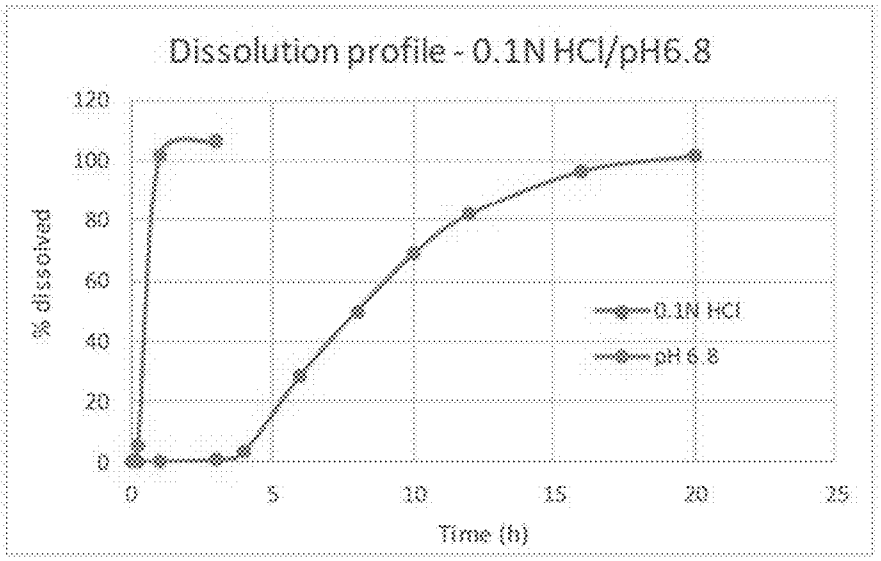


Figure 45

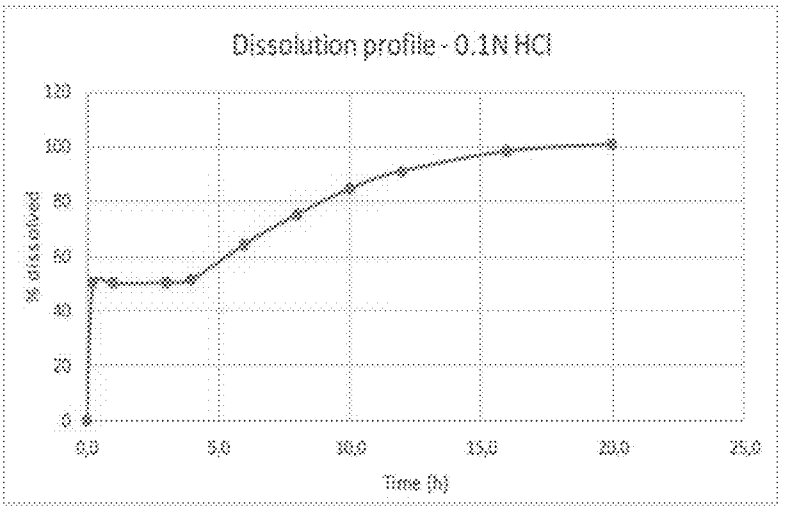


Figure 46

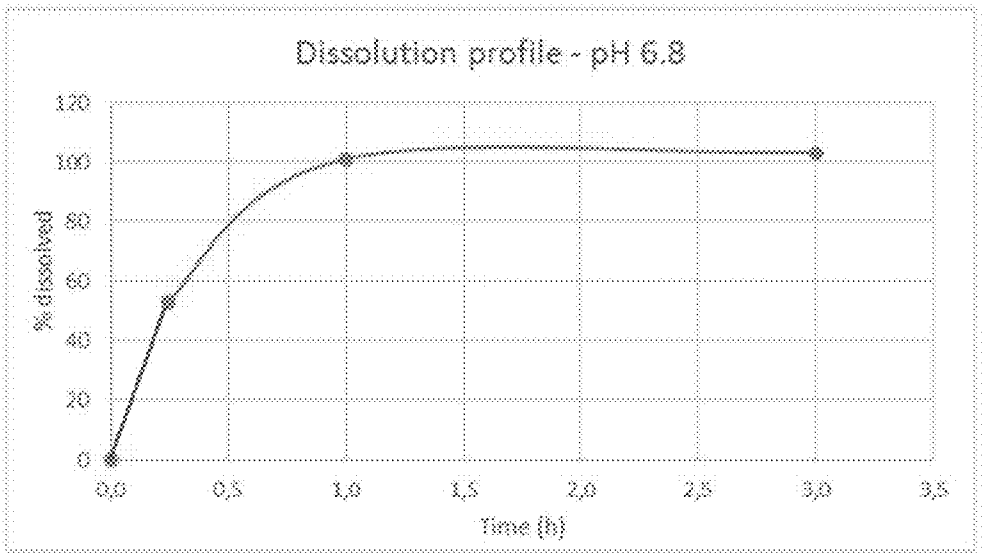


Figure 47

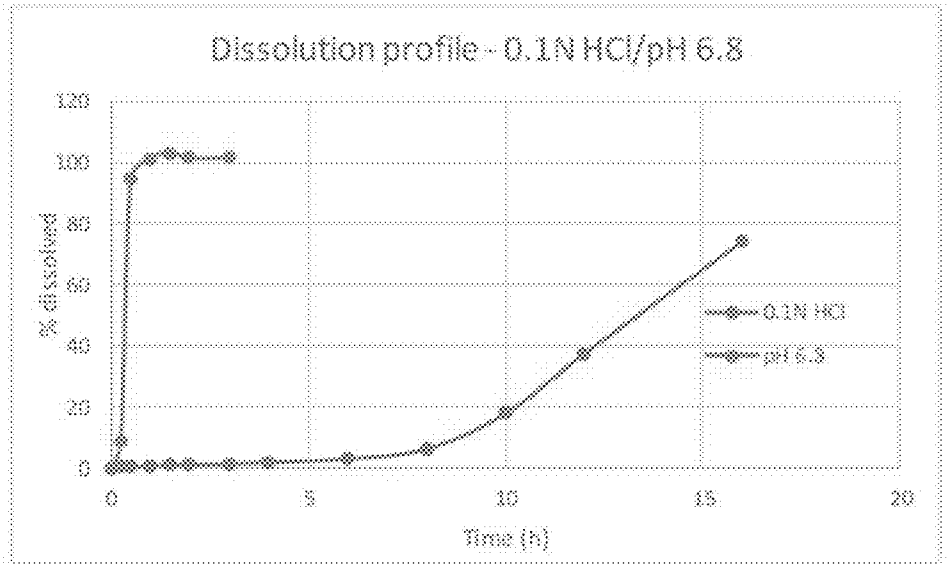


Figure 48

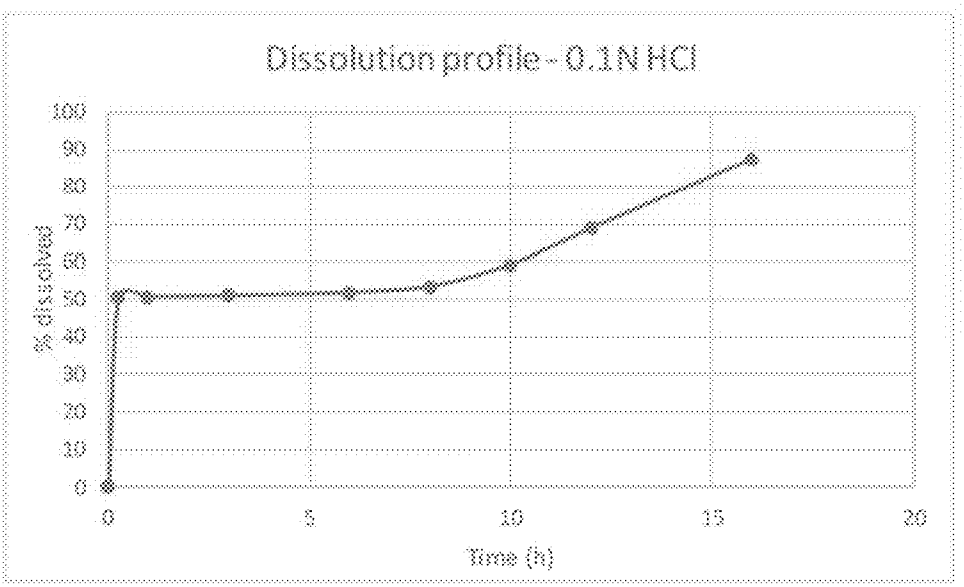


Figure 49

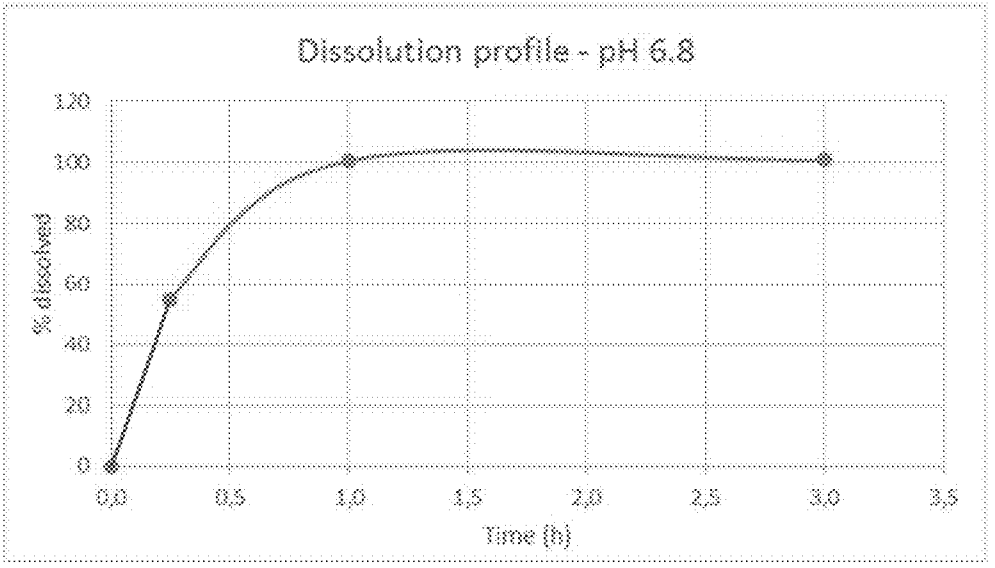


Figure 50

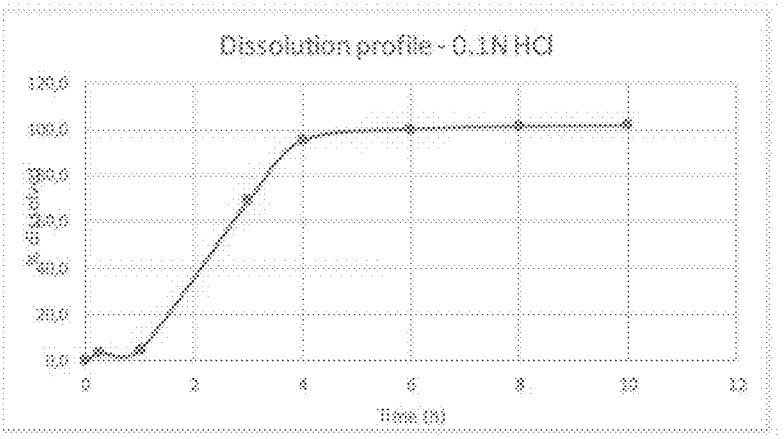


Figure 51

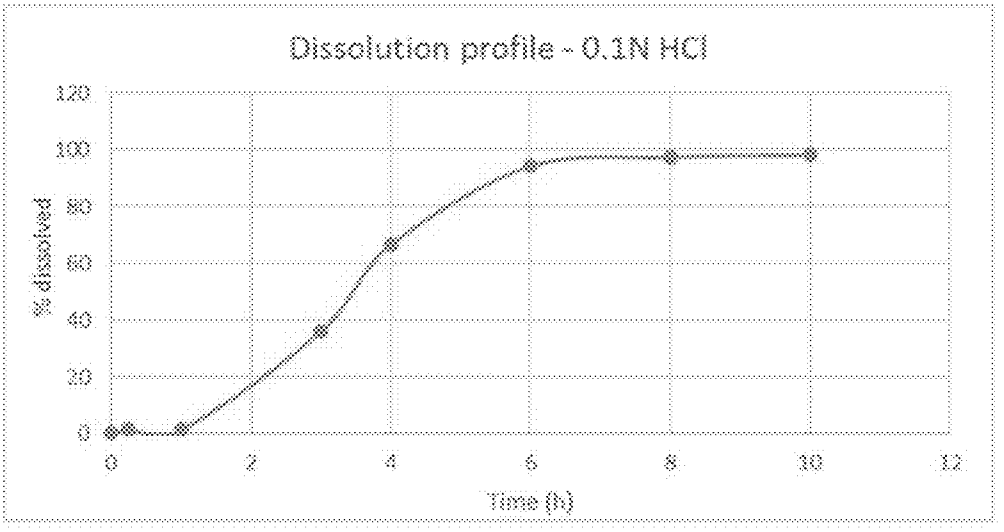


Figure 52

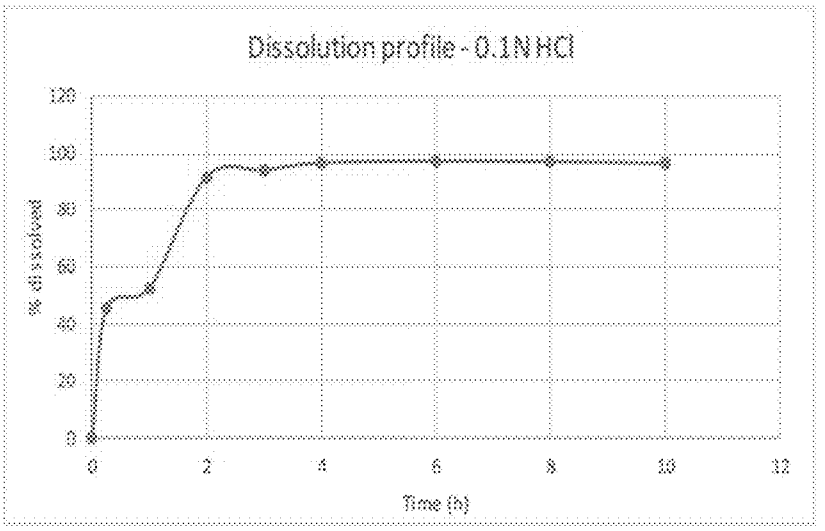


Figure 53

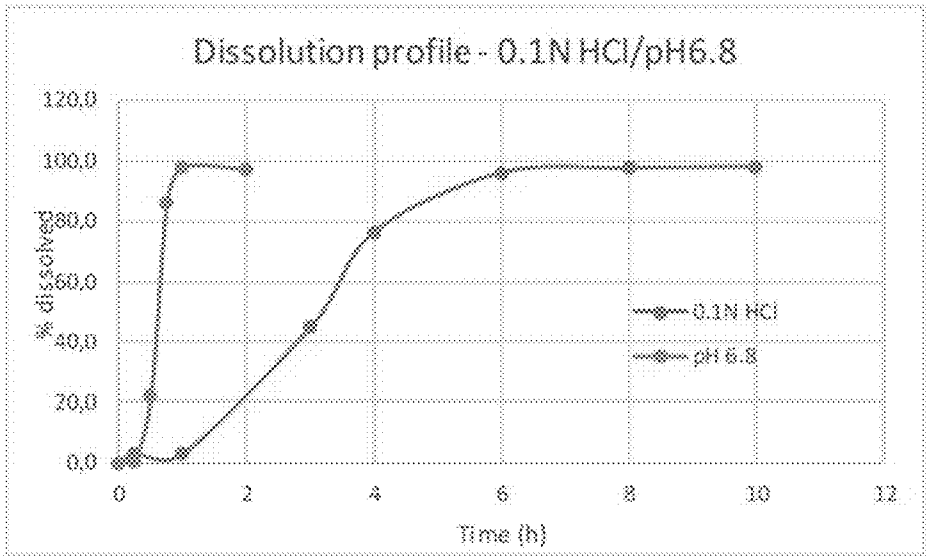


Figure 54

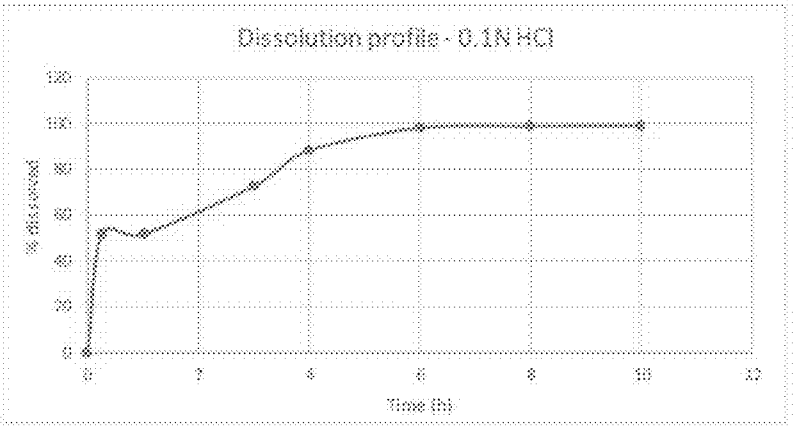


Figure 55

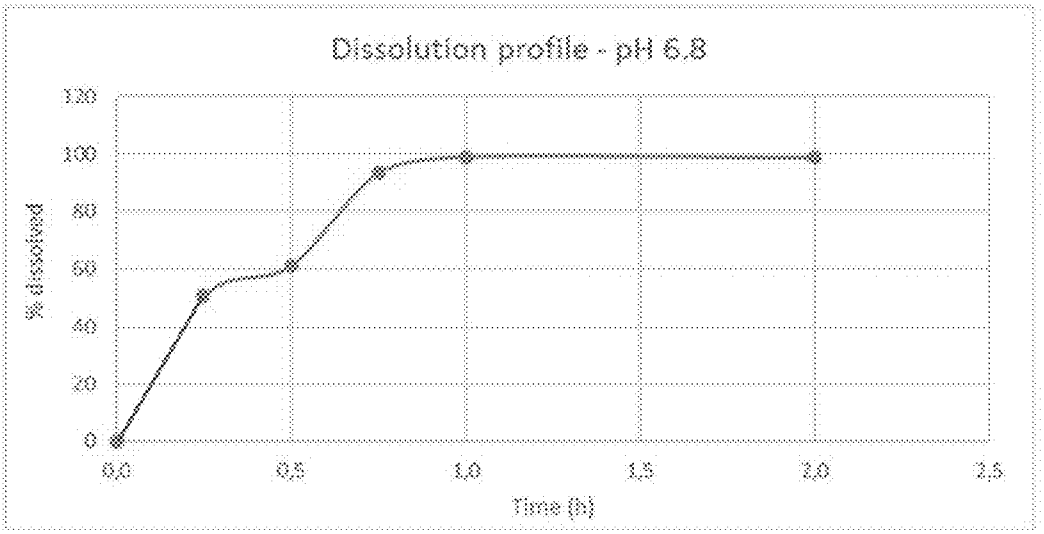


Figure 56

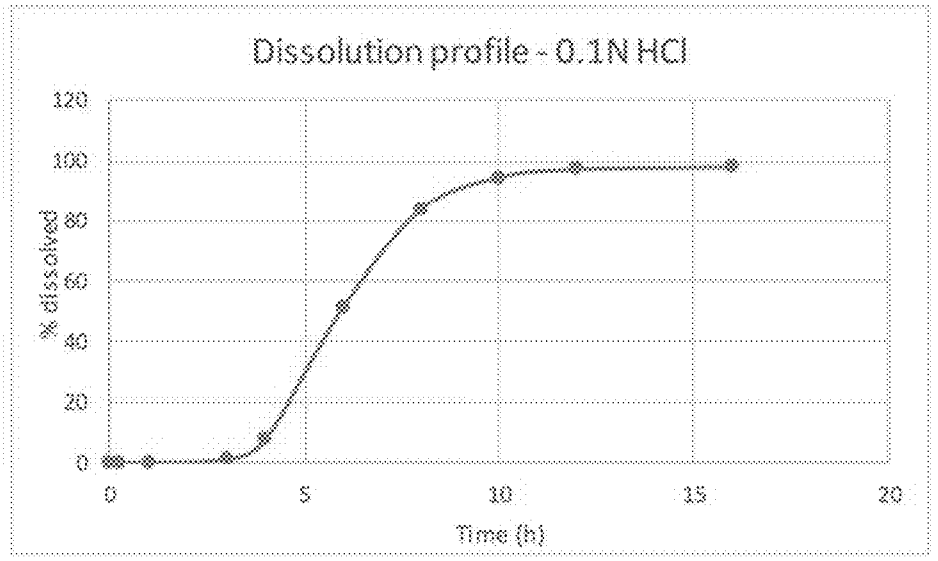


Figure 57

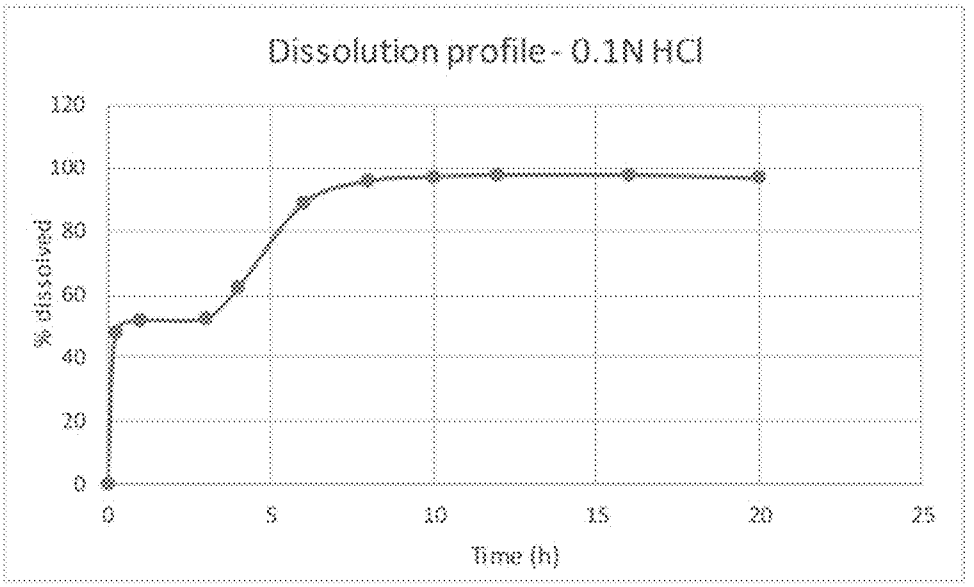


Figure 58

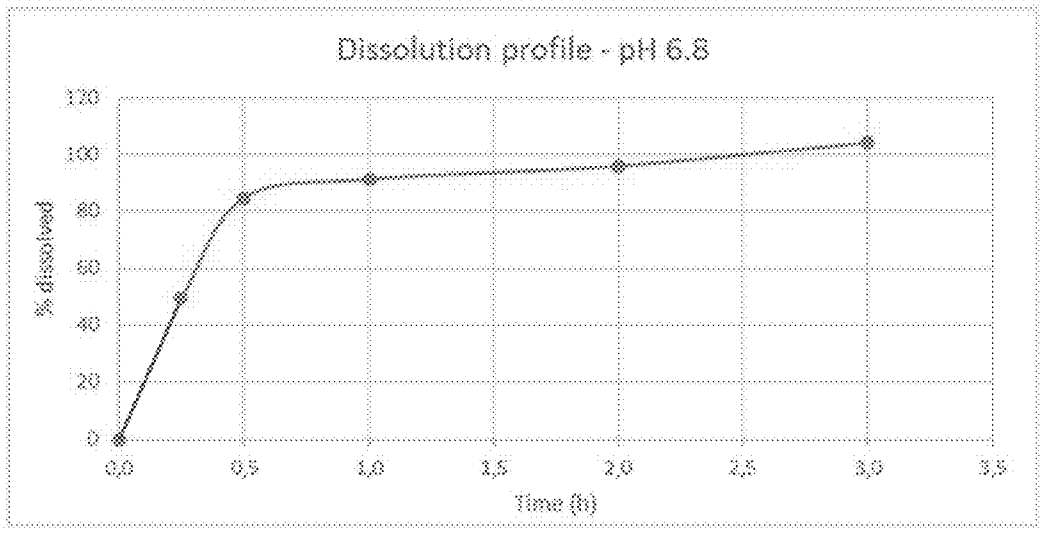


Figure 59

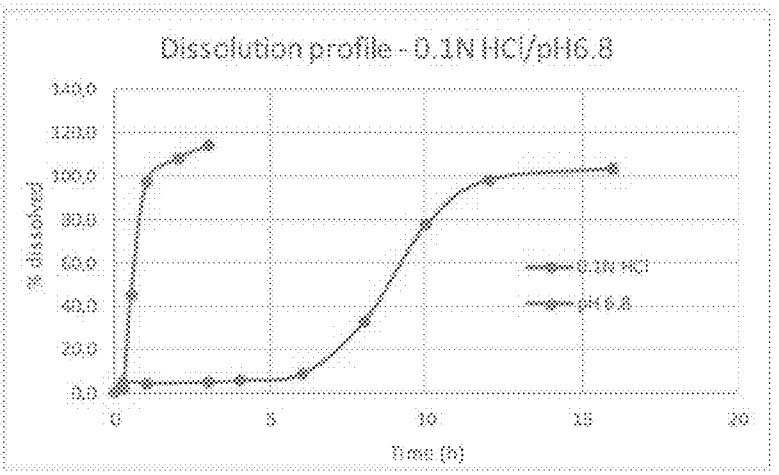


Figure 60

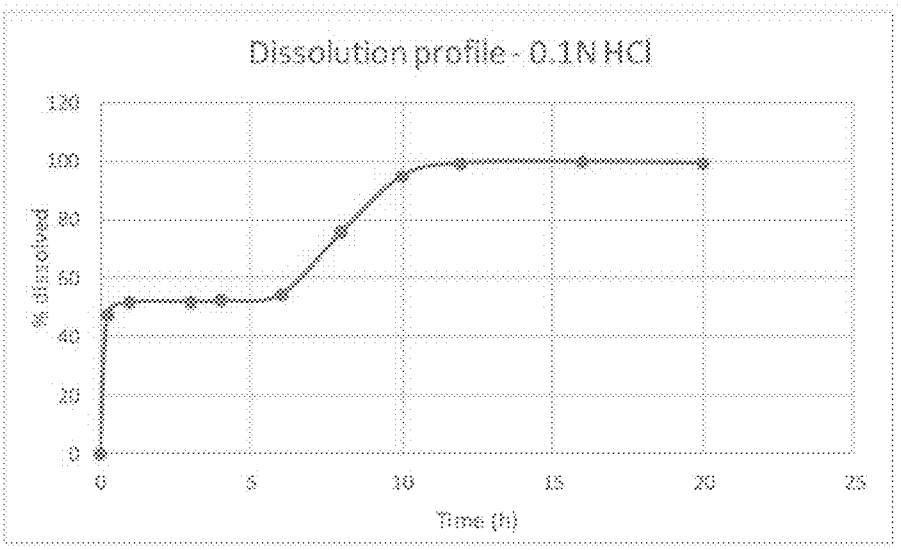


Figure 61

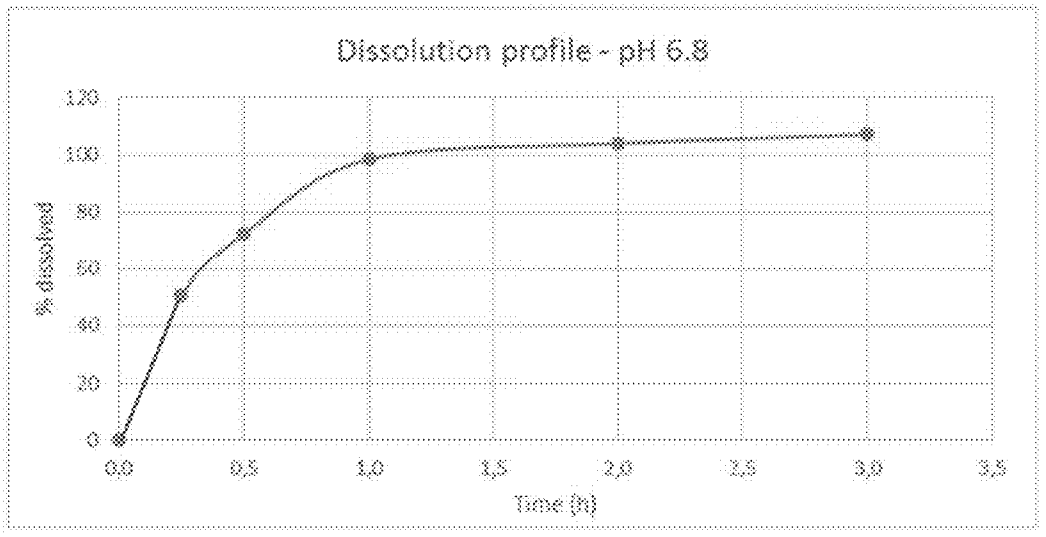


Figure 62

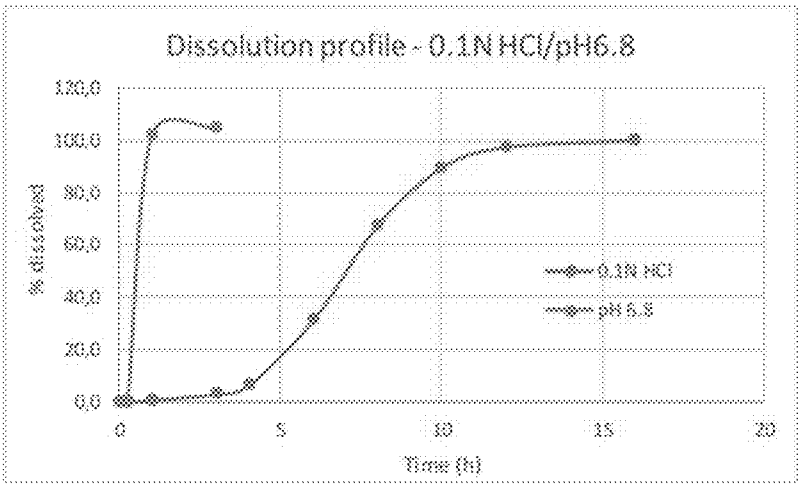


Figure 63

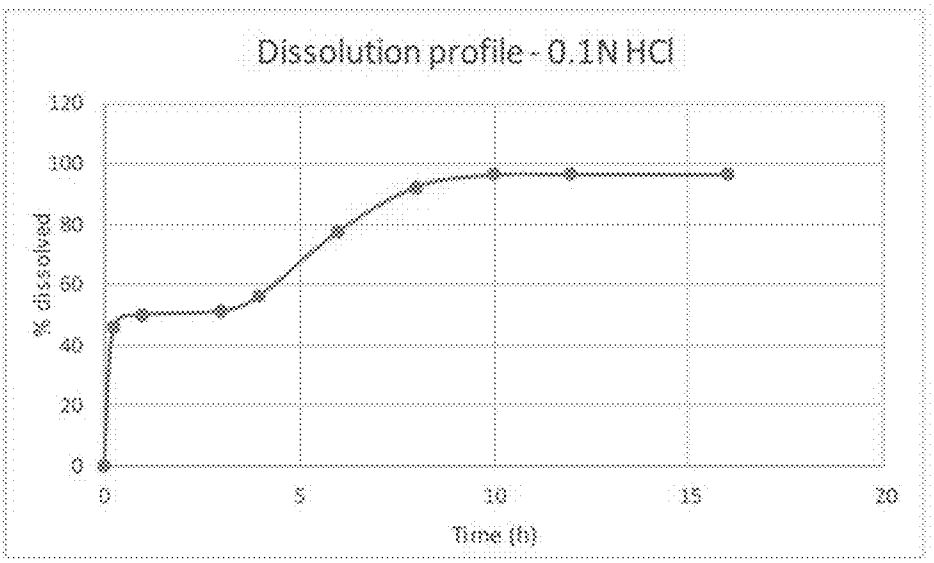


Figure 64

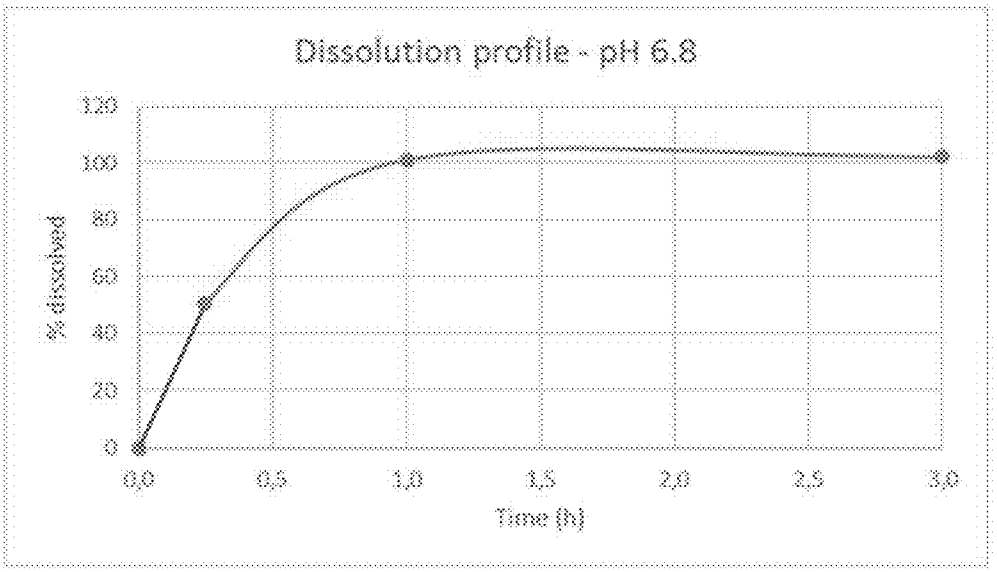


Figure 65

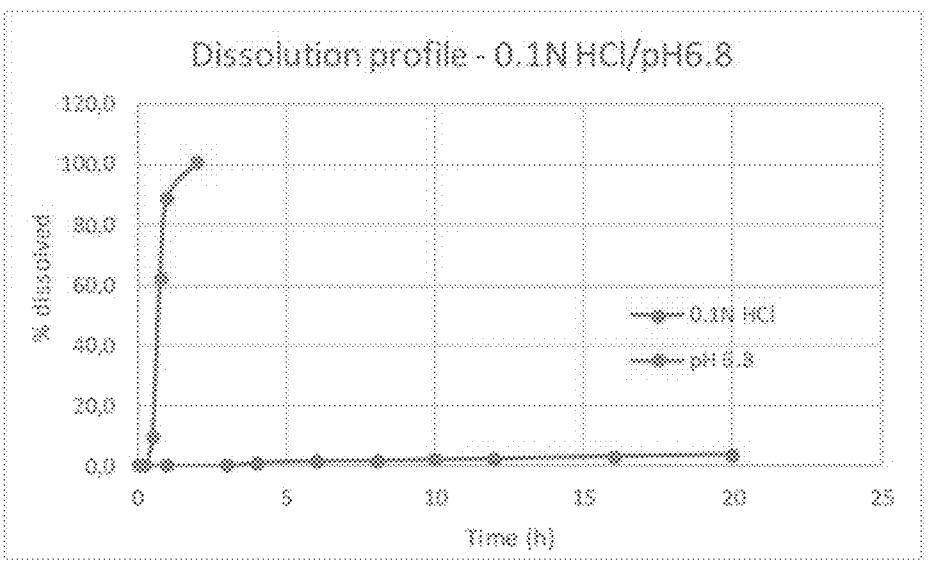


Figure 66

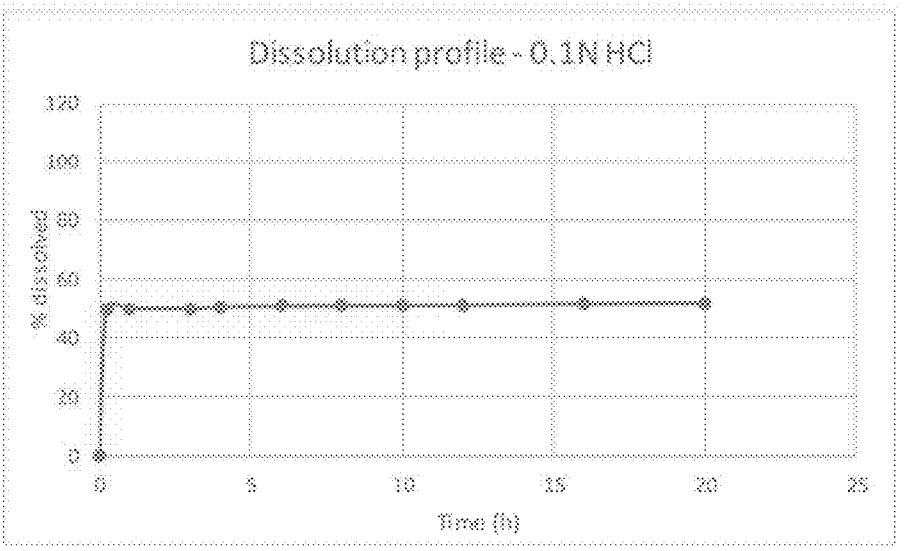


Figure 67

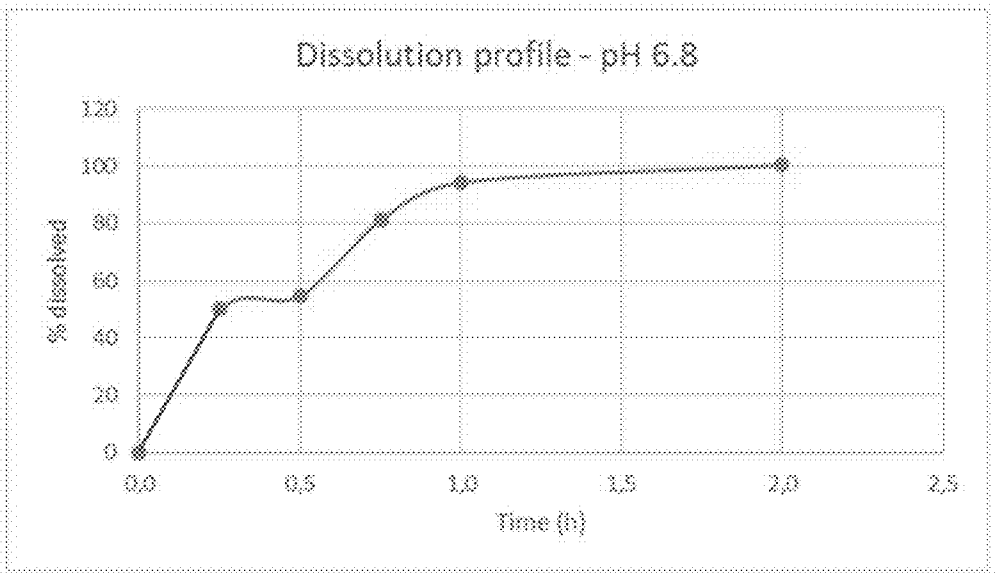


Figure 68

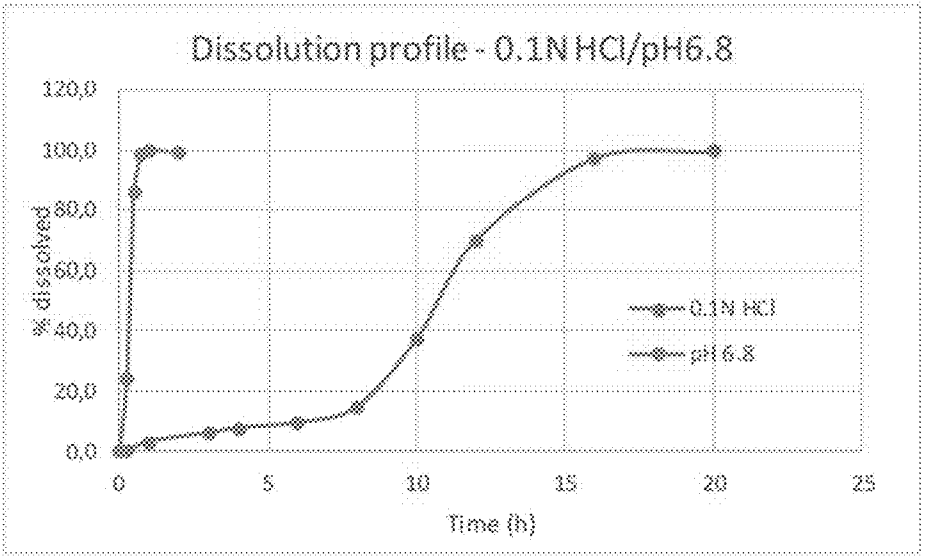


Figure 69

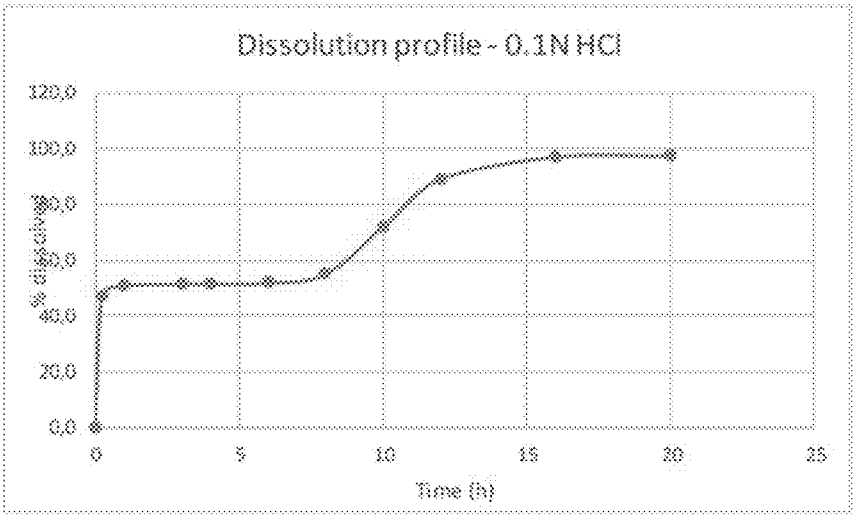


Figure 70

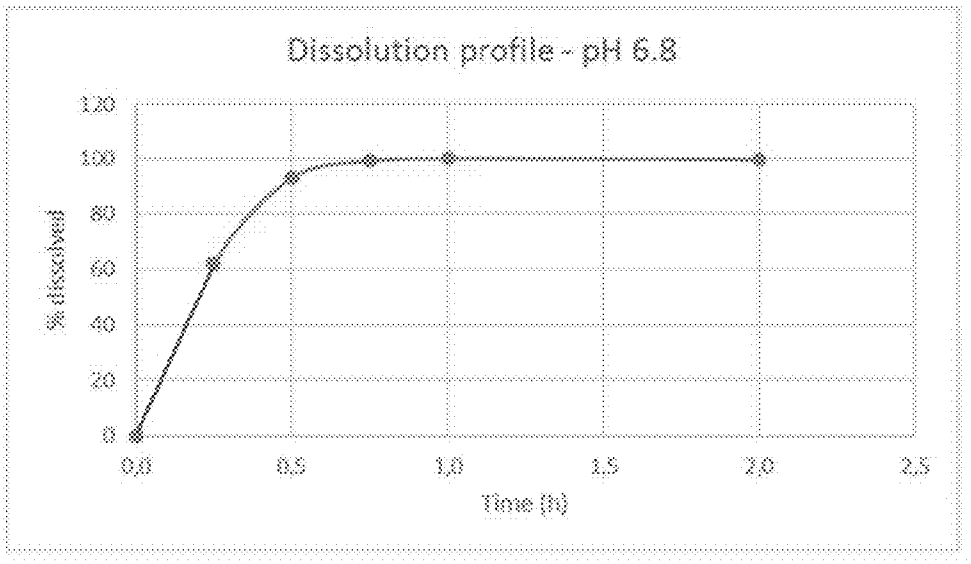


Figure 71

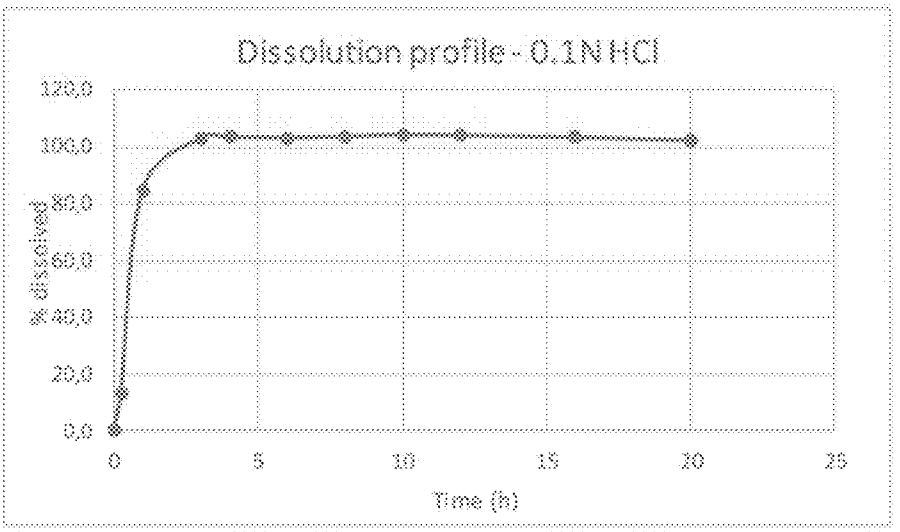


Figure 72

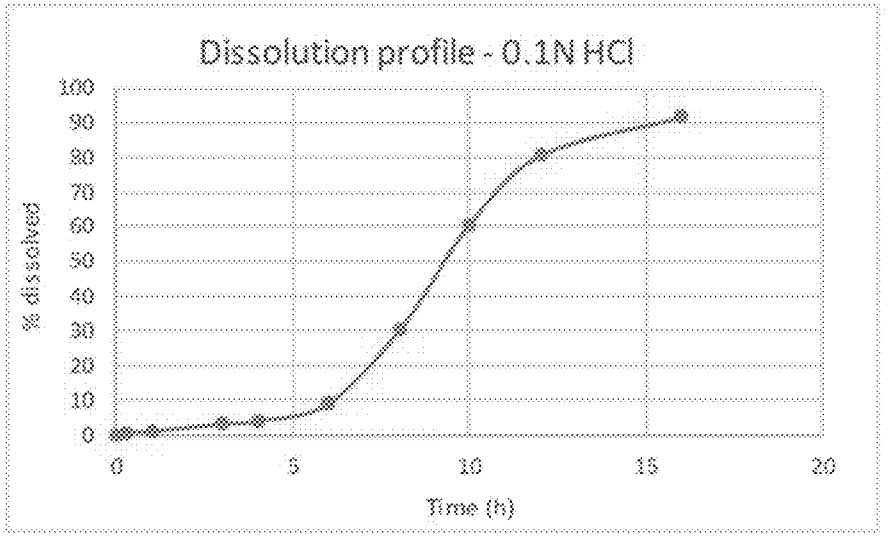


Figure 73

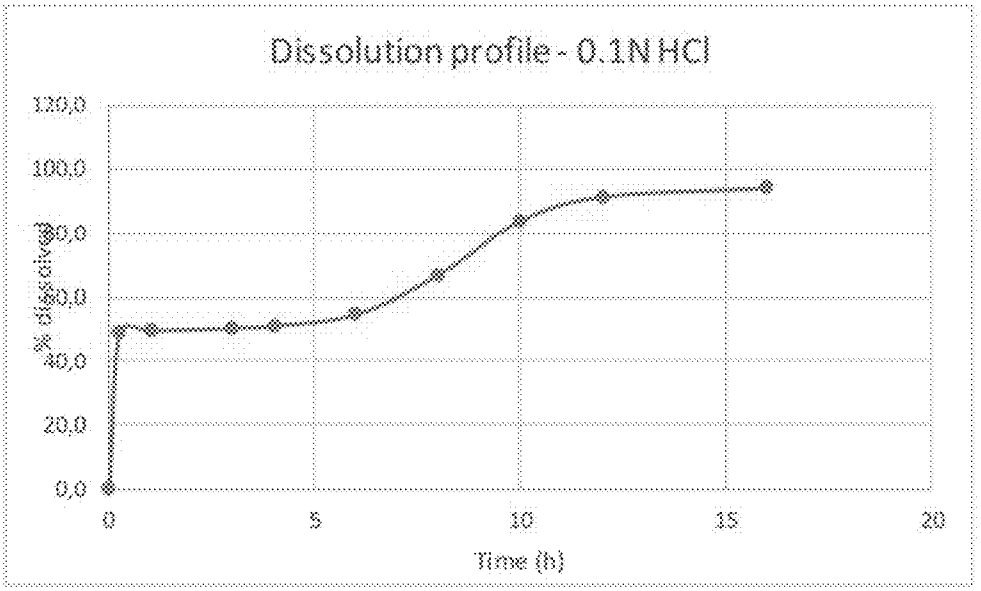


Figure 74

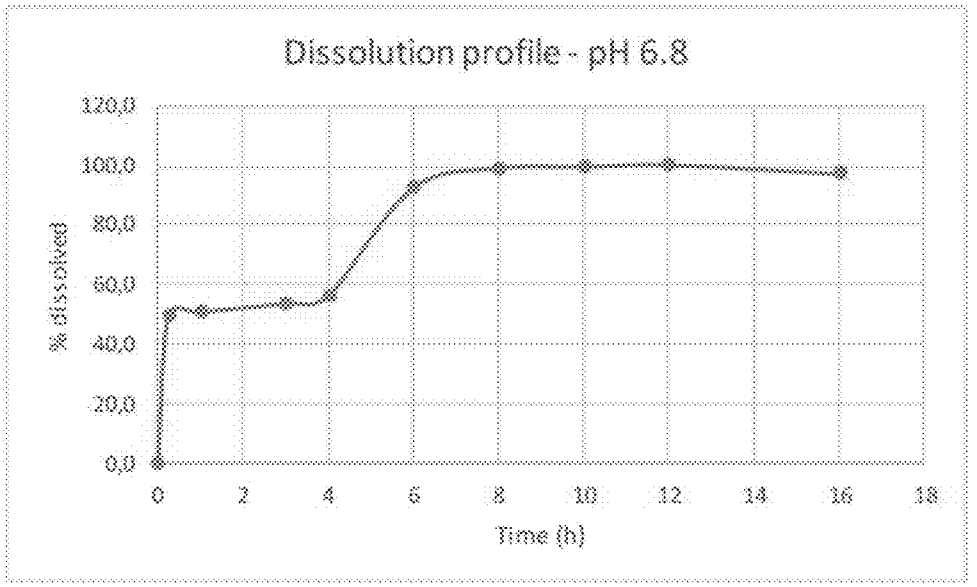


Figure 75

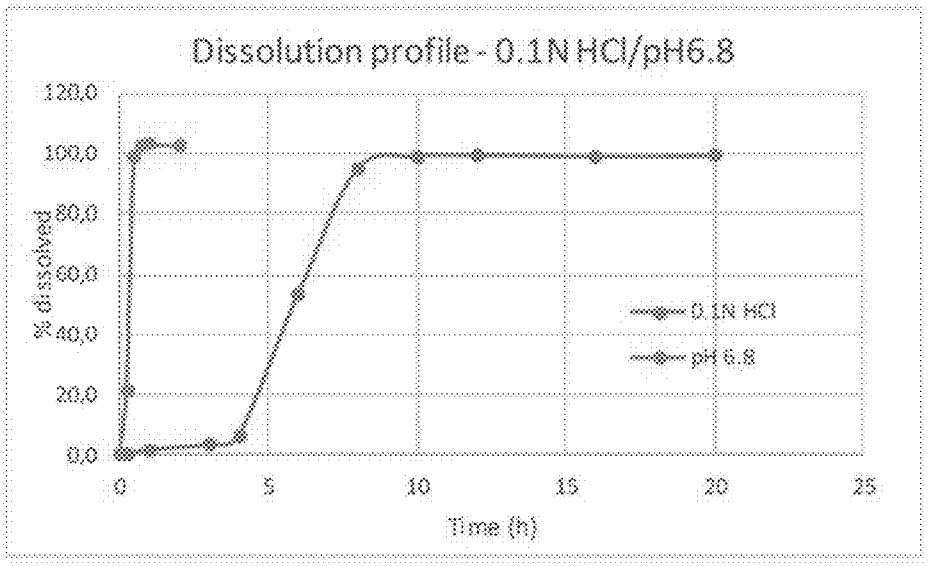


Figure 76

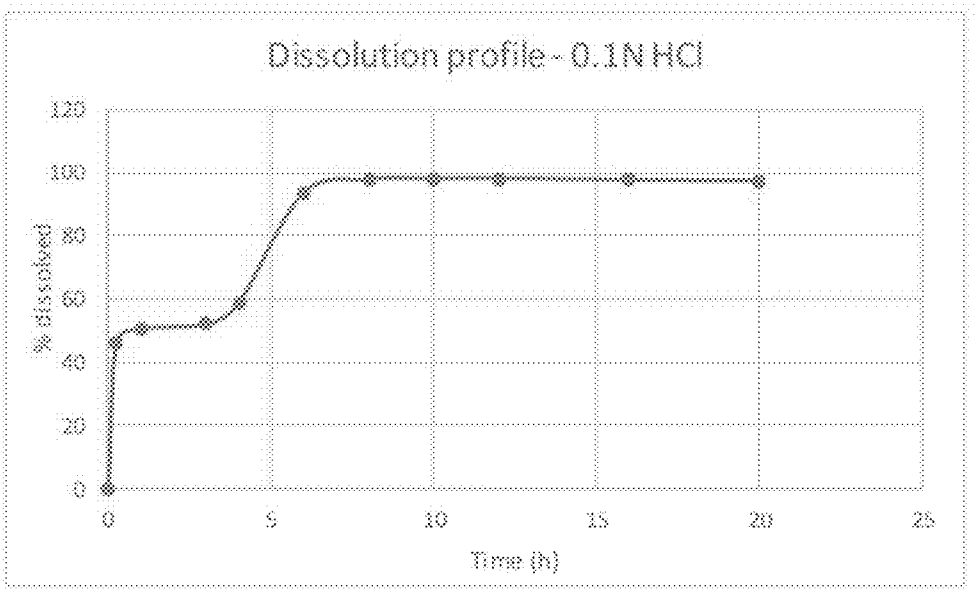


Figure 77

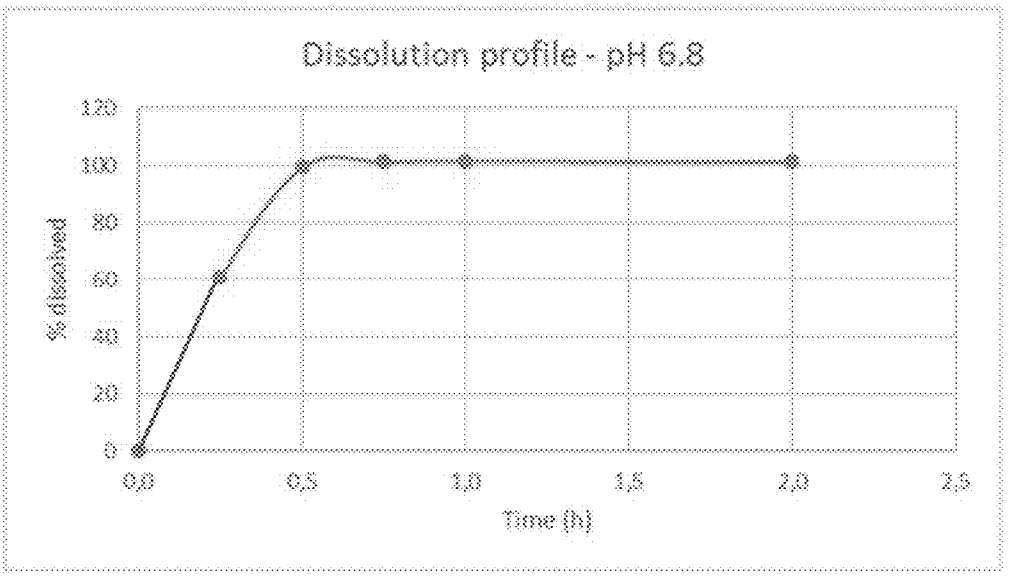


Figure 78

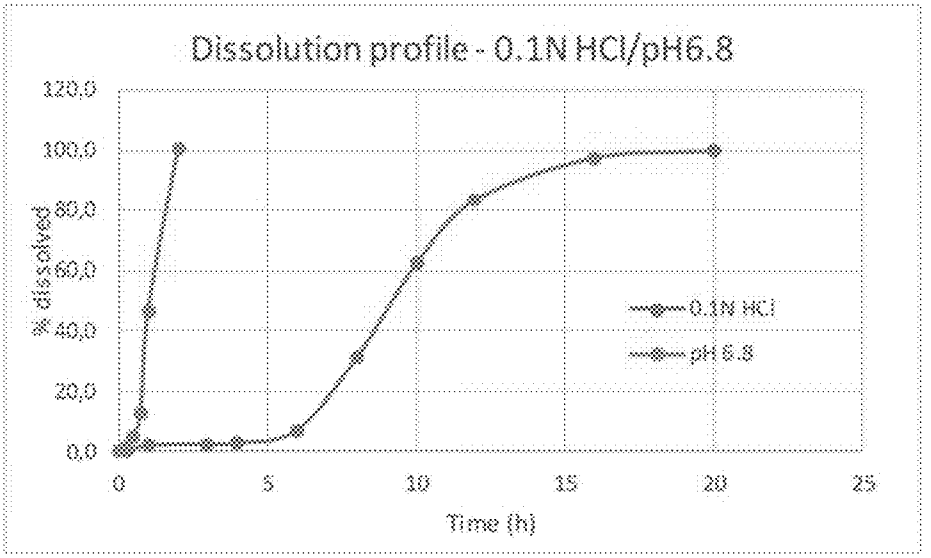


Figure 79

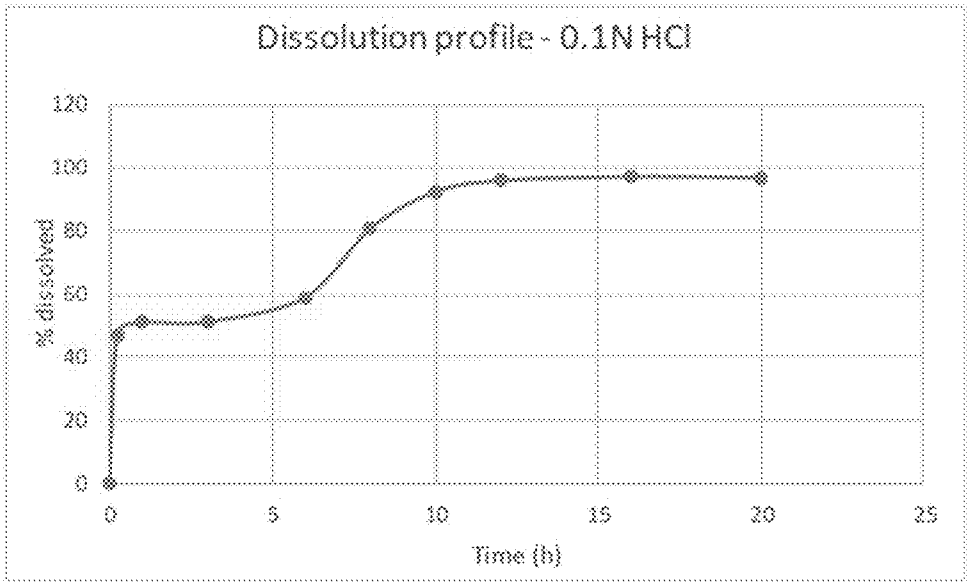


Figure 80

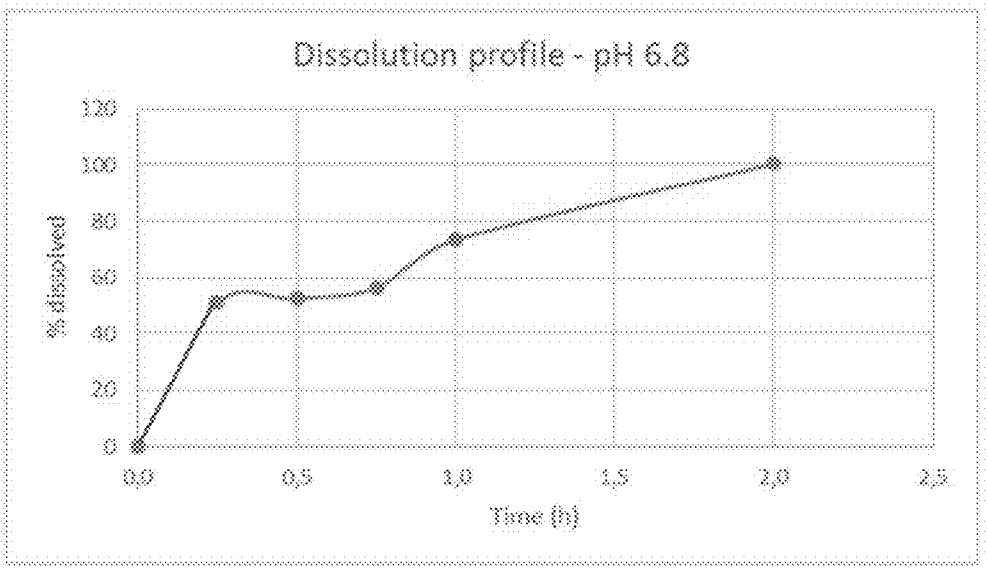


Figure 81

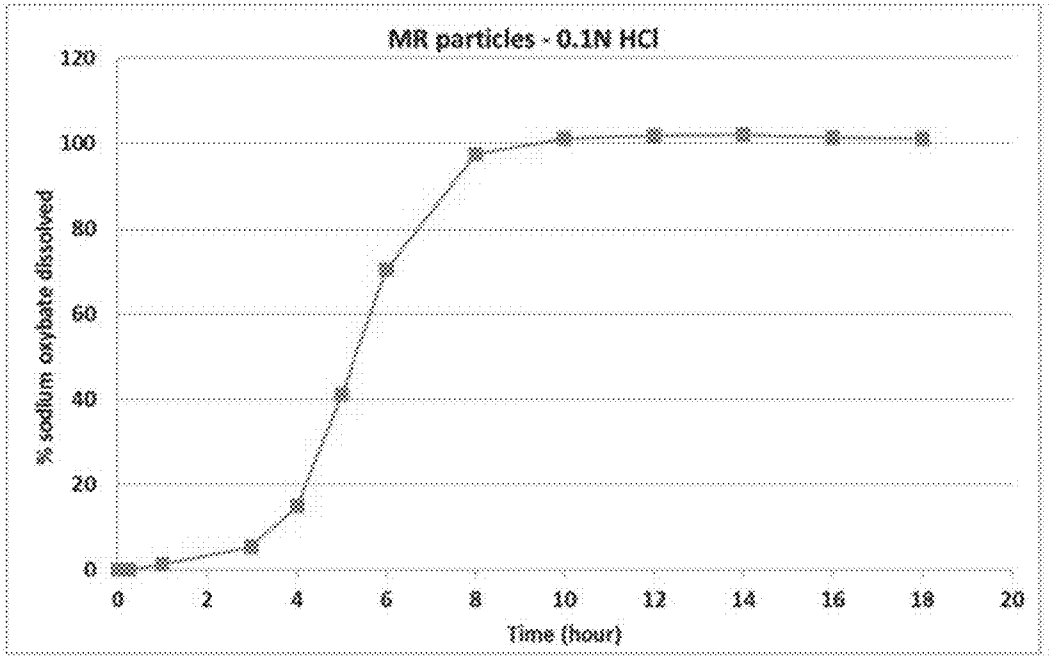


Figure 82

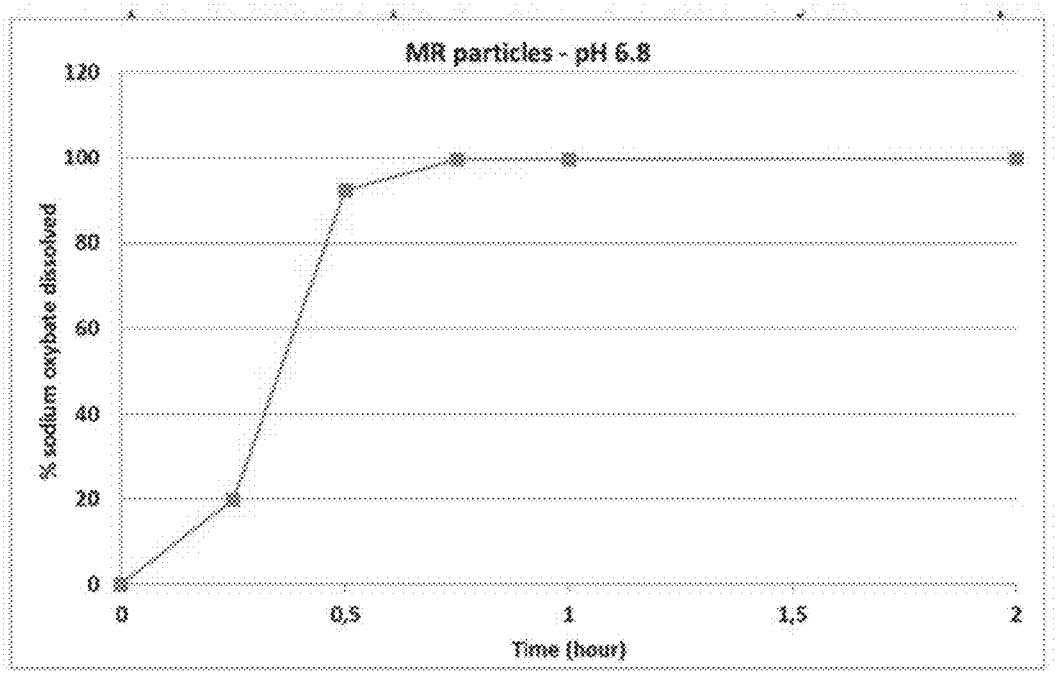


Figure 83

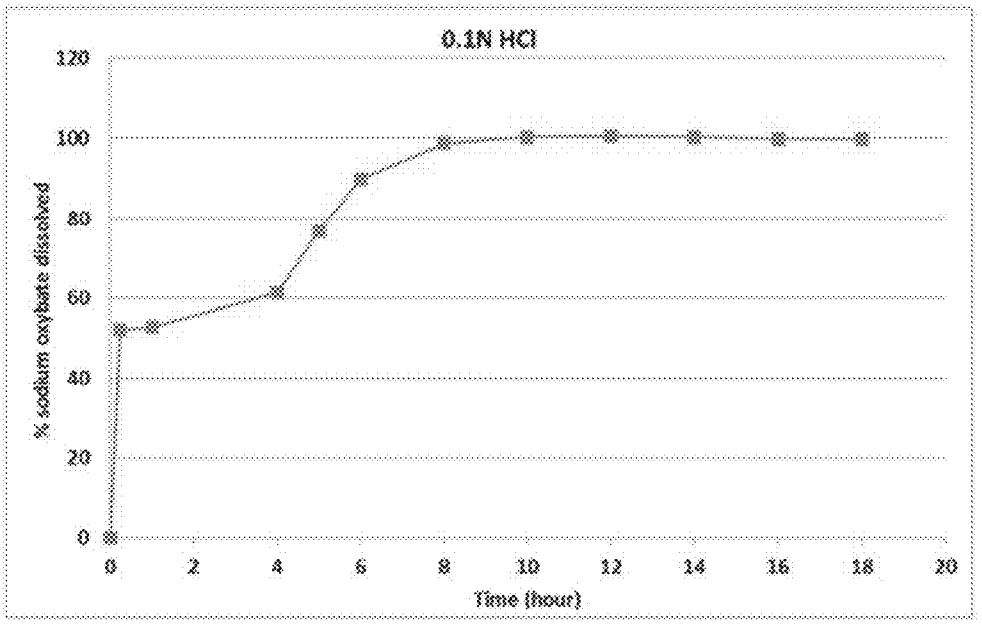


Figure 84

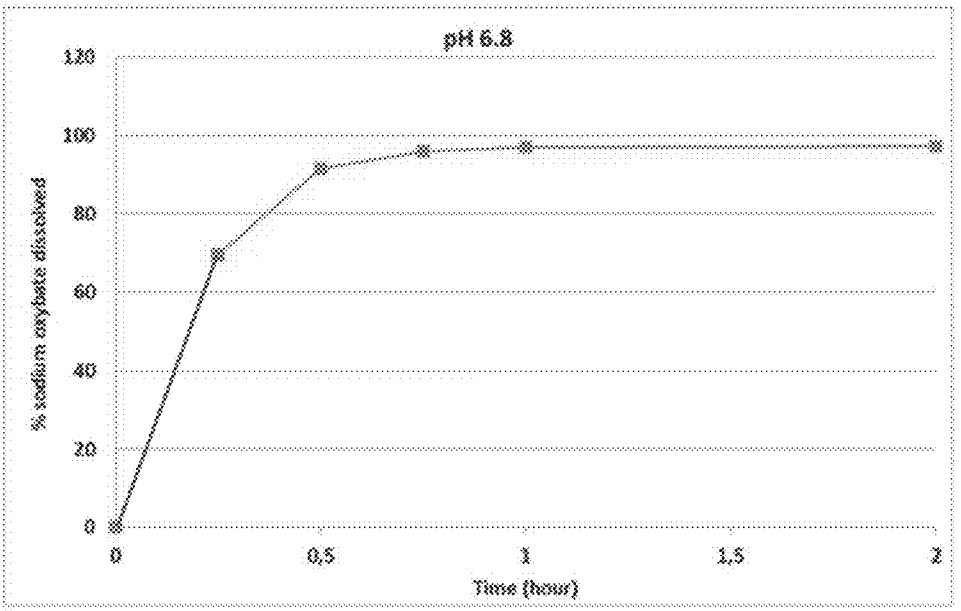


Figure 85

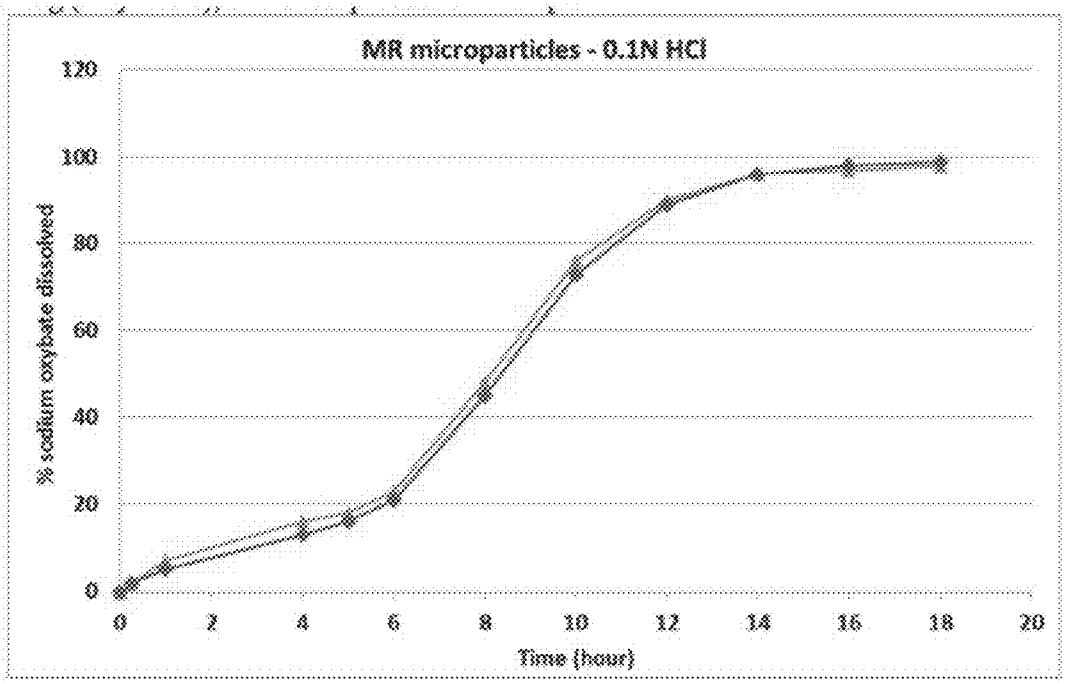


Figure 86

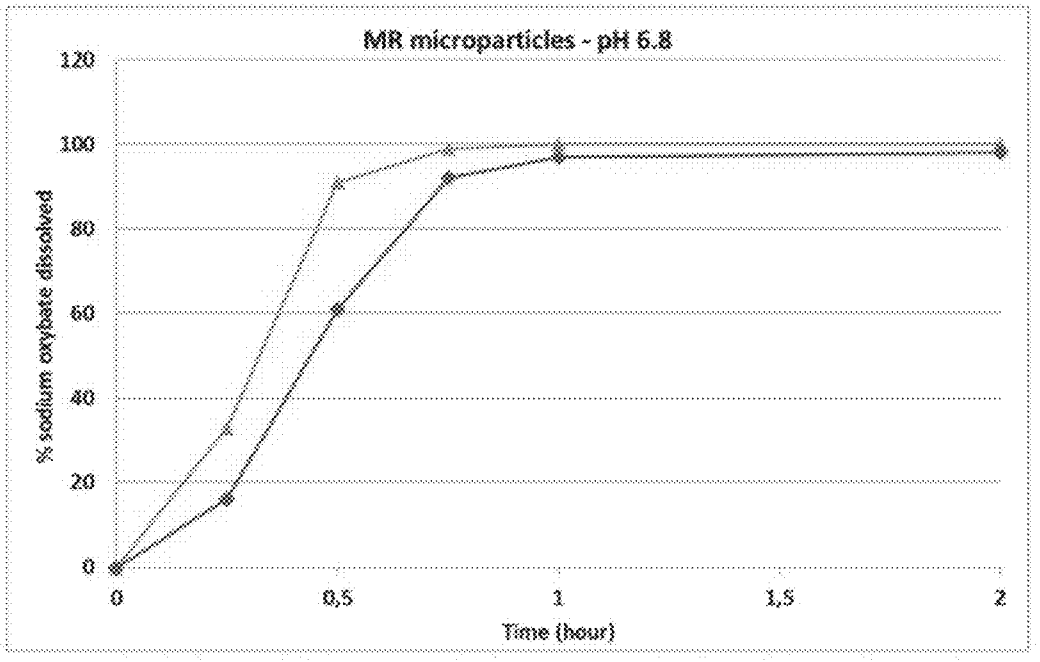


Figure 87

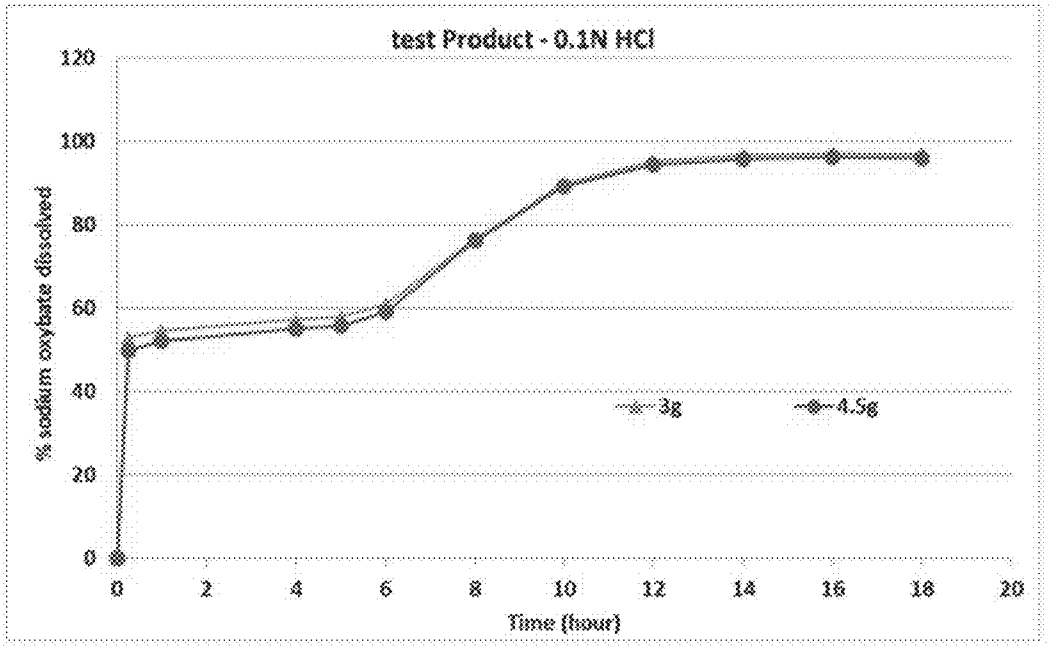


Figure 88

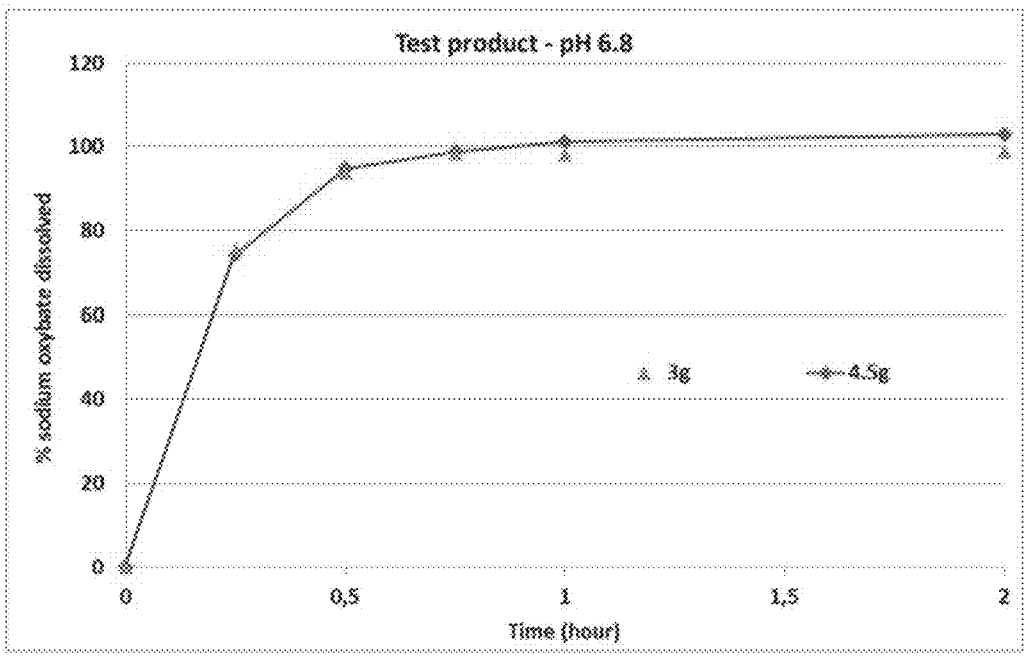

Test product - pH 6.8
% sodium oxybate dissolved
120
100
80
60
40
20
0
0
0,5
1
1,5
2
Time (hour)
3g
4.5g

Figure 89

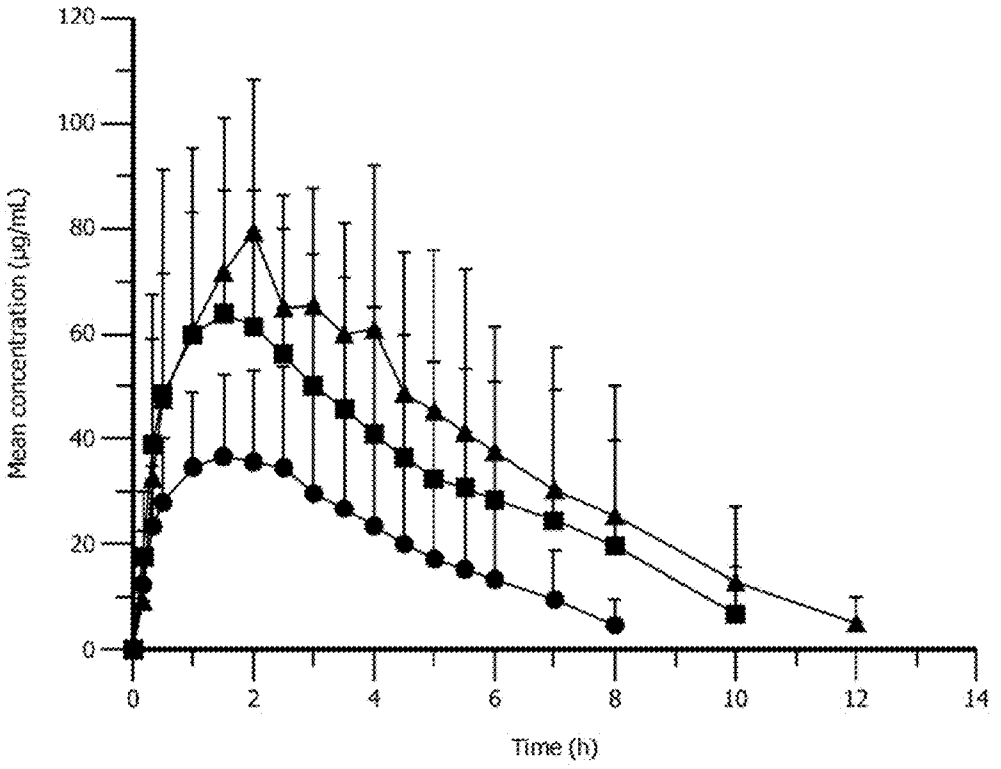

120
100
80
60
40
20
0
Mean concentration (µg/mL)
0
2
4
6
8
10
12
14
Time (h)

Figure 90

MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS

PRIOR APPLICATIONS

[0001] This application claims priority to United States Provisional Patent Application Nos. 62/365,812 (filed Jul. 22, 2016), 62/399,413 (filed Sep. 25, 2016), and 62/474,330 (filed Mar. 21, 2017). The content of the foregoing applications is hereby incorporated by reference and made a part hereof as if fully contained herein.

FIELD OF THE INVENTION

[0002] The present invention relates to modified release formulations of gamma-hydroxybutyrate having improved pharmacokinetic (PK) properties, and to therapeutic uses thereof.

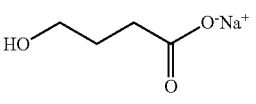
BACKGROUND

[0003] Narcolepsy is a devastating disabling condition. The cardinal symptoms are excessive daytime sleepiness (EDS), cataplexy (a sudden loss of muscle tone triggered by strong emotions, seen in approximately 60% of patients), hypnogogic hallucination (HH), sleep paralysis (SP), and disturbed nocturnal sleep (DNS). Other than EDS, DNS is the most common symptom seen among narcolepsy patients.

[0004] The diagnosis of narcolepsy rests in part on clinical grounds. When narcolepsy is suspected, it is standard practice to administer an overnight polysomnogram (PSG) followed by a multiple sleep latency test (MSLT) to document the rapid eye movement (REM) abnormality that characterizes the disorder. On the MSLT a mean sleep latency less than or equal to 8 minutes and two or more sleep onset REM periods (SOREMPs) are required to confirm a diagnosis of Type 1 or Type 2 narcolepsy. It is also possible, but infrequently preferred, that narcolepsy be diagnosed by measuring hypocretin in the cerebrospinal fluid (CSF) in cases where the PSG and/or MSLT is not completed. For these cases, a hypocretin concentration of less than 110 pg/nL confirms a narcolepsy Type 1 diagnosis.

[0005] One of the major treatments for narcolepsy is sodium oxybate, a neuroactive agent with a variety of Central Nervous System (CNS) pharmacological properties. The species is present endogenously in many tissues, where it acts as a neurotransmitter on a gamma-hydroxybutyrate (GHB) receptor (GHBR), and possesses neuromodulatory properties with significant effects on dopamine and gamma-Aminobutyric Acid (GABA). Studies have suggested that sodium oxybate improves Rapid Eye Movement Sleep (REM sleep, REMS) of narcoleptics in contrast to antidepressant drugs.

[0006] Sodium oxybate is also known as sodium 4-hydroxybutanoate, or gamma-hydroxybutyric acid sodium salt, and has the following chemical structure:



[0007] Sodium oxybate is marketed commercially in the United States as Xyrem®. The product is formulated as an immediate release liquid solution that is taken once immediately before bed, and a second time approximately 2.5 to 4 hours later, in equal doses. Sleep-onset can be dramatic and fast, and patients are advised to be sitting in bed when consuming the dose. The most commonly reported side effects are confusion, depressive syndrome, incontinence and sleepwalking.

[0008] When initiating treatment with sodium oxybate, careful titration up to an adequate level is essential both to obtain positive results and avoid adverse effects. The recommended starting dose is 4.5 g divided into 2 equal doses of 2.25 g, the first taken at bedtime and the second taken 2.5 to 4 hours later. The starting dosage can be decreased to 3.0 g/day or increased to as high as 9.0 g/day in increments of 1.5 g/day (0.75 g per dose). Two weeks are recommended between dosage adjustments to optimize reduction of daytime symptoms and minimize side effects. The ideal dose will provide an effective eight hours of sleep but, at the end of eight hours, very little of the drug will remain in the patient's bloodstream to affect the patient's wakefulness.

[0009] The requirement to take Xyrem® twice each night is a substantial inconvenience to narcolepsy patients. The patient must typically set an alarm to take the second dose, which can interrupt ongoing productive sleep. Several efforts have been made to provide a once-nightly modified release dosage form of sodium oxybate, but none has yet received approval from the United States Food and Drug Administration ("FDA") or proven effective in the clinic.

[0010] One of the biggest drawbacks of these once-nightly formulations is the reduction in bioavailability that occurs when sodium oxybate is formulated in a modified release dosage form, as measured by the blood concentration/time area under the curve ("AUC"). U.S. 2012/0076865 A1 by Allphin et al. ("Allphin"), for example, conducted two separate crossover bioavailability trials involving three separate modified release formulations and an immediate release solution, and reported the following bioavailability results:

Summary of PK Parameterse 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	0.6	4.50	130.79	350.84	351.2
SD	0.27	0.13	(0.5, 4.75)	31.52	116.74	116.74
CV %	21.93	22.61		24.1	33.27	33.24
Mean	1.19	0.58		127.3	333.33	333.72
Treatment B						
N	18	18	19	19	19	18
Mean	0.62	1.22	2.00	41.78	188.23	196.25
SD	0.16	0.40	(1.50, 5.00)	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	50.49	221.64	222.60
SD	0.16	0.23	(1.00, 5.00)	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

-continued

Summary of PK Parameterse 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	30	30	30	30	30	30
Mean	1.08	0.71	4.50	114.59	301.28	301.59
SD	0.31	0.27	(0.50, 5.50)	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	25.10	64.44	65.58
SD	0.14	0.47	(0.50, 2.50)	7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.10	61.31	62.55
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00	59.52	242.30	243.80
SD	0.20	0.64	(0.50, 5.00)	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

Treatment A: Two 3 g IR doses administered four hours apart

Treatment B: One 6 g CR dose administered at time zero (no IR component)

Treatment C: One 6 g CR dose administered at time zero (no IR component)

Treatment D: One 4 g dose including IR and CR fractions administered at time zero

Treatment E: One 8 g dose including IR and CR fractions administered at time zero

[0011] As can be seen, mean AUC_{inf}, which measures the total exposure of the body to sodium oxybate for a given dose, was significantly less for the doses having a modified release component when compared to the immediate release doses. Mean AUC_{inf} for Treatment B, which included the exact same dose of sodium oxybate as Treatment A, was only 56% of the mean AUC_{inf} for Treatment A; mean AUC_{inf} for Treatment C, which also included the same dose of sodium oxybate as Treatment A, was only 63% of the mean AUC_{inf} for Treatment A; mean AUC_{inf} for Treatment E was only 81% of the mean AUC_{inf} of Treatment A, even though Treatment E dosed 2 g more of sodium oxybate than Treatment A, which, compared to same dose, represented only 61% of the mean AUC_{inf} of Treatment A. Mean AUC_{inf} for Treatment D was only 22% of the mean AUC_{inf} of Treatment A, although Treatment D dosed 2 g less of sodium oxybate than Treatment A, which, compared to same dose, represented only 33% of the mean AUC_{inf} of Treatment A. As shown in FIGS. 12 and 14 of U.S. 2012/0076865 A1, Allphin's formulations also suffered from an excess of sodium oxybate remaining in the bloodstream at 8 hours.

[0012] U.S. Pat. No. 8,193,211 to Liang et al. ("Liang") reports even lower bioavailability from his once-nightly formulations. Liang developed several enterically coated delayed release formulations of sodium oxybate, and tested these formulations in dogs alongside an immediate release formulation to compare the relative pharmacokinetics (PK) of these formulations. The results of Liang's testing are reported below:

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%

DR1-w/ Acid: Two 1 g DR capsules administered at time zero

DR1-No Acid: Two 1 g DR capsules administered at time zero

IR: Two 1 g IR capsules administered at time zero

DR2: Two 1 g DR capsules administered at time zero

[0013] As can be seen, by encapsulating the sodium oxybate in an enteric/delayed release coating, Liang decreased the AUC of the sodium oxybate significantly. One of the formulations, DR1-w/Acid, had a relative bioavailability of only 22% compared to the immediate release dosage form. DR2 had the greatest relative bioavailability, but still only 53% compared to the immediate release dosage form. One can easily calculate that any of the envisioned combinations of immediate release (IR) components and delayed release (DR) components as described in col. 5 lines 3 to 28 of U.S. Pat. No. 8,193,211 will not give a relative bioavailability greater than 78%.

[0014] All of these formulations are inconvenient for at least two reasons: (1) the low relative bioavailability necessitates an increase in the dose compared to current IR treatments which already require a large dose (4.5 to 9 g a day), and (2) when provided in the form of pills, a patient must swallow around 4 to 9 pills per dose, which is a serious inconvenience for the patient and potential drawback for patient compliance.

[0015] Various other techniques are known for formulating modified release dosage forms including, for example, the techniques described in U.S. Pat. No. 8,101,209 to Legrand et al. ("Legrand"). Legrand provides a system ensuring that the active ingredient is released with certainty from the modified release dosage form by means of a dual mechanism of "time-dependent" and "pH-dependent" release. Legrand did not describe any dosage forms for delivering sodium oxybate or other forms of gamma-hydroxybutyrate.

[0016] Another drawback of Xyrem® is the high level of the daily dose, generally 7.5 g or 9 g of sodium oxybate taken daily over long periods of time. This represents a very high sodium intake which is not recommended in persons with high blood pressure, risk of cardiovascular disease, stroke or coronary heart disease (See WHO. Guideline: Sodium intake for adults and children. Geneva, World Health Organization (WHO), 2012.).

[0017] Accordingly, one object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that are administered only once at bed-time with improved dissolution and pharmacokinetic profiles.

[0018] Another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that optimize the bioavailability of the gamma-hydroxybutyrate, and roughly approximate the bioavailability of an equal dose of an immediate release liquid solution of sodium oxybate administered twice nightly.

[0019] Still another object of the present invention is to provide once-nightly modified release formulations of gamma-hydroxybutyrate that roughly approximate or exceed the bioavailability of an equal dose of an immediate release solution of sodium oxybate administered twice nightly, across the entire therapeutic range of sodium oxybate doses.

[0020] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate which, 8 hours after administration, produce very little residual drug content in the bloodstream of most patients but still similar to the one observed after administration of an equal dose of an immediate release liquid solution of sodium oxybate administered twice nightly.

[0021] Yet another object of the present invention is to improve the therapeutic effectiveness and safety profile of gamma-hydroxybutyrate based on novel dissolution and pharmacokinetic profiles.

[0022] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that yield a similar pharmacokinetic profile compared to an immediate release liquid solution of sodium oxybate administered twice nightly while potentially giving a reduced dose.

[0023] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that allow once daily administration and reduced dose compared to the commercial treatment Xyrem®.

[0024] Yet another object of the present invention is to provide a convenient dosage form of gamma-hydroxybutyrate that can be easily swallowed.

[0025] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that are administered only once at bed-time with improved dissolution and pharmacokinetic profiles and reduced sodium content compared to an immediate release liquid solution of sodium oxybate administered twice nightly.

SUMMARY OF INVENTION

[0026] As the prior art demonstrates, it is extremely difficult to find a modified release formulation of gamma-hydroxybutyrate which, when administered only once nightly, has a comparable bioavailability to an immediate release liquid solution of sodium oxybate administered twice nightly. Even if such a formulation could be found, it probably still would not be satisfactory because the dose of gamma-hydroxybutyrate differs among individuals, and the size of the dose affects the amount of drug absorbed through the GI tract. I.e., even if the prior art formulations achieved comparable bioavailability at one dose—which they do not—they would not be comparable at other doses.

[0027] The inventors have discovered a novel relationship between the in vitro release profile of gamma-hydroxybutyrate modified release formulations and in vivo absorption which permits, for the first time, a modified release formulation of gamma-hydroxybutyrate that approximates the bioavailability of a twice-nightly equipotent immediate release liquid solution of sodium oxybate, and that does so across a range of therapeutic doses. In particular, the inventors have discovered that a modified release formulation of gamma-hydroxybutyrate that rapidly releases half of its gamma-hydroxybutyrate in 0.1N hydrochloric acid dissolution medium, and rapidly releases the other half of its gamma-hydroxybutyrate in phosphate buffer pH 6.8 dissolution medium, approximates or exceeds the in vivo bioavailability of an equipotent immediate release liquid solution of sodium oxybate administered twice nightly. This can be seen by comparing the formulations of Examples 1 and 4, which satisfy the dissolution requirements of the present invention and achieve the necessary bioavailability for a commercial formulation, with the Comparative formulation of Example 7, which exhibited a dissolution profile similar to prior art dissolution profiles, and did not achieve the necessary bioavailability for a commercial formulation.

[0028] This phenomenon is observed especially with higher doses of gamma-hydroxybutyrate. For example, the inventors have discovered that a modified release composition of gamma-hydroxybutyrate according to the invention administered once approximately two hours after a standardized evening meal at the dose equivalent to 7.5 g of sodium oxybate results in a similar pharmacokinetic profile as an immediate release liquid solution of sodium oxybate given in two separate equal doses of 4.5 g of sodium oxybate each administered at t_0 and t_{4h}.

[0029] The modified release formulations of gamma-hydroxybutyrate preferably have both immediate release and modified release portions. The release of gamma-hydroxybutyrate from the immediate release portion is practically uninhibited, and occurs almost immediately in 0.1N hydrochloric acid dissolution medium. In contrast, while the modified release portion also preferably releases its gamma-hydroxybutyrate almost immediately when fully triggered, the release is not triggered until a predetermined lag-time or the drug is subjected to a suitable dissolution medium such as a phosphate buffer pH 6.8 dissolution medium. Without wishing to be bound by any theory, it is believed that this rapid release in two dissolution media compresses the blood concentration vs. time curve in vivo, resulting in a relative bioavailability of gamma-hydroxybutyrate comparable to or greater than an equipotent dose of an immediate-release liquid solution of sodium oxybate administered twice nightly.

[0030] Formulations that achieve this improved bioavailability can be described using several different pharmacokinetic and in vitro dissolution parameters. In a first principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL.

[0031] In a second principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL, and a mean C_{8h} that is

from 50% to 130% of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0032] In a third principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0033] In a fourth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0034] In a fifth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0035] In a sixth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and (b) the formulation releases (i) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (ii) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0036] In a seventh principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0037] In an eighth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and (d) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0038] In a ninth principal embodiment, the invention provides a modified release formulation of gamma-hydroxy-

butyrate, preferably comprising immediate release and modified release portions, wherein 4.5 g, 6 g, 7.5 g, and 9 g doses of the formulation have been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0039] In a tenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein 4.5 g and 9 g doses of the formulation have been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0040] In an eleventh principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 6.0 g or 7.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **12** or FIG. **13** for the corresponding strength.

[0041] In a twelfth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **22**.

[0042] In a thirteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **7** and FIG. **8**.

[0043] In a fourteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **20** and FIG. **21**.

[0044] In a fifteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein said modified release portion yields a dissolution profile substantially as depicted in FIG. **3** or FIG. **16**.

[0045] In a sixteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **25** and FIG. **26**.

[0046] In a seventeenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **27** and FIG. **28**.

[0047] In an eighteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate yielding a dissolution profile substantially as shown in any one of FIGS. **29** through **89**.

[0048] A nineteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 7.5 g or 9.0 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **90** for the corresponding strength.

[0049] A twentieth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **26** and FIG. **28**.

[0050] Still further embodiments relate to methods of using the formulations of the present invention to treat narcolepsy and associated disorders and symptoms, and to physical aspects of the formulations of the present invention. Additional principal embodiments and sub-embodiments thereto will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION OF THE FIGURES

[0051] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments of the invention and together with the description serve to explain the principles of the invention.

[0052] FIG. **1** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 1.

[0053] FIG. **2** plots a time release dissolution profile of IR microparticles of gamma-hydroxybutyrate of Example 1 (♦) and 1bis (■) in a 0.1N HCl dissolution medium.

[0054] FIG. **3** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 1 in two sequential dissolution media (0.1 N HCl/phosphate buffer pH 6.8).

[0055] FIG. **4** plots a time release dissolution profile of MR microparticles (▲ symbols) of Example 1 in two sequential dissolution media (0.1 N HCl/phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (● symbols).

[0056] FIG. **5** plots a time release dissolution profile of the finished formulation of Example 1 in deionized water.

[0057] FIG. **6** plots a time release dissolution profile of the finished composition of Example 1 in deionized water (▲ symbols), overlaid against dissolution profile described in FIG. 2 of USP 2012/0076865 (● symbols).

[0058] FIG. **7** plots time release dissolution profiles in 0.1N HCl of four separate batches of finished compositions produced in accordance with Example 1 or Example 1bis.

[0059] FIG. **8** plots time release dissolution profiles in phosphate buffer pH 6.8 of four separate batches of finished compositions produced in accordance with Example 1 or Example 1bis.

[0060] FIG. **9** plots time release dissolution profiles in 0.1N HCl of MR microparticles of gamma-hydroxybutyrate produced in accordance with Example 1 at 75 rpm (■ symbols) and 100 rpm (▲ symbols).

[0061] FIG. **10** plots time release dissolution profiles in 0.1N HCl of finished composition produced in accordance with Example 1 performed with paddle rotation speed set at 75 rpm (■ symbols) and 100 rpm (▲ symbols).

[0062] FIG. **11** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time for two different modified release formulations of gamma-hydroxybutyrate tested in vivo according to the methods of Example 3. Time profiles are given for a 4.5 g dose of the finished composition of Example 1bis administered once (● symbols) (N=26) and a 4.5 g dose of Xyrem® administered in two divided doses (- symbols) (N=15).

[0063] FIG. **12** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time after a Single Oral Administration of 4.5 g (● symbols) and 6 g (▲ symbols) of finished composition of Example 1bis in the same 7 subjects tested in vivo according to the methods of Example 3.

[0064] FIG. **13** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time of three separate doses of finished composition prepared according to Example 1bis tested in vivo according to the methods of Example 3. Mean time profiles are given for a single oral administration of 4.5 g (N=26) (●), 6.0 g (N=19) (▲) or 7.5 g (■) doses (N=1).

[0065] FIG. **14** plots the mean plasma gamma-hydroxybutyrate Concentrations (microgram/mL) of a Single dose of 7.5 g (■) of finished composition prepared according to Example 1bis compared to 2×4.5 g Xyrem® post-fed (Source NDA 21-196 review).

[0066] FIG. **15** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 4.

[0067] FIG. **16** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 4 in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8).

[0068] FIG. **17** plots a time release dissolution profile of MR microparticles (▲ symbols) of Example 4 in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (● symbols).

[0069] FIG. **18** plots a time release dissolution profile of the finished composition of Example 4 in deionized water.

[0070] FIG. **19** plots a time release dissolution profile of the finished composition of Example 4 in deionized water (● symbols), overlaid against dissolution profile described in FIG. 2 of USP 2012/0076865 (▲ symbols).

[0071] FIG. **20** plots time release dissolution profiles in 0.1N HCl of three separate batches of finished compositions produced in accordance with Example 4 or 4bis.

[0072] FIG. **21** plots a time release dissolution profile in phosphate buffer pH 6.8 of a finished composition produced in accordance with Example 4.

[0073] FIG. **22** plots mean plasma gamma-hydroxybutyrate concentration (microgram/mL) time profiles after a Single Dose of 4.5 g (■) of finished composition of Example 4bis, N=15 compared to 2×2.25 g Xyrem® post fed, N=15.

[0074] FIG. **23** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 7.

[0075] FIG. **24** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 7 (▲ symbols) in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (● symbols).

[0076] FIG. **25** plots the Min (■) and Max (▲) values of a preferred dissolution profile in 0.1N HCl of finished composition according to the invention.

[0077] FIG. **26** plots the Min (■) and Max (▲) values of a preferred dissolution profile in phosphate buffer pH 6.8 of finished composition according to the invention.

[0078] FIG. **27** plots the Min (■) and Max (▲) values of another preferred dissolution profile in phosphate buffer pH 6.8 of finished composition according to the invention.

[0079] FIG. **28** plots the Min (■) and Max (▲) values of another preferred dissolution profile in 0.1N HCl of finished composition according to the invention.

[0080] FIG. **29** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus 2 for the formulation of Example 9.1 5 minutes and 15 minutes after reconstitution in water.

[0081] FIG. **30** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus 2 for the formulation of Example 9.2 5 minutes and 15 minutes after reconstitution in water.

[0082] FIG. **31** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus 2 for the formulation of Example 9.3 5 minutes and 15 minutes after reconstitution in water.

[0083] FIG. **32** depicts the dissolution profile determined in 0.1N HCl using a USP apparatus 2 of a 9 g dose of the formulation of Example 10 with and without rinsing.

[0084] FIG. **33** depicts the dissolution profile of the MR portion of the formulation of Example 11a in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0085] FIG. **34** depicts the dissolution profile of the formulation of Example 11a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0086] FIG. **35** depicts the dissolution profile of the formulation of Example 11a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0087] FIG. **36** depicts the dissolution profile of the MR portion of the formulation of Example 11b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0088] FIG. **37** depicts the dissolution profile of the formulation of Example 11b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0089] FIG. **38** depicts the dissolution profile of the formulation of Example 11b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0090] FIG. **39** depicts the dissolution profile of the formulation of Example 11c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0091] FIG. **40** depicts the dissolution profile of the formulation of Example 11c in pH6.8 phosphate buffer (0.05M

monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0092] FIG. **41** depicts the dissolution profile of the MR portion of the formulation of Example 12a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0093] FIG. **42** depicts the dissolution profile of the formulation of Example 12a using a USP apparatus 2 in 0.1N HCl.

[0094] FIG. **43** depicts the dissolution profile of the formulation of Example 12b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0095] FIG. **44** depicts the dissolution profile of the formulation of Example 12b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0096] FIG. **45** depicts the dissolution profile of the MR portion of the formulation of Example 13 in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0097] FIG. **46** depicts the dissolution profile of the formulation of Example 13 in 900 ml of 0.1N HCl using a USP apparatus 2.

[0098] FIG. **47** depicts the dissolution profile of the formulation of Example 13 in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0099] FIG. **48** depicts the dissolution profile of the MR portion of the formulation of Example 14 in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0100] FIG. **49** depicts the dissolution profile of the formulation of Example 14 in 900 ml of 0.1N HCl using a USP apparatus 2.

[0101] FIG. **50** depicts the dissolution profile of the formulation of Example 14 in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0102] FIG. **51** depicts the dissolution profile of the MR portion of the formulation of Example 15a (coating weight 35%) in 900 ml of 0.1N HCl using a USP apparatus 2.

[0103] FIG. **52** depicts the dissolution profile of the MR portion of the formulation of Example 15a (coating weight 50%) in 900 ml of 0.1N HCl using a USP apparatus 2.

[0104] FIG. **53** depicts the dissolution profile of the formulation of Example 15a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0105] FIG. **54** depicts the dissolution profile of the MR portion of the formulation of Example 15b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0106] FIG. **55** depicts the dissolution profile of the formulation of Example 15b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0107] FIG. **56** depicts the dissolution profile of the formulation of Example 15b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0108] FIG. **57** depicts the dissolution profile of the MR portion of the formulation of Example 15c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0109] FIG. **58** depicts the dissolution profile of the formulation of Example 15c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0110] FIG. **59** depicts the dissolution profile of the formulation of Example 15c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0111] FIG. **60** depicts the dissolution profile of the MR portion of the formulation of Example 15d in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0112] FIG. **61** depicts the dissolution profile of the formulation of Example 15d in 900 ml of 0.1N HCl using a USP apparatus 2.

[0113] FIG. **62** depicts the dissolution profile of the formulation of Example 15d in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0114] FIG. **63** depicts the dissolution profile of the MR portion of the formulation of Example 16a in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0115] FIG. **64** depicts the dissolution profile of the formulation of Example 16a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0116] FIG. **65** depicts the dissolution profile of the formulation of Example 16a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0117] FIG. **66** depicts the dissolution profile of the MR portion of the formulation of Example 16b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0118] FIG. **67** depicts the dissolution profile of the formulation of Example 16b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0119] FIG. **68** depicts the dissolution profile of the formulation of Example 16b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0120] FIG. **69** depicts the dissolution profile of the MR portion of the formulation of Example 16c in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0121] FIG. **70** depicts the dissolution profile of the formulation of Example 16c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0122] FIG. **71** depicts the dissolution profile of the formulation of Example 16c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0123] FIG. **72** depicts the dissolution profile of the MR portion of the formulation of Example 16d in 900 ml of 0.1N HCl using a USP apparatus 2.

[0124] FIG. **73** depicts the dissolution profile of the MR portion of the formulation of Example 17a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0125] FIG. **74** depicts the dissolution profile of the formulation of Example 17a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0126] FIG. **75** depicts the dissolution profile of the formulation of Example 17a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0127] FIG. **76** depicts the dissolution profile of the MR portion of the formulation of Example 17b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0128] FIG. **77** depicts the dissolution profile of the formulation of Example 17b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0129] FIG. **78** depicts the dissolution profile of the formulation of Example 17b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0130] FIG. **79** depicts the dissolution profile of the MR portion of the formulation of Example 17c in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0131] FIG. **80** depicts the dissolution profile of the formulation of Example 17c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0132] FIG. **81** depicts the dissolution profile of the formulation of Example 17c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0133] FIG. **82** depicts a preferred dissolution profile of sodium oxybate MR microparticles in 900 ml 0.1N HCl using a USP apparatus 2 at 75 rpm.

[0134] FIG. **83** depicts a preferred dissolution profile of sodium oxybate MR microparticles in 900 ml pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2 at 75 rpm.

[0135] FIG. **84** depicts a preferred dissolution profile of a sodium oxybate finished formulation comprising IR and MR microparticles in 900 ml 0.1N HCl using a USP apparatus 2 at 75 rpm.

[0136] FIG. **85** depicts a preferred dissolution profile of a sodium oxybate finished formulation comprising IR and MR microparticles in 900 ml pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2 at 75 rpm.

[0137] FIG. **86** is a dissolution profile in 0.1N HCl of two separate batches of the sodium oxybate MR microparticles present in the finished composition of Example 18.

[0138] FIG. **87** is a dissolution profile in phosphate buffer pH 6.8 of two separate batches of the sodium oxybate MR microparticles present in the finished composition of Example 18.

[0139] FIG. **88** is a dissolution profile in 0.1N HCl of two unit doses of 3 g (▲ symbols) and 4.5 g (● symbols) of the finished composition of Example 18.

[0140] FIG. **89** is a dissolution profile in phosphate buffer pH 6.8 of two unit doses of 3 g (▲ symbols) and 4.5 g (● symbols) of the finished composition of Example 18.

[0141] FIG. **90** plots mean plasma gamma-hydroxybutyrate concentrations (microgram/mL)+SD—time profiles after a single oral administration of 4.5 g (● symbols), 7.5 g (■ symbols) and 9 g (▲ symbols) of the finished composition of Example 18.

DETAILED DESCRIPTION OF THE INVENTION

[0142] The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein.

Definitions and Use of Terms

[0143] Wherever an analysis or test is required to understand a given property or characteristic recited herein, it will be understood that the analysis or test is performed in accordance with applicable guidances, draft guidances, regulations and monographs of the United States Food and Drug Administration ("FDA") and United States Pharmacopoeia ("USP") applicable to drug products in the United States in force as of Nov. 1, 2015 unless otherwise specified. Clinical endpoints can be judged with reference to standards adopted by the American Academy of Sleep Medicine, including standards published at C Iber, S Ancoli-Israel, A Chesson, S F Quan. The AASM Manual for the Scoring of Sleep and Associated Events. Westchester, Ill.: American Academy of Sleep Medicine; 2007.

[0144] When a pharmacokinetic comparison is made between a formulation described or claimed herein and a reference product, it will be understood that the comparison is preferably performed in a suitable designed cross-over trial, although it will also be understood that a cross-over trial is not required unless specifically stated. It will also be understood that the comparison can be made either directly or indirectly. For example, even if a formulation has not been tested directly against a reference formulation, it can still satisfy a comparison to the reference formulation if it has been tested against a different formulation, and the comparison with the reference formulation can be deduced therefrom.

[0145] As used in this specification and in the claims which follow, the singular forms "a," "an" and "the" include plural referents unless the context dictates otherwise. Thus, for example, reference to "an ingredient" includes mixtures of ingredients, reference to "an active pharmaceutical agent" includes more than one active pharmaceutical agent, and the like.

[0146] "Bioavailability" means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

[0147] "Relative bioavailability" or "Rel BA" or "RBA" means the percentage of mean AUC_{inf} of the tested product relative to the mean AUC_{inf} of the reference product. Unless otherwise specified, relative bioavailability refers to the percentage of the mean AUC_{inf} observed for a full dose of the test product relative to the mean AUC_{inf} observed for two ½-doses of an immediate release liquid solution administered four hours apart.

[0148] "Bioequivalence" means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

[0149] When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively

combining any one of the lower end variables with any one of the upper end variables that is mathematically and physically possible. Thus, for example, if a formulation may contain from 1 to 10 weight parts of a particular ingredient, or 2 to 8 parts of a particular ingredient, it will be understood that the formulation may also contain from 2 to 10 parts of the ingredient. In like manner, if a formulation may contain greater than 1 or 2 weight parts of an ingredient and up to 10 or 9 weight parts of the ingredient, it will be understood that the formulation may contain 1-10 weight parts of the ingredient, 2-9 weight parts of the ingredient, etc. unless otherwise specified, the boundaries of the range (lower and upper ends of the range) are included in the claimed range.

[0150] In like manner, when various sub-embodiments of a senior (i.e. principal) embodiment are described herein, it will be understood that the sub-embodiments for the senior embodiment can be combined to define another sub-embodiment. Thus, for example, when a principal embodiment includes sub-embodiments 1, 2 and 3, it will be understood that the principal embodiment can be further limited by any one of sub-embodiments 1, 2 and 3, or any combination of sub-embodiments 1, 2 and 3 that is mathematically and physically possible. In like manner, it will be understood that the principal embodiments described herein can be combined in any manner that is mathematically and physically possible, and that the invention extends to such combinations.

[0151] When used herein the term "about" or "substantially" or "approximately" will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength due to manufacturing variation and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered bioequivalent to the recited strength, as described in FDA's March 2003 Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations.

[0152] When used herein the term "gamma-hydroxybutyrate" or GHB, unless otherwise specified, refers to the free base of gamma hydroxy-butyrate, a pharmaceutically acceptable salt of gamma-hydroxybutyric acid, and combinations thereof, their hydrates, solvates, complexes or tautomers forms. Gamma-hydroxybutyric acid salts can be selected from the sodium salt of gamma-hydroxybutyric acid or sodium oxybate, the potassium salt of gamma-hydroxybutyric acid, the magnesium salt of gamma-hydroxybutyric acid, the calcium salt of gamma-hydroxybutyric acid, the lithium salt of gamma-hydroxybutyric, the tetra ammonium salt of gamma-hydroxybutyric acid or any other pharmaceutically acceptable salt forms of gamma-hydroxybutyric acid.

[0153] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. The term "formulation" or "composition" refers to the quantitative and qualitative characteristics of a drug product or dosage form prepared in accordance with the current invention.

[0154] As used herein the doses and strengths of gamma-hydroxybutyrate are expressed in equivalent-gram (g) weights of sodium oxybate unless stated expressly to the contrary. Thus, when considering a dose of gamma-hydroxybutyrate other than the sodium salt of gamma-hydroxybutyrate, one must convert the recited dose or strength from sodium oxybate to the gamma-hydroxybutyrate under evaluation. Thus, if an embodiment is said to provide a 4.5 g dose of gamma-hydroxybutyrate, because the form of gamma-hydroxybutyrate is not specified, it will be understood that the dose encompasses a 4.5 g dose of sodium oxybate, a 5.1 g dose of potassium gamma-hydroxybutyrate (assuming a 126.09 g/mol MW for sodium oxybate and a 142.20 g/mol MW for potassium gamma-hydroxybutyrate), and a 3.7 g dose of the free base (assuming a 126.09 g/mol MW for sodium oxybate and a 104.1 g/mol MW for the free base of gamma-hydroxybutyrate), or by the weight of any mixture of salts of gamma-hydroxybutyric acid that provides the same amount of GHB as 4.5 g of sodium oxybate.

[0155] As used herein "microparticle" means any discreet particle of solid material. The particle can be made of a single material or have a complex structure with core and shells and be made of several materials. The terms "microparticle", "particle", "microspheres" or "pellet" are interchangeable and have the same meaning. Unless otherwise specified, the microparticle has no particular particle size or diameter and is not limited to particles with volume mean diameter D(4,3) below 1 mm.

[0156] As used herein, the "volume mean diameter D(4,3)" is calculated according to the following formula:

$$D(4,3)=\Sigma(d^4_i \cdot n_i)/\Sigma(d^3_i \cdot n_i)$$

wherein the diameter d of a given particle is the diameter of a hard sphere having the same volume as the volume of that particle.

[0157] As used herein, the terms "finished composition", "finished formulation" or "formulation" are interchangeable and designate the modified release formulation of gamma-hydroxybutyrate preferably comprising modified release microparticles of gamma-hydroxybutyrate, immediate release microparticles of gamma-hydroxybutyrate, and any other excipients.

[0158] As used herein and in the claims that follow, an "immediate release (IR) portion" of a formulation includes physically discreet portions of a formulation, mechanistically discreet portions of a formulation, and pharmacokinetically discreet portions of a formulation that lend to or support a defined IR pharmacokinetic characteristic. Thus, for example, any formulation that releases active ingredient at the rate and extent required of the immediate release portion of the formulations of the present invention includes an "immediate release portion," even if the immediate release portion is physically integrated in what might otherwise be considered an extended release formulation. Thus, the IR portion can be structurally discreet or structurally indiscreet from (i.e. integrated with) the MR portion. In a preferred embodiment, the IR portion and MR portion are provided as particles, and in an even more preferred sub-embodiment the IR portion and MR portion are provided as particles discreet from each other.

[0159] As used here in, "immediate release formulation" or "immediate release portion" refers to a composition that releases at least 80% of its gamma-hydroxybutyrate in 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in a 0.1N HCl dissolution medium at a temperature of 37° C. and a paddle speed of 75 rpm.

[0160] In like manner, a "modified-release (MR) portion" includes that portion of a formulation or dosage form that lends to or supports a particular MR pharmacokinetic characteristic, regardless of the physical formulation in which the MR portion is integrated. The modified release drug delivery systems are designed to deliver drugs at a specific time or over a period of time after administration, or at a specific location in the body. The USP defines a modified release system as one in which the time course or location of drug release or both, are chosen to accomplish objectives of therapeutic effectiveness or convenience not fulfilled by conventional IR dosage forms. More specifically, MR solid oral dosage forms include extended release (ER) and delayed-release (DR) products. A DR product is one that releases a drug all at once at a time other than promptly after administration. Typically, coatings (e.g., enteric coatings) are used to delay the release of the drug substance until the dosage form has passed through the acidic medium of the stomach. An ER product is formulated to make the drug available over an extended period after ingestion, thus allowing a reduction in dosing frequency compared to a drug presented as a conventional dosage form, e.g. a solution or an immediate release dosage form. For oral applications, the term "extended-release" is usually interchangeable with "sustained-release", "prolonged-release" or "controlled-release".

[0161] Traditionally, extended-release systems provided constant drug release to maintain a steady concentration of drug. For some drugs, however, zero-order delivery may not be optimal and more complex and sophisticated systems have been developed to provide multi-phase delivery. One can distinguish among four categories of oral MR delivery systems: (1) delayed-release using enteric coatings, (2) site-specific or timed release (e.g. for colonic delivery), (3) extended-release (e.g., zero-order, first-order, biphasic release, etc.), and (4), programmed release (e.g., pulsatile, delayed extended release, etc.) See *Modified Oral Drug Delivery Systems* at page 34 in Gibaldi's DRUG DELIVERY SYSTEMS IN PHARMACEUTICAL CARE, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, 2007 and *Rational Design of Oral Modified-release Drug Delivery Systems* at page 469 in DEVELOPING SOLID ORAL DOSAGE FORMS: PHARMACEUTICAL THEORY AND PRACTICE, Academic Press, Elsevier, 2009. As used herein, "modified release formulation" or "modified release portion" in one embodiment refers to a composition that releases its gamma-hydroxybutyrate according a multiphase delivery that is comprised in the fourth class of MR products, e.g. delayed extended release. As such it differs from the delayed release products that are classified in the first class of MR products.

[0162] As used herein the terms "coating", "coating layer," "coating film," "film coating" and like terms are interchangeable and have the same meaning. The terms refer to the coating applied to a particle comprising the gamma-hydroxybutyrate that controls the modified release of the gamma-hydroxybutyrate.

[0163] In all pharmacokinetic testing described herein, unless otherwise stated, the dosage form, or the initial dosage form if the dosing regimen calls for more than one administration, is administered approximately two hours after consumption of a standardized dinner consisting of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

[0164] A "similar PK profile" or "comparable bioavailability" means that the mean AUC_{inf} of a test product is from 80% to 125% of the mean AUC_{inf} of a reference product in a suitably designed cross-over trial, and that the mean plasma concentration at 8 hours (C_{8h}) of the test product is from 50% to 130% of the mean plasma concentration at 8 hours (C_{8h}) of the reference product.

[0165] Type 1 Narcolepsy (NT1) refers to narcolepsy characterized by excessive daytime sleepiness ("EDS") and cataplexy. Type 2 Narcolepsy (NT2) refers to narcolepsy characterized by excessive daytime sleepiness without cataplexy. A diagnosis of narcolepsy (with or without cataplexy) can be confirmed by one or a combination of (i) an overnight polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) performed within the last 2 years, (ii) a full documentary evidence confirming diagnosis from the PSG and MSLT from a sleep laboratory must be made available, (iii) current symptoms of narcolepsy including: current complaint of EDS for the last 3 months (ESS greater than 10), (iv) mean MWT less than 8 minutes, (v) mean number of cataplexy events of 8 per week on baseline Sleep/Cataplexy Diary, and/or (vi) presence of cataplexy for the last 3 months and 28 events per week during screening period.

[0166] Unless otherwise specified herein, percentages, ratios and numeric values recited herein are based on weight; averages and means are arithmetic means; all pharmacokinetic measurements based on the measurement of bodily fluids are based on plasma concentrations.

[0167] It will be understood, when defining a composition by its pharmacokinetic or dissolution properties herein, that the formulation can in the alternative be defined as "means for" achieving the recited pharmacokinetic or dissolution properties. Thus, a formulation in which the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour can instead be defined as a formulation comprising "means for" or "modified release means for" releasing less than 20% of its gamma-hydroxybutyrate at one hour. It will be further understood that the preferred structures for achieving the recited pharmacokinetic or dissolution properties are the structures described in the examples hereof that accomplish the recited pharmacokinetic or dissolution properties.

Discussion of Principal Embodiments

[0168] The invention can be described in terms of principal embodiments, which in turn can be recombined to make other principal embodiments, and limited by sub-embodiments to make other principal embodiments.

[0169] A first principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 300, 325, 340, 375, 400, 425, or 450 hr×microgram/mL, most preferably greater than 340 hr×microgram/mL.

[0170] A second principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 265, 285, 300, 315, 325, 340, 350, 375, 400, 425, or 450 hr×microgram/mL, most preferably greater than 340 hr×microgram/mL, and a mean C_{8h} that is from

50% to 130%, from 60% to 130%, from 70% to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, from 90% to 110%, from 50% to 95%, from 60% to 90%, most preferably from 60% to 90% or 60% to 130% of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate (e.g. Xyrem®) administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0171] A third principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0172] A fourth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion preferably releases greater than 80% or 90% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0173] A fifth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60%, 70%, or 80%, preferably greater than 80%, of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0174] A sixth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 300, 325, 340, 375, 400, 425, or 450 hr×microgram/mL, preferably 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70% to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, from 90% to 110%, from 50% to 95%, or from 60% to 90%, preferably from 60% to 90% or from 60% to 130%, of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of gamma-hydroxybutyrate (e.g. Xyrem®) administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and (b) the formulation releases (i) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (ii) from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0175] A seventh principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% or 10% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at three hours, two hours or one hour, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monoba-

sic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0176] An eighth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at one hour, two hours, or three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% or 10% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (c) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at three hours, two hours, or one hour, when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and (d) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0177] A ninth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 4.5 g, 6 g, 7.5 g, and 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85% or 90% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal. The relative bioavailability is even higher with larger doses, and with a 6.0 g or 7.5 g or 9.0 g dose is preferably greater than 90, 95 or 100% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0178] A tenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, wherein a 4.5 g and a 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0179] An eleventh principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **12** or FIG. **13** for the corresponding strength.

[0180] A twelfth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **22**.

[0181] A thirteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **7** and FIG. **8**.

[0182] A fourteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **20** and FIG. **21**.

[0183] A fifteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions that yields a dissolution profile substantially as depicted in FIG. **3** or **16**.

[0184] In a sixteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **25** and FIG. **26**.

[0185] In a seventeenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **27** and FIG. **28**.

[0186] In an eighteenth principal embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate yielding a dissolution profile substantially as shown in any one of FIGS. **29** through **89**. It will be understood that this seventeenth principal embodiment can be limited only to one of these dissolution profiles.

[0187] A nineteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 7.5 g or 9.0 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **90** for the corresponding strength.

[0188] In any of these principal embodiments, the formulation is preferably effective to treat narcolepsy Type 1 or Type 2. The formulation is also preferably effective to induce sleep for six to eight, most preferably eight consecutive hours.

[0189] In any of these principal embodiments, the formulation preferably comprises immediate release and modified release portions, wherein the modified release portion comprises gamma hydroxybutyrate particles coated by a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C., and the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35. The polymers comprising free carboxylic groups preferably have a pH dissolution trigger of from 5.5 to 6.97 and are preferably methacrylic acid copolymers having a pH dissolution trigger of from 5.5 to 6.97.

Principal Structural Embodiments

[0190] In a first principal structural embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

[0191] In a second principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, a suspending or viscosifying agent, and an acidifying agent, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

[0192] In a third principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

[0193] In a fourth principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

[0194] In a fifth principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a methacrylic acid copolymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

Discussion of Pharmacokinetic and Dissolution Sub-Embodiments

[0195] As mentioned in the definitions section of this document, each of the sub-embodiments can be used to further characterize and limit each of the foregoing principal embodiments. In addition, more than one of the following sub-embodiments can be combined and used to further characterize and limit each of the foregoing principal embodiments, in any manner that is mathematically and physically possible.

[0196] In various sub-embodiments of the foregoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean AUC_{inf} of greater than 245, 265, 285, 300, 315, 325, 340, 350, 375, 400, 425, or 450 hr×microgram/mL when administered once approximately two hours after a standardized evening meal. An upper limit on mean AUC_{inf} for such 7.5 g dose can be set at 500 or 550 hr×microgram/mL.

[0197] In additional sub-embodiments of the foregoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean C_{max} of greater than 65, 70, 75, 80, 85, or 90 microgram/mL when administered once approximately two hours after a standardized evening meal. An upper limit on mean C_{max} for such 7.5 g dose can be set at 125 or 100 microgram/mL.

[0198] In additional sub-embodiments of the forgoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70 to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, or from 90% to 110% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of gamma-hydroxybutyrate administered at t_0 and t_{4h} in two equally divided doses, when administered approximately two hours after a standardized evening meal.

[0199] In one sub-embodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr·microgram/mL, and a mean C_{8h} that is from 50% to 130% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0200] Further sub-embodiments can be characterized based on the dissolution properties of the entire (or finished) modified release formulation of gamma-hydroxybutyrate in 0.1N hydrochloric acid dissolution medium. Thus, in additional sub-embodiments the entire modified release formulation of gamma-hydroxybutyrate releases greater than 30%, 35%, 40%, or 45%, and less than 70%, 65%, 60%, or 55%, of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0201] Further sub-embodiments can be defined based on the dissolution properties of the modified release portion of the formulation of gamma-hydroxybutyrate in a phosphate buffer pH 6.8 dissolution medium. Thus, in additional sub-

embodiments the modified release portion releases greater than 80%, 85%, 90%, 95%, 98% or even 99% of its gamma-hydroxybutyrate at 3, 2, 1, 0.5 or 0.25 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0202] Still further embodiments can be defined based on the dissolution properties of the modified release portion of the modified release formulation of gamma-hydroxybutyrate in a 0.1N HCl dissolution medium. Thus, in additional sub-embodiments the modified release portion releases less than 20%, 15%, 10%, 5%, or even 2% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0203] In additional embodiments, the modified release portion releases less than 20%, 15%, 10%, 5%, or even 2% of its gamma-hydroxybutyrate at one hour and at three hours and more than 30%, 35%, 40%, 45% of its gamma-hydroxybutyrate at ten hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0204] Further embodiments can be defined based on the dissolution properties of the immediate release portion of the modified release formulation of gamma-hydroxybutyrate in a 0.1N HCl dissolution medium. Thus, in additional sub-embodiments the immediate release portion releases greater than 80%, 85%, 90%, 95%, 98% or even 99% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0205] In another sub-embodiment, the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0206] In another subembodiment, the formulation comprises immediate release and modified release portions, and (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0207] In another sub-embodiment, the formulation comprises immediate release and modified release portions, and (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65% of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0208] Still further sub-embodiments can be defined based on a pharmacokinetic comparison of the modified release formulation of gamma-hydroxybutyrate to an immediate release solution of gamma-hydroxybutyrate. Therefore, in additional sub-embodiments the modified release formulation of gamma-hydroxybutyrate, preferably in a 4.5 g, 6.0 g, 7.5 g, and 9.0 g dose, has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85%, 90%, or 95% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0209] In additional sub-embodiments of the forgoing principal embodiments the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 4.5 g and 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85% or 90% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal

[0210] In additional sub-embodiments, a 6.0 g or 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85%, 90%, 95% or 100% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0211] The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined by comparing the area under the concentration/time curve for eight hours to the area under the concentration/time curve calculated to infinity. Thus, in still further sub-embodiments a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate of the present invention has been shown to achieve a ratio of AUC_{8h} to AUC_{inf} of greater than 0.80, 0.85, 0.90, 0.95 or 0.98 when administered once approximately two hours after a standardized evening meal.

[0212] In still further sub-embodiments, the modified release formulations of gamma-hydroxybutyrate are defined based on the concentration of gamma-hydroxybutyrate in the blood stream 8 hours after administration. Therefore, in other sub-embodiments the formulation can be characterized by a 4.5 g dose of the modified release formulation of gamma-hydroxybutyrate that has been shown to achieve a mean C_{8h} Of from 4.7 to 9.0, from 5.4 to 8.3, from 6.1 to 7.6, from 3.5 to 7.0, or from 4.0 to 5.5 microgram/mL, a 6.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{8h} of from 6.3 to 16.7, from 7.3 to 15.4, from 8.2 to 14.1, from 8.9 to 16.7, from 10.2 to 15.4, or from 11.5 to 14.1 microgram/mL; or a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{8h} of from 13.0 to 40.3, from 16.0 to 26.0, 15.0 to 25.0, from 17.5 to 22.0, from 21.6 to 40.3, from 24.7 to 37.2, or from 27.8 to 34.1 microgram/mL, when administered once approximately two hours after a standardized evening meal.

[0213] The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined by the concentration/time and dissolution curves that they produce when tested according to the examples of the present invention. Therefore, in other sub-embodiments, a 4.5 g, 6.0 g, or 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate of the present invention has been shown to achieve a time/concentration curve substantially as shown in FIGS. **13** (*a*), (*b*) and (*c*) respectively herein. In another principal embodiment or sub-embodiment, the formulation has been shown to achieve a dissolution curve substantially as shown in FIGS. **7** and **8** or FIGS. **20** and **21** herein.

[0214] The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined based on the time required to reach maximum blood concentration of gamma-hydroxybutyrate. Thus, in additional sub-embodiments, the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a median T_{max} of 1.25 to 3.25 hours, preferably of about 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, or 3.25 hours when administered once approximately two hours after a standardized evening meal. A lower limit on the median T_{max} in any of the foregoing ranges can alternatively be set at 0.5 or 1.0 hours.

[0215] Additional embodiments can be defined by comparing a dose of the modified release formulation of gamma-hydroxybutyrate, administered once nightly, to the same dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a median T_{max} within one hundred fifty, one hundred twenty, ninety, sixty or thirty minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

[0216] In still another sub-embodiment a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

[0217] Additional embodiments can be defined by comparing the pharmacokinetic profile of a dose of the modified release formulation of gamma-hydroxybutyrate administered once nightly to the same dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{3h} to the mean C_{max} of the first half dose of the immediate release liquid solution of sodium oxybate from 0.6 to 1.2, preferably from 0.7 to 1.1 and most preferably from 0.8 to 1. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{4h} to the mean C_{max} of the first half dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1.1, preferably from 0.6 to 1 and most preferably from 0.7 to 0.9. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean $C_{4.5h}$ to the mean C_{max} of the first half dose of the immediate release liquid solution of gamma-hydroxybutyrate from 0.5 to 1, preferably from 0.5 to 0.9 and most preferably from 0.6 to 0.8.

[0218] Additional sub-embodiments can be defined by the range of mean blood concentrations of gamma-hydroxybutyrate achieved 3, 4, 4.5 or 5 hours after administration once nightly by a modified release formulation of gamma-hydroxybutyrate according to the invention at the dose of 7.5 g. Thus, in another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{3h} of 43 to 81 microgram/mL, preferably 49 to 75 microgram/mL and more preferably 55 to 69 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{4h} of 40 to 75 microgram/mL, preferably 45 to 69 microgram/mL and more preferably 51 to 64 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean $C_{4.5h}$ of 35 to 67 microgram/mL, preferably 40 to 62 microgram/mL and more preferably 45 to 56 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{5h} of 31 to 59 microgram/mL, preferably 36 to 55 microgram/mL and more preferably 40 to 50 microgram/mL.

[0219] In another subembodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 300 hr*microgram/mL and a mean C_{max} of greater than 70 microgram/mL when administered once approximately two hours after a standardized evening meal.

[0220] In still another subembodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 350 hr*microgram/mL and a mean C_{max} of greater than 80 microgram/mL when administered once approximately two hours after a standardized evening meal.

[0221] In another subembodiment, a 4.5, 6.0, 7.5 and 9.0 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95%, 90 or 85% of the mean C_{8h}

provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0222] Additional embodiments can be defined by comparing the pharmacokinetic profile of a dose of the modified release formulation of gamma-hydroxybutyrate administered once nightly to another dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a similar pharmacokinetic profile to the pharmacokinetic profile provided by a 2×4.5 g dose of sodium oxybate as an immediate release liquid solution administered for the first 4.5 g two hours after a standardized evening meal and for the second 4.5 g dose, 4 hours after the first dose. Thus, in another sub-embodiment a modified release formulation of gamma-hydroxybutyrate according to the invention administered at the dose of 7.5 g has been shown to achieve a ratio of its mean C_{3h} to the mean C_{max} of the first 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1.1, preferably from 0.6 to 1 and most preferably from 0.7 to 0.9. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{4h} to the mean C_{max} of the first 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1, preferably from 0.6 to 0.9 and most preferably from 0.7 to 0.8. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean $C_{4.5h}$ to the mean C_{max} of the 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.4 to 0.9, preferably from 0.5 to 0.8 and most preferably from 0.6 to 0.7.

[0223] In another subembodiment, the modified release formulation of gamma-hydroxybutyrate comprises immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0224] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0225] (a) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0226] (i) from 40% to 65% at 1 hour,

[0227] (ii) from 40% to 65% at 3 hours,

[0228] (iii) from 47% to 85% at 8 hours,

[0229] (iv) greater or equal to 60% at 10 hours,

[0230] (v) greater or equal to 80% at 16 hours, and

[0231] (b) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0232] (i) from 43% to 94% at 0.25 hour,

[0233] (ii) greater or equal to 65% at 0.35 hour, and

[0234] (iii) greater or equal to 88% at 1 hour.

[0235] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0236] (a) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0237] (i) from 40% to 65% at 1 hour,

[0238] (ii) from 40% to 65% at 3 hours,

[0239] (iii) greater or equal to 47% at 8 hours,

[0240] (iv) greater or equal to 60% at 10 hours,

[0241] (v) greater or equal to 80% at 16 hours, and

[0242] (b) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0243] (i) from 43% to 94% at 0.25 hour,

[0244] (ii) greater or equal to 65% at 0.35 hour, and

[0245] (iii) greater or equal to 88% at 1 hour.

[0246] In another preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0247] (a) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0248] (i) from 40% to 65% at 1 hour,

[0249] (ii) from 40% to 65% at 3 hours,

[0250] (iii) from 47% to 85% at 8 hours,

[0251] (iv) greater or equal to 60% at 10 hours,

[0252] (v) greater or equal to 80% at 16 hours, and

[0253] (b) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0254] (i) from 45% to 67% at 1 hour, and

[0255] (ii) greater or equal to 65% at 3 hours.

[0256] In another preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0257] (a) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0258] (i) from 40% to 65% at 1 hour,

[0259] (ii) from 40% to 65% at 3 hours,

[0260] (iii) greater or equal to 47% at 8 hours,

[0261] (iv) greater or equal to 60% at 10 hours,

[0262] (v) greater or equal to 80% at 16 hours, and

[0263] (b) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0264] (i) from 45% to 67% at 1 hour, and

[0265] (ii) greater or equal to 65% at 3 hours.

[0266] In still another subembodiment, the formulation achieves an in vitro dissolution profile: (a) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) from 40% to 65% at 1 hour, (ii) from 40% to 65% at 3 hours, (iii) greater than 45% at 8 hours, and (b) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) greater than 40% at 0.5 hour, and (ii) greater than 85% at 1 hour.

[0267] Alternatively, the formulation can be described as achieving an in vitro dissolution profile measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) from 40% to 65% at 1 hour, (ii) from 40% to 65% at 3 hours, and (iii) greater than 45% at 8 hours.

[0268] In another alternative, the formulation can be described as achieving an in vitro dissolution profile measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) greater than 40% at 0.5 hour, and (ii) greater than 85% at 1 hour.

Structural Sub-Embodiments

[0269] The modified release formulations of gamma-hydroxybutyrate of the present invention can be provided in any dosage form that is suitable for oral administration, including tablets, capsules, liquids, orally dissolving tablets, and the like, but they are preferably provided as dry particulate formulations (i.e. granules, powders, coated particles, microparticles, pellets, microspheres, etc.), in a sachet or other suitable discreet packaging units. A preferred particulate formulation will be mixed with tap water shortly before administration, preferably 50 mL.

[0270] In one subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; and (b) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

[0271] In one subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; and (b) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 40/60 to 60/40.

[0272] In another subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40.

[0273] In another subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/3 5 or 40/60 to 60/40; and (e) the film coating is from 10 to 50% of the weight of the microparticles.

[0274] In another subembodiment the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40; and (e) the coating is from 10 to 50% of the weight of the particles.

[0275] In a particularly preferred sub-embodiment of the immediately preceding sub-embodiments, the polymer carrying free carboxylic groups comprises from 100% poly (methacrylic acid, ethyl acrylate) 1:1 and 0% poly (methacrylic acid, methylmethacrylate) 1:2 to 2% poly (methacrylic acid, ethyl acrylate) 1:1 and 98% poly (methacrylic acid, methylmethacrylate) 1:2; and the hydrophobic compound comprises hydrogenated vegetable oil.

[0276] In a preferred embodiment, the formulation includes excipients to improve the viscosity and the pourability of the mixture of the particulate formulation with tap water. As such, the particulate formulation comprises, besides the immediate release and modified release particles of gamma-hydroxybutyrate, one or more suspending or viscosifying agents or lubricants.

[0277] Preferred suspending or viscosifying agents are chosen from the group consisting of xanthan gum, medium viscosity sodium carboxymethyl cellulose, mixtures of microcrystalline cellulose and sodium carboxymethyl cellulose, mixtures of microcrystalline cellulose and guar gum, medium viscosity hydroxyethyl cellulose, agar, sodium alginate, mixtures of sodium alginate and calcium alginate, gellan gum, carrageenan gum grade iota, kappa or lambda, and medium viscosity hydroxypropylmethyl cellulose.

[0278] Medium viscosity sodium carboxymethyl cellulose corresponds to grade of sodium carboxymethyl cellulose

whose viscosity, for a 2% solution in water at 25° C., is greater than 200 mPa·s and lower than 3100 mPa·s.

[0279] Medium viscosity hydroxyethyl cellulose corresponds to a grade of hydroxyethyl cellulose whose viscosity, for a 2% solution in water at 25° C., is greater than 250 mPa·s and lower than 6500 mPa·s. Medium viscosity hydroxypropylmethyl cellulose corresponds to a grade of hydroxypropylmethyl cellulose whose viscosity, for a 2% solution in water at 20° C., is greater than 80 mPa·s. and lower than 3800 mPa·s.

[0280] Preferred suspending or viscosifying agents are xanthan gum, especially Xantural 75™ from Kelco, hydroxyethylcellulose, especially Natrosol 250M™ from Ashland, Kappa carrageenan gum, especially Gelcarin PH812™ from FMC Biopolymer, and lambda carrageenan gum, especially Viscarin PH209™ from FMC Biopolymer.

[0281] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate comprises from 1 to 15% of viscosifying or suspending agents, preferably from 2 to 10%, more preferably from 2 to 5%, and most preferably from 2 to 3% of the formulation.

[0282] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate is in the form of a powder that is intended to be dispersed in water prior to administration and further comprises from 1 to 15% of a suspending or viscosifying agent selected from a mixture of xanthan gum, carrageenan gum and hydroxyethylcellulose or xanthan gum and carrageenan gum.

[0283] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate is in the form of a powder that is intended to be dispersed in water prior to administration and further comprises: from 1.2 to 15% of an acidifying agent selected from malic acid and tartaric acid; and from 1 to 15% of a suspending or viscosifying agent selected from a mixture of xanthan gum, carrageenan gum and hydroxyethylcellulose or xanthan gum and carrageenan gum.

[0284] In a most preferred embodiment, the modified release formulation of gamma-hydroxybutyrate comprises about 1% of lambda carrageenan gum or Viscarin PH209™, about 1% of medium viscosity grade of hydroxyethyl cellulose or Natrosol 250M™, and about 0.7% of xanthan gum or Xantural 75™. For a 4.5 g dose unit, these percentages will typically equate to about 50 mg xanthan gum (Xantural 75™), about 75 mg carragenan gum (Viscarin PH209™), and about 75 mg hydroxyethylcellulose (Natrasol 250M™).

[0285] Alternative packages of viscosifying or suspending agents, for a 4.5 g dose, include about 50 mg xanthan gum (Xantural 75™) and about 100 mg carragenan gum (Gelcarin PH812™), or about 50 mg xanthan gum (Xantural 75™), about 75 mg hydroxyethylcellulose (Natrasol 250M™) and about 75 mg carragenan gum (Viscarin PH109™)

[0286] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate further comprises a lubricant or a glidant, besides the immediate release and modified release particles of gamma-hydroxybutyrate. Preferred lubricants and glidants are chosen from the group consisting of salts of stearic acid, in particular magnesium stearate, calcium stearate or zinc stearate, esters of stearic acid, in particular glyceryl monostearate or glyceryl palmitostearate, stearic acid, glycerol behenate, sodium stearyl fumarate, talc, and colloidal silicon dioxide.

[0287] The preferred lubricant or glidant is magnesium stearate.

[0288] The lubricant or glidant can be used in the particulate formulation in an amount of from 0.1 to 5%. The preferred amount is about 0.5%.

[0289] Most preferably, the modified release formulation of gamma-hydroxybutyrate comprises about 0.5% of magnesium stearate.

[0290] A preferred modified release formulation of gamma-hydroxybutyrate further comprises an acidifying agent. The acidifying agent helps to ensure that the release profile of the formulation in 0.1N HCl will remain substantially unchanged for at least 15 minutes after mixing, which is approximately the maximum length of time a patient might require before consuming the dose after mixing the formulation with tap water.

[0291] In one particular subembodiment the formulation is a powder, and further comprising an acidifying agent and a suspending or viscosifying agent, preferably in the weight percentages recited herein.

[0292] The preferred acidifying agents are chosen from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid. In a preferred embodiment, the acidifying agent is present in the formulation from 1.2 to 15%, preferably from 1.2 to 10%, preferably from 1.2 to 5%. Preferred acidifying agents are tartaric acid and malic acid, with malic acid being most preferred.

[0293] When tartaric acid is employed, it is preferably employed in an amount of from 1 to 10%, from 2.5 to 7.5%, or about 5%. In a most preferred embodiment, the amount of malic acid in the modified release formulation of gamma-hydroxybutyrate is from 1.2 to 15%, preferably from 1.2 to 10%, preferably from 1.2 to 5%, and most preferably 1.6% or 3.2%.

[0294] In a most preferred embodiment, the amount of malic acid in the modified release formulation of gamma hydroxybutyrate is about 1.6%.

[0295] The modified release formulation of gamma-hydroxybutyrate preferably includes an immediate release portion and a modified release portion of gamma-hydroxybutyrate, and in a particularly preferred embodiment, the formulation is a particulate formulation that includes a plurality of immediate release gamma-hydroxybutyrate particles and a plurality of modified release gamma-hydroxybutyrate particles. The molar ratio of gamma-hydroxybutyrate in the immediate release and modified release portions preferably ranges from 0.11:1 to 1.86:1, from 0.17:1 to 1.5:1, from 0.25:1 to 1.22:1, from 0.33:1 to 1.22:1, from 0.42:1 to 1.22:1, from 0.53:1 to 1.22:1, from 0.66:1 to 1.22:1, from 0.66:1 to 1.5:1, from 0.8:1 to 1.22:1, and preferably is about 1:1. The molar percentage of gamma-hydroxybutyrate in the immediate release portion relative to the total of gamma-hydroxybutyrate in the formulation preferably ranges from 10% to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%. In a preferred embodiment, the molar percentage of the gamma-hydroxybutyrate in the immediate release portion relative to the total of gamma-hydroxybutyrate in the formulation is about 50%. The molar percentage of gamma-hydroxybutyrate in the modified release portion relative to the total of gamma-hydroxybu-

tyrate in the formulation preferably ranges from 90% to 35%, from 85 to 40%, from 80 to 45%, from 75 to 45%, from 70 to 45%, from 65 to 45%, from 60 to 45%, from 60 to 40%, or from 55 to 45%, preferably from 60% to 40%. In a preferred embodiment, the molar ratio of the gamma-hydroxybutyrate in the modified release portion relative to the total of gamma-hydroxybutyrate in the formulation is about 50%. The weight percentage of the IR microparticles relative to the total weight of IR microparticles and MR microparticles, preferably ranges from 7.2% to 58.2%, from 11.0% to 52.9%, from 14.9% to 47.8%, from 18.9% to 47.8%, from 23.1% to 47.8%, from 27.4% to 47.8%, from 31.8% to 47.8%, from 31.8% to 52.9%, or from 36.4% to 47.8%. In other embodiments, the weight percentage of the IR microparticles relative to the total weight of IR microparticles and MR microparticles preferably ranges from 5.9% to 63.2%, from 9.1% to 58.1%, from 12.4% to 53.1%, from 19.9% to 53.1%, from 19.6% to 53.1%, from 23.4% to 53.1%, from 27.4% to 53.1% from 27.4% to 58.1%, preferably from 31.7% to 53.1%.

[0296] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to 450 microns and 50% of its sodium oxybate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0297] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to 170 microns and 50% of its sodium oxybate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0298] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its sodium oxybate content in modified release particles consisting of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0299] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone™ K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its sodium oxybate content in modified release particles consisting of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent).

[0300] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent).

[0301] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent).

[0302] In a preferred embodiment, the finished formulation comprises 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline

cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0303] In a preferred embodiment, the finished formulation comprises 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0304] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of calcium salt of gamma-hydroxybutyric acid mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0305] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of calcium salt of gamma-hydroxybutyric acid mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

Other Characteristics of Immediate Release Portion

[0306] The immediate release portion of the formulation can take any form capable of achieving an immediate release of the gamma-hydroxybutyrate when ingested. For example, when the formulation is a particulate formulation, the formulation can include unmodified "raw" gamma-hydroxybutyrate, rapidly dissolving gamma-hydroxybutyrate granules, particles or microparticles comprised of a core covered by a gamma-hydroxybutyrate loaded layer containing a binder such as povidone.

[0307] The IR granules or particles of gamma-hydroxybutyrate can be made using any manufacturing process suitable to produce the required particles, including:

[0308] agglomeration of the gamma-hydroxybutyrate sprayed preferably in the molten state, such as the Glatt ProCell™ technique,

[0309] extrusion and spheronization of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,

[0310] wet granulation of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,

[0311] compacting of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,

[0312] granulation and spheronization of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, the spheronization being carried out for example in a fluidized bed apparatus equipped with a rotor, in particular using the Glatt CPS™ technique,

[0313] spraying of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, for example in a fluidized bed type apparatus equipped with zig-zag filter, in particular using the Glatt MicroPx™ technique, or

[0314] spraying, for example in a fluidized bed apparatus optionally equipped with a partition tube or Wurster tube, the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, in dispersion or in solution in an aqueous or organic solvent on a core.

[0315] Preferably, the immediate release portion of the formulation is in the form of microparticles comprising the immediate release gamma-hydroxybutyrate and optional pharmaceutically acceptable excipients. In a preferred embodiment, the immediate release microparticles of gamma-hydroxybutyrate have a volume mean diameter D(4, 3) of from 10 to 1000 microns, preferably from 95 to 600

microns, more preferably from 150 to 400 microns. Most preferably their volume mean diameter is about 270 microns.

[0316] The preferred immediate release particles of gamma-hydroxybutyrate of the present invention comprises a core and a layer deposited on the core that contains the gamma-hydroxybutyrate. The core can be any particle chosen from the group consisting of:

[0317] crystals or spheres of lactose, sucrose (such as Compressuc™ PS from Tereos), microcrystalline cellulose (such as Avicel™ from FMC Biopolymer, Cellet™ from Pharmatrans or Celphere™ from Asahi Kasei), sodium chloride, calcium carbonate (such as Omyapure™ 35 from Omya), sodium hydrogen carbonate, dicalcium phosphate (such as Dicafos™ AC 92-12 from Budenheim) or tricalcium phosphate (such as Tricafos™ SC93-15 from Budenheim);

[0318] composite spheres or granules, for example sugar spheres comprising sucrose and starch (such as Suglets™ from NP Pharm), spheres of calcium carbonate and starch (such as Destab™ 90 S Ultra 250 from Particle Dynamics) or spheres of calcium carbonate and maltodextrin (such as Hubercal™ CCG4100 from Huber).

[0319] The core can also comprise other particles of pharmaceutically acceptable excipients such as particles of hydroxypropyl cellulose (such as Klucel™ from Aqualon Hercules), guar gum particles (such as Grinsted™ Guar from Danisco), xanthan particles (such as Xantural™ 180 from CP Kelco).

[0320] According to a particular embodiment of the invention, the cores are sugar spheres or microcrystalline cellulose spheres, such as Cellets™ 90, Cellets™ 100 or Cellets™ 127 marketed by Pharmatrans, or also Celphere™ CP 203, Celphere™ CP305, Celphere™ SCP 100. Preferably the core is a microcrystalline cellulose sphere. Most preferably the core is a Cellets™ 127 from Pharmatrans.

[0321] The core preferably has a mean volume diameter of about 95 to about 450 microns, preferably about 95 to about 170 microns, most preferably about 140 microns.

[0322] The layer deposited onto the core comprises the immediate release gamma-hydroxybutyrate. Preferably the layer also comprises a binder, which can be chosen from the group consisting of:

[0323] low molecular weight hydroxypropyl cellulose (such as Klucel™ EF from Aqualon-Hercules), low molecular weight hydroxypropyl methylcellulose (or hypromellose) (such as Methocel™ E3 or E5 from Dow), or low molecular weight methylcellulose (such as Methocel™ A1 5 from Dow);

[0324] low molecular weight polyvinyl pyrrolidone (or povidone) (such as Plasdone™ K29/32 from ISP or Kollidon™ 30 from BASF), vinyl pyrrolidone and vinyl acetate copolymer (or copovidone) (such as Plasdone: S630 from ISP or Kollidon™ VA 64 from BASF);

[0325] dextrose, pregelatinized starch, maltodextrin; and mixtures thereof.

[0326] Low molecular weight hydroxypropyl cellulose corresponds to grades of hydroxypropyl cellulose having a molecular weight of less than 800,000 g/mol, preferably less than or equal to 400,000 g/mol, and in particular less than or equal to 100,000 g/mol. Low molecular weight hydroxypropyl methylcellulose (or hypromellose) corresponds to grades of hydroxypropyl methylcellulose the solution viscosity of which, for a 2% solution in water and at 20° C., is less than or equal to 1,000 mPa·s, preferably less than or equal to 100 mPa·s and in particular less than or equal to 15 mPa·s. Low molecular weight polyvinyl pyrrolidone (or povidone) corresponds to grades of polyvinyl pyrrolidone having a molecular weight of less than or equal to 1,000,000 g/mol, preferably less than or equal to 800,000 g/mol, and in particular less than or equal to 100,000 g/mol.

[0327] Preferably, the binding agent is chosen from low molecular weight polyvinylpyrrolidone or povidone (for example, Plasdone™ K29/32 from ISP), low molecular weight hydroxypropyl cellulose (for example, Klucel™ EF from Aqualon-Hercules), low molecular weight hydroxypropyl methylcellulose or hypromellose (for example, Methocel™ E3 or E5 from Dow) and mixtures thereof.

[0328] The preferred binder is povidone K30 or K29/32, especially Plasdone™ K29/32 from ISP. The binder can be present in an amount of 0 to 80%, 0 to 70%, 0 to 60%, 0 to 50%, 0 to 40%, 0 to 30%, 0 to 25%, 0 to 20%, 0 to 15%, 0 to 10%, or from 1 to 9%, most preferably 5% of binder based on the total weight of the immediate release coating.

[0329] The preferred amount of binder is 5% of binder over the total mass of gamma-hydroxybutyrate and binder.

[0330] The layer deposited on the core can represent at least 10% by weight, and even greater than 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85 or 90% by weight of the total weight of the immediate release particle of gamma-hydroxybutyrate. Most preferably, the layer deposited on the core represents about 85% of the weight of the immediate release particle of gamma-hydroxybutyrate.

[0331] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0332] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns.

[0333] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns.

[0334] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0335] According to another preferred embodiment, the immediate-release particles comprise 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0336] According to another preferred embodiment, the immediate-release particles comprise 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0337] According to another preferred embodiment, the immediate-release particles comprise 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0338] According to another embodiment, the immediate-release particles are manufactured by dissolving the gamma-hydroxybutyrate and the Povidone K30 in a mixture of water/ethanol 40/60 w/w and spraying the resulting solution onto the surface of the microcrystalline cellulose spheres.

Other Characteristics of Modified Release Portion

[0339] The modified release portion can be any formulation that provides the desired in vitro dissolution profile of gamma-hydroxybutyrate. The modified release portion is preferably comprised of modified release particles, obtained by coating immediate release particles of gamma-hydroxybutyrate with a coating (or coating film) that inhibits the immediate release of the gamma-hydroxybutyrate. In one sub-embodiment the modified release portion comprises particles comprising: (a) an inert core; (b) a coating; and (c) a layer comprising the gamma hydroxybutyrate interposed between the core and the coating.

[0340] In a preferred embodiment, the modified release portion comprises a time-dependent release mechanism and a pH-dependent release mechanism.

[0341] In a preferred embodiment, the coating film comprises at least one polymer carrying free carboxylic groups, and at least one hydrophobic compound preferably characterized by a melting point equal or greater than 40° C.

[0342] The polymer carrying free carboxylic groups is preferably selected from: (meth)acrylic acid/alkyl (meth) acrylate copolymers or methacrylic acid and methylmethacrylate copolymers or methacrylic acid and ethyl acrylate copolymers or methacrylic acid copolymers type A, B or C, cellulose derivatives carrying free carboxylic groups, preferably cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethylethyl cellulose, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, zein, shellac, alginate and mixtures thereof.

[0343] In a preferred embodiment, the methacrylic acid copolymers are chosen from the group consisting of poly (methacrylic acid, methyl methacrylate) 1:1 or Eudragit™ L100 or equivalent, poly (methacrylic acid, ethyl acrylate) 1:1 or Eudragit™ L100-55 or equivalent and poly (methacrylic acid, methyl methacrylate) 1:2 or Eudragit™ S 100 or equivalent.

[0344] In another subembodiment the coating comprises a polymer carrying free carboxylic groups wherein the free carboxylic groups are substantially ionized at pH 7.5.

[0345] The hydrophobic compound with a melting point equal or greater than 40° C. can be selected from the group consisting of hydrogenated vegetable oils, vegetable waxes, wax yellow, wax white, wax microcrystalline, lanolin, anhydrous milk fat, hard fat suppository base, lauroyl macrogol glycerides, polyglyceryl diisostearate, diesters or triesters of glycerol with a fatty acid, and mixtures thereof.

[0346] Even more preferably, the hydrophobic compound with a melting point equal or greater than 40° C. is chosen from the group of following products: hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candellila wax, tristearin, tripalmitin, trimyristin, yellow wax, hard fat or fat that is useful as suppository bases, anhydrous dairy fats, lanolin, glyceryl palmitostearate, glyceryl stearate, lauryl macrogol glycerides, polyglyceryl diisostearate, diethylene glycol monostearate, ethylene glycol monostearate, omega 3 fatty acids, and mixtures thereof. A particularly preferred subgroup of products comprises hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candelilla wax, tristearin, tripalmitin, trimyristin, beeswax, hydrogenated poly-1 decene, carnauba wax, and mixtures thereof.

[0347] In practice, and without this being limiting, it is preferable the hydrophobic compound with a melting point equal or greater than 40° C. to be chosen from the group of products sold under the following trademarks: Dynasan™, Cutina™, Hydrobase™, Dub™, Castorwax™, Croduret™, Compritol™, Sterotex™, Lubritab™, Apifil™, Akofine™, Softisan™, Hydrocote™, Livopol™, Super Hartolan™, MGLA™, Corona™, Protalan™, Akosoft™, Akosol™, Cremao™, Massupol™, Novata™, Suppocire™, Wecobee™, Witepsol™, Lanolin™, Incromega™, Estaram™, Suppoweiss™, Gelucire™, Precirol™, Emulcire™, Plurol Diisostéarique™, Geleol™, Hydrine™, Monthyle™, Kahlwax™ and mixtures thereof; and, preferably, from the group of products sold under the following trademarks: Dynasan™ P60, Dynasan™114, Dynasan™116, Dynasan™118, Cutina™ HR, Hydrobase™ 66-68, Dub™ HPH, Compritol™ 888, Sterotex™ NF, Sterotex™ K, Lubritab™, and mixtures thereof.

[0348] A particularly suitable coating is composed of a mixture of hydrogenated vegetable oil and a methacrylic acid copolymer. The exact structure and amount of each component, and the amount of coating applied to the particle, controls the release rate and release triggers. Eudragit® methacrylic acid copolymers, namely the methacrylic acid—methyl methacrylate copolymers and the methacrylic acid—ethyl acrylate copolymers, have a pH-dependent solubility: typically, the pH triggering the release of the active ingredient from the microparticles is set by the choice and mixture of appropriate Eudragit® polymers. In the case of gamma hydroxybutyrate modified release microparticles, the theoretical pH triggering the release is preferably from 5.5 to 6.97 or 6.9, more preferably 6.5 up to 6.9. By "pH trigger" is meant the minimum pH above which dissolution of the polymer occurs.

[0349] In a particular embodiment, the coating comprises a hydrophobic compound with a melting point equal or greater than 40° C. and a polymer carrying free carboxylic groups are present in a weight ratio from 0.4 or 0.5 to 4, preferably from 0.6 or 0.67 to 2.5, most preferably from 0.6 or 0.67 to 2.33; most preferably about 1.5.

[0350] A particularly suitable coating is composed of a mixture of hydrogenated vegetable oil and a methacrylic acid copolymer with a theoretical pH triggering the release from 6.5 up to 6.97 in a weight ratio from 0.4 or 0.5 to 4, preferably from 0.6 or 0.67 to 2.5, most preferably from 0.6 or 0.67 to 2.33; most preferably of about 1.5.

[0351] The modified release particles of gamma-hydroxybutyrate preferably have a volume mean diameter of from 100 to 1200 microns, from 100 to 500 microns, from 200 to 800 microns, and preferably of about 320 microns.

[0352] The coating can preferably represent 10 to 50%, 15 to 45%, 20 to 40%, or 25 to 35% by weight of the total weight of the coated modified release particles. Preferably, the coating represents 25-30% by weight of the total weight of the modified release particles of gamma-hydroxybutyrate.

[0353] In a preferred embodiment, the coating layer of the modified release particles of gamma-hydroxybutyrate is obtained by spraying, in particular in a fluidized bed appa-

ratus, a solution, suspension or dispersion comprising the coating composition as defined previously onto the immediate release particles of gamma-hydroxybutyrate, in particular the immediate release particles of gamma-hydroxybutyrate as previously described. Preferably, the coating is formed by spraying in a fluidized bed equipped with a Wurster or partition tube and according to an upward spray orientation or bottom spray a solution of the coating excipients in hot isopropyl alcohol.

[0354] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of gamma-hydroxybutyrate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of gamma-hydroxybutyrate.

[0355] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of gamma-hydroxybutyrate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of gamma-hydroxybutyrate.

[0356] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of sodium oxybate.

[0357] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of sodium oxybate.

[0358] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of gamma-hydroxybutyrate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent).

[0359] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of gamma-hydroxybutyrate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S 100 or equivalent).

[0360] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0361] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

Packaging

[0362] The modified release formulation of gamma-hydroxybutyrate is preferably supplied in sachets or stick-packs comprising a particulate formulation. The sachets are preferably available in several different doses, comprising gamma-hydroxybutyrate in amounts equivalents to 0.5 g, 1.0 g, 1.5 g, 3.0 g, 4.5 g, 6.0 g, 7.5 g, 9.0 g, 10.5 g and/or 12 g of sodium oxybate. Depending on the dose required, one or more of these sachets can be opened, and its contents mixed with tap water to provide the nightly dose of gamma-hydroxybutyrate.

Methods of Treatment

[0363] The invention further provides a method of treating a disorder treatable with gamma-hydroxybutyrate in a human subject in need thereof comprising orally administering a single bedtime daily dose to said human amounts of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate in the formulation of the present invention. The invention further provides methods of treating narcolepsy, types 1 and/or 2, by orally administering at bedtime a

therapeutically effective amount of a gamma-hydroxybutyrate formulation characterized by the novel gamma-hydroxybutyrate pharmacokinetics or dissolution properties of the present invention. The modified release formulation of the present invention is effective to treat narcolepsy Type 1 or Type 2, wherein said treatment of narcolepsy is defined as reducing excessive daytime sleepiness or reducing the frequency of cataplectic attacks. The therapeutically effective amount preferably comprises equivalents from 3.0 to 12.0 g of sodium oxybate, more preferably from to 9.0 g of sodium oxybate, and most preferably 4.5, 6.0, 7.5 or 9.0 g of sodium oxybate. The effectiveness of the treatment can be measured by one or any combination of the following criteria:

[0364] Increase the mean sleep latency, preferably as determined on the Maintenance of Wakefulness Test (MWT)

[0365] Improve the Clinical Global Impression (CGI) rating of sleepiness

[0366] Decrease the number of cataplexy attacks (NCA) preferably determined from the cataplexy frequency item in the Sleep and Symptoms Daily Diary

[0367] Decrease the disturbed nocturnal sleep (DNS), the disturbed nocturnal events or the adverse respiratory events preferably as determined by polysomnographic (PSG) measures of sleep fragmentation

[0368] Decrease the excessive daytime sleepiness (EDS) preferably as measured by patient report via the Epworth Sleepiness Scale (ESS)

[0369] Decrease the daytime sleepiness as measured by the Maintenance of Wakefulness Test based on EEG measures of wakefulness

[0370] Decrease PSG transitions from N/2 to N/3 and REM sleep to wake and N1 sleep (as determined by C Iber, S Ancoli-Israel, A Chesson, S F Quan. *The AASM Manual for the Scoring of Sleep and Associated Events*. Westchester, Ill.: American Academy of Sleep Medicine; 2007).

[0371] Decrease the number of arousals or wakenings, preferably obtained from a PSG as defined by the American Academy of Sleep Medicine

[0372] Improve the sleep quality, preferably obtained from one or more of (i) the Sleep and Symptom Daily Diary, (ii) Visual Analog Scale (VAS) for sleep quality and sleep diary, and (iii) VAS for the refreshing nature of sleep

[0373] Decrease the Hypnagogic Hallucinations (HH) or sleep paralysis (SP) symptoms in NT1 narcolepsy patients, preferably as measured by the Sleep and Symptom Daily Diary

[0374] In a preferred embodiment, the treatment of the present invention is superior, as measured by any one or combination of the foregoing criteria, to an equal dose administered twice nightly of an immediate release liquid solution of sodium oxybate, with the second dose administered 4 hours after the first dose.

[0375] The invention further provides a method of treatment of narcolepsy Type 1 or Type 2 wherein, compared to a dosing regimen consisting of administering half the dose at to and another half of the dose at t_{4h} of an immediate release liquid solution of sodium oxybate, a single bedtime daily dose administration of a therapeutically effective amount of the formulation of the invention has been shown to produce less confusion, less depressive syndrome, less incontinence, less nausea or less sleepwalking.

Additional Embodiments

[0376] In one additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0377] In a second additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0378] In a third additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0379] In a fourth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed

of 75 rpm, and (b) from 40% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0380] In a fifth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hour3 when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 40% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0381] In a sixth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 40% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0382] In a seventh additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 40% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0383] In a eighth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 40% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0384] In a ninth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 40 to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

EXAMPLES

Example 1. Formulations

[0385] Tables 1a-1d provide the qualitative and quantitative compositions of sodium oxybate IR microparticles, MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **1**.

[0386] Briefly, sodium oxybate immediate release (IR) microparticles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone™ K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 270 microns were obtained.

[0387] Sodium oxybate modified release (MR) microparticles were prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S 100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), were dissolved in 1542.9 g of isopropanol at 78° C. The solution was sprayed entirely onto 400.0 g of the sodium oxybate IR

microparticles described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR microparticles with mean volume diameter of about 320 microns were obtained.

[0388] The finished composition, which contains a 50:50 mixture of MR and IR microparticles calculated on their sodium oxybate content, was prepared as follows: 353.36 g of the above IR microparticles, 504.80 g of the above MR microparticles, 14.27 g of malic acid (D/L malic acid), 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.51 g of magnesium stearate were mixed. Individual samples of 7.11 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 1a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		2.786

TABLE 1b

Composition of MR Microparticles

Component	Function	Quantity per 4.5 g dose (g)
IR Microparticles	Core of MR microparticles	2.786
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.981

TABLE 1c

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

TABLE 1c-continued

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

TABLE 1d

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

Example 1bis: Alternative Formulation

[0389] An alternative formulation to the formulation described in example 1 is described in Example 1bis.

[0390] Sodium oxybate immediate release (IR) microparticles were prepared by coating the IR microparticles described in example 1 with a top coat layer. Microparticles were prepared as follows: 170.0 of hydroxypropyl cellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the IR microparticles of Example 1 in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 298 microns were obtained (see Table 1bis-*a*).

[0391] Sodium oxybate modified release (MR) microparticles were prepared as described in example 1 (see Table 1b).

[0392] The finished composition, which contains a 50:50 mixture of MR and IR microparticles based on their sodium oxybate content, was prepared as follows: 412.22 g of the above IR microparticles, 530.00 g of the above MR microparticles, 29.96 g of malic acid (D/L malic acid), 4.96 g of xanthan gum (Xantural™ 75 from Kelco), 4.96 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 9.92 g of magnesium stearate were mixed. Individual samples of 7.45 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose in an immediate-release fraction and half of the dose in a modified release fraction) were weighed (see Table 1bis-*b* and ibis-*c*).

TABLE 1bis-a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Hydroxypropyl cellulose	Top coat	0.310
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Total		3.096

TABLE 1bis-b

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of sodium oxybate	3.096
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.037
Colloidal silicon dioxide	Gliding agent	0.037
Magnesium stearate	Lubricant	0.075
Total		7.451

TABLE 1bis-c

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydroxypropyl cellulose	Top coat	0.310
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.037
Colloidal silicon dioxide	Gliding agent	0.037
Magnesium stearate	Lubricant	0.075
Total		7.451

[0393] Compared to the finished composition described in example 1, this alternative composition has the following characteristics: same MR microparticles, same IR microparticles but with a top coat, increased amount of malic acid, only one suspending agent (xanthan gum) and presence of a glidant.

[0394] Finished compositions from Example 1 and 1bis exhibit substantially the same in-vitro dissolution profiles (see FIGS. **7** and **8**).

Example 2: In Vitro Release Profiles of IR, MR and Finished Compositions of Formulations of Examples 1 and 1bis

Dissolution Testing of IR Microparticles

[0395] The dissolution profile of 2786 mg of IR microparticles of Example 1, corresponding to 2250 mg of sodium oxybate per vessel, was determined in 0.1N HCl dissolution medium using a USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile of the IR microparticles is shown in FIG. **2** and Table 2a. All the sodium oxybate was released at 1 hour.

TABLE 2a

Percent Sodium Oxybate Released in 0.1N HCl for IR microparticles of sodium oxybate prepared according to Example 1

Time (min)	% released
0	0
5	94
10	97
15	97
30	98
60	98

Dissolution Testing of IR Microparticles from Example 1bis

[0396] The dissolution profile of 3096 mg of IR microparticles of Example 1bis, corresponding to 2250 mg of sodium oxybate per vessel, was determined in 0.1N HCl dissolution medium using a USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile of the IR microparticles is shown in FIG. **2** and Table 2b. All the sodium oxybate was released at 1 hour.

TABLE 2b

Percent Sodium Oxybate Released in 0.1N HCl for IR microparticles of sodium oxybate prepared according Example 1bis

Time (min)	% Released
0	0
5	91
10	99
15	100
30	101
60	100

Dissolution Testing of MR Microparticles from Example 1—Protocol (2 h 0.1N HCl/Phosphate Buffer pH 6.8)

[0397] 49.1 g of MR microparticles from Example 1 were mixed with 0.5 g of magnesium stearate (from Peter Graven) and 0.25 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4040 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

[0398] After 2 hours in 750 mL of 0.1N HCl medium, 6.5 g of monobasic potassium phosphate was added to the dissolution vessel. pH and volume were then respectively adjusted to 6.8 and 950 mL, as needed by the addition of NaOH and water. The potassium phosphate concentration was equal to 0.05 M in the dissolution medium after pH and volume adjustment.

[0399] The release profile of the MR microparticles is shown in FIG. **3** and Table 2c. The sodium oxybate was not

released in the 0.1N HCl dissolution medium during two hours. After the switch to pH 6.8 dissolution medium, all the sodium oxybate was released within 30 minutes.

TABLE 2c

Percent Sodium Oxybate Released in two sequential dissolution media (0.1 HCl for 2 hours, then phosphate buffer pH 6.8) for MR microparticles of sodium oxybate prepared according to Example 1

Time (h)	% released
0	0
1	1
2	2
2.25	33
2.5	97
3	103
4	104
6	103

[0400] FIG. **4** overlays the dissolution profile of the MR microparticles of Example 1 with the dissolution profile for MR microparticles reported in Supernus U.S. Pat. No. 8,193,211, FIG. 3. It shows that the dissolution profiles are different and that the MR microparticles according to the present invention release greater than 80% of their sodium oxybate at 3 hours, whereas the MR microparticles described in Supernus U.S. Pat. No. 8,193,211, FIG. 3 do not and exhibit a much slower release profile.

Dissolution Testing of Finished Composition According to Example 1 in Deionized Water

[0401] The dissolution profile of the quantity equivalent to 4.5 g sodium oxybate of the finished composition according Example 1 was determined in 900 mL of deionized water using the USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 50 rpm. The release profile is shown in FIG. **5** and Table 2d. The IR fraction of sodium oxybate was solubilized in 15 minutes. The release of sodium oxybate from the modified-release fraction started after approximately 4 hours with 90% of the total dose released at 6 hours.

TABLE 2d

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 1

Time (h)	% released
0	0
0.25	53
1	52
2	54
3	55
4	58
5	69
6	92
7	96
8	97

[0402] An overlay of the release profile of the finished formulation of Example 1 versus that reported in USP 2012/0076865 FIG. **2** is shown in FIG. **6**. It shows that the dissolution profiles are different. The formulation described in USP 2012/0076865 FIG. **2** does not exhibit a lag phase after the dissolution of the immediate release part.

Release Testing of Different Batches of MR Microparticles and Finished Dosage Forms

[0403] In vitro release profiles obtained in 900 mL of 0.1N HCl dissolution medium for different batches of modified release (MR) microparticles prepared according to Example 1 are described below in Table 2e. The dissolution profile of 4040 mg of microparticles corresponding to 2250 mg of sodium oxybate per vessel is determined using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 2e

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium from different manufacturing lots of MR Particles of Example 1

Time	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5	Lot 6	Lot 7	Lot 8
0.25	2.22	0.62	0.42	0.86	0.56	1.03	0.69	0.26
1.0	2.59	1.14	1.23	1.48	0.96	2.15	1.43	0.97
2.00	3.07	1.71	2.09	1.94	1.36	3.16	2.17	1.39
3	3.55	2.31	2.75	2.29	1.76	4.08	2.82	1.80
4.0	4.23	3.03	3.53	2.75	2.18	4.92	3.50	2.31
6	7.99	7.68	8.69	5.33	3.78	7.52	5.70	8.10
8.0	37.44	33.84	33.84	26.20	17.00	21.59	21.02	37.27
10	77.09	69.85	65.51	61.77	49.89	50.98	53.48	67.64
12	91.26	85.72	84.25	83.55	77.65	75.68	78.00	82.66
16	96.15	90.48	95.35	97.34	96.94	95.19	96.17	90.35

[0404] In vitro release profiles obtained in 0.1N HCl for three batches of finished composition comprising IR (50% w/w sodium oxybate dose) and MR microparticles (50% w/w sodium oxybate dose), prepared as described in Example 1, are provided in Table 2f. The sodium oxybate dose per vessel was 4.5 g, 6 g and 7.5 g respectively and dissolution was determined in 900 mL of 0.1N HCl dissolution medium using the USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 2f

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for three batches of finished composition prepared according to Example 1

Time (hour)	Batch 1	Batch 2	Batch 3
0.5	50	49	50
1	50	50	50
3	50	50	50
6	52	52	53
8	61	64	63
12	90	93	97
16	96	94	95

[0405] FIG. **7** and Table 2 g depict dissolution profiles determined using a USP apparatus 2 in a 900 mL in 0.1N HCl dissolution medium of four finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases from 10 to 65% of its sodium oxybate at 1 and 3 hours and releases greater than 60% at 10 hours.

TABLE 2g

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for four batches of finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis

Time (hour)	Example 1bis	Example 1bis	Example 1	Example 1
0	0	0	0	0
0.25	Nd	Nd	52	50
0.5	51	50	Nd	Nd
1	51	50	54	51
3	51	50	54	52
6	55	52	55	53
8	72	61	60	57
10	Nd	Nd	73	70
12	86	90	85	83
16	88	96	96	94
20	Nd	Nd	99	98

Nd: not determined

[0406] FIG. **8** and Table 2h depict dissolution profiles determined using a USP apparatus 2 in a 900 mL phosphate buffer pH 6.8 dissolution medium for four finished compositions prepared according to Example 1 or 1bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases more than 80% of its sodium oxybate at 3 hours.

TABLE 2h

Percent Sodium Oxybate Released in phosphate buffer pH 6.8 Dissolution Medium for four batches of finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis

Time (hour)	Example 1bis	Example 1bis	Example 1	Example 1
0	0	0	0	0
0.25	Nd	Nd	75	84
0.5	99	98	Nd	Nd
1	101	101	100	102
1.5	101	101	106	108
2	100	100	Nd	Nd
3	103	100	Nd	Nd
4	103	100	Nd	Nd
6	102	99	101	102
8	103	99	101	105
10	103	99	101	Nd
12	101	99	101	102
16	Nd	Nd	100	101
20	Nd	Nd	99	98

Nd: not determined

Release Testing of MR Microparticles and Finished Compositions Effect of Paddle Speed:

[0407] FIG. **9** and Table 2i depict dissolution profiles in 0.1N HCl of a batch of MR microparticles prepared according to Example 1. The dissolution profile of 4040 mg of microparticles corresponding to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2. The dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 or 100 rpm.

TABLE 2i

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for MR microparticles prepared according to Example 1

Time (hour)	75 rpm	100 rpm
0	0	0
0.25	1	1

TABLE 2i-continued

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for MR microparticles prepared according to Example 1

Time (hour)	75 rpm	100 rpm
1	2	1
2	2	2
3	3	2
4	3	3
6	6	5
8	28	26
10	65	62
12	86	84
16	97	97

[0408] FIG. **10** and Table 2j depict dissolution profiles in 0.1N HCl of a finished composition prepared according to Example 1. The dose per vessel was 4.5 g and dissolution was determined in 900 mL of dissolution medium using the USP apparatus 2. The dissolution medium temperature was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 75 or 100 rpm.

[0409] Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 2j

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for finished composition prepared according to Example 1

Time (hour)	75 rpm	100 rpm
0	0	0
0.25	48	47
1	53	52
3	54	53
6	56	56
8	65	65
10	82	79
12	92	89
16	97	96
20	98	98

Example 3. In Vivo Pharmacokinetic Study of Finished Composition According to Example 1bis

[0410] Pharmacokinetic testing was undertaken in vivo in healthy human volunteers according to the principles described in FDA's March 2003 Guidance for Industry on BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS. All testing was performed in subjects two hours after eating a standardized dinner. Xyrem® doses were administered in two equipotent doses four hours apart. All other tested doses were manufactured as described in Example 1bis. The standardized dinner consisted of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

[0411] The finished composition of Example 1bis given as a 4.5 g once-nightly dose rather than a standard Xyrem® dosing twice (2×2.25 g) nightly 4 hours apart, produced a dramatically different pharmacokinetic profile than Xyrem® as shown in FIG. **11**. As summarized below (Tables 3a and 3b), 4.5 g nighttime doses of finished composition of the invention equivalent to twice-nightly doses of Xyrem® (2×2.25 g) provided somewhat less total exposure to sodium

oxybate with a later median T_{max} than the initial Xyrem® dose. The relative bioavailability was about 88%. Composition according to the invention avoids the high second-dose peak concentration of Xyrem® and therefore does not exhibit the substantial between-dose fluctuations in concentration, while achieving a comparable mean C_{8h}.

TABLE 3a

Pharmacokinetic Parameters of finished composition of Example 1bis vs. Xyrem ®

	Mean Cmax (μg/mL) (% CV)	Mean AUCinf (h*μg/mL)	Median Tmax (hour) (min-max)
Finished composition of Example 1bis 4.5 g	44.35 (38)	188.88 (44)	1.5 (0.5-4)
Xyrem ® 2 × 2.25 g	1st dose: 33.41 (41) 2nd dose: 65.91 (40)	214.32 (48)	1st dose: 1.00 (0.5-2) 2nd dose: 4.50 (4.33-6.5)

[0412] The pharmacokinetic profile of a single 6 g dose of finished composition produced according to Example 1bis was also tested and found to have a similar pharmacokinetic profile as the 4.5 g dose. FIG. **12** provides a pharmacokinetic profile comparison of a single 4.5 g or 6 g dose of finished composition according to Example 1bis in the same 7 subjects. The pharmacokinetic profile for a 7.5 g dose of finished formulation produced according to Example ibis was also obtained. FIG. **13** and Table 3c provide data on a single 4.5 g, 6 g and 7.5 g dose, showing effects on T_{max}, C_{max}, C_{8h}, AUC_{8h} and AUC_{inf} related to dose strength. The 7.5 g dose achieved a mean C_{8h} equal to about 31 microgram/mL which represents approximately 128.5% of the C_{8h} obtained for Xyrem® dosed 2×3.75 g which was extrapolated to be approximately 24.07 microgram/mL from published data. The 7.5 g dose achieved a ratio of AUC_{8h} to AUC_{inf} of about 0.89, whereas the ratio was 0.83 and 0.93 for the 4.5 g and 6 g doses respectively.

TABLE 3b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 1bis and Xyrem ®

Time (hour)	Finished composition Example 1bis 4.5 g (2 h after meal) pooled mean (N = 26)	Finished composition Example 1bis 6.0 g (2 h after meal) pooled mean (N = 19)	Finished composition Example 1bis 7.5 g (2 h after meal) (N = 11)	Xyrem ® (2 × 2.25 g) part I (N = 15)
0	0.00	0.00	0.00	0.00
0.5	29.31	36.44	43.19	27.44
1	34.93	49.97	63.32	28.97
1.5	36.63	54.66	73.40	26.12
2	36.78	54.82	67.96	21.11
2.5	33.35	53.05	66.59	NA
3	30.28	50.25	62.13	13.93
3.5	27.30	47.22	59.45	10.25
4	23.66	43.06	57.40	6.92
4.5	19.89	39.13	50.85	57.33
5	16.55	34.28	45.09	52.27
5.5	13.62	32.11	44.94	43.55
6	12.40	25.84	42.36	35.20
6.5	11.25	22.36	41.02	27.44
7	11.27	18.07	40.76	19.36
7.5	9.65	15.41	35.83	13.88
8	6.86	12.80	30.94	9.24
10	1.08	2.38	7.99	2.64
12	NC	0.52	1.47	NC

NC: Not Calculated

TABLE 3c

Pharmacokinetic Parameters of 4.5 g, 6 g, and 7.5 g of finished composition produced according to Example 1bis

Finished composition according to Example 1bis	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h*μg/mL) (% CV)	Mean $AUC_{8\ h}$ (h*μg/mL) (% CV)	Median T_{max} (h) (min-max)	Mean $C_{8\ h}$ (μg/mL) (% CV)
4.5 g	44.35 (38)	188.88 (47)	174.68 (48)	1.5 (0.5-4)	6.86 (84)
6 g	65.46 (35)	307.34 (48)	290.97 (47)	3 (0.5-5.5)	12.8 (82)
7.5 g	88.21 (30)	454.99 (34)	404.88 (31)	2 (0.5-6)	30.94 (34)

[0413] FIG. **14** and table 3d compare the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g of a finished composition according to Example 1bis to the same parameters calculated for 2×4.5 g, i.e. 9 g total dose of Xyrem®. The data show that a 7.5 g dose of a formulation according to the invention given once nightly exhibits a similar PK profile to 9 g of Xyrem® given in two separate equal doses.

TABLE 3d

Pharmacokinetic Parameters of 7.5 g of finished composition produced according to Example 1bis compared to 2 × 4.5 g of Xyrem ®

	Mean $C_{8\ h}$ (µg/mL)	Mean AUC_{inf} (µg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®	Ratio (%) $C_{8\ h}$ composition to $C_{8\ h}$ Xyrem ®
Xyrem ® 2 × 4.5 g	28.9	518	NA	NA
Finished composition according to Example 1bis 7.5 g	30.9	455	88%	107%

Example 4. Alternative Formulation

[0414] Tables 4a-4d provide the qualitative and quantitative compositions of IR microparticles, MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **15**.

[0415] Briefly, sodium oxybate immediate release (IR) microparticle were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone™ K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus. IR microparticles with volume mean diameter of about 270 microns were obtained.

[0416] Sodium oxybate modified release (MR) microparticles were prepared as follows: 4.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55), 49.3 g of Methacrylic acid copolymer Type B (Eudragit™ S100), 80 g of Hydrogenated cottonseed oil (Lubritab™), were dissolved in 1200.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR microparticles prepared above in a fluid bed spray coater apparatus with an inlet temperature 48° C., spraying rate around 11 g per min and atomization pressure 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR microparticles with volume mean diameter of about 330 microns were obtained.

[0417] The finished composition, which contained a 50:50 mixture of MR and IR microparticles calculated on their sodium oxybate content, was prepared as follows: 27.86 g of IR microparticles, 37.15 g of MR microparticles, 1.13 g of malic acid (D/L malic acid), 0.50 g of xanthan gum (Xantural™ 75 from Kelco), 0.75 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 0.75 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.34 g of magnesium stearate were mixed. Individual samples of 6.85 g (corresponding to a 4.5 g sodium oxybate dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 4a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		2.786

TABLE 4b

Composition of MR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
IR Microparticles	Core of MR Microparticles	2.786
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.715

TABLE 4c

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.715
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.848

TABLE 4d

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.848

Example 4bis

[0418] An alternative formulation to example 4 is described in example 4bis. Sodium oxybate immediate release (IR) microparticles were prepared by coating the IR microparticles described in example 4 with a top coat layer. IR Microparticles were prepared as follows: 170.0 of hydroxypropyl cellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the IR microparticles of Example 4 in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 298 microns were obtained (see Table 4bis-a).

[0419] Sodium oxybate modified release (MR) microparticles were prepared as described in example 4 (see Table 4b).

[0420] The finished composition, which contains a 50:50 mixture of MR and IR microparticles calculated based on sodium oxybate content, was prepared as follows: 424.99 g of the above IR microparticles, 509.98 g of the above MR microparticles, 30.89 g of malic acid (D/L malic acid), 4.93 g of xanthan gum (Xantural™ 75 from Kelco), 4.93 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 9.86 g of magnesium stearate were mixed. Individual samples of 7.18 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose as an immediate-release fraction and half of the dose as a modified release fraction) were weighed. (see Tables 4bis-b and 4bis-c).

TABLE 4bis-a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Hydroxypropyl cellulose	Top coat	0.310
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Total		3.096

TABLE 4bis-b

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.715
IR microparticles	Immediate release fraction of sodium oxybate	3.096
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.036
Colloidal silicon dioxide	Gliding agent	0.036
Magnesium stearate	Lubricant	0.072
Total		7.180

TABLE 4bis-c

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydroxypropyl cellulose	Top coat	0.310
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.036
Colloidal silicon dioxide	Gliding agent	0.036
Magnesium stearate	Lubricant	0.072
Total		7.180

[0421] Compared to the finished composition described in example 4, this alternative composition has the following characteristics: same MR microparticles, same IR microparticles but with a top coat, increased amount of malic acid, only one suspending agent (xanthan gum) and presence of a glidant.

Example 5 In Vitro Release Profiles of IR, MR and Finished Compositions of Formulation of Example 4 and 4bis

[0422] Dissolution Testing of MR Microparticles from Example 4—Protocol (2 h 0.1N HCl/Phosphate Buffer pH 6.8)

[0423] 49.1 g of MR microparticles from Example 4 were mixed with 0.5 g of magnesium stearate (from Peter Greven) and 0.25 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik).

[0424] The dissolution profile of 3770 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

[0425] After 2 hours in 750 mL of 0.1N HCl dissolution medium, 6.5 g of monobasic potassium phosphate was added in the dissolution vessel. pH and volume were then respectively adjusted to 6.8 and 950 mL. The potassium phosphate concentration was equal to 0.05 M in the dissolution medium after pH and volume adjustment. The release profile is shown in FIG. **16** and Table 5a.

TABLE 5a

Percent Sodium Oxybate Released in two sequential dissolution media (0.1N HCl for two hours, then phosphate buffer pH 6.8) for MR microparticles of sodium oxybate prepared according to Example 4

Time (h)	% sodium oxybate dissolved
0	0
1	1
2	2
2.25	9
2.5	40
3	89
4	102
6	103

[0426] The sodium oxybate was not released in the 0.1N HCl medium during two hours. After the switch at pH 6.8, 40% of the API was released after 30 minutes and 90% of API after 1 hour. FIG. **17** overlays the dissolution profile of the MR microparticles of Example 4 with the dissolution profile for MR microparticles reported in Supernus U.S. Pat. No. 8,193,211, FIG. 3. It shows that the dissolution profiles are different and especially that the MR microparticles according to the invention release greater than 80% of its sodium oxybate at 3 hours, whereas the MR microparticles described in Supernus U.S. Pat. No. 8,193,211, FIG. 3 do not and exhibit a much slower releasing profile.

Dissolution Testing of Finished Composition According to Example 4 in Deionized Water:

[0427] The dissolution profile of the quantity equivalent to 4.5 g of sodium oxybate of the finished composition of the Example 4 was determined in 900 mL of deionized water using the USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 50 rpm. The release profile of is shown in FIG. **18** and Table 5b.

TABLE 5b

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 4

Time (hour)	Example 4
0	0
0.25	52
1	55
2	53
3	54
4	52
5	54
6	60
7	78
8	90

[0428] The IR fraction of sodium oxybate was solubilized in 15 minutes. The release of sodium oxybate from the modified release fraction started after 5 hours with 90% of the total dose released at 8 hours.

[0429] An overlay of the release profile of the finished composition of the Example 4 versus that reported in USP 2012/0076865 FIG. 2 is shown in FIG. **19**. It shows that the dissolution profiles are different. The formulation described in USP 2012/0076865 FIG. 2 does not exhibit a lag phase after the dissolution of the immediate release part.

[0430] FIG. **20** and Table 5c depict dissolution profiles determined using a USP apparatus 2 in a 900 mL in 0.1N HCl dissolution medium of three finished compositions prepared according to Example 4bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases from 10 to 65% of its sodium oxybate at 1 and 3 hours and releases greater than 60% at 10 hours.

TABLE 5c

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for three batches of finished composition prepared according to Example 4bis

Time (Hour)	Batch 1	Batch 2	Batch 3
0	0	0	0
0.25	50	Nd	Nd
0.5	51	50	49
0.75	51	Nd	Nd
1	51	51	51
1.5	51	Nd	Nd
2	51	Nd	Nd
3	51	52	53
4	51	Nd	Nd
6	55	57	57
8	74	70	71
10	89	Nd	Nd
12	93	90	92
16	94	95	97

Nd = not determined

[0431] FIG. **21** and Table 5d depict dissolution profile determined using a USP apparatus 2 in a 900 mL phosphate buffer pH 6.8 dissolution medium for a finished composition prepared according to Example 4bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 100 rpm. It shows that the composition according to the invention releases more than 80% of its sodium oxybate at 3 hours.

TABLE 5d

Percent Sodium Oxybate Released in phosphate buffer pH 6.8 Dissolution Medium for finished composition prepared according to Example 4bis

Time (Hour)	Example 4bis
0	0
0.25	54
0.5	54
0.75	55
1.0	56
1.5	63
2	77
3	103
4	105
6	105
8	102
10	101
12	104
16	100

Example 6. In Vivo Pharmacokinetic Study of Finished Composition According to Example 4bis

[0432] Pharmacokinetic testing was undertaken in vivo in healthy human volunteers according to the principles described in FDA's March 2003 Guidance for Industry on Bioavalability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. All testing was performed in subjects two hours after eating a standardized dinner. Xyrem® doses were administered in two equipotent doses four hours apart. All other tested doses were manufactured as described in Example 4bis. The standardized dinner consisted of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

[0433] The finished composition of Example 4bis given as a 4.5 g once-nightly dose rather than a standard Xyrem® dosing twice (2×2.25 g) nightly 4 hours apart, produced a dramatically different pharmacokinetic profile than Xyrem® as shown in FIG. **22**. As summarized below (Tables 6a and 6b), 4.5 g nighttime doses of finished composition of the invention equivalent to twice-nightly doses of Xyrem® (2×2.25 g) provided somewhat less total exposure to sodium oxybate with a later median T_{max} than the initial Xyrem® dose. The relative bioavailability was about 88%. Composition according to the invention avoids the high second-dose peak concentration of Xyrem® and therefore does not exhibit the substantial between-dose fluctuations in concentration, while achieving a comparable mean C_{8h}.

TABLE 6b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 4bis and Xyrem ®

Time (hour)	Finished composition Example 4bis 4.5 g (2 h after meal) (N = 15)	Xyrem ® (2 × 2.25 g) (N = 15)
0	0.00	0.00
0.5	23.80	27.44
1	33.26	28.97
1.5	35.60	26.12
2	35.57	21.11
2.5	33.81	13.93
3	30.96	10.25
3.5	28.73	6.92
4	26.06	42.32
4.5	23.27	57.33
5	18.68	52.27
5.5	16.67	43.55
6	15.55	35.20
6.5	13.07	27.44
7	11.75	19.36
7.5	9.20	13.88
8	6.85	9.24
10	1.94	2.64
12	NC	NC

NC: Not Calculated

[0434] The 4.5 g dose achieved a mean C_{8h} equal to about 6.85 microgram/mL which represents approximately 74.1% of the C_{8h} obtained for Xyrem® dosed 2×2.25 g. The ratio of AUC_{8h} to AUC_{inf} was about 0.89.

Example 7. In Vitro and In Vivo Pharmacokinetic Study of a Comparative Formulation

[0435] A formulation having an in vitro dissolution profile comparable to the formulation reported in FIG. 3 of U.S. Pat. No. 8,193,211 was prepared to confirm the in vitro/in vivo correlations reported herein. Tables 7a-7c provide the qualitative and quantitative compositions of the MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **23**.

[0436] Briefly, sodium oxybate immediate release (IR) microparticles were prepared according to Example 1bis. Sodium oxybate modified release (MR) microparticles were prepared in two steps:

[0437] Step 1: 106.7 g of water insoluble polymer Ethylcellulose (Ethocel™ 20 Premium), 10.7 g of polyvinylpyrrolidone (Plasdone™ K30 from ISP), 10.7 g of castor oil (from Olvea) and 5.3 g of Polyoxyl 40 Hydrogenated Castor

TABLE 6a

Pharmacokinetic Parameters of finished composition of Example 4bis vs. Xyrem ®

	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h*μg/mL) (% CV)	Mean $AUC_{8\ h}$ (h*μg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (μg/mL) (% CV)
Finished composition of Example 4bis 4.5 g	43.47 (49)	188.96 (57)	179.69 (57)	2 (0.5-7)	6.85 (118)
Xyrem ® 2 × 2.25 g	1^{st} dose: 33.41 (41) 2^{nd} dose: 65.91 (40)	214.32 (48)	202.78 (46)	1^{st} dose: 1.0 (0.5-2) 2^{nd} dose: 4.5 (4.33-6.5)	9.24 (127)

Oil (Kolliphor RH40 from BASF), were dissolved in a mixture of 828.0 g of acetone, 552.0 g of isopropanol and 153.3 g of water. The solution was sprayed entirely on 400.0 g of immediate release microparticles of sodium oxybate prepared above in a fluid bed spray coater apparatus Glatt G.P.C.G.1.1 with inlet temperature 57° C., spraying rate around 14.5 g per min and atomization pressure 2.5 bar. Microparticles with volume mean diameter of about 310 microns were obtained.

[0438] Step 2: 15.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 30.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 67.5 g of Hydrogenated cottonseed oil (Lubritab™), were dissolved in 1012.5 g of isopropanol at 78° C. The solution was sprayed entirely on 450.0 g of the above prepared microparticles in a fluid bed spray coater apparatus with an inlet temperature 47° C., spraying rate around 10.5 g per min and atomization pressure 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR Microparticles with volume mean diameter of 335 microns were obtained.

[0439] The finished composition, which contains a 60:40 mixture of MR and IR microparticles calculated based on their sodium oxybate content, was prepared as follows: 326.69 g of the above IR microparticles, 735.04 g of the above MR microparticles, 23.74 g of malic acid (D/L malic acid), 5.54 g of xanthan gum (Xantural™ 75 from Kelco), 5.54 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 11.08 g of magnesium stearate were mixed. Individual samples of 8.40 g (corresponding to a 4.5 g dose of sodium oxybate with 40% of the dose as immediate-release fraction and 60% of the dose as modified release fraction) were weighed.

TABLE 7a

Composition of MR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
IR Microparticles	Core of MR Microparticles	2.786
Ethylcellulose 20	Coating excipient	0.743
Povidone K30	Coating excipient	0.074
Polyoxyl 40 Hydrogenated Castor Oil	Coating excipient	0.037
Castor oil	Coating excipient	0.074
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.124
Methacrylic acid Copolymer Type B	Coating excipient	0.248
Ethyl alcohol	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Water	Solvent	Eliminated during processing
Isopropyl alcohol	Solvent	Eliminated during processing
Total		4.644

TABLE 7b

Qualitative Composition of Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	5.573
IR microparticles	Immediate release fraction of sodium oxybate	2.477
Malic acid	Acidifying agent	0.180
Xanthan gum	Suspending agent	0.042
Colloidal silicon dioxide	Gliding agent	0.042
Magnesium stearate	Lubricant	0.084
Total		8.398

TABLE 7c

Quantitative Composition of Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	der and coating excipient	0.326
Hydroxypropyl cellulose	Top coat	0.248
Ethylcellulose 20	Coating excipient	0.892
Polyoxyl 40 Hydrogenated Castor Oil	Coating excipient	0.045
Castor oil	Coating excipient	0.089
Hydrogenated Vegetable Oil	Coating excipient	0.669
Methacrylic acid Copolymer Type C	Coating excipient	0.149
Methacrylic acid Copolymer Type B	Coating excipient	0.297
Malic acid	Acidifying agent	0.180
Xanthan gum	Suspending agent	0.042
Colloidal silicon dioxide	Gliding agent	0.042
Magnesium stearate	Lubricant	0.084
Total		8.398

[0440] The dissolution profile obtained for the MR microparticles in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8) is shown in FIG. **24** and Table 7d. These data show that the dissolution profile of the MR microparticles produced according the comparative Example 7 was quite similar to the dissolution profile of FIG. 3 from U.S. Pat. No. 8,193,211. In particular, the MR microparticles according to the comparative Example 7 do not release more than 80% of its sodium oxybate at 3 hours.

TABLE 7d

Dissolution profile obtained for the MR microparticles of Example 7 in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8)

Time (hour)	Example 7
0	0
1	0
2	1
2.25	5
2.5	44
3	74
64	89
6	96

[0441] The finished composition of Comparative Example 7 was tested in the same pharmacokinetic study than the finished composition of Example 1 and 4. As summarized below (Tables 7e), 4.5 g nighttime dose of finished composition of the comparative Example 7 compared to twice-nightly doses of Xyrem® (2×2.25 g) provided much less total exposure to sodium oxybate with a relative bioavailability of 67%.

TABLE 7e

Pharmacokinetic Parameters of finished composition of Comparative Example 7 vs. Xyrem ®

	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h * μg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean C_{8h} (μg/mL) (% CV)
Finished composition of Comparative Example 7 4.5 g	28.99 (45)	143.90 (53)	1.5 (0.5-8)	7.79 (82)
Xyrem ® 2 × 2.25 g	1st dose: 33.41 (41) 2nd dose: 65.91 (40)	214.32 (48)	1st dose: 1.0 (0.5-2) 2nd dose: 4.5 (4.33-6.5)	9.24 (127)

TABLE 7f

Mean plasma concentration (microgram/mL) of gamma-hydroxybutyrate versus time of finished composition of Comparative Example 7 and Xyrem ®

Time (hour)	Comparative Example 7 @ 4.5 g (2 h after meal) pooled mean (N = 27)	Comparative Example 7 @ 6.0 g (2 h after meal) pooled mean (N = 18)	Comparative Example 7 @ 7.5 g (2 h after meal) (N = 12)	Xyrem ® (2 × 2.25 g) part I (N = 15)
0	0.00	0.00	0.00	0.00
0.5	18.84	25.54	31.40	27.44
1	23.93	35.80	46.78	28.97
1.5	24.31	38.59	58.29	26.12
2	24.32	40.78	57.47	21.11
2.5	23.10	38.03	52.25	13.93
3	20.05	35.76	49.00	10.25
3.5	17.47	33.99	45.66	6.92
4	16.48	30.47	40.52	0.00
4.5	15.44	26.87	37.70	57.33
5	14.10	25.59	36.82	52.27
5.5	12.60	24.63	35.93	43.55
6	11.68	23.90	34.47	35.20
6.5	11.45	23.98	31.60	27.44

TABLE 7f-continued

Mean plasma concentration (microgram/mL) of gamma-hydroxybutyrate versus time of finished composition of Comparative Example 7 and Xyrem ®

Time (hour)	Comparative Example 7 @ 4.5 g (2 h after meal) pooled mean (N = 27)	Comparative Example 7 @ 6.0 g (2 h after meal) pooled mean (N = 18)	Comparative Example 7 @ 7.5 g (2 h after meal) (N = 12)	Xyrem ® (2 × 2.25 g) part I (N = 15)
7	10.64	20.94	31.89	19.36
7.5	9.35	17.93	29.69	13.88
8	7.79	14.36	25.80	9.24
10	1.98	3.71	11.00	2.64
12	0.59	0.78	3.63	NC

NC: not calculated

[0442] The pharmacokinetic profiles of single 6 g and 7.5 g doses of the finished composition produced according to comparative Example 7 were also generated. Table 7 g provides data on a single 4.5 g, 6 g and 7.5 g dose, showing effects on C_{max}, C_{8h}, AUC_{8h} and AUC_{inf} related to dose strength.

TABLE 7g

Pharmacokinetic Parameters of 4.5 g, 6 g, and 7.5 g of finished composition produced according Comparative Example 7

Finished composition Comparative of Example 7	Mean C_{max} (μg/mL) (% CV)	Mean AUCinf (h * μg/mL) (% CV)	Mean $AUC_{8\ h}$ (h * μg/mL) (% CV)	Median T_{max} (min-max) (h) (% CV)	Mean $C_{8\ h}$ (μg/mL) (% CV)
4.5 g	28.98 (45)	143.90 (53)	128.83 (55)	1.5 (0.5-8)	7.79 (82)
6 g	45.64 (35)	248.24 (47)	225.00 (47)	2 (0.5-6.5)	14.36 (77)
7.5 g	63.31 (33)	379.83 (54)	316.18 (48)	1.75 (1-4.5)	25.80 (74)

Example 8. Alternative Formulations

Example 8.1

[0443] Modified release formulation of gamma-hydroxybutyrate comprising immediate release microparticles of potassium salt of gamma-hydroxybutyric acid and modified release microparticles of sodium salt of gamma-hydroxybutyric acid (sodium oxybate).

[0444] Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid can be prepared as follows: 1615.0 g of potassium salt of gamma-hydroxybutyric acid and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone™ K29/32 from ISP) are solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution is entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus.

[0445] Immediate release (IR) microparticles of sodium salt of gamma-hydroxybutyric acid were prepared as follows: 1615.0 g of sodium salt of gamma-hydroxybutyric acid and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone K29/32 from ISP) were solubilized in 1894.3 g of

absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans Sanaq) in a fluid bed spray coater apparatus.

[0446] Sodium oxybate modified release (MR) microparticles are prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S 100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), are dissolved in 1542.9 g of isopropanol at 78° C. The solution is sprayed entirely onto 400.0 g of the sodium oxybate IR microparticles described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles are dried for two hours with inlet temperature set to 56° C. MR microparticles with mean volume diameter of about 320 microns were obtained.

[0447] The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 398.51 g of the above IR microparticles, 504.80 g of the above MR microparticles, 16.09 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.75 g of magnesium stearate were mixed. Individual samples of 7.49 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8a

Composition of IR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Potassium salt of hydroxybutyric acid	Drug substance	2.537
Microcrystalline cellulose spheres	Core	0.471
Povidone K30	Binder and excipient in diffusion coating	0.134
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		3.142

TABLE 8b

Composition of MR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Povidone K30	Binder	0.118
Microcrystalline cellulose spheres	Core	0.419

TABLE 8b-continued

Composition of MR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Ethyl alcohol	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Water	Solvent	Eliminated during processing
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.981

TABLE 8c

Qualitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid	3.142
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.487

TABLE 8d

Quantitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	2.25
Potassium salt of gamma-hydroxybutyric acid	Drug substance	2.537
Microcrystalline cellulose spheres	Core	0.890
Povidone K30	Binder	0.252
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.487

Example 8.2

[0448] Modified release formulation of gamma-hydroxybutyrate comprising immediate release microparticles of potassium salt of gamma-hydroxybutyric acid, immediate

release microparticles of magnesium salt of gamma-hydroxybutyric acid, immediate release microparticles of calcium salt of gamma-hydroxybutyric acid and modified release microparticles of sodium salt of gamma-hydroxybutyric acid (sodium oxybate).

[0449] Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid are prepared according to example 8.1.

[0450] Immediate release (IR) microparticles of magnesium salt of gamma-hydroxybutyric acid or calcium salt of gamma-hydroxybutyric acid can be prepared using the same manufacturing process by replacing the potassium salt of gamma-hydroxybutyric acid by the same weight of respectively magnesium salt of gamma-hydroxybutyric acid or calcium salt of gamma-hydroxybutyric acid.

[0451] Sodium oxybate modified release (MR) microparticles are prepared according to example 8.1.

[0452] The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 132.84 g of the IR microparticles of potassium salt of gamma-hydroxybutyric acid, 215.32 g of the IR microparticles of magnesium salt of gamma-hydroxybutyric acid, 230.05 g of the IR microparticles of calcium salt of gamma-hydroxybutyric acid, 504.80 g of the MR microparticles of sodium oxybate, 23.35 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 5.69 g of magnesium stearate were mixed. Individual samples of 8.96 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8e

Qualitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid + immediate release fraction of magnesium salt of gamma-hydroxybutyric acid + immediate release fraction of calcium salt of gamma-hydroxybutyric acid	4.559
Malic acid	Acidifying agent	0.184
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.97

TABLE 8f

Quantitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	2.25
Potassium salt of gamma-hydroxybutyric acid	Drug substance	0.84

TABLE 8f-continued

Quantitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
Magnesium salt of gamma-hydroxybutyric acid	Drug substance	1.37
Calcium salt of gamma-hydroxybutyric acid	Drug substance	1.46
Microcrystalline cellulose spheres	Core	1.102
Povidone K30	Binder	0.312
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.184
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.96

Example 8.3: Modified Release Formulation of Gamma-Hydroxybutyrate Comprising Immediate Release Microparticles of Potassium Salt of Gamma-Hydroxybutyric Acid and Modified Release Microparticles of Calcium Salt of Gamma-Hydroxybutyric Acid

[0453] Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid are prepared according to example 8.1.

[0454] Immediate release (IR) microparticles of calcium salt of gamma-hydroxybutyric acid can be prepared using the manufacturing process described in example 8.1 for immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid by replacing the potassium salt of gamma-hydroxybutyric acid by the same weight of calcium salt of gamma-hydroxybutyric acid. These Immediate release (IR) microparticles of calcium salt of gamma-hydroxybutyric acid are used to manufacture modified release (MR) microparticles of calcium salt of gamma-hydroxybutyric acid as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), are dissolved in 1542.9 g of isopropanol at 78° C. The solution is sprayed entirely onto 400.0 g of the immediate release microparticles of calcium salt of gamma-hydroxybutyric acid described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles are dried for two hours with inlet temperature set to 56° C.

[0455] The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 398.53 g of the IR microparticles of potassium salt of gamma-hydroxybutyric acid, 492.87 g of the MR microparticles of sodium oxybate, 16.10 g of D/L malic acid, 6.34 g of xanthan gum (Xantural 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.69 g of magnesium stearate were mixed. Individual samples of 7.39 g of the mixture (amount equiva-

lent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8g

Qualitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of calcium salt of gamma-hydroxybutyric acid	3.887
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid	3.143
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

TABLE 8h

Quantitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
7Potassium salt of gamma-hydroxybutyric acid	Drug substance	2.54
Calcium salt of gamma-hydroxybutyric acid	Drug substance	2.19
Microcrystalline cellulose spheres	Core	0.880
Povidone K30	Binder	0.249
Hydrogenated Vegetable Oil	Coating excipient	0.700
Methacrylic acid Copolymer Type C	Coating excipient	0.155
Methacrylic acid Copolymer Type B	Coating excipient	0.311
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

Example 9. Alternative Formulations with Differing Concentrations of Acidic Agents

[0456] Different prototypes were developed to evaluate the effect of acidic agent on the dissolution stability of the formulation dispersed in water. Experimental data with 0.8%, 1.6% and 15% malic acid are detailed below.

Example 9.1—1.6% Malic Acid

[0457] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0458] MR coated particles were prepared as follows: 39.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80. g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 180.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 49° C., spraying rate around 11.6 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 324 microns were obtained.

[0459] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 655.1 g of the above IR particles, 936.4 g of the above MR particles, 26.5 g of Malic acid (D/L malic acid regular from Bartek), 11.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 17.6 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 17.6 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 8.2 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.11 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0460] FIG. **29** and Table 9a below depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9a

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	47	48
1	53	52
3	53	53
6	55	54
8	59	60
10	74	77
12	87	88
16	96	97
20	97	98

Example 9.2—0.8% Malic Acid

[0461] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 273 microns were obtained.

[0462] MR coated particles were prepared as follows: 39.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 180.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was

sprayed entirely on 700.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 47° C., spraying rate around 10.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 60° C. Sodium oxybate MR coated particles with mean diameter of 309 microns were obtained.

[0463] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 100.0 g of the above IR particles, 142.9 g of the above MR particles, 2.0 g of Malic acid (D/L malic acid regular from Bartek), 1.2 g of xanthan gum (Xantural™ 75 from CP Kelco), 1.2 g of hydrophilic fumed silica (Aerosil™ 200 from Degussa) and 2.5 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.93 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0464] FIG. **30** and Table 9b below depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9b

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	51	51
1	51	52
3	51	53
6	52	62
8	60	86
10	77	96
12	90	98
16	98	98

Example 9.3—15% Malic Acid

[0465] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 255 microns were obtained.

[0466] MR coated particles were prepared as follows: 22.8 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1544.8 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 49° C., spraying rate around 12.0 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 298 microns were obtained.

[0467] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 36.2 g of the above IR particles, 51.8 g of the above MR particles, 16.1 g of Malic acid (D/L malic acid regular from Bartek), 0.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 1.0 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 1.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.6 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 8.25 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0468] FIG. **31** and Table 9c below depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9c

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	48	49
1	51	51
3	51	51
4	51	51
6	52	51
8	56	56
10	71	71
12	86	85
16	97	96
20	99	98

Example 10. Alternative Formulations

[0469] Suspending agents are present in the formulation to limit microparticles settling after reconstitution. Without suspending agents, microparticles starts settling as soon as shaking stops. In presence of the suspending agents, full microparticles settling does not occur in less than 1 minute. The following data illustrates the good pourability of the suspension assessed by the high recovery of sodium oxybate content in the dissolution test:

[0470] IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 271 microns were obtained.

[0471] MR coated particles were prepared as follows: 39.9 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 80.1 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 180.0 g of hydrogenated

cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of sodium oxybate IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 11.5 g per min and atomization pressure 1.6 bar. MR coated particles were dried for 2 hours with inlet temperature set to 56° C. MR particles of sodium oxybate with mean diameter of 321 microns were obtained.

[0472] The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 634.0 g of the above IR particles, 907.6 g of the above MR particles, 25.7 g of malic acid (D/L malic acid regular from Bartek), 11.4 g of xanthan gum (Xantural™ 75 from CP Kelco), 17.1 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 17.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 8.1 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 14.20 g (corresponding to a 9 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0473] FIG. **32** and Table 10a below depict dissolution profiles of 9 g doses determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel. Dissolution profile was determined with and without rinsing step.

TABLE 10a

Time (h)	with rinsing	without rinsing
0	0	0
0.25	47	46
1	51	51
3	53	52
6.0	54	53
8	61	60
10	77	74
12	91	88
16	98	95
20	98	96

Example 11. Alternative Formulations with a Different Ratio of IR and MR Fractions

[0474] Different prototypes were prepared and evaluated to determine the effect of IR/MR ratio.

Example 11a—15% IR/85% IR with MR pH*6.5 Microparticles

[0475] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1896.2 g of absolute ethyl alcohol and 1264.4 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 275 microns were obtained.

[0476] MR coated particles were prepared as follows: 22.8 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.1 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 47° C., spraying rate around 10.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 330 microns were obtained.

[0477] 17.1 g of MR microparticles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown in FIG. **33**, Table 11a, and Table 11b.

TABLE 11a

Dissolution data - 0.1N HCl

Time (hour)	% dissolved
0	0.0
0.25	1
1	1
3	2
4	3
6	6
8	24
10	59
12	83
16	95
20	97

TABLE 11b

Dissolution data - 50 mM phosphate buffer pH 6.8

Time (hour)	% dissolved
0	0
0.25	18
0.5	80
0.75	97
1	97
2	97

[0478] The qualitative composition of 4.5 g dose units comprising 15% of the dose as IR fraction and 85% of the dose as MR fraction is described in Table 11c.

TABLE 11c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	6.767
IR microparticles	Immediate release fraction of sodium oxybate	0.836

TABLE 11c-continued

Component	Function	Quantity per 4.5 g dose (g)
Malic acid	Acidifying agent	0.034
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.039
Total		7.876

[0479] The finished composition, which contains a 85:15 mixture of MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 100.0 g of the above IR particles, 809.5 g of the above MR particles, 4.0 g of malic acid (D/L malic acid regular from Bartek), 6.0 g of xanthan gum (Xantural™ 75 from CP Kelco), 9.0 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.7 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.88 g (corresponding to a 4.5 g dose with 15% of the dose as immediate-release fraction and 85% of the dose as modified release fraction) were weighed.

[0480] After reconstitution with 50 ml of tap water and a rinsing volume of 10 ml of tap water, the finished composition will display the dissolution profiles in FIGS. **34** and **35** and Tables 11d and Ile in 840 ml of 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 11d

Time (hour)	% dissolved
0	0.0
0.25	16
1	16
3	17
4	17
6	20
8	35
10	65
12	85
16	96

TABLE 11e

Time (hour)	% dissolved
0	0
0.25	30
0.5	83
0.75	97
1	98
2	98

Example 11b—30% IR/70% MR with MR pH*6.2 Microparticles

[0481] IR particles were prepared as follows: 1615.1 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0482] MR coated particles were prepared as follows: 36.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 32.1 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 103.0 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.5 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 12.0 g per min and atomization pressure 1.3 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 323 microns were obtained.

[0483] 17.0 g of sodium oxybate MR particles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile of 4050 mg of the mixture which correspond to 2280 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl dissolution medium using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile in 0.1N HCl is shown in FIG. **36** and Table 11f.

TABLE 11f

Time (hour)	% dissolved
0.0	0
0.3	1
1.0	3
3.0	4
4.0	4
6.0	8
8.0	40
10.0	81
12.0	95
16.0	100
20.0	99

[0484] The finished composition, which contains a 70:30 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 92.1 g of the above IR particles, 306.5 g of the above MR particles, 7.5 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.0 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.62 g (corresponding to a 4.5 g dose with 30% of the dose as immediate-release fraction and 70% of the dose as modified release fraction) were weighed.

[0485] FIGS. **37** and **38** and Tables 11 g and 11h below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 11g

Time (hour)	% dissolved in 0.1N HCl
0.0	0.0
0.3	29
1.0	31
3.0	32
4.0	32
6.0	35
8.0	70
10.0	94
12.0	99
16.0	99

TABLE 11h

Time (h)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	64
0.5	87
1	100
2	100
3	102

Example 11c—65% IR/35% MR with MR pH*6.5 Microparticles

[0486] IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 270 microns were obtained.

[0487] MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 45.8 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.1 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 47° C., spraying rate around 10.8 g per min and atomization pressure 1.3 bar. MR coated particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 330 microns were obtained.

[0488] Refer to the Example 1 1a for the dissolution profile of the MR microparticles. The qualitative composition of 4.5 g dose units comprising 65% of the dose as IR fraction and 35% of the dose as MR fraction is described in Table 11i.

TABLE 11i

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	2.786
IR microparticles	Immediate release fraction of sodium oxybate	3.622

TABLE 11i-continued

Component	Function	Quantity per 4.5 g dose (g)
Malic acid	Acidifying agent	0.110
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.752

[0489] The finished composition, which contains a 85:15 mixture of sodium oxybate MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 100.0 g of the above IR particles, 76.9 g of the above MR coated particles, 3.0 g of Malic acid (D/L malic acid regular from Bartek), 1.4 g of xanthan gum (Xantural™ 75 from CP Kelco), 2.1 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 2. Ig of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.75 g (corresponding to a 4.5 g dose with 65% of the dose as immediate-release fraction and 35% of the dose as modified release fraction) were weighed.

[0490] Dissolution profile: After reconstitution with 50 ml tap water and rinsing with 10 ml of tap water, the finished composition will display the dissolution profiles in FIGS. **39** and **40** and Tables 11j and 11k in 840 ml of 0.1N HCl and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 11j

Time (hour)	% dissolved in 0.1N HCl
0	0.0
0.25	65
1	65
3	66
4	66
6	67
8	73
10	86
12	94
16	98
20	99

TABLE 11k

Time (hour)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	71
0.5	93
0.75	99
1	99
2	99

Example 12. Alternative Formulations with IR Fraction Obtained Using Different Manufacturing Processes

[0491] Prototype formulations were developed to test the impact of different manufacturing processes on the dissolution of the formulations.

Example 12a—IR Portion=Raw Sodium Oxybate

[0492] IR particles to serve as cores of the MR coated microparticles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 256 microns were obtained.

[0493] MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 45.8 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1542.9 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 10 g per min and atomization pressure 1.3 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 308 microns were obtained.

[0494] 25.2 g of MR microparticles were mixed with 0.26 g of magnesium stearate (from Peter Greven) and 0.13 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl dissolution medium using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile in 0.1N HCl is shown in FIG. **41** and Table 12a.

TABLE 12a

Time (hour)	% dissolved
0	0
0.25	1
1	1
3	2
4	3
6	14
8	40
10	65
12	78
16	89

[0495] The finished composition, which contains a 50:50 mixture of sodium oxybate MR coated particles and raw sodium oxybate as IR fraction calculated on their sodium oxybate content, was prepared as follows: 36 g of raw sodium oxybate, 63.7 g of the above MR coated particles, 1.8 g of malic acid (D/L malic acid regular from Bartek), 1.6 g of xanthan gum (Xantural™ 75 from CP Kelco), 2.4 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 0.047 g of an apple aroma and 0.3 g of hydrophilic fumed silica (Aerosil 200 from Degussa) were mixed in a Roue-Roehn mixer. Individual doses of 6.66 g (corresponding to a 4.5 g dose with half of the dose as raw sodium oxybate as IR fraction and half of the dose as modified release fraction) were weighed.

[0496] FIG. **42** and Table 12b below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 12b

Time (hour)	% dissolved
0	0
0.25	50
1	52
4	55
6	57
8	70
10	82
12	87
16	93

Considering that the 0.1N HCl dissolution profile of the MR coated particles is similar to the MR microparticles from examples 1 and 1bis, the dissolution profile in pH 6.8 phosphate buffer of the finished composition is expected to be similar to the profile depicted in FIG. **8**, insofar as the MR particles are similar and only the nature of the immediate-release fraction was changed.

Example 12b—IR=Microparticles Obtained by Extrusion-Spheronization

[0497] IR particles were prepared as follows: 97 g of sodium oxybate and 3 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were mixed with 7.5 g of water. The mixture was extruded through a 400 micron mesh and spheronized at 1500 rpm for 1.5 min in an extruder-spheronizer Fuji-Paudal MG-55. After drying for 4 hours at 45° C. in a ventilated oven, microparticles were sieved between 150 microns and 500 microns.

[0498] MR coated particles were prepared as described in Example 14.

[0499] The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 67.4 g of the above IR particles obtained by extrusion-spheronization, 115.6 g of the above MR coated particles, 3.3 g of malic acid (D/L malic acid regular from Bartek), 0.9 g of xanthan gum (Xantural™ 75 from CP Kelco), 0.9 g of hydrophilic fumed silica (Aerosil 200 from Degussa) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.54 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0500] FIG. **43** and Table 12c below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 12c

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	51
1	53
4	54
6	54
8	56
10	65
12	79
16	92

[0501] Based on the dissolution profile of the MR coated particles in pH 6.8 phosphate buffer, finished compositions are expected to have the dissolution profile in pH 6.8 phosphate buffer given in Table 12d and FIG. **44**.

TABLE 12d

Time (h)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	55
0.50	97
1	101
1.5	102
2	101
3	101

Example 13. Alternative Formulation without Binder

[0502] IR particles were prepared as follows: 1700.0 g of Sodium Oxybate are solubilized in 1899.4 g of absolute ethyl alcohol and 1261.3 g of water. The solution is entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 244 microns are obtained.

[0503] MR coated particles were prepared as follows: 17.1 g of methacrylic acid copolymer type C (Eudragit L100-55 from Evonik), 34.3 g of methacrylic acid copolymer type B (Eudragit S100 from Evonik), 77.1 g of hydrogenated cottonseed oil (Lubritab from JRS), are dissolved in 1157.9 g of isopropanol at 78° C. The solution is sprayed entirely on 300.0 g of IR particles prepared above in a fluid bed spray coater apparatus Glatt G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 10.7 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 289 microns are obtained.

[0504] 25.3 g of MR coated microparticles were mixed with 0.12 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which correspond to 2368 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown below in FIG. **45** and Tables 13a and 13b.

TABLE 13a

Dissolution data - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	0
3	1
4	3
6	29
8	50
10	69
12	82
16	97
20	102

TABLE 13b

Dissolution data - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	5
1	102
3	106

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 13c.

TABLE 13c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.841
IR microparticles	Immediate release fraction of sodium oxybate	2.647
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.835

[0505] After reconstitution with 50 ml of tap water and rinsing with 10 ml of tap water, the finished composition is expected to provide the following dissolution profiles in FIGS. **46** and **47** and Tables 13d and 13e in 840 ml of 0.1N HCl and pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 13d

Time (h)	% dissolved in 0.1N HCl
0.0	0
0.3	50
1.0	50
3.0	50
4.0	52
6.0	64
8.0	75

TABLE 13d-continued

Time (h)	% dissolved in 0.1N HCl
10.0	84
12.0	91
16.0	98
20.0	101

TABLE 13e

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	53
1.0	101
3	103

Example 14. MR Particles with Larger Core Size (160 Microns)

[0506] Different prototypes were also developed to evaluate the impact of the core size on the dissolution of the formulation.

[0507] IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 100 from Pharmatrans) (D[4,3]=160 microns) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 310 microns were obtained.

[0508] MR coated particles were prepared as follows: 25.7 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 51.5 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 115.7 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1735.7 g of isopropanol at 78° C. The solution was sprayed entirely on 450.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 47° C., spraying rate around 9.6 g per min and atomization pressure 1.6 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 370 microns were obtained.

[0509] 49.3 g of sodium oxybate MR particles were mixed with 0.52 g of magnesium stearate (from Peter Greven) and 0.26 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile in 0.1N HCl and pH 6.8 phosphate buffer is shown below in FIG. **48** and Tables 14a and 14b.

TABLE 14a

Dissolution data - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0

TABLE 14a-continued

Dissolution data - 0.1N HCl	
Time (h)	% dissolved
1	1
3	2
6	3
8	7
10	18
12	37
16	75

TABLE 14b

Dissolution data - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	9
0.5	95
1	101
3	101

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 14c.

TABLE 14c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	2.786
IR microparticles	Immediate release fraction of sodium oxybate	3.981
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.115

[0510] After reconstitution with 50 ml of tap water and rinsing with 10 ml of tap water, the finished composition is expected to provide the dissolution profiles in FIGS. **49** and **50** and Table 14d and 14e in 840 ml of 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 14d

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	51
4	51
6	52
8	53
10	59
12	69
16	87

TABLE 14e

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	55
1	101
3	101

Example 15. MR Microparticles with Different Ratios of Lubritab™ and Eudragit™

[0511] Different prototypes were developed to evaluate the effect of the ratio between Lubritab™ and Eudragit™ on the formulation.

Example 15a—30% Lubritab™; Cellets™ 127; Coating Level=35%

[0512] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 100 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

[0513] MR coated particles were prepared as follows: 50.2 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 100.6 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 64.6 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1943.5 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.0 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 403 microns were obtained.

[0514] 17.9 g of sodium oxybate MR microparticles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4308 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **51** and Table 15a.

TABLE 15a

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	3
1	5
3	69
4	96
6	101
8	102
10	102

[0515] Alternative MR coated particles of sodium oxybate were prepared according to the above manufacturing protocol with the coating level adjusted to 50% instead of 35%. The dissolution profile of the alternative sodium oxybate MR particles was determined using the same protocol as above. The 0.1N HCl dissolution profile is shown in FIG. **52** and Table 15b.

TABLE 15b

Time (h)	% dissolved
0	0
0.25	1
1	1
3	36
4	67
6	95
8	98
10	98

[0516] The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR microparticles, 235.8 g of the above sodium oxybate MR microparticles with a coating level of 30%, 6.2 g of malic acid (D/L malic acid regular from Bartek), 2.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carragenan gum (Viscarin™ PH109 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.0 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.42 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0517] FIG. **53** and Table 15c below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15c

Time (hour)	% dissolved
0	0
0.25	45
1	52
2	92
3	94
4	97
6	97
8	97
10	96

Example 15b—Celphere™ CP203 as neutral cores and coating level=35%

[0518] IR particles were prepared as follows: 665.0 g of Sodium Oxybate and 35.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 781.2 g of absolute ethyl alcohol and 521.6 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Celphere™ CP203 from Asahi Kasei—mean diameter D[4,3]=250

microns) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 398 microns were obtained.

[0519] MR coated particles were prepared as follows: 37.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 75.4 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 48.5 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1458.0 g of isopropanol at 78° C. The solution was sprayed entirely on 300.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 11.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 491 microns were obtained.

[0520] 17.0 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 5210 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **54** and Tables 15d and 15e.

TABLE 15d

Dissolution data - 0.1N HCl

Time (hour)	% dissolved
0	0
0.25	3
1	3
3	45
4	77
6	96
8	98
10	98

TABLE 15e

Dissolution data - 50 mM pH 6.8 phosphate buffer

Time (h)	% dissolved
0	0
0.25	1
0.5	22
0.75	87
1	98
2	97

[0521] The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 15f.

TABLE 15f

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	5.205
IR microparticles	Immediate release fraction of sodium oxybate	3.383

TABLE 15f-continued

Component	Function	Quantity per 4.5 g dose (g)
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulo	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.946

[0522] After reconstitution, the finished composition is expected to exhibit the dissolution profiles in FIGS. **55** and **56** and Tables 15g and 15h in 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 15 g

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	51
1	51
3	73
4	88
6	98
8	99
10	99

TABLE 15h

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	50
0.5	61
0.75	93
1	99
2	99

Example 15c—40% Lubritab™ (Coating Level=40%)

[0523] IR pellets were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267. Ig of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0524] MR coated particles were prepared as follows: 40.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 80.5 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1799.4 g of isopropanol at 78° C. The solution was sprayed entirely on 300.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.5 g per min and

atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 348 microns were obtained.

[0525] 20.0 g of MR coated particles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4700 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **57** and Table 15i.

TABLE 15i

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	0
1	0
3	1
4	8
6	52
8	84
10	95
12	97
16	98

[0526] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 156.0 g of the above IR particles, 260.0 g of the above MR coated particles, 6.3 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.2 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.2 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.2 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.78 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0527] FIGS. **58** and **59** and Tables 15j and 15k below depict dissolution profiles determined in 0.1N HCl and pH 6.8 buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15j

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	48
1	52
3	52
4	62
6	89
8	96
10	97
12	98

TABLE 15j-continued

Time (h)	% dissolved in 0.1N HCl
16	98
20	97

TABLE 15k

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	49
0.5	85
1	91
2	96
3	104

Example 15d—70% Lubritab™ (Coating Level 25%)

[0528] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

[0529] MR coated particles were prepared as follows: 13.3 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 26.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 93.3 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1200.3 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.6 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 313 microns were obtained.

[0530] 17.0 g of MR coated particles were mixed with 0.06 g of magnesium stearate (from Peter Greven). The dissolution profile of 3750 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **60** and Tables 15l and 15m.

TABLE 15l

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0.0
0.25	5
1	4
3	5
4	5

TABLE 15l-continued

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
6	8
8	33
10	78
12	98
16	103

[0531] 15m. Dissolution Profile in 50 mM pH 6.8 Phosphate Buffer

Time (h)	% dissolved
0	0.0
0.25	1
0.5	45
1	97
2	108
3	114

[0532] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR particles, 204.3 g of the above MR coated particles, 6.2 g of Malic acid (D/L malic acid regular from Bartek), 2.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 4. Ig of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.85 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0533] FIG. **61** and Table 15n depict the dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15n

Time (h)	% dissolved
0	0
0.25	48
1	52
3	52
4	52
6	55
8	76
10	95
12	100
16	100
20	100

Based on the dissolution profile of the MR coated particles in pH 6.8 phosphate buffer, single dose units are expected to have the dissolution profile in pH6.8 buffer shown in FIG. **62** and in Table 15o.

TABLE 15o

Time (h)	% dissolved in pH 6.8 buffer
0	0.0
0.25	51
0.5	72
1	99
2	104
3	107

Example 16. Evaluation of Different Hydrophobic Compounds in the Coating

[0534] Prototypes with different hydrophobic coatings were prepared and evaluated to determine the effect of coating type on the dissolution of the formulations.

Example 16a—Glyceryl Dibehenate (Compritol™ AT0888)

[0535] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267. Ig of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0536] MR coated particles were prepared as follows: 22.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of glyceryl dibehenate (Compritol™ ATO 888 from Gattefossé), were dissolved in 1371.8 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 322 microns were obtained.

[0537] 17.0 g of MR coated particles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **63** and Tables 16a and 16b.

TABLE 16a

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	1
3	3
4	6
6	31
8	67

TABLE 16a-continued

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
10	90
12	98
16	100

TABLE 16b

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	1
1	102
3	105

[0538] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 181.1 g of the above IR particles, 258.7 g of the above MR coated particles, 7.3 g of Malic acid (D/L malic acid regular from Bartek), 3.3 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.9 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.9 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.3 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.12 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0539] FIG. **64** and Table 16c depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 16c

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	46
1	50
3	51
4	56
6	78
8	92
10	96
12	97
16	96

Based on the dissolution profile of the MR microparticles alone in pH 6.8 phosphate buffer, single dose units are expected to have the dissolution profile at pH6.8 shown in FIG. **65** and in Table 16d.

TABLE 16d

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	50
1	101
3	102

Example 16b—60% Candelilla Wax with Coating Level of 20%

[0540] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 255 microns were obtained.

[0541] MR coated particles were prepared as follows: 13.3 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 26.7 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 60.0 g of candelilla wax (Kahlwax™ 2039L from Brenntag), were dissolved in 902.2 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 12.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 289 microns were obtained.

[0542] 21.2 g of MR microparticles were mixed with 0.11 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2570 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown below in FIG. **66** and Tables 16e and 16f.

TABLE 16e

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	0
3	0
4	1
6	2
8	2
10	2
12	2
16	3
20	4

TABLE 16f

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	0
0.5	10
0.75	62
1	89
2	101

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 16 g.

TABLE 16g

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.483
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.033
Total		6.615

[0543] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 200.0 g of the above IR particles, 250.0 g of the above MR coated particles, 8.1 g of Malic acid (D/L malic acid regular from Bartek), 3.6 g of xanthan gum (Xantural™ 75 from CP Kelco), 5.4 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 5.4 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.4 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.61 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0544] After reconstitution, the finished composition is expected to provide the dissolution profiles in FIGS. **67** and **68** and Tables 16h and 16i in 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 16h

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	50
3	50
4	50
6	51
8	51
10	51
12	51
16	52
20	52

TABLE 16i

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	50
0.5	55
0.75	81
1	94
2	100

Example 16c—40% Candelilla Wax (Coating Level=20%)

[0545] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 270 microns were obtained.

[0546] MR coated particles were prepared as follows: 20.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 40.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 40.0 g of candelilla wax (Kahlwax™ 2039L from Brenntag), were dissolved in 904.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.9 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 302 microns were obtained.

[0547] 17.0 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 3500 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **69** and Tables 16j and 16k. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

TABLE 16j

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	3
3	6
4	8
6	9

TABLE 16j-continued

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
8	15
10	37
12	70
16	97
20	100

TABLE 16k

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	24
0.5	86
0.75	99
1	100
2	100

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 16l.

TABLE 16l

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.483
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.033
Total		6.615

[0548] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 122.7 g of the above IR particles, 153.2 g of the above MR coated particles, 5.0 g of malic acid (D/L malic acid regular from Bartek), 2.2 g of xanthan gum (Xantural™ 75 from CP Kelco), 3.3 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 3.3 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.5 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.62 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0549] FIG. **70** and Table 16m depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 16m

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	47
1	51
3	51
4	52
6	52
8	55
10	72
12	89
16	97

Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished compositions are expected to provide the dissolution profile in pH 6.8 phosphate buffer shown in FIG. **71** and in Table 16n.

TABLE 16n

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	62
0.5	93
0.75	99
1	100
2	100

Example 16d—60% Cetyl Alcohol (Kolliwax™ CA)

[0550] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1898.7 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

[0551] MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of cetyl alcohol (Kolliwax™ CA from BASF), were dissolved in 1472.5 g of isopropanol and 77.7 g of water at room temperature. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 14.5 g per min and atomization pressure 2.5 bar. Sodium oxybate MR coated particles with mean diameter of 315 microns were obtained.

[0552] 16.4 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium is given in FIG. **72** and Table 16o. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

TABLE 16o

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	13
1	84
3	103
4	103
6	103
8	103
10	104
12	104
16	103
20	102

Example 17. Effect of Eudragit™ Selection in the Coating of the MR Microparticles

[0553] Further prototypes were developed and evaluate to determine the effect of the Eudragit™ selected on the dissolution of the MR microparticles.

Example 17a—100% Eudragit™ S100

[0554] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 285 microns were obtained.

[0555] Sodium oxybate IR seal-coated particles were prepared by coating the IR particles described above with a seal-coat layer: 170.0 g of hydroxypropylcellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the above IR particles in a fluid bed spray coater apparatus. Sodium oxybate IR particles with volume mean diameter of about 298 microns were obtained.

[0556] MR coated particles were prepared as follows: 100.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 150.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2250.0 g of isopropanol at 78° C. The solution was sprayed entirely on 750.0 g of the above IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 12.0 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 307 microns were obtained.

[0557] The dissolution profile of 2100 mg of the mixture which corresponds to 1253 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 500 ml of 0.1N HCl medium is reported in FIG. **73** and Table 17a. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17a

Time (h)	% dissolved
0	0
0.25	0
1	1
3	3
4	4
6	9
8	30
10	60
12	81
16	92

[0558] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 425.0 g of the above IR seal-coated particles, 510.0 g of the above MR coated particles, 30.9 g of malic acid (D/L malic acid regular from Bartek), 4.9 g of xanthan gum (Xantural™ 180 from CP Kelco), 4.9 g of Aerosil™ 200 (amorphous anhydrous colloidal silicon dioxide from Evonik) and 9.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.18 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0559] FIG. **74** and Table 17b below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17b

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	50
3	50
4	51
6	55
8	67
10	84
12	91
16	94

[0560] FIG. **75** and Table 17c depict the dissolution profile determined using a USP apparatus 2 in phosphate buffer pH 6.8 (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of pH 6.8 dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17c

Time (hour)	% dissolved
0	0
0.25	50

TABLE 17c-continued

Time (hour)	% dissolved
1	51
3	54
4	56
6	93
8	99
10	100
12	100
16	97

Example 17b—100% Eudragit™ L100-55

[0561] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.1 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1896.2 g of absolute ethyl alcohol and 1264.4 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 275 microns were obtained.

[0562] MR coated particles were prepared as follows: 68.7 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.2 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 46° C., spraying rate around 12.7 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 328 microns were obtained.

[0563] 17.0 g of MR microparticles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile in of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **76** and Tables 17d and 17e. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17d

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	2
3	3
4	6
6	53
8	95
10	99
12	99
16	99
20	99

TABLE 17e

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	21
0.5	99
0.75	103
1	103
2	103

[0564] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR particles, 219.0 g of the above MR coated particles, 6.2 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 4. Ig of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.12 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0565] FIG. **77** and Table 17f depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17f

Time (hour)	% dissolved
0	0
0.25	46
1	51
3	52
4	59
6	94
8	98
10	98
12	98
16	98

[0566] Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished compositions are expected to provide the dissolution profile in pH 6.8 phosphate buffer in FIG. **78** and Table 17 g.

TABLE 17g

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	61
0.5	99
0.75	101
1	101
2	101

Example 17c—Mixture Eudragit™ L100-S100 (50-50)

[0567] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267. Ig of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0568] MR coated particles were prepared as follows: 34.3 g of Methacrylic acid copolymer Type A (Eudragit™ L100 from Evonik), 34.3 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 316 microns were obtained.

[0569] 24.0 g of MR microparticles were mixed with 0.12 g of magnesium stearate (from Peter Greven). The dissolution profile of 4050 mg of the mixture which corresponds to 2280 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **79** and Tables 17h and 17i. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17h

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	2
3	2
4	3
6	7
8	31
10	62
12	83
16	98
20	100

TABLE 17i

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	2
0.5	5
0.75	13
1	47
2	101

[0570] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 223.0 g of the above IR particles, 318.4 g of the above MR coated particles, 11.2 g of malic acid (D/L malic acid regular from Bartek), 4.0 g of xanthan gum (Xantural™ 75 from CP Kelco), 6.0 g of carragenan gum (Viscarin™ PH209 from FMC Biopolymer), 6.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.14 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0571] FIG. **80** and Table 17j depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17j

Time (hour)	% dissolved
0	0
0.25	47
1	51
3	51
6	59
8	80
10	92
12	96
16	97

Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished composition are expected to have the dissolution profile in pH 6.8 phosphate buffer given in FIG. **81** and Table 17k.

TABLE 17k

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	51
0.5	53
0.75	56
1	73
2	100

Example 18. In Vivo Pharmacokinetic Study of Finished Composition According to Example 1 (Dose Escalating Study)

[0572] Pharmacokinetic testing was undertaken in vivo in healthy human volunteers. Pharmacokinetic parameters were normalized by the dose. To assess the dose-proportionality, log-transformed dose-normalized PK parameters were pairwise compared according to the statistical methodology described in FDA's 2013 Draft Guidance entitled BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS FOR DRUGS SUBMITTED UNDER AN ANDA (2013). All testing was performed in subjects two hours after eating a standardized dinner. A test product with finished composition of Example 1 and manufactured

at larger scale was administered in sequential ascending doses, 4.5 g, 7.5 g and 9 g, one week apart. The tested samples were manufactured as described in Table 1c for 4.5 g and quantities were homothetically adjusted for the other strengths. The dissolution profiles of the MR portions of the test product are presented in FIGS. **86** and **87**. The dissolution profiles of the test product are presented in FIGS. **88** and **89**. The individual concentrations of gamma-hydroxybutyrate and derived PK parameters are summarized below (Tables 18a and 18b) and in FIG. **90**.

TABLE 18a

Pharmacokinetic Parameters of 4.5 g, 7.5 g, and 9 g

Finished composition of test product	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (μg/mL*h) (% CV)	Mean $AUC_{8\,h}$ (μg/mL*h) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\,h}$ (μg/mL) (% CV)
4.5 g	42.9 (37)	191 (50)	174 (55)	1.71 (0.333-4)	4.76 (105)
7.5 g	72.0 (32)	357 (48)	320 (46)	1.5 (0.333-7)	19.7 (101)
9.0 g	84.5 (34)	443 (46)	379 (41)	2 (0.5-4)	25.5 (97)

[0573] AUC and C_{max} values increased more than dose-proportionally with increasing doses of gamma-hydroxybutyrate formulated as the test product.

TABLE 18b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of test product

Time (hr)	Test product 4.5 g (2 h after meal) (N = 20)	Test product 7.5 g (2 h after meal) (N = 20)	Test product 9 g (2 h after meal) (N = 12)
0	0.00	0.00	0.00
0.167	12.5	17.7	9.34
0.333	23.4	39.0	32.7
0.5	28.1	48.4	47.5
1	34.7	59.8	60.9
1.5	36.7	63.8	71.6
2	35.7	61.6	79.3
2.5	34.7	56.0	64.9
3	29.8	50.1	65.3
3.5	26.9	46.0	60.0
4	23.5	40.9	60.8
4.5	20.1	36.6	48.8
5	17.3	32.7	45.3
5.5	15.4	30.8	41.3
6	13.4	28.7	37.6
7	9.66	24.7	30.5
8	4.76	19.7	25.5
10	0.727	6.97	13.0
12	0.211	1.35	5.13
14	NC	0.392	0.820

NC: Not Calculated

[0574] Table 18c compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 4.5 g of the test product to the same parameters calculated 2×2.25 g, i.e. 4.5 g total dose of Xyrem®.

TABLE 18c

Comparison to 4.5 g divided dose of Xyrem ®

	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 2.25 g *	9.24	NA	214	NA
Test product 4.5 g	4.76	52%	191	89%

* data from the pilot PK study of example 3

[0575] Table 18d compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g of the test product to the same parameters calculated 2×3.75 g, i.e. 7.5 g total dose of Xyrem®.

TABLE 18d

Comparison to 7.5 g divided dose of Xyrem ®

	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 3.75 g * (extrapolation from 2 × 4.5 g *)	24.1	NA	432	NA
Test product 7.5 g	19.7	82%	357	83%

* based on data from NDA #21-196

[0576] Table 18e compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g and 9 g of the test product to the same parameters calculated for 2×4.5 g, i.e. 9 g total dose of Xyrem®.

TABLE 18e

Comparison to 9 g divided dose of Xyrem ®

	Mean $C_{8\ h}$ (μg/mL)	Ratio (%) $C_{8\ h}$ composition to $C_{8\ h}$ Xyrem ®	Mean AUC_{inf} (μg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 4.5 g *	28.9	NA	518	NA
Test product 7.5 g	19.7	68%	357	69%
Test product 9 g	25.5	88%	443	86%

* data from NDA #21-196

[0577] For the finished composition administered at 4.5 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max}(Xyrem®) is 1.03. The ratio C_{4h}/C_{max}(Xyrem®) is 0.81. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.69.

[0578] For the finished composition administered at 7.5 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max}(Xyrem®) is 0.77. The ratio C_{4h}/C_{max}(Xyrem®) is 0.63. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.57.

[0579] For the finished composition administered at 9 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max}(Xyrem®) is 0.84. The ratio C_{4h}/C_{max}(Xyrem®) is 0.78. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.63.

[0580] For the finished composition administered at 7.5 g compared to Xyrem® at 2×4.5 g, i.e. total dose of 9 g, the ratio C_{3h}/C_{max}(Xyrem®) is 0.65. The ratio C_{4h}/C_{max}(Xyrem®) is 0.53. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.47.

[0581] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

1. (canceled)

2. A modified release formulation of gamma-hydroxybutyrate, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr*microgram/mL, and a mean C_{8h} that is from 50% to 130% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at to and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

3. (canceled)

4. A modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein:

a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm,

b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and

c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

5. (canceled)

6. (canceled)

7. (canceled)

8. A modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein:

a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm;

b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm;

c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and

d) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

9. (canceled)

10. (canceled)

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. (canceled)

16. (canceled)

17. (canceled)

18. (canceled)

19. (canceled)

20. (canceled)

21. (canceled)

22. The formulation of claim **4**, comprising immediate release and modified release portions, wherein said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

23. (canceled)

24. (canceled)

25. (canceled)

26. The formulation of claim **4**, wherein the formulation achieves an in vitro dissolution profile:

a) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 40% to 65% at 1 hour,

(ii) from 40% to 65% at 3 hours,

(iii) from 47% to 85% at 8 hours,

(iv) greater or equal to 60% at 10 hours,

(v) greater or equal to 80% at 16 hours, and

b) measured in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 43% to 94% at 0.25 hour,

(ii) greater or equal to 65% at 0.35 hour, and

(iii) greater or equal to 88% at 1 hour.

27. (canceled)

28. The formulation of claim **4**, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr·microgram/mL, and a mean C_{8h} that is from 50% to 130% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at to and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

29. (canceled)

30. (canceled)

31. (canceled)

32. (canceled)

33. The formulation of claim **4**, wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 40/60 to 60/40.

34. (canceled)

35. The formulation of claim **4**, wherein:

a) the modified release portion comprises coated particles of gamma-hydroxybutyrate;

b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and

c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

36. The formulation of claim **4**, wherein:

a) the modified release portion comprises coated particles of gamma-hydroxybutyrate;

b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.;

c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups to is from 0.4 to 4;

d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

e) the coating is from 10 to 50% of the weight of the particles.

37. The formulation of claim **4**, wherein:

a) the modified release portion comprises coated particles of gamma-hydroxybutyrate;

b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.;

c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4;

d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

e) the coating is from 10 to 50% of the weight of the particles.

38. (canceled)

39. The formulation of claim **35** wherein the polymer carrying free carboxylic groups is selected from the group consisting of: (meth)acrylic acid/alkyl (meth)acrylate copolymers or methacrylic acid and methyl methacrylate copolymers or methacrylic acid and ethyl acrylate copolymers or methacrylic acid copolymers type A, B or C, cellulose derivatives carrying free carboxylic groups, cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate carboxymethylethyl cellulose, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, zein, shellac, alginate, and mixtures thereof.

40. The formulation of claim **35** wherein the polymer carrying free carboxylic groups is selected from the group consisting of copolymers of methacrylic acid and ethyl acrylate 1:1, copolymers of methacrylic acid and methylmethacrylate 1:2, and mixtures thereof.

41. The formulation of claim **35** wherein the hydrophobic compound is selected from the group consisting of hydrogenated vegetable oils, vegetable waxes, wax yellow, wax white, wax microcrystalline, lanolin, anhydrous milk fat, hard fat suppository base, lauroyl macrogol glycerides, polyglyceryl diisostearate, diesters or triesters of glycerol with a fatty acid, and mixtures thereof.

42. The formulation of claim **35** wherein the hydrophobic compound is selected from the group consisting of hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candelilla wax, tristearin, tripalmitin, trimyristin, yellow wax, hard fat or fat that is useful as suppository bases, anhydrous dairy fats, lanolin, glyceryl palmitostearate, glyceryl stearate, lauryl macrogol glycerides, polyglyceryl diisostearate, diethylene glycol monostearate, ethylene glycol monostearate, omega 3 fatty acids, and mixtures thereof.

43. The formulation of claim **35** wherein the hydrophobic compound is selected from the group consisting of hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candelilla wax, tristearin, tripalmitin, trimyristin, beeswax, hydrogenated poly-1 decene, carnauba wax, and mixtures thereof.

44. The formulation of claim **35** wherein:

a) the polymer carrying free carboxylic groups comprises from 100% poly (methacrylic acid, ethyl acrylate) 1:1 and 0% poly (methacrylic acid, methylmethacrylate)

1:2 to 2% poly (methacrylic acid, ethyl acrylate) 1:1 and 98% poly (methacrylic acid, methylmethacrylate) 1:2; and

b) the hydrophobic compound comprises hydrogenated vegetable oil.

45. (canceled)

46. (canceled)

47. The formulation of claim **34** in the form of a powder that is intended to be dispersed in water prior to administration, further comprising an acidifying agent and a suspending or viscosifying agent.

48. (canceled)

49. The formulation of claim **34** in the form of a powder that is intended to be dispersed in water prior to administration, further comprising from 1 to 15% of a viscosifying or suspending agent.

50. (canceled)

51. (canceled)

52. (canceled)

53. (canceled)

54. (canceled)

55. (canceled)

56. The formulation of claim **4** wherein a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the formulation or any combination thereof has been shown to achieve a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

57. (canceled)

58. (canceled)

59. (canceled)

60. The formulation of claim **4** wherein the modified release portion and the immediate release portion comprise structurally discreet modified release particles and immediate release particles.

61. The formulation of claim **4** wherein the modified release portion and the immediate release portion comprise structurally indiscreet particles.

62. (canceled)

63. (canceled)

64. The formulation of claim **4** in a dosage form selected from the group consisting of tablets, powders and capsules.

65. The formulation of claim **4** wherein the gamma-hydroxybutyrate is in the form of sodium oxybate.

66. The formulation of claim **4** in the form of a powder.

67. The formulation of claim **4** effective to treat narcolepsy Type 1 or Type 2, wherein said treatment of narcolepsy is defined as reducing excessive daytime sleepiness or reducing the frequency of cataplectic attacks.

68. The formulation of claim **4** effective to induce sleep for eight consecutive hours.

69. (canceled)

70. (canceled)

71. (canceled)

72. (canceled)

73. The formulation of claim **4**, wherein the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

74. The formulation of claim **8**, wherein said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

* * * * *

EXHIBIT F

And Definition

ənd, ən; ănd *when stressed*

ands

Meanings | **Synonyms** | **Sentences**

Definition Source | **Origin** | **Conjunction** | **Noun** | **Abbreviation**

conjuntion

Together with or along with; in addition to; as well as. Used to connect words, phrases, or clauses that have the same grammatical function in a construction.

American Heritage •••

In addition; also; as well as.

Apples and pears; a red and white dress; he begged and borrowed.

Webster's New World •••

Added to; plus.

Two and two makes four.

American Heritage •••

Plus; added to.

6 and 2 equals 8

Webster's New World •••

Used to indicate result.

Give the boy a chance, and he might surprise you.

American Heritage •••

More Conjuntion Definitions (11)

Synonyms:

further | et sequens | und so weiter | moreover | furthermore | et-cetera | et al.

connective | besides | including | also | plus | et-alii | as-well-as | in addition to

Antonyms:

not

noun

An addition or stipulation.

The offer is final—no ifs, ands, or buts.

American Heritage •••

A logical operator that returns a true value only if both operands are true.

American Heritage •••

Synonyms:

polysyndeton ampersand

abbreviation

Andante.

American Heritage •••

Andorra.

American Heritage •••

Andorran.

American Heritage •••

(astronomy) Andromeda Constellation.

Wiktionary •••

(astronomy) Andromeda Galaxy.

Wiktionary •••

More Abbreviation Definitions (2)

suffix

(Now chiefly dialectal, Scotland) Used to form the present participle of verbs, equivalent to **-*ing*.**

Livand, nurischand, ravand, snipand.

Wiktionary •••

(rare or no longer productive) A suffix of Anglo-Saxon origin forming adjectives from verbs analogous to *-ing*.

Wiktionary •••

(no longer productive) A noun suffix, usually denoting agency, similar to *-er*.

Errand, thousand, weasand.

Friend, fiend, bond, husband, healand.

Wiktionary •••

A suffix forming nouns denoting patients or recipients of actions, such as compiland.

Wiktionary •••

prefix

(no longer productive) A prefix of Old English origin meaning "against", "back", "in return", "away", represented in Modern English by *a-*, *an-*, *on-*, and in altered form by the reverse-action prefix *un-* (i.e. *unbuckle*). Also as the initial letter *d* in *dread* (< Old English *ondrǣdan*).

Along.

Answer.

Onfang.

Onset.

Wiktionary •••

idiom

and so forth

- And other unspecified things of the same class:

  bought groceries, went to the bank, picked up the dry cleaning, and so forth.

- Further in the same manner.

American Heritage •••

and then some

With considerably more in addition:

This project will take all our skill and then some.

American Heritage •••

Idioms, Phrasal Verbs Related to And

and so forth

and then some

Origin of And

> From Middle English *and-*, *ond-*, from Old English *and-*, *ond-* (“against, back”), from Proto-

> Cognate with Dutch *ont-*, German *ant-*, *ent-*, *emp-*, Icelandic *and-*, Gothic **-** (and-), Latin ante (“before”), Ancient Greek *ἀντί* (anti, “against”).
>
> *From Wiktionary*

> From Middle English *-and*, *-end*, *-ant*, *-nd*, from Old English *-ende*, *-ande*, present participle ending of verbs, and Old English *-end*, *-nd*, agent ending, both from Proto-Germanic **-andz* (present participle suffix), from Proto-Indo-European **-anto-*. More at -ing.
>
> *From Wiktionary*

> From Latin gerundive termination *-andus*, *-endus*. More at -end.
>
> *From Wiktionary*

> Middle English *from* Old English en in Indo-European roots
>
> *From American Heritage Dictionary of the English Language, 5th Edition*

> From **and**
>
> *From American Heritage Dictionary of the English Language, 5th Edition*

And Sentence Examples

The boy laughed cheerfully **and** jumped out.

He laughed at that, **and** his laugh was merry **and** frank.

She stopped **and** gazed up at his face.

He parked the truck in front of the house **and** headed down the hill.

Then they turned bottom side up, **and** continued to roll slowly over until they were right side up again.

More Sentences ›

EXHIBIT G

US 20190274990A1

(19) **United States**

(12) **Patent Application Publication**

Megret et al.

(10) **Pub. No.: US 2019/0274990 A1**

(43) **Pub. Date: Sep. 12, 2019**

(54) **MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS**

(71) Applicant: **Flamel Ireland Limited**, Dublin (IE)

(72) Inventors: **Claire Megret**, Lyon (FR); **Herve Guillard**, Villeurbanne (FR); **Jean-Francois Dubuisson**, Lyon (FR)

(21) Appl. No.: **16/420,321**

(22) Filed: **May 23, 2019**

Related U.S. Application Data

(63) Continuation of application No. 16/281,235, filed on Feb. 21, 2019, which is a continuation of application No. 15/655,924, filed on Jul. 21, 2017, now Pat. No. 10,272,062.

(60) Provisional application No. 62/365,812, filed on Jul. 22, 2016, provisional application No. 62/399,413, filed on Sep. 25, 2016, provisional application No. 62/474,330, filed on Mar. 21, 2017.

Publication Classification

(51) **Int. Cl.**

A61K 31/22	(2006.01)
A61K 9/14	(2006.01)
A61K 9/50	(2006.01)
A61K 31/19	(2006.01)
A61K 9/16	(2006.01)

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

CPC ***A61K 31/22*** (2013.01); ***A61K 9/14*** (2013.01); ***A61K 9/5015*** (2013.01); ***A61K 9/5026*** (2013.01); ***A61K 9/1676*** (2013.01); ***A61K 9/5042*** (2013.01); ***A61K 9/5078*** (2013.01); ***A61K 9/5084*** (2013.01); ***A61K 31/19*** (2013.01)

(57) **ABSTRACT**

Modified release formulations of gamma-hydroxybutyrate having improved dissolution and pharmacokinetic properties are provided, and therapeutic uses thereof.

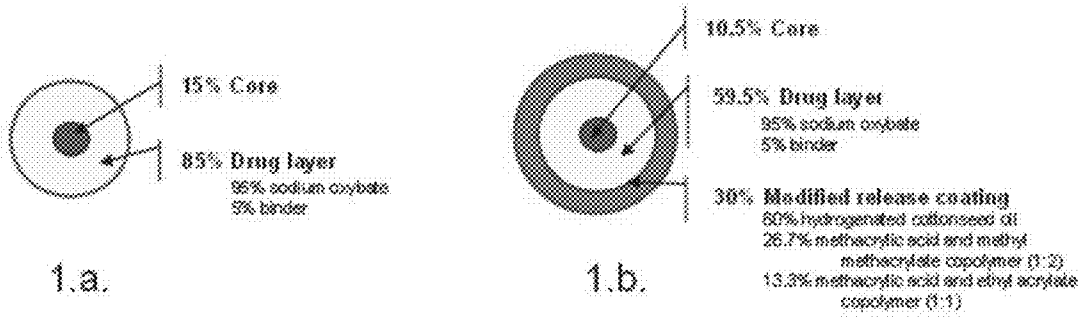


Figure 1

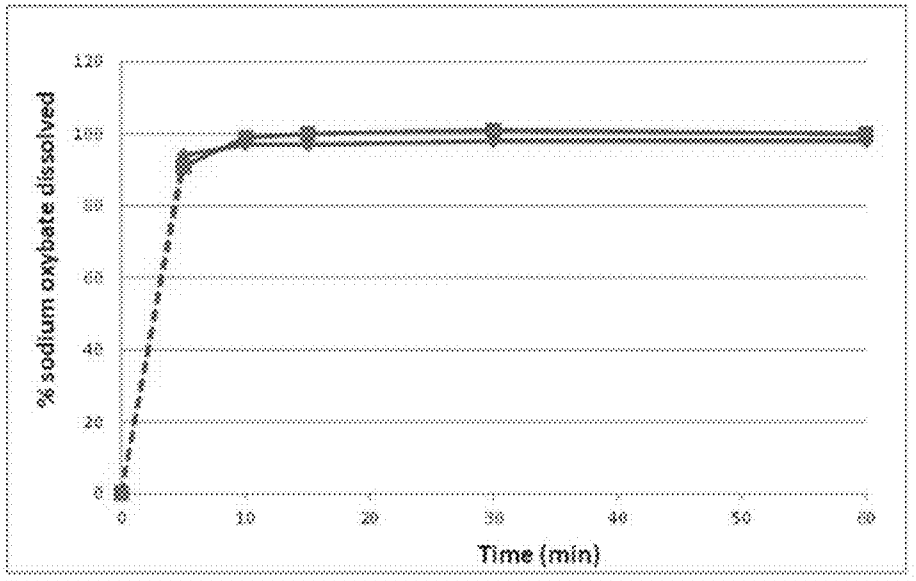


Figure 2

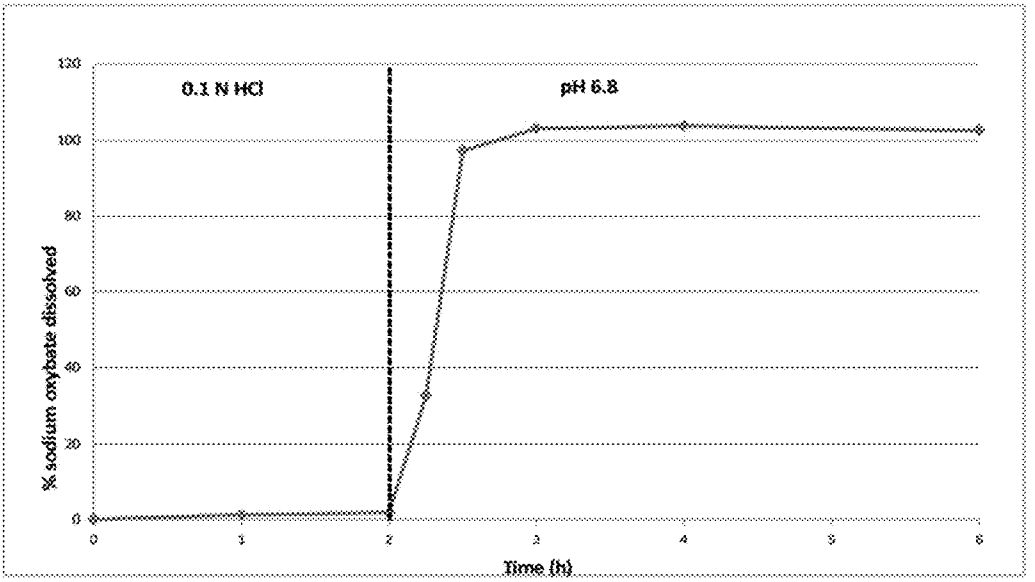


Figure 3

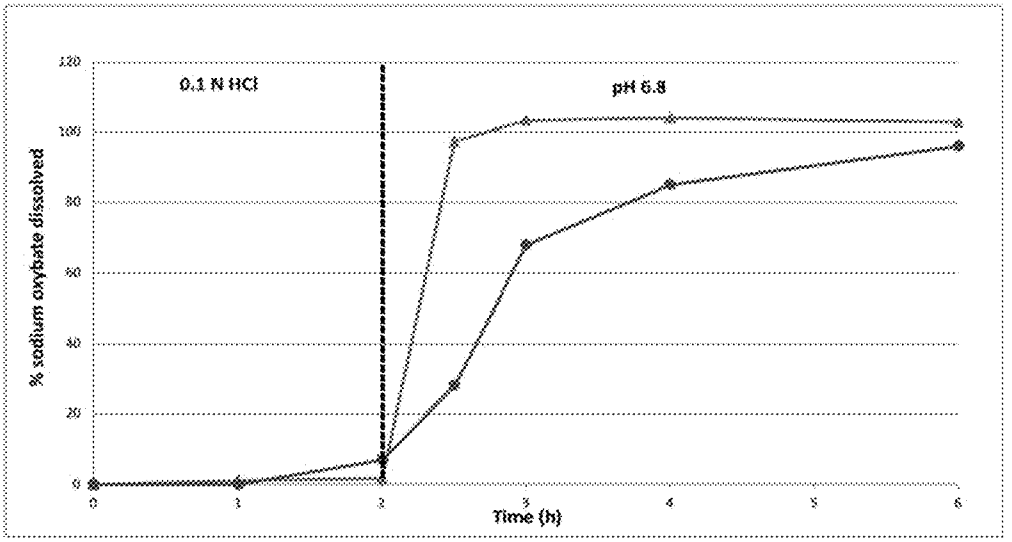


Figure 4

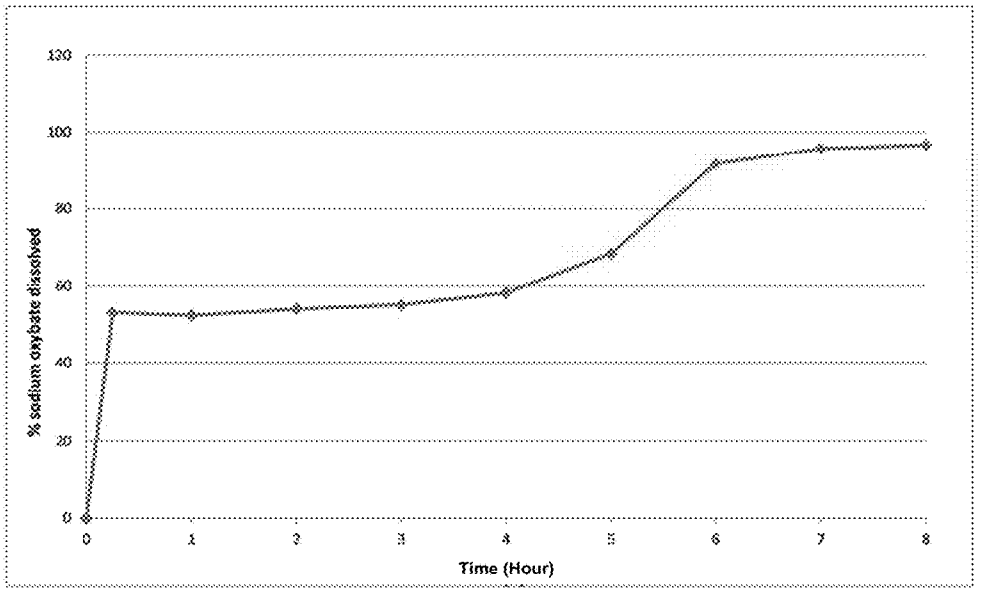


Figure 5

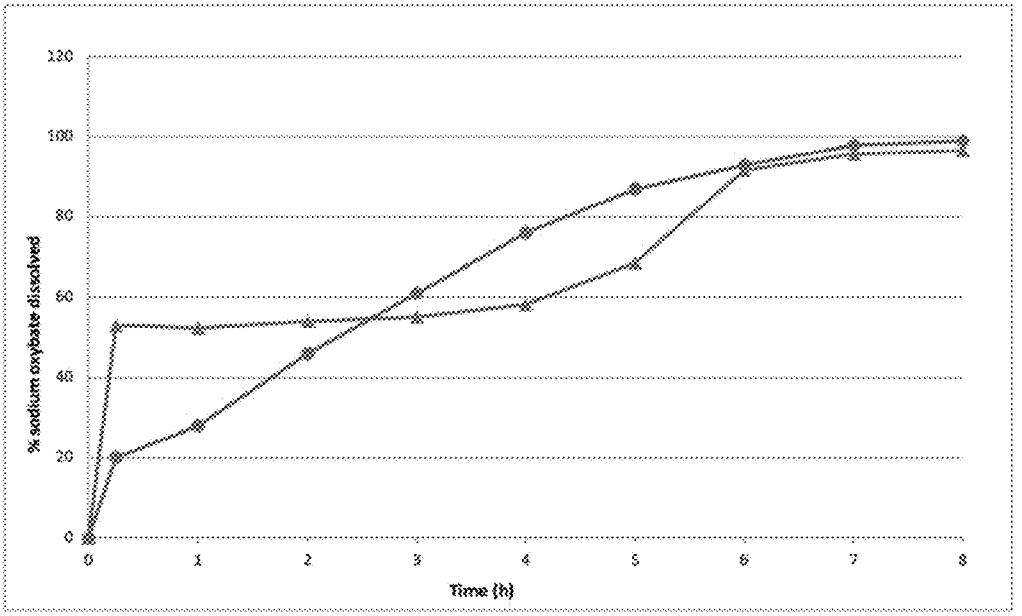


Figure 6

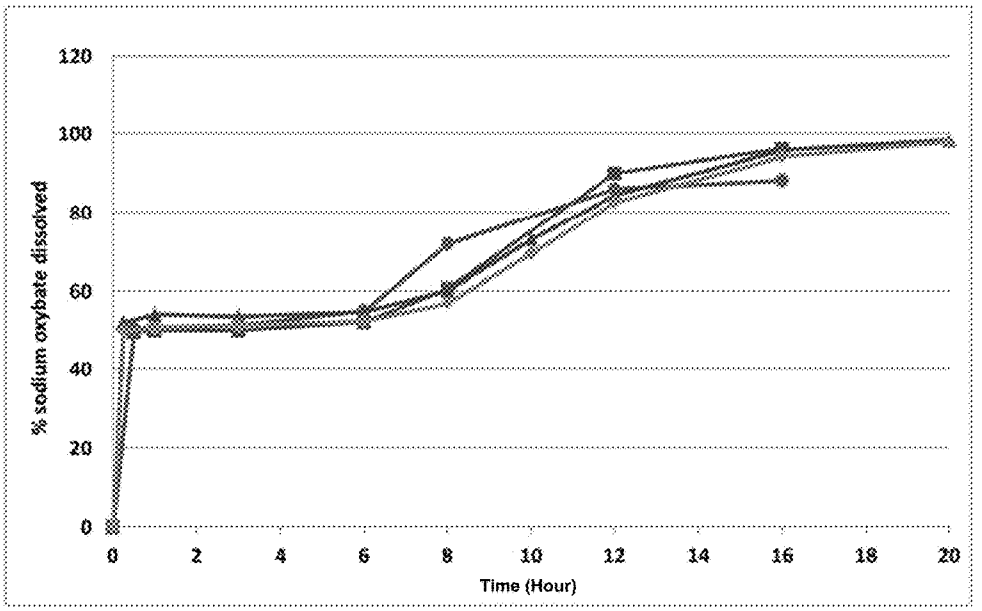


Figure 7

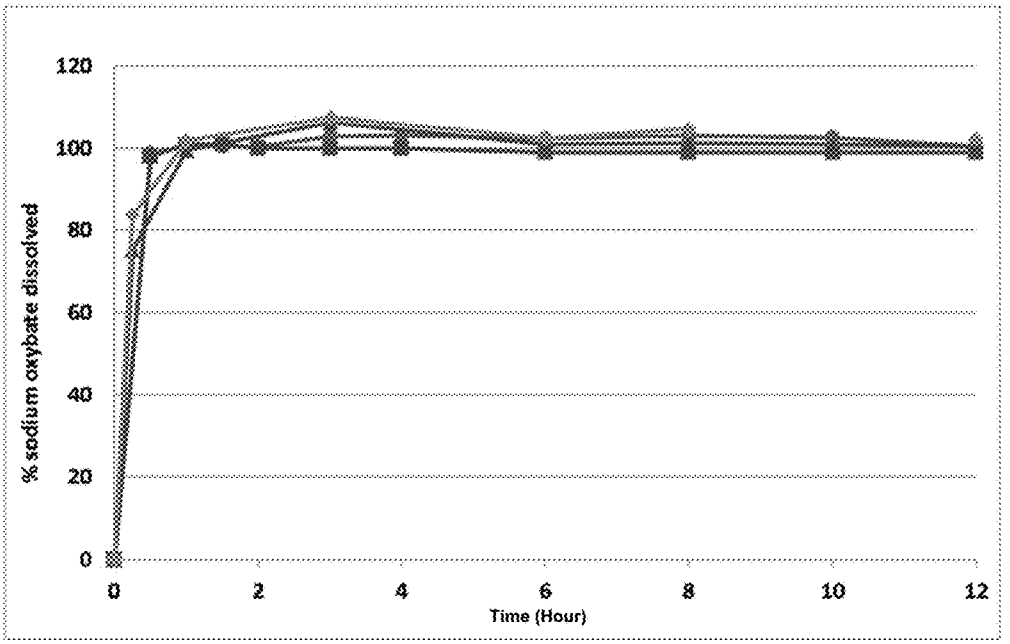


Figure 8

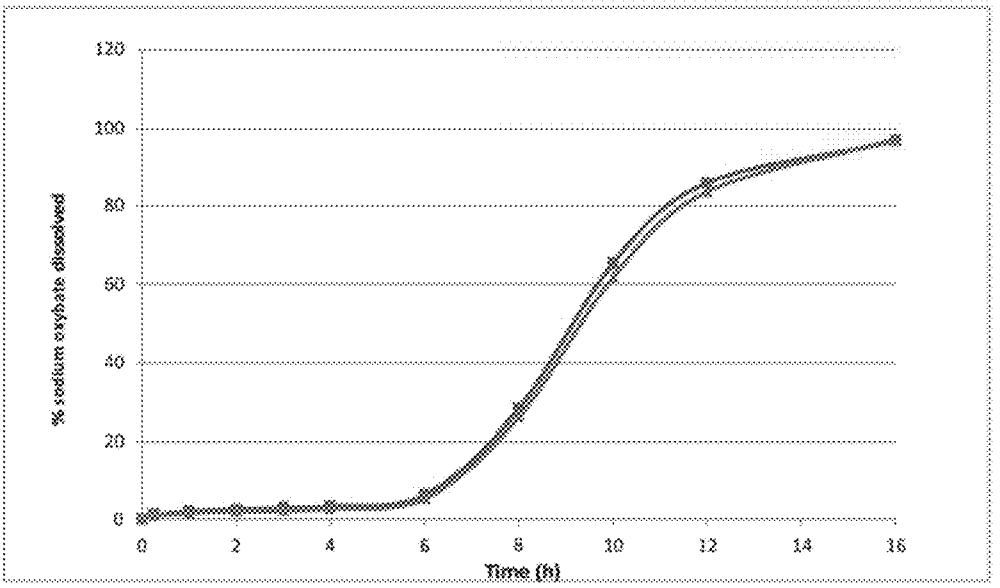


Figure 9

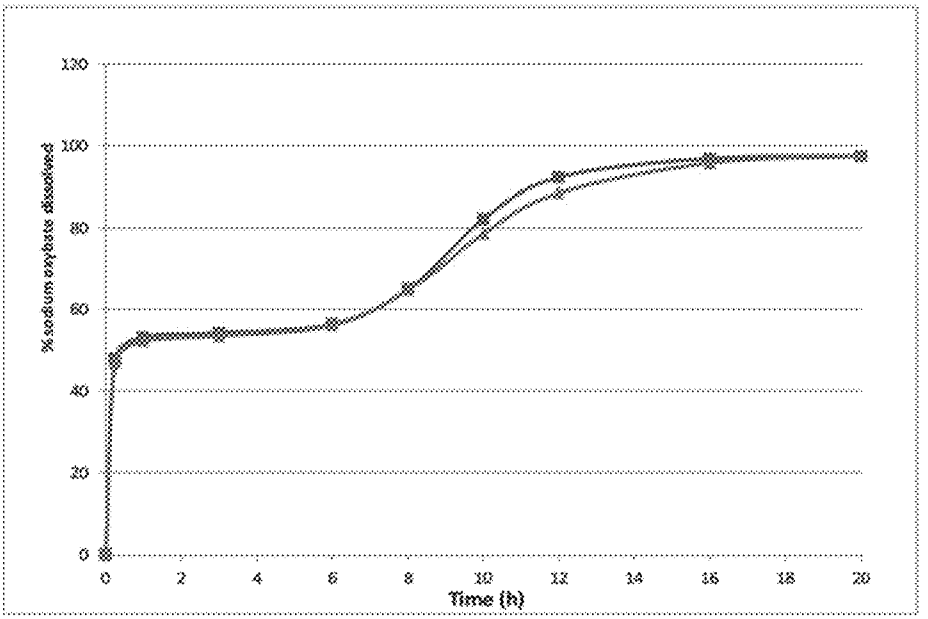


Figure 10

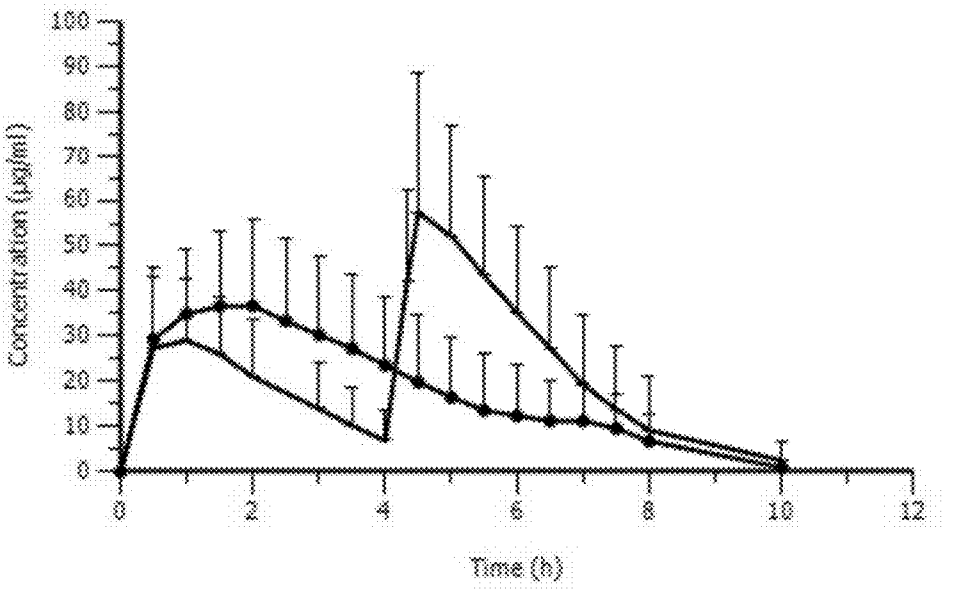


Figure 11

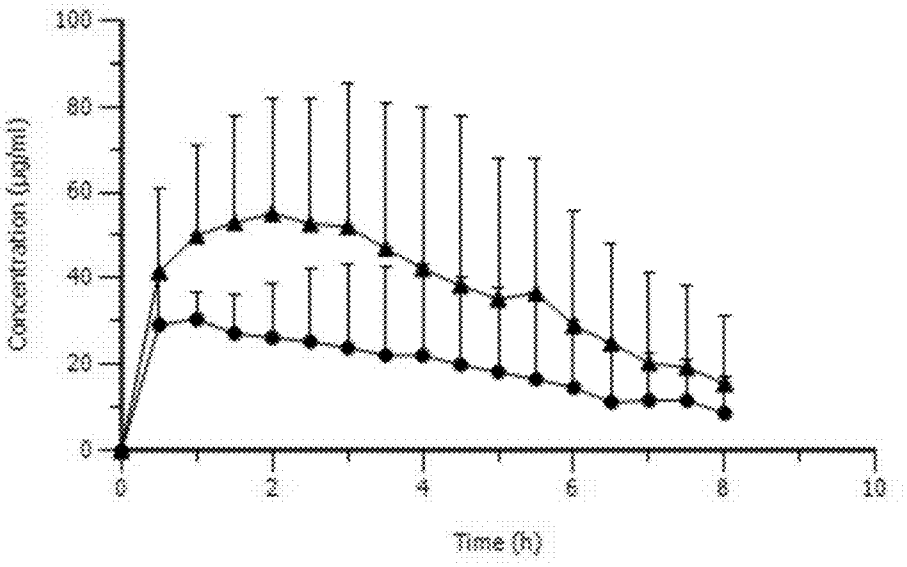


Figure 12

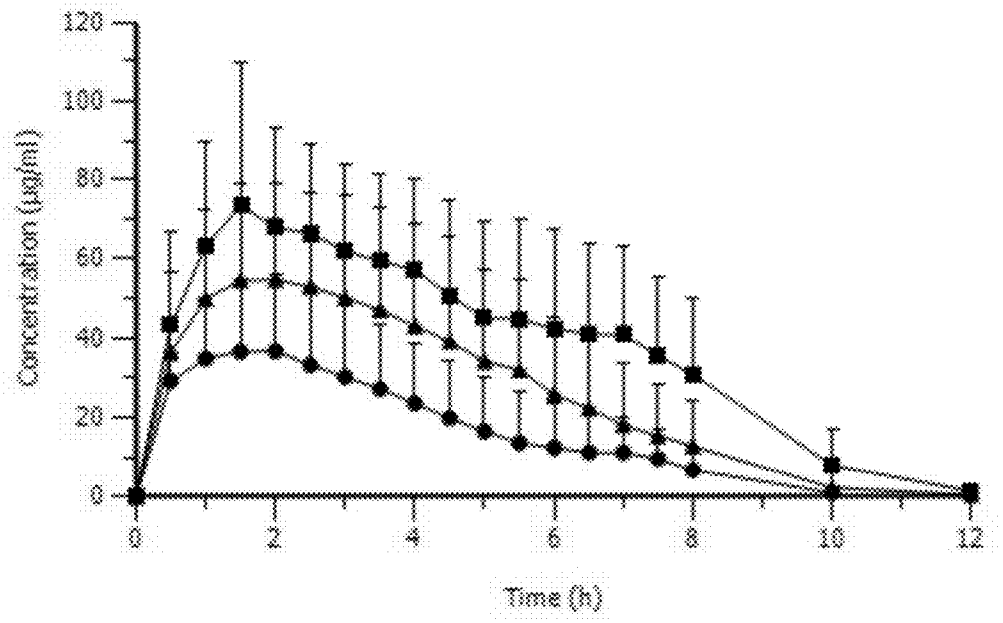


Figure 13

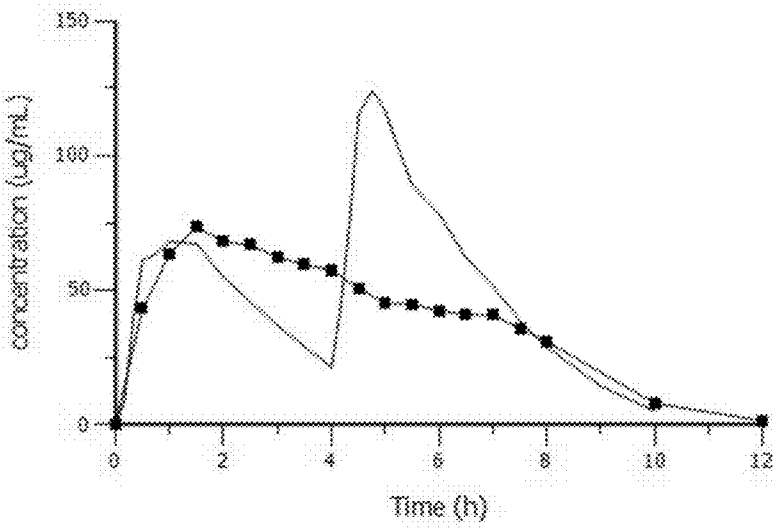


Figure 14

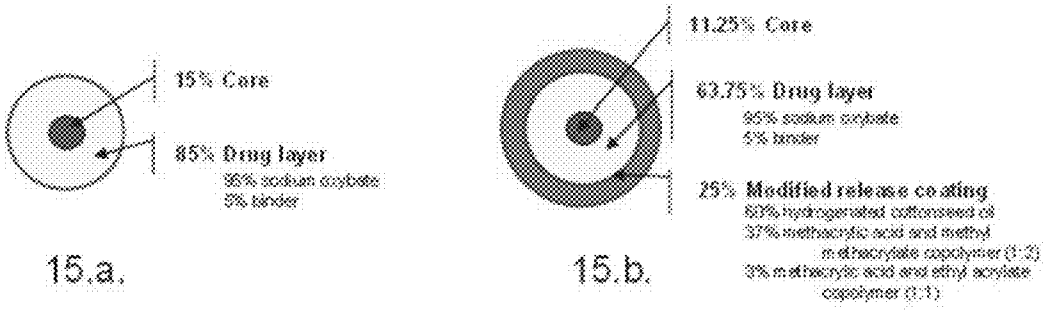


Figure 15

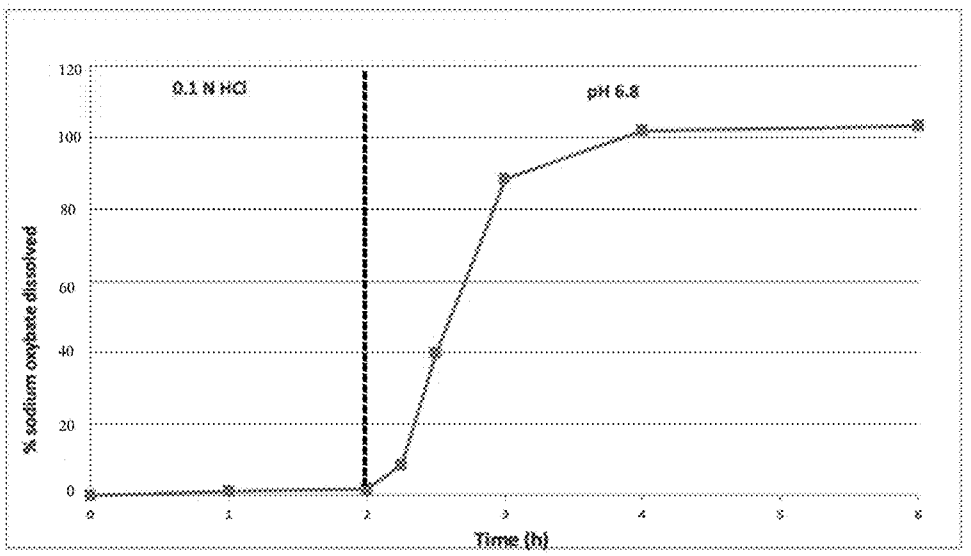


Figure 16

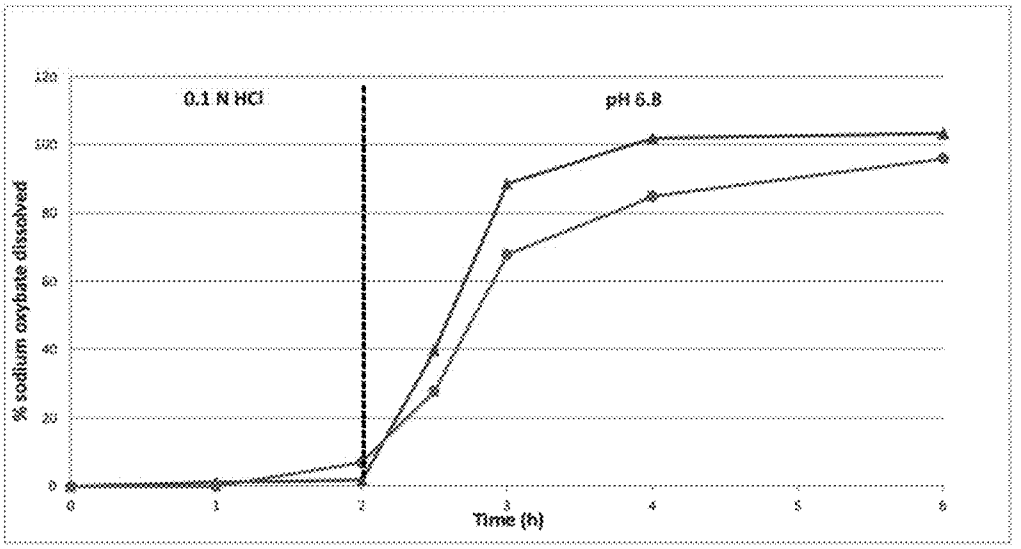


Figure 17

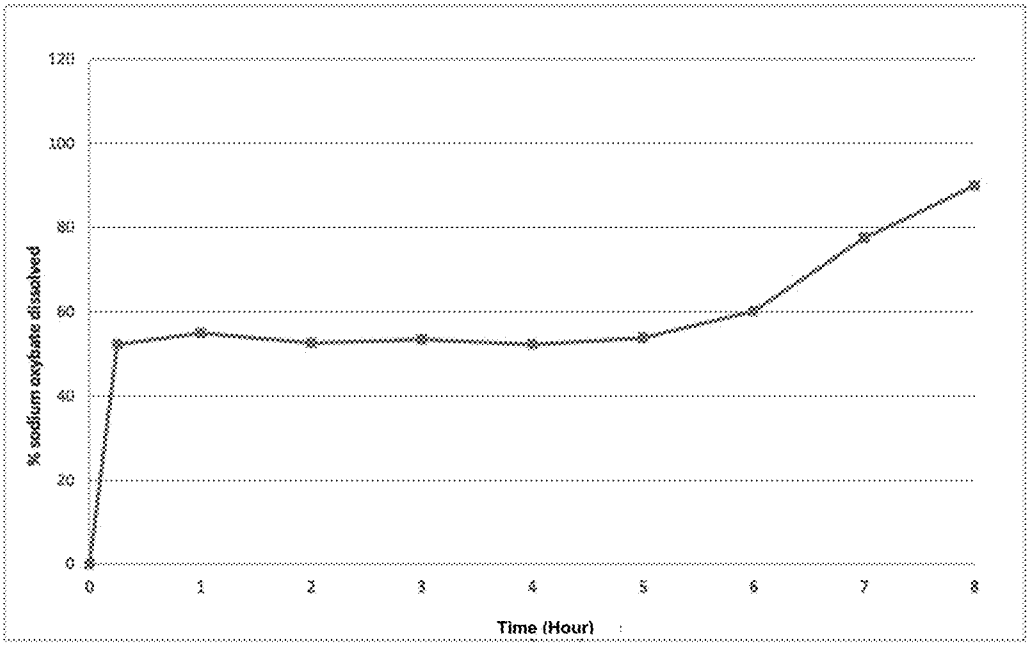


Figure 18

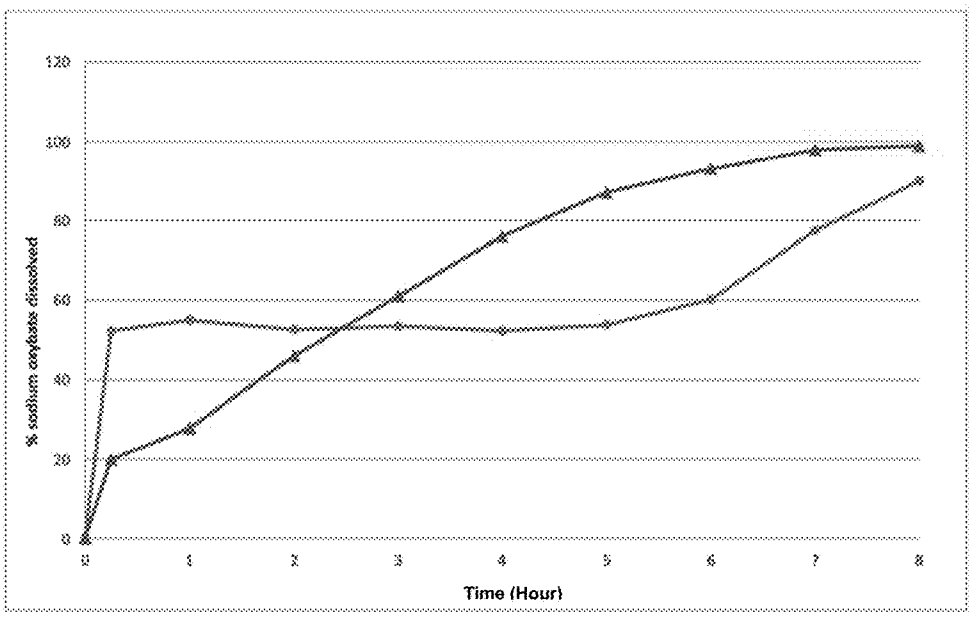


Figure 19

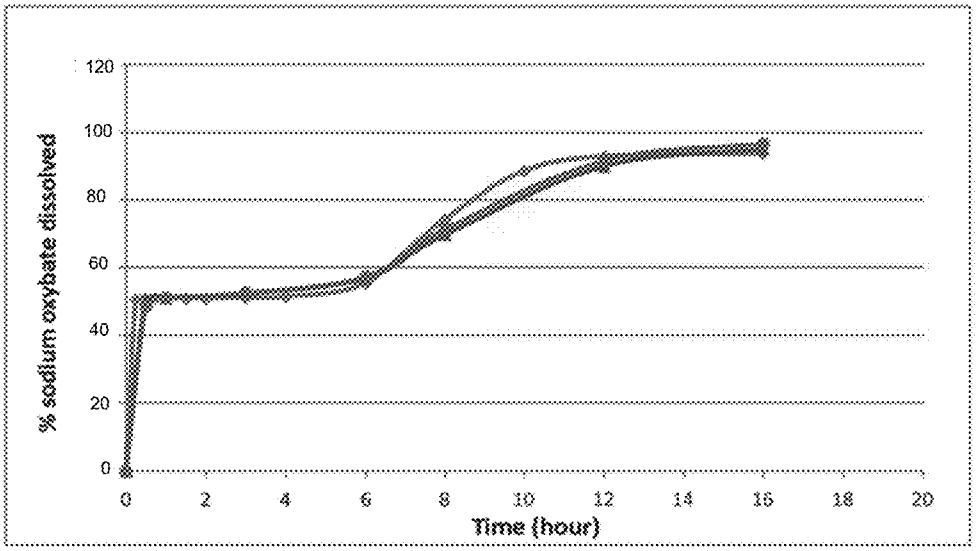


Figure 20

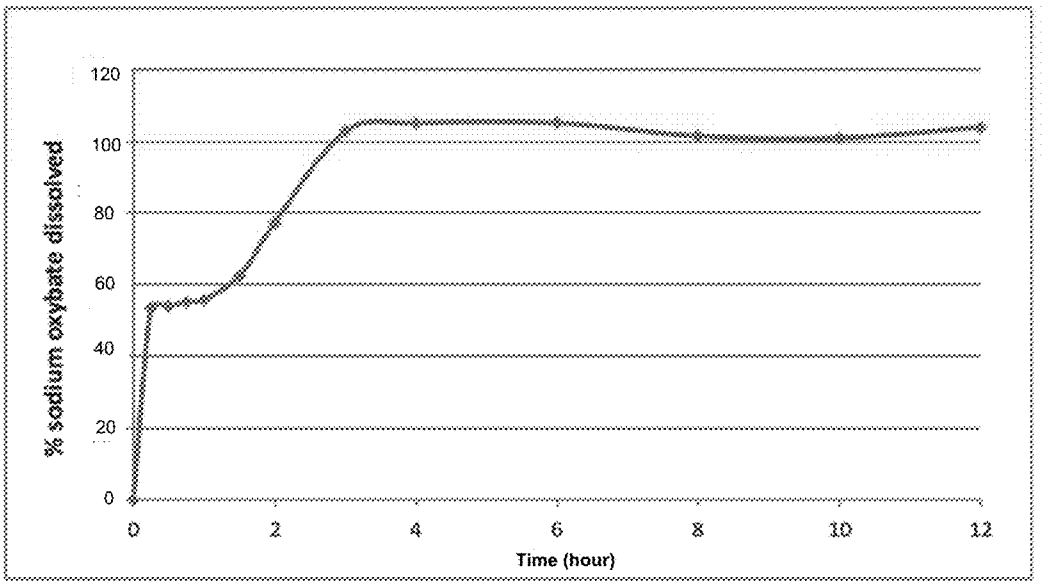


Figure 21

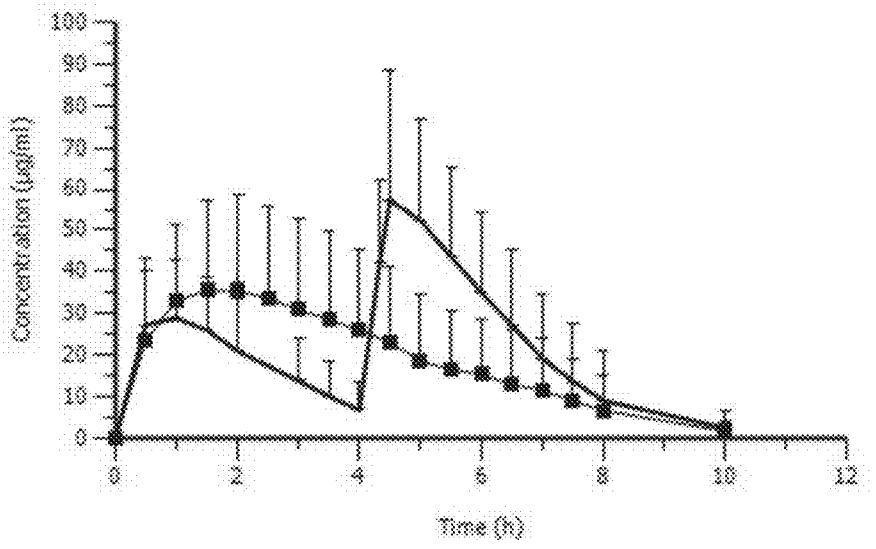
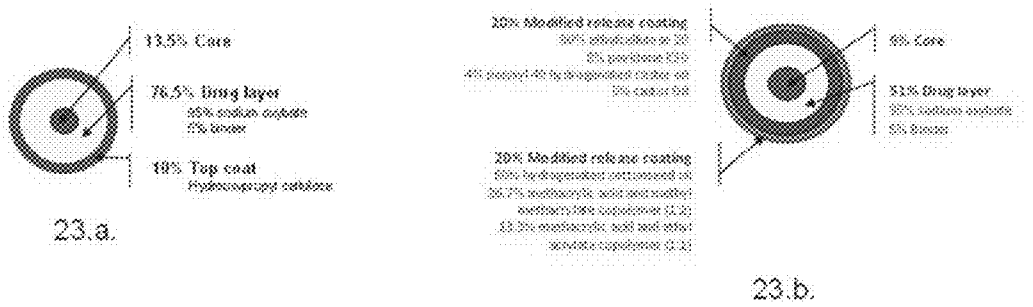


Figure 22



23.a. 23.b.

Figure 23

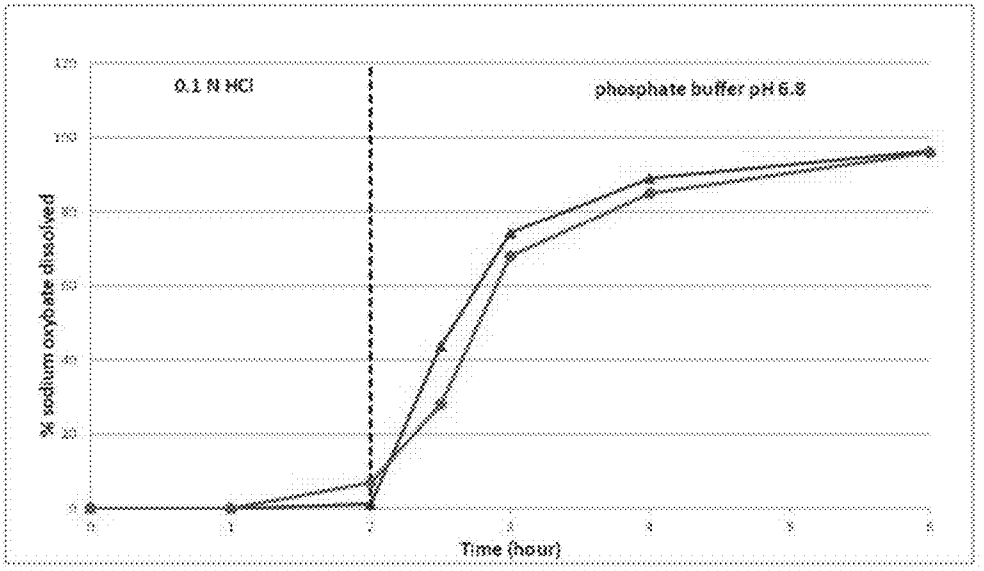


Figure 24

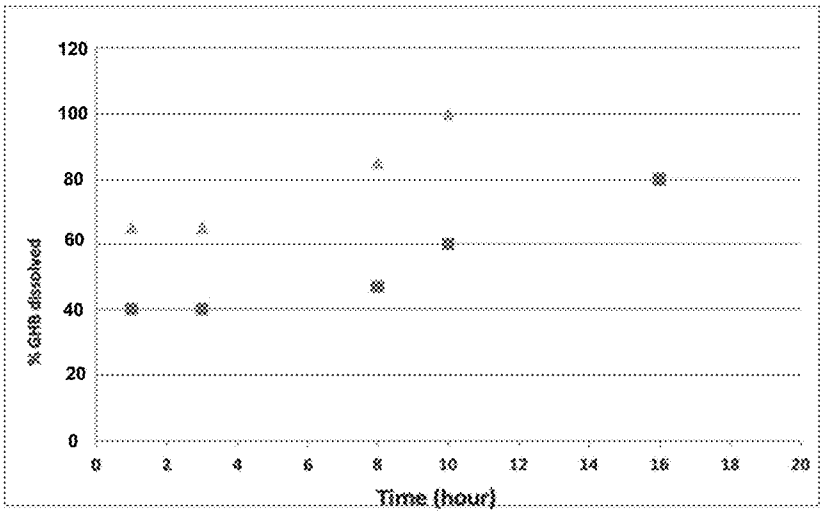


Figure 25

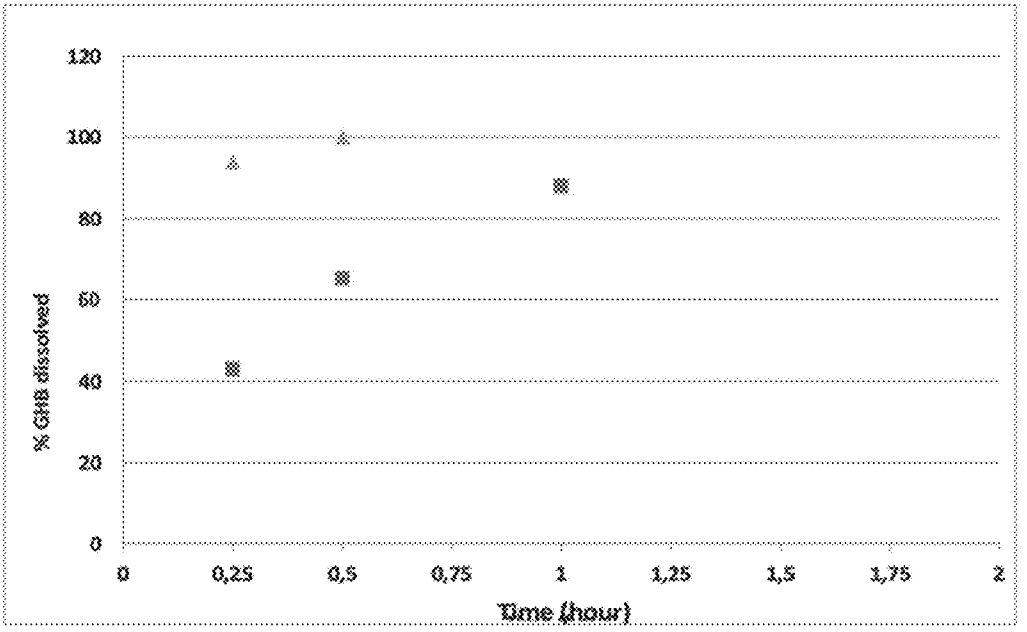


Figure 26

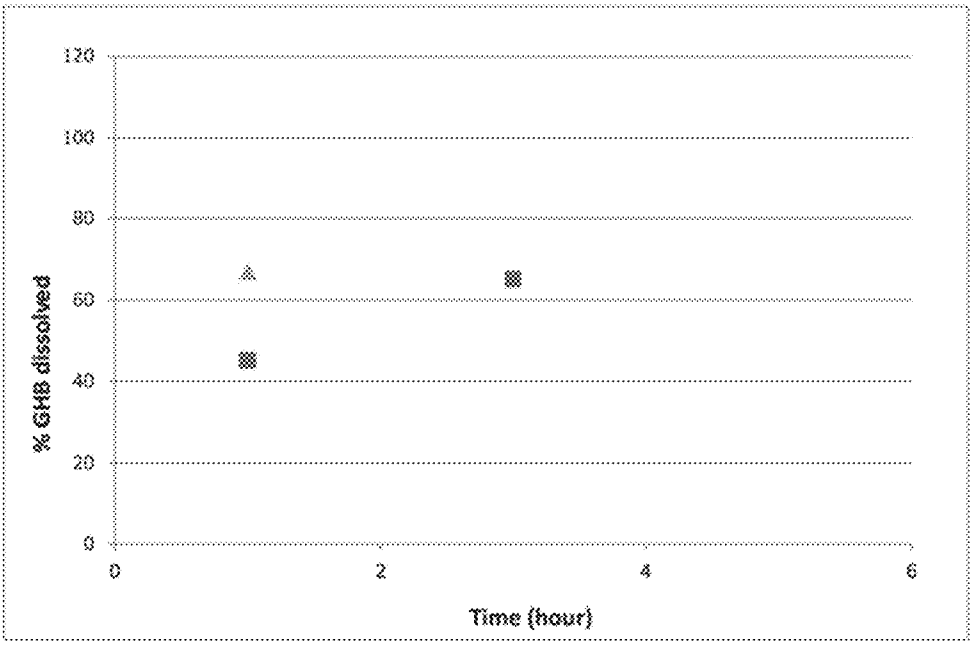


Figure 27

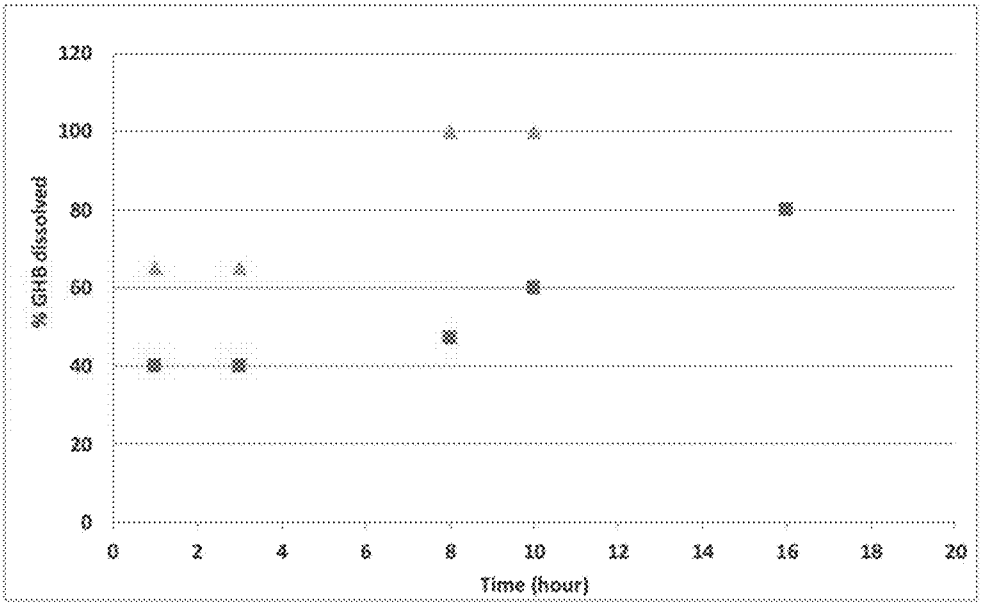


Figure 28

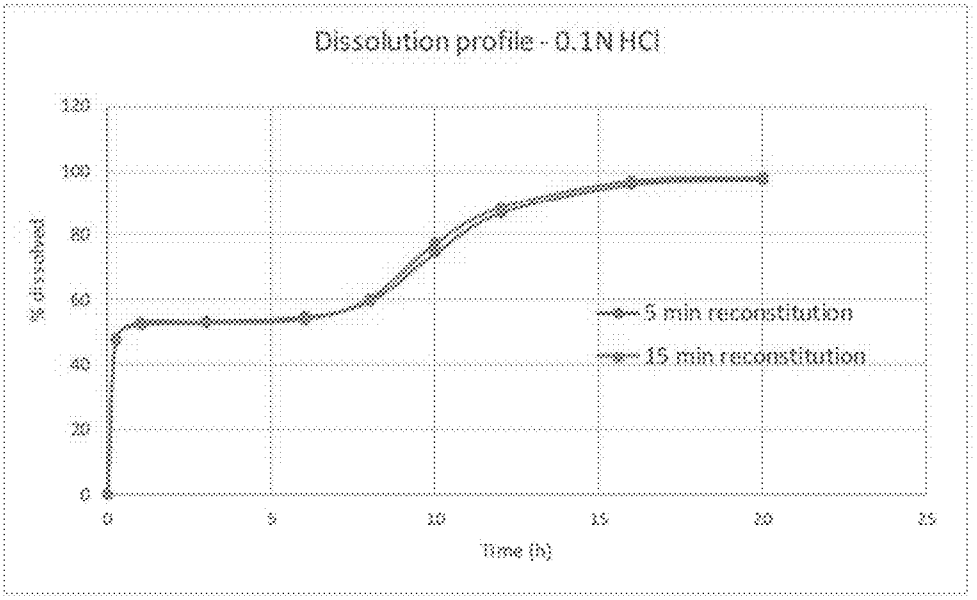


Figure 29

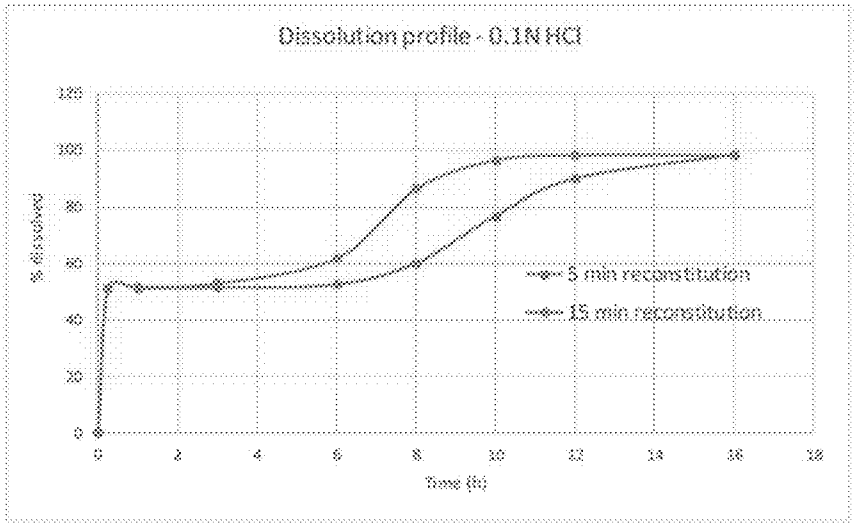


Figure 30

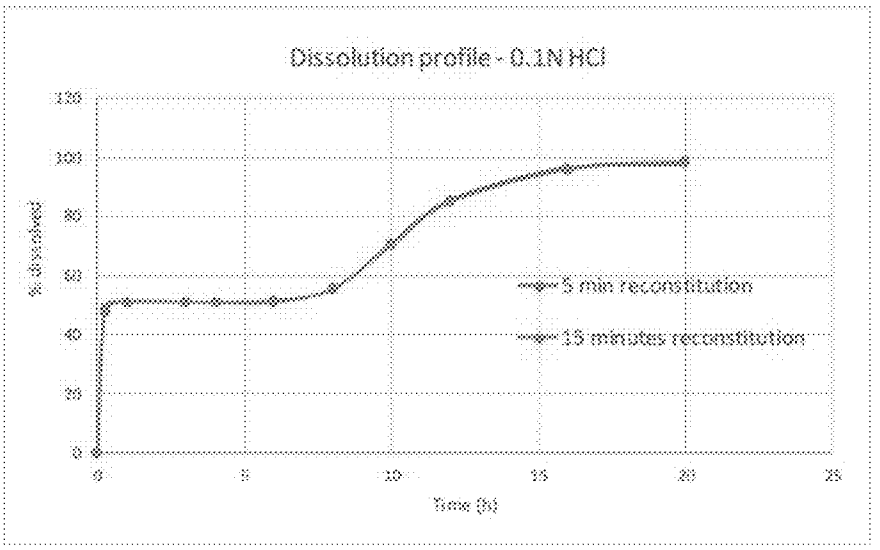


Figure 31

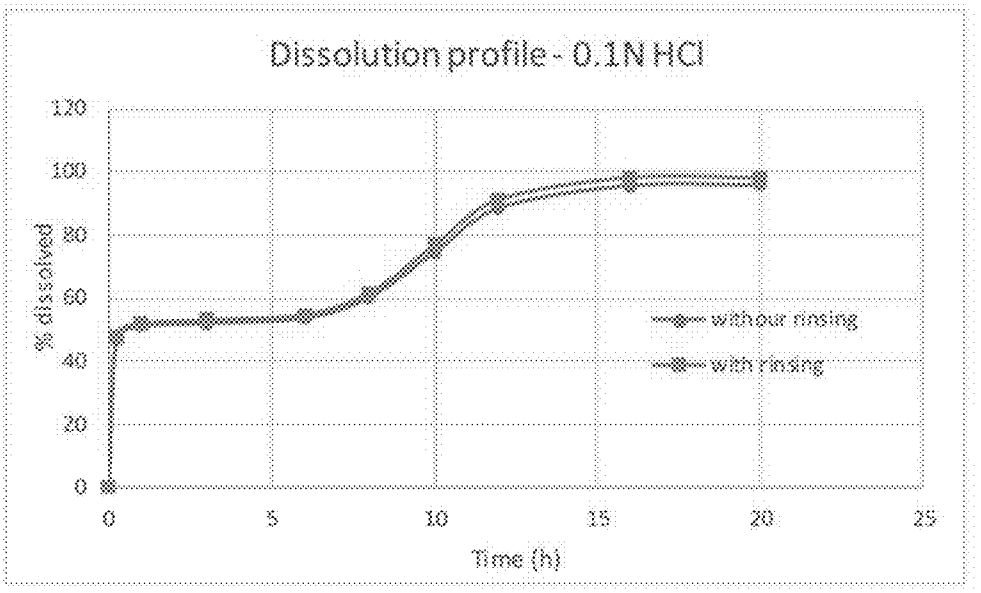


Figure 32

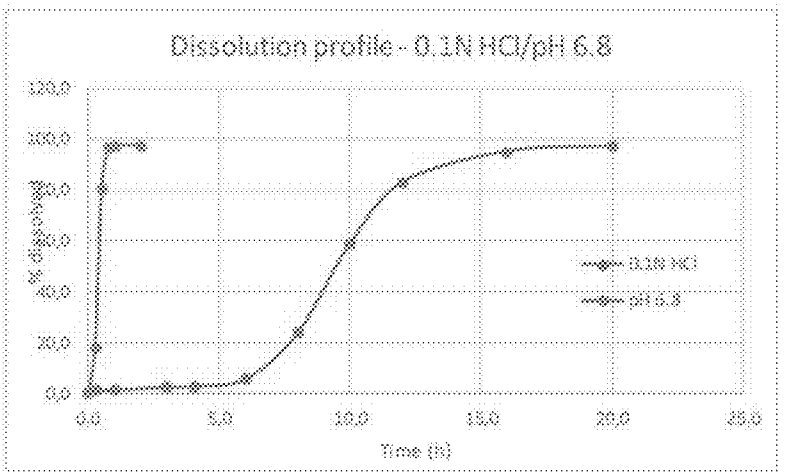


Figure 33

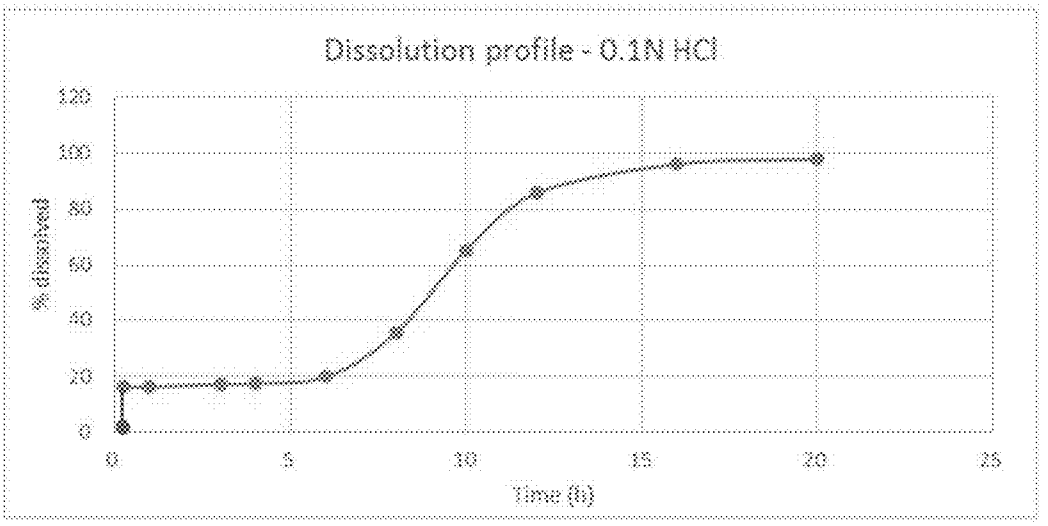


Figure 34

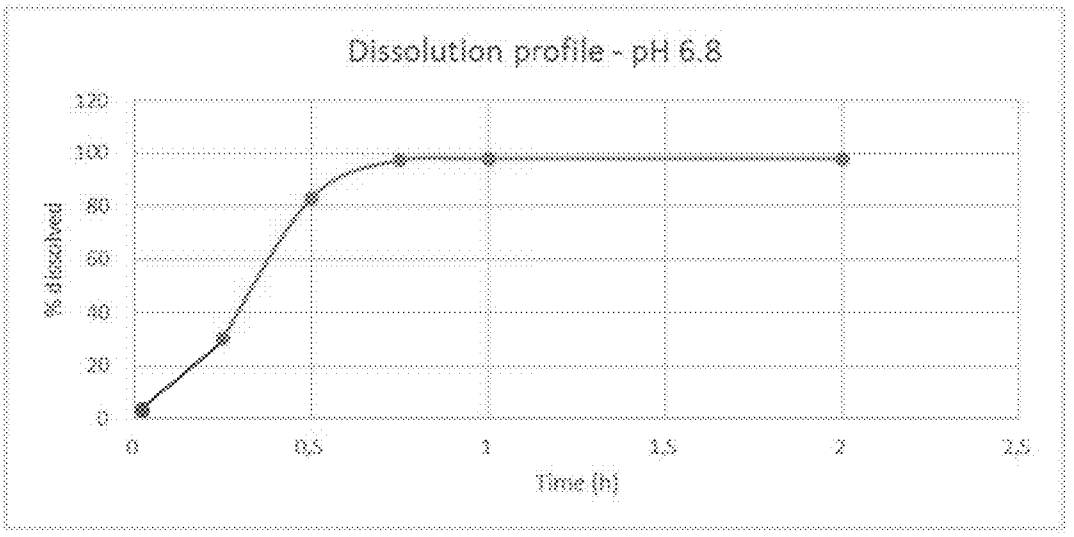


Figure 35

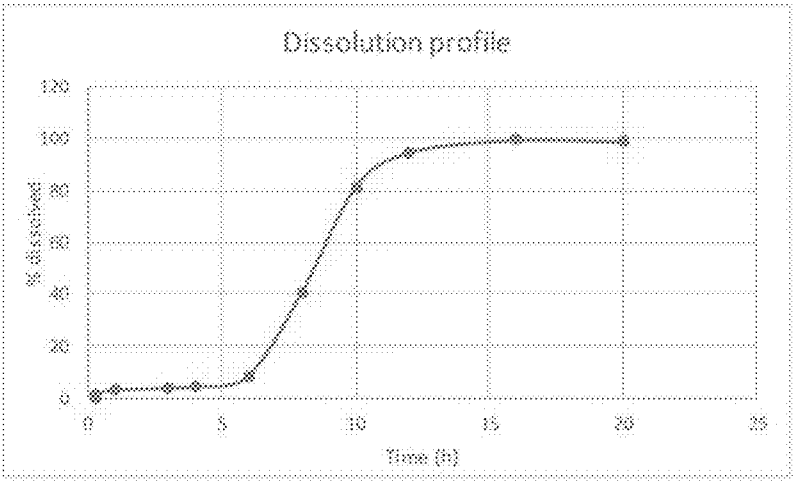


Figure 36

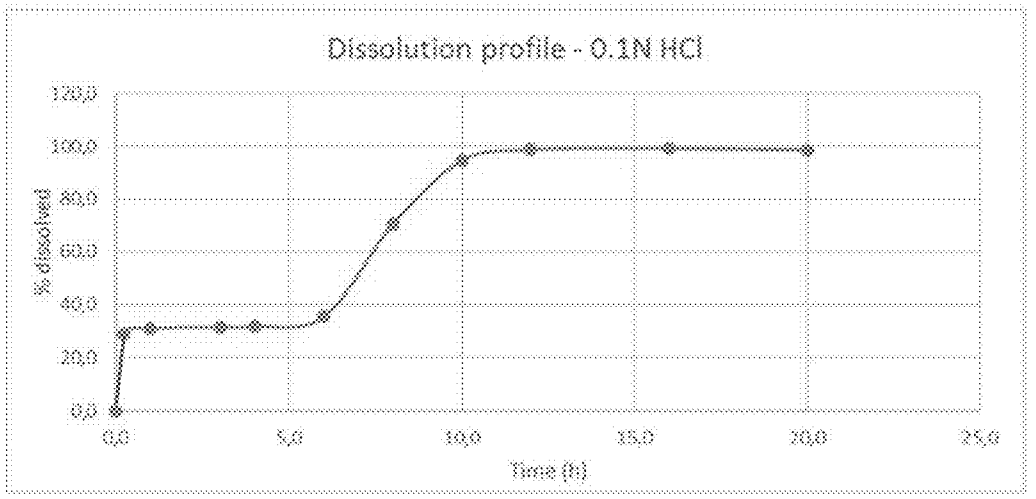


Figure 37

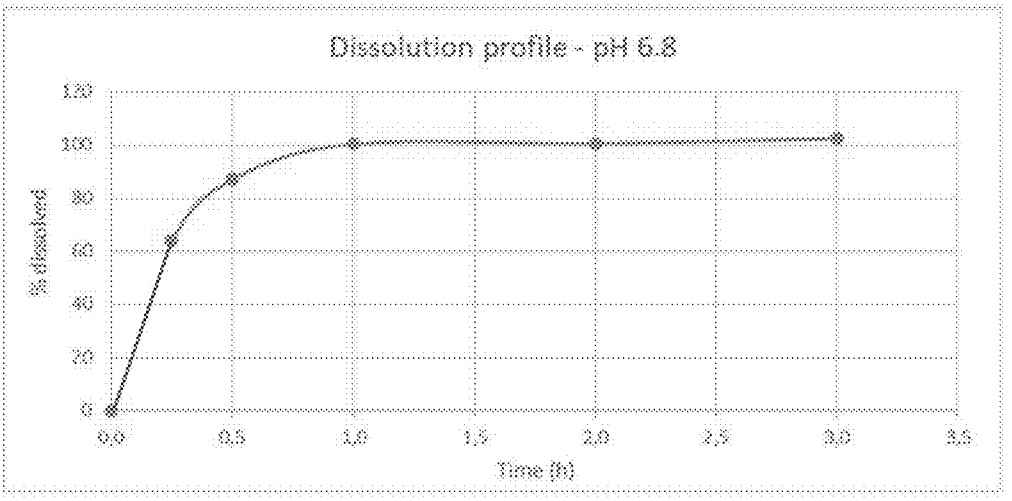


Figure 38

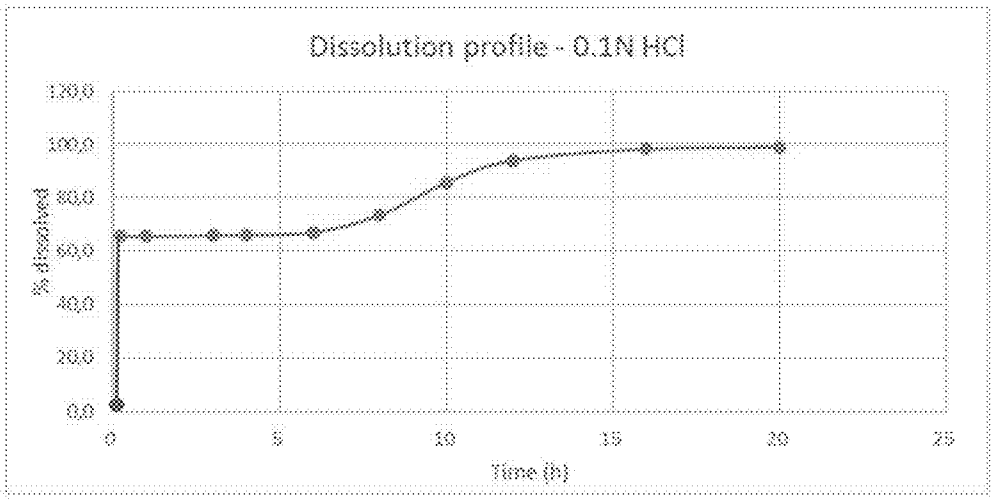


Figure 39

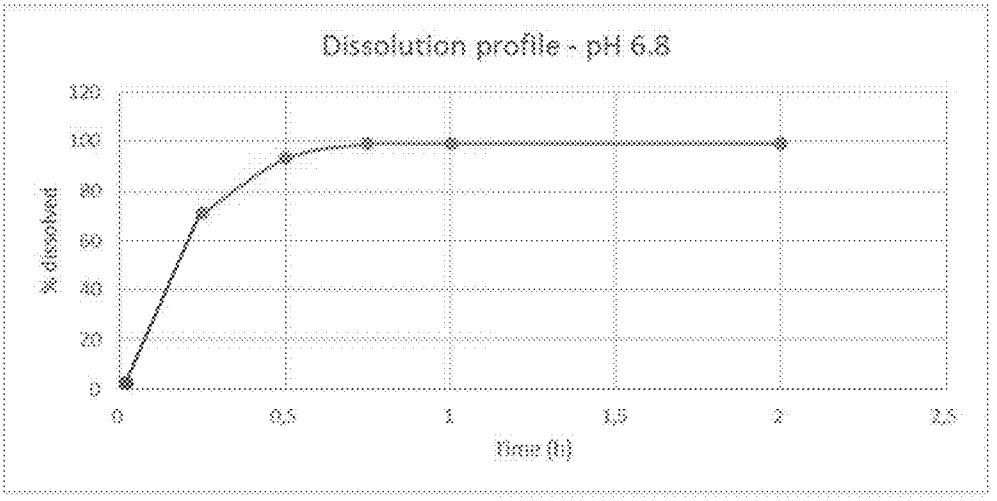


Figure 40

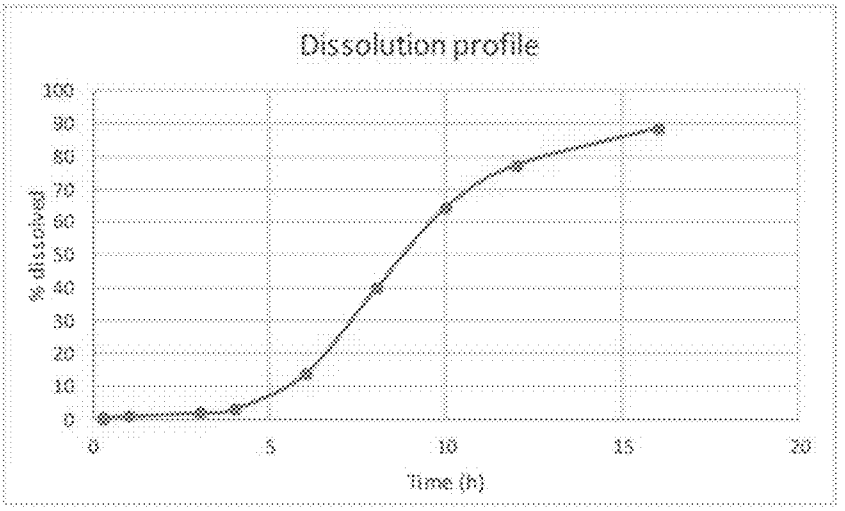


Figure 41

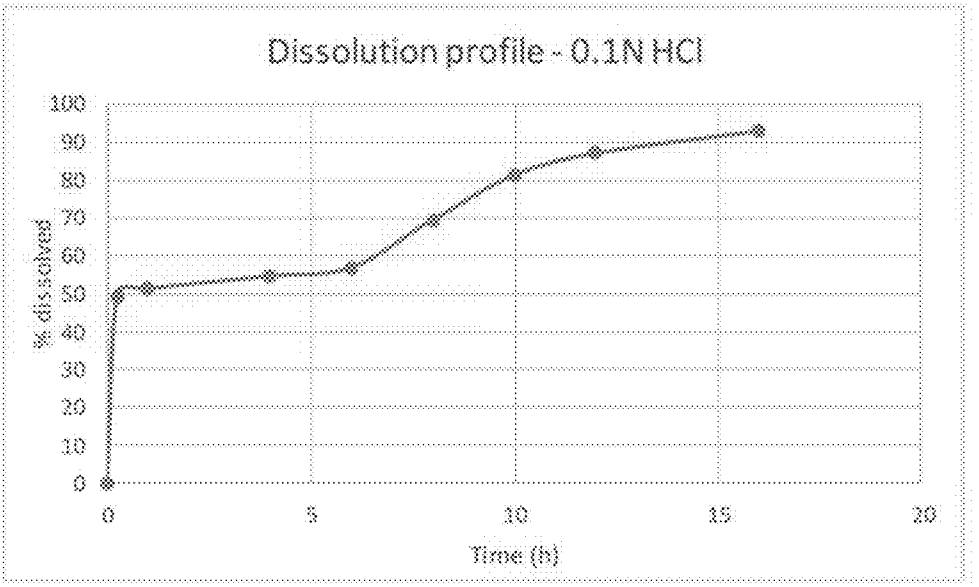


Figure 42

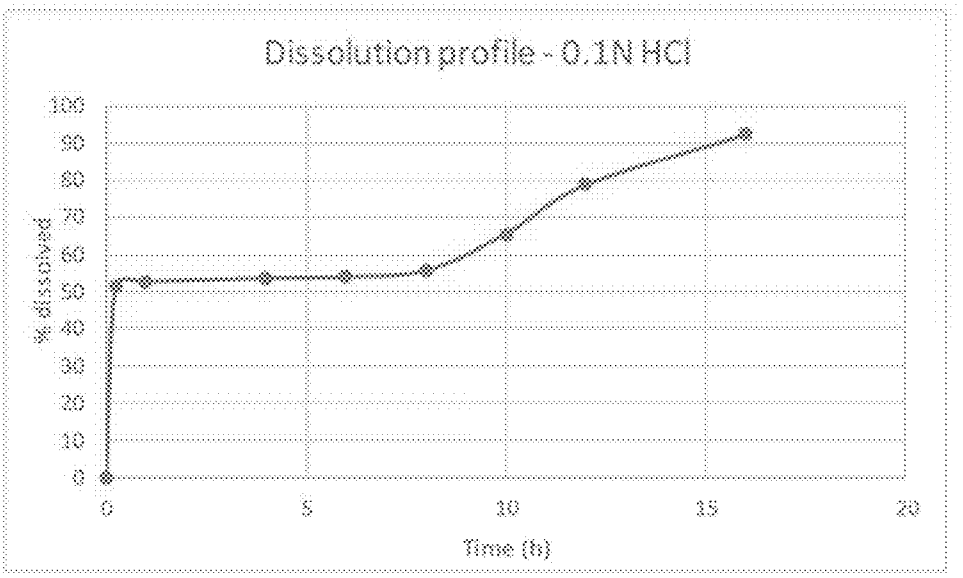


Figure 43

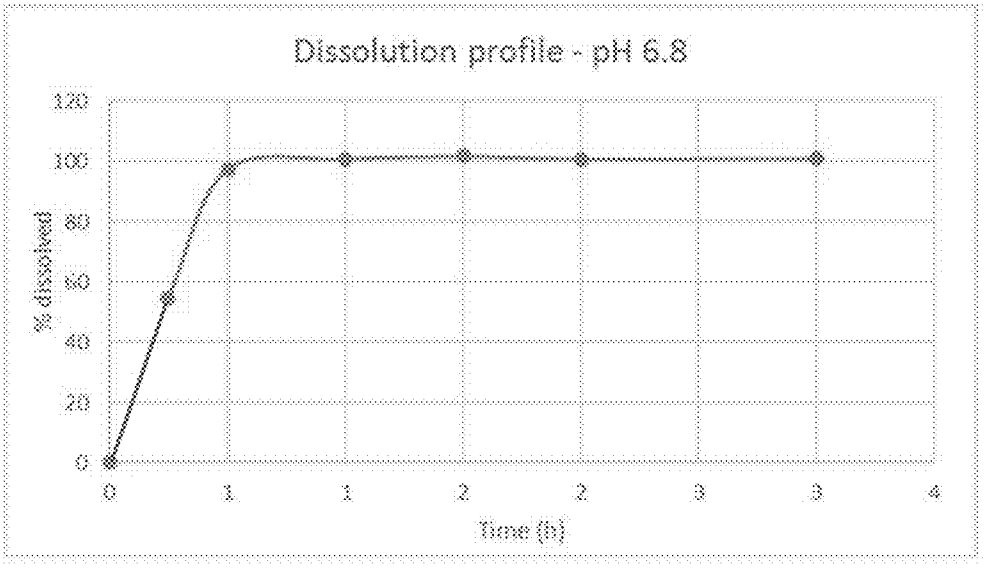


Figure 44

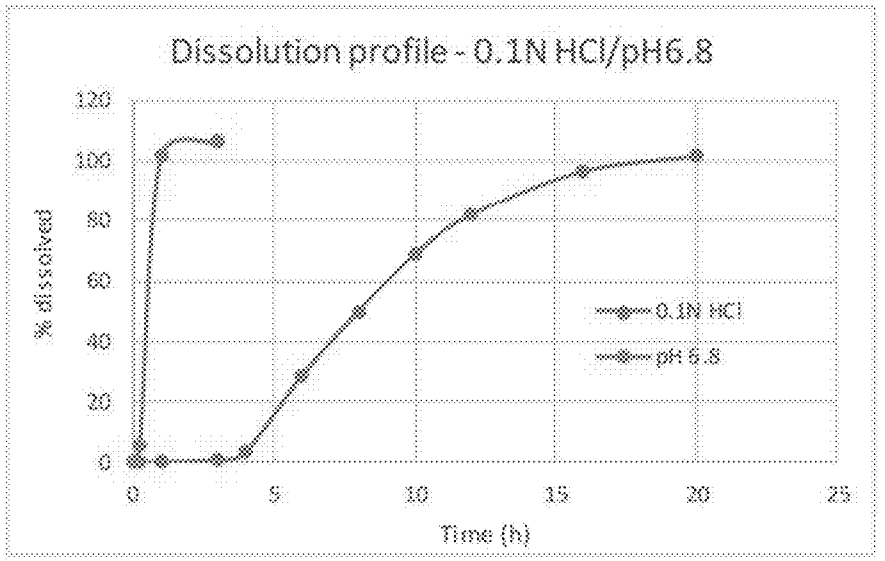


Figure 45

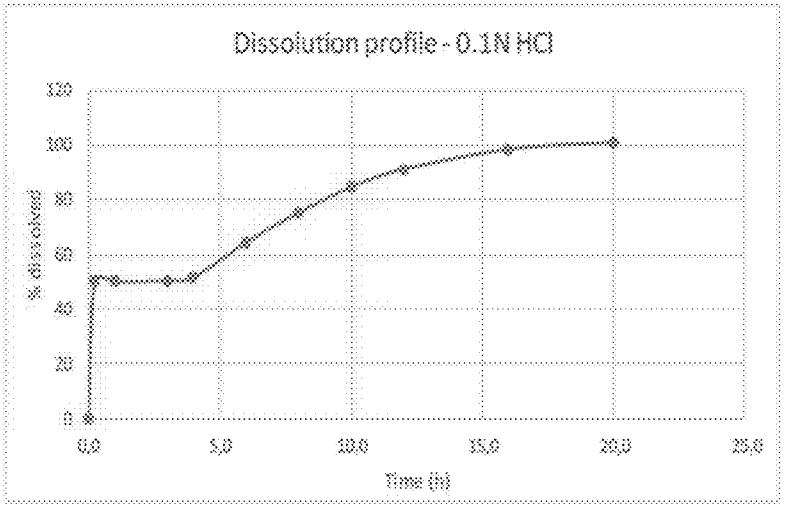


Figure 46

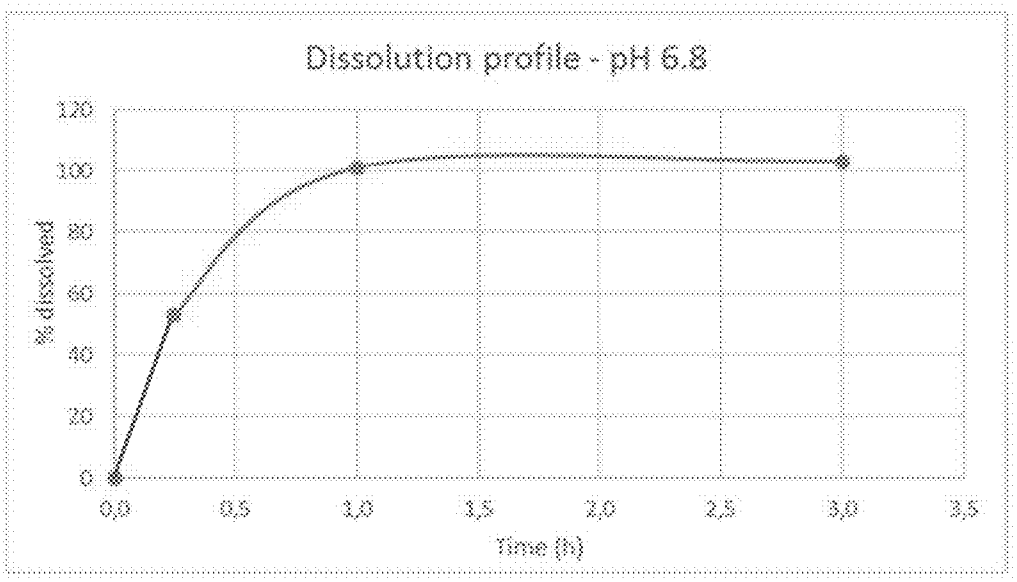


Figure 47

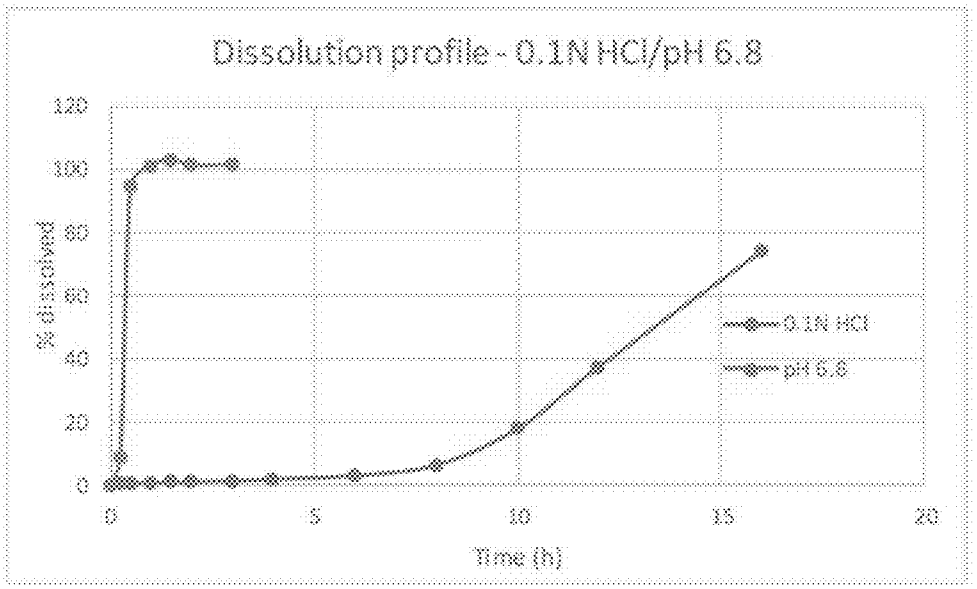


Figure 48

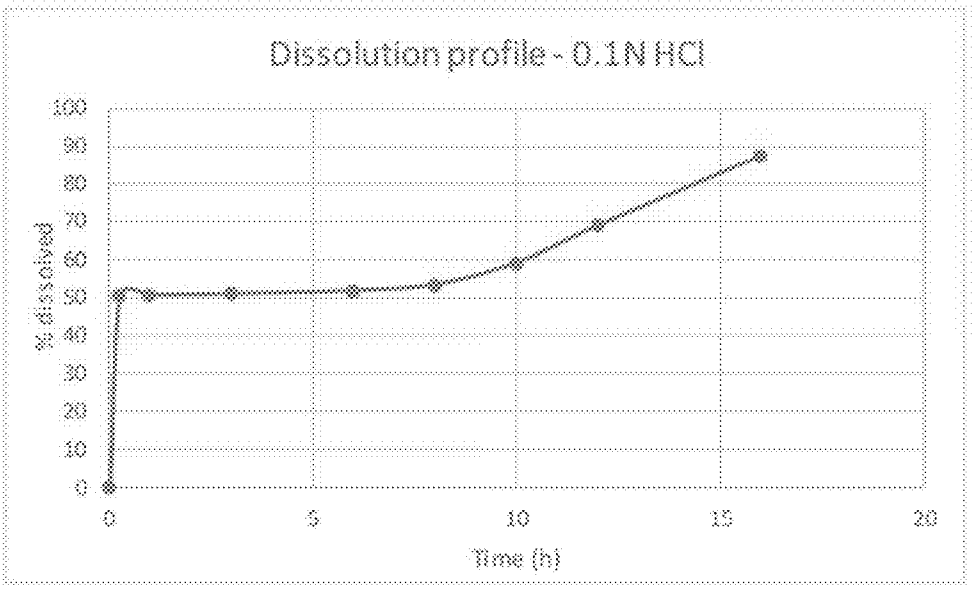


Figure 49

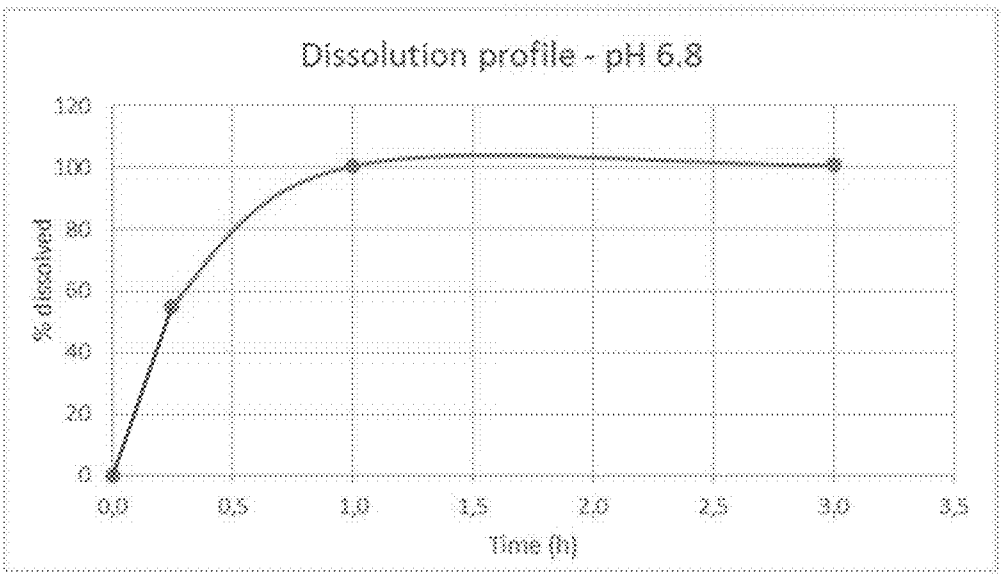


Figure 50

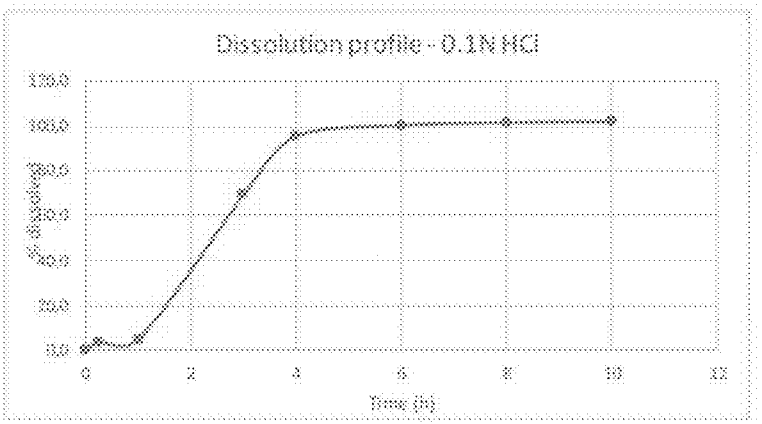


Figure 51

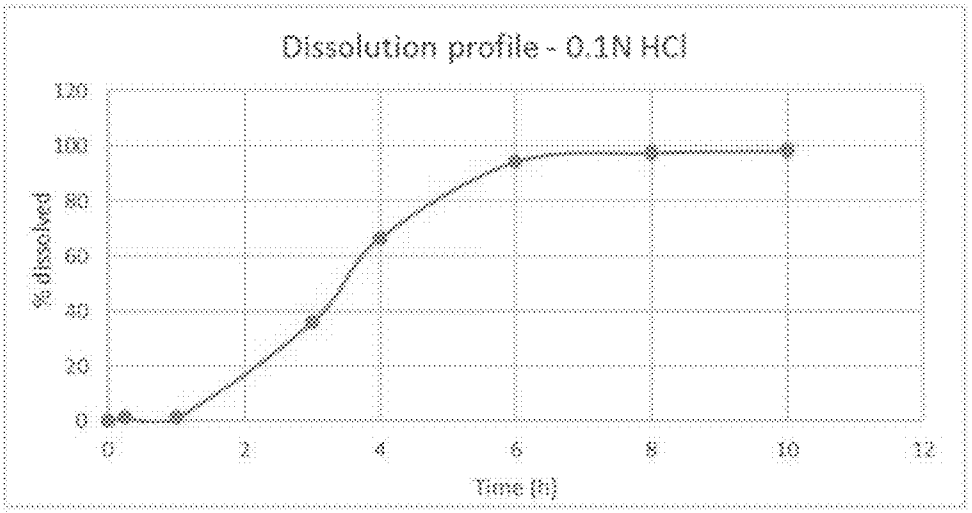


Figure 52

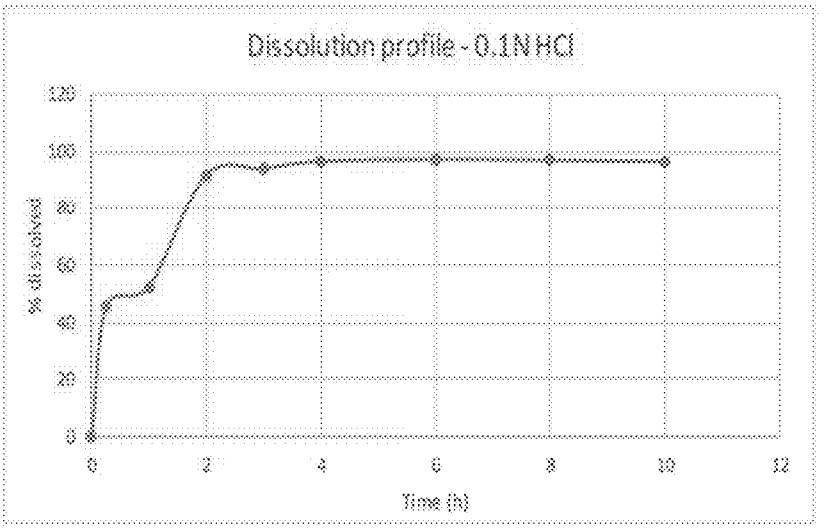


Figure 53

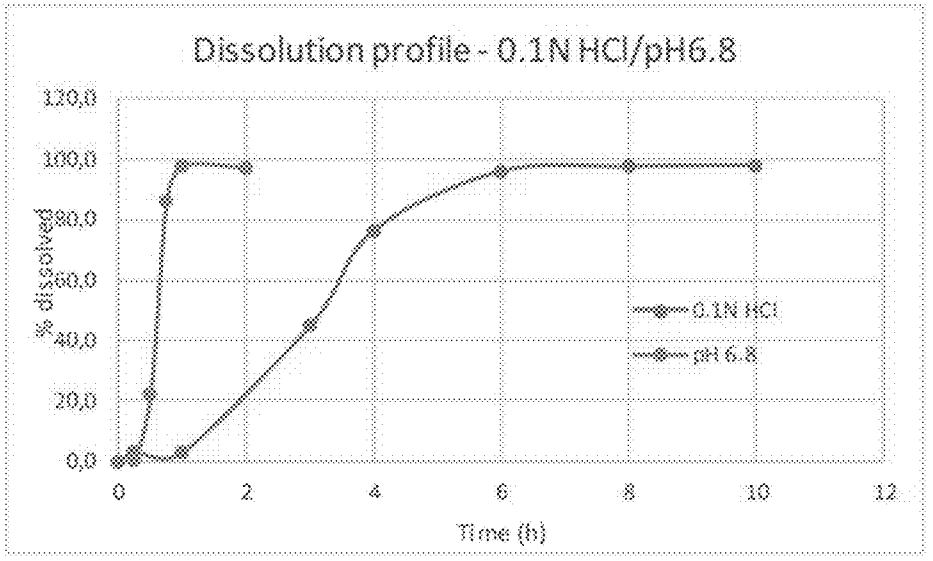


Figure 54

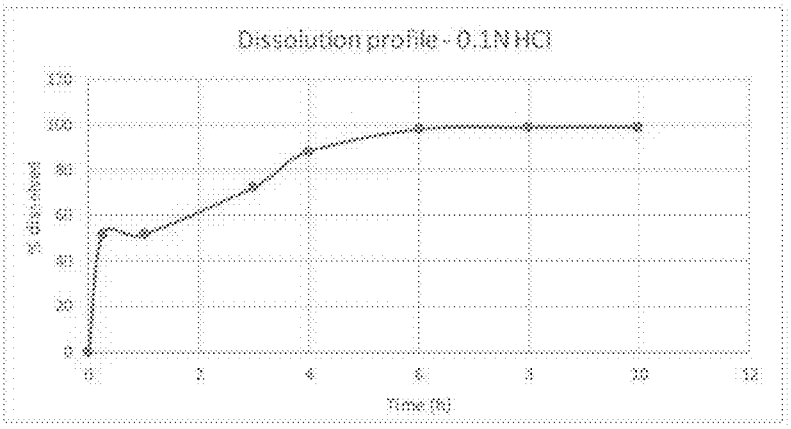


Figure 55

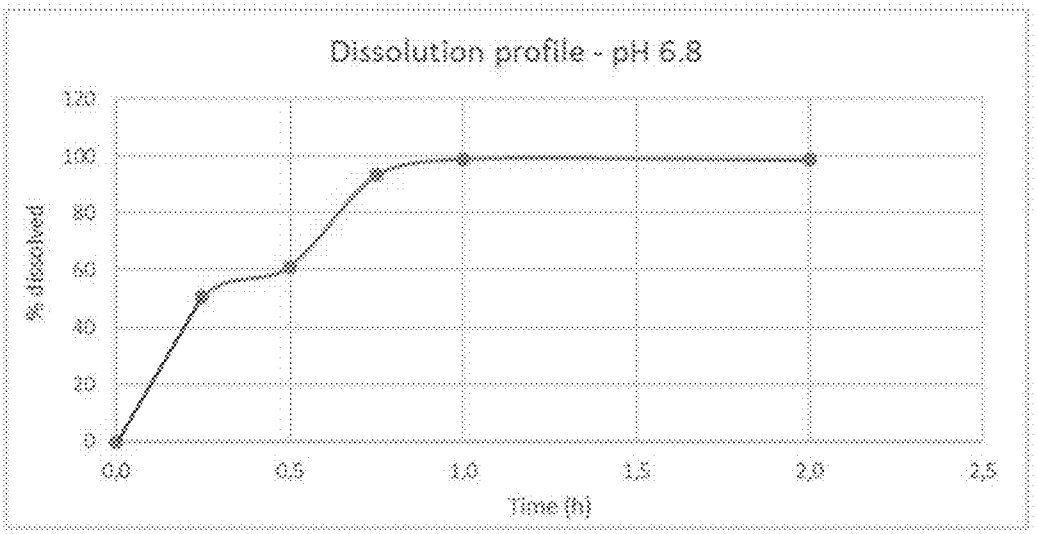


Figure 56

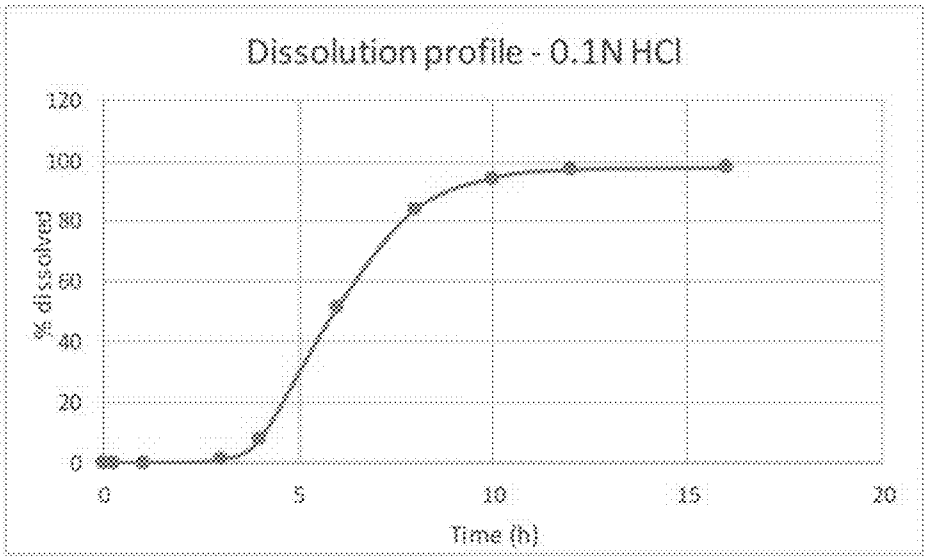


Figure 57

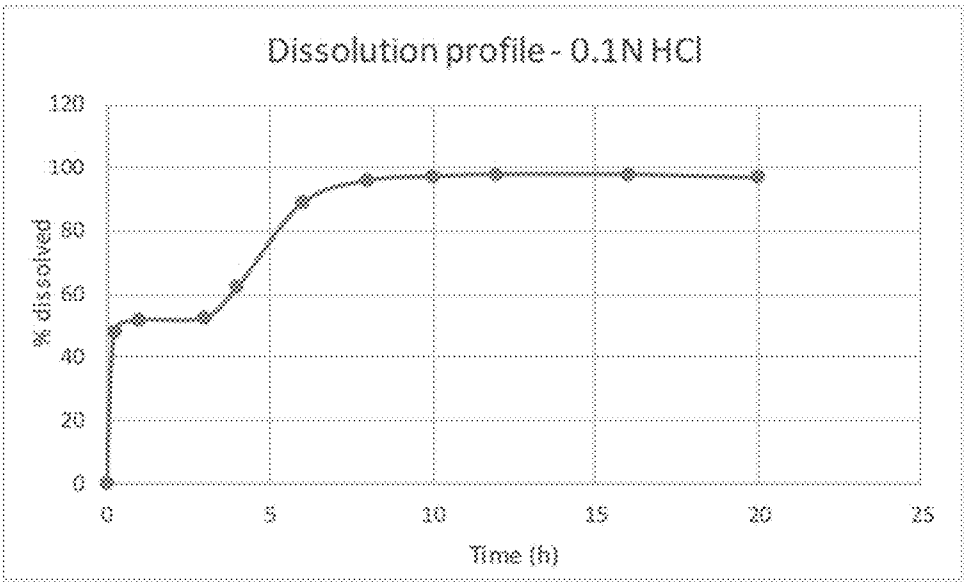


Figure 58

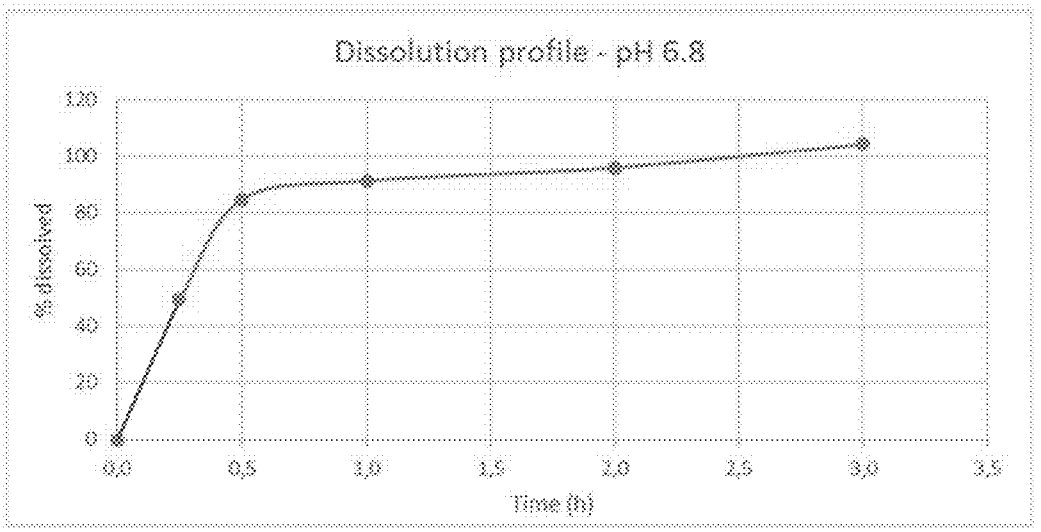


Figure 59

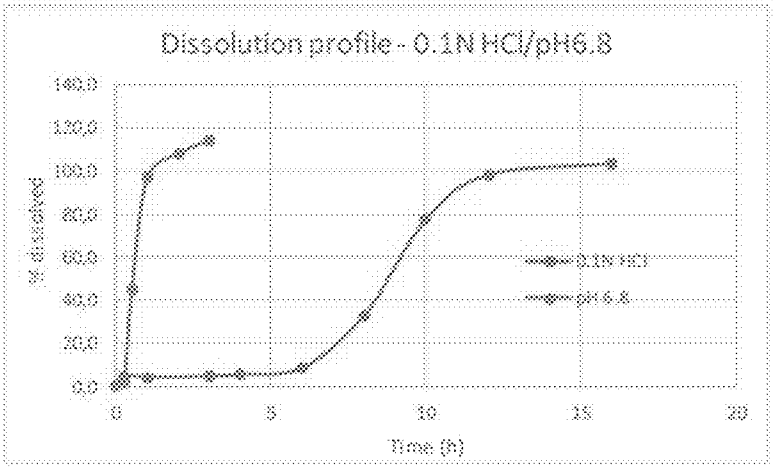


Figure 60

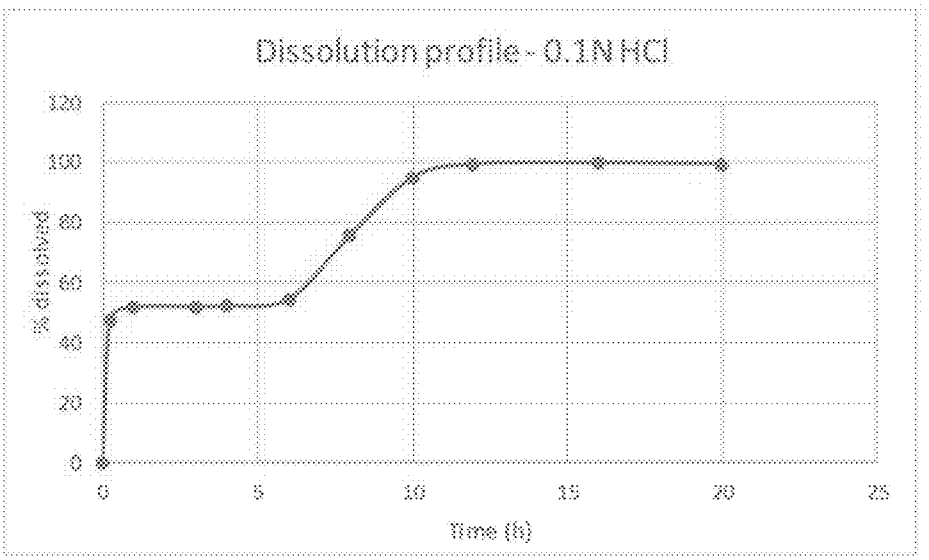


Figure 61

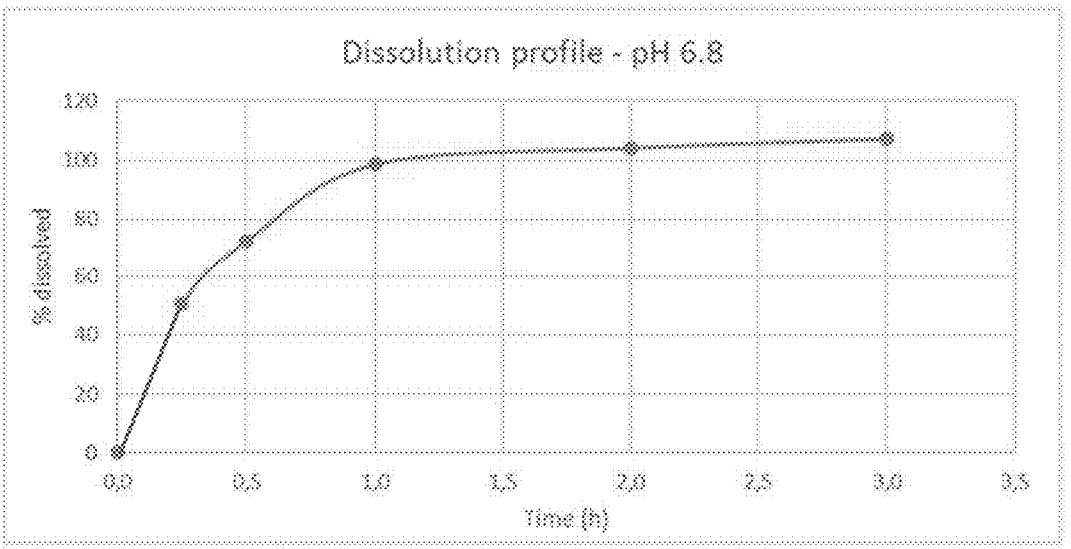


Figure 62

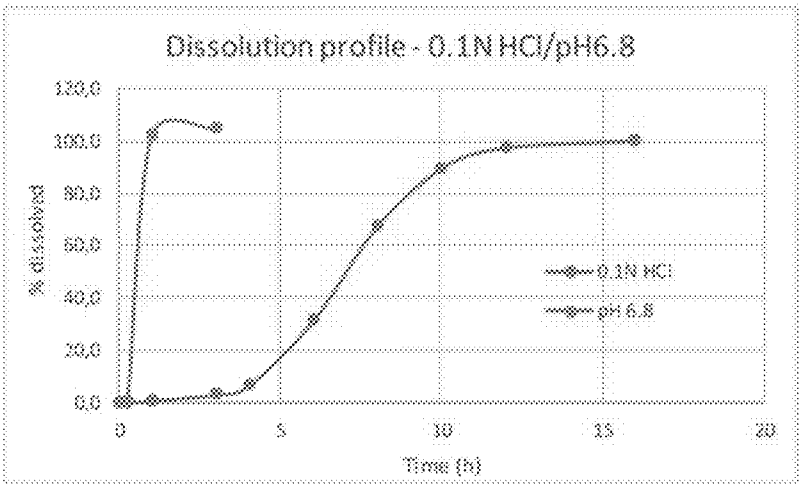


Figure 63

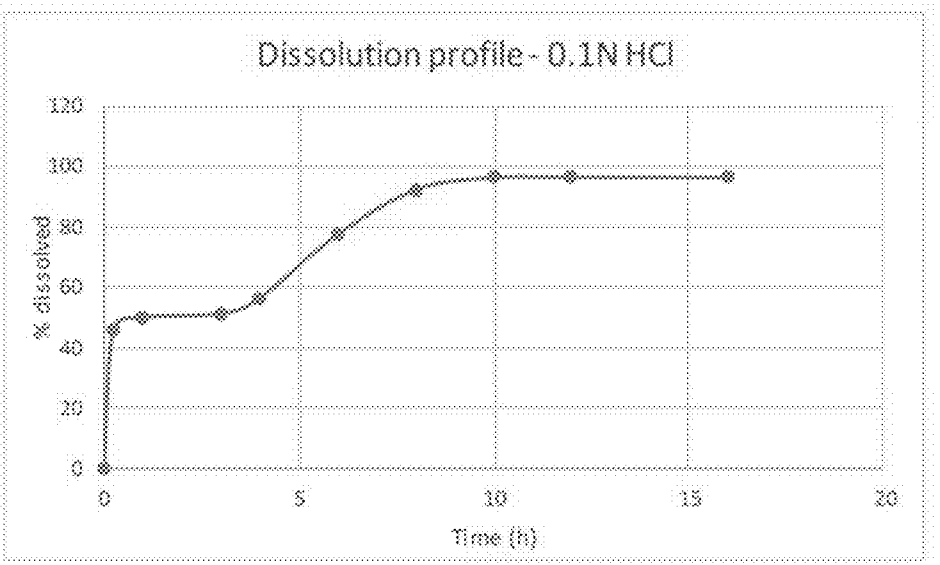


Figure 64

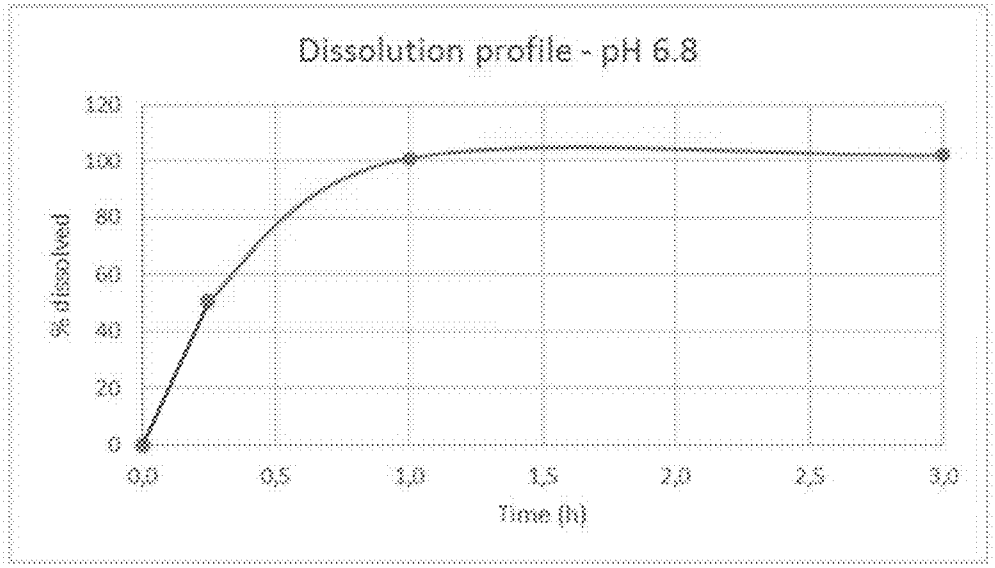


Figure 65

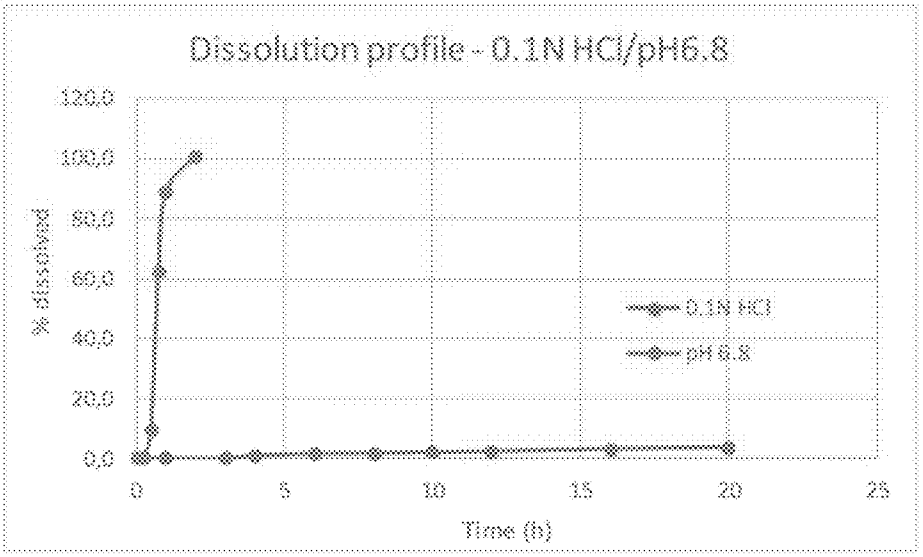


Figure 66

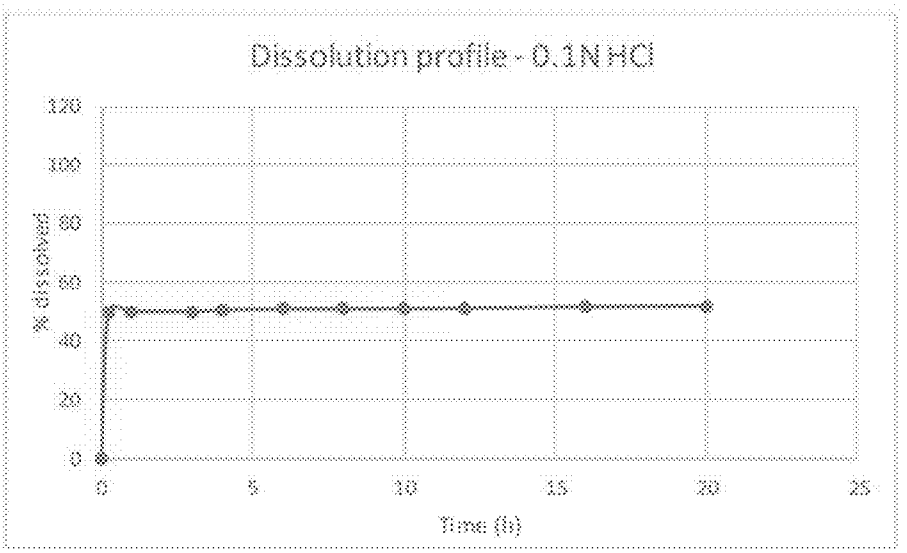


Figure 67

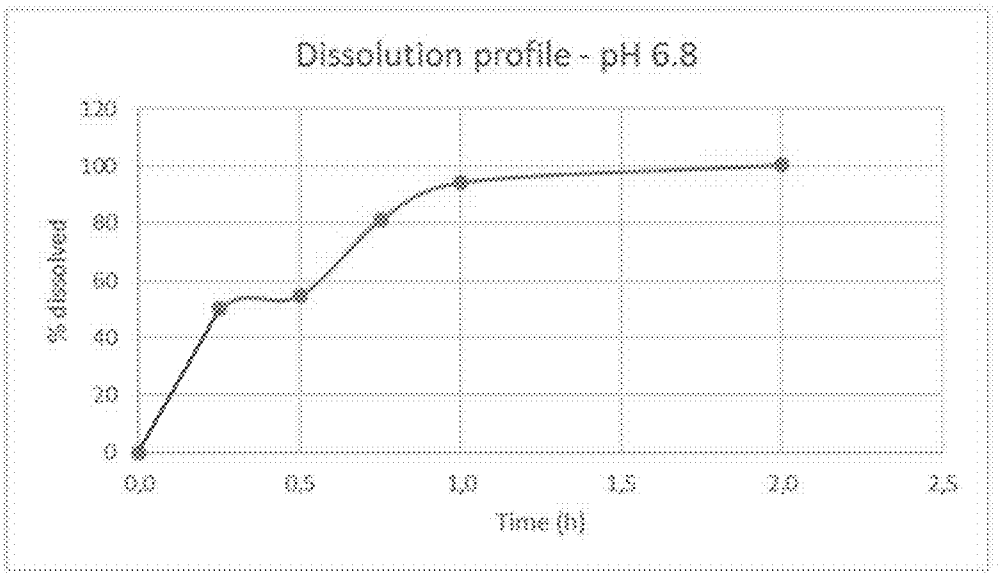


Figure 68

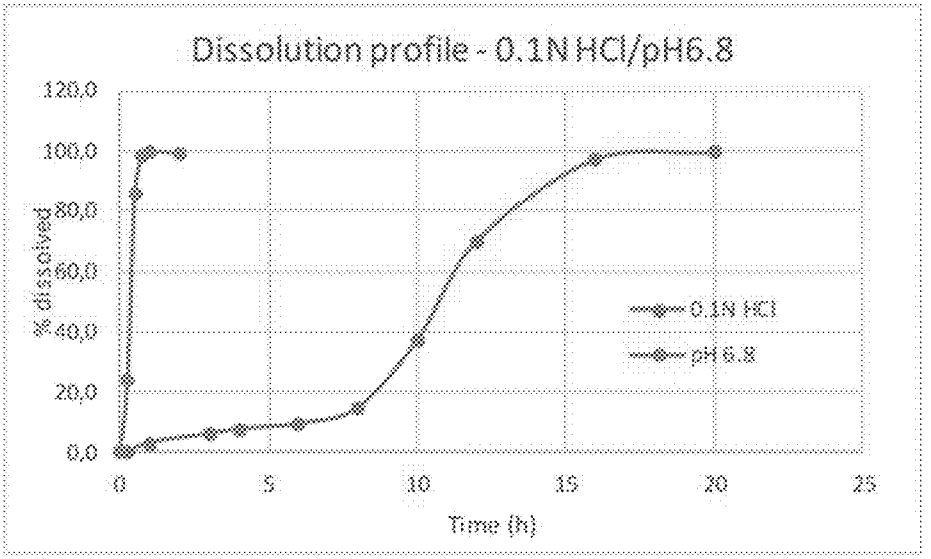


Figure 69

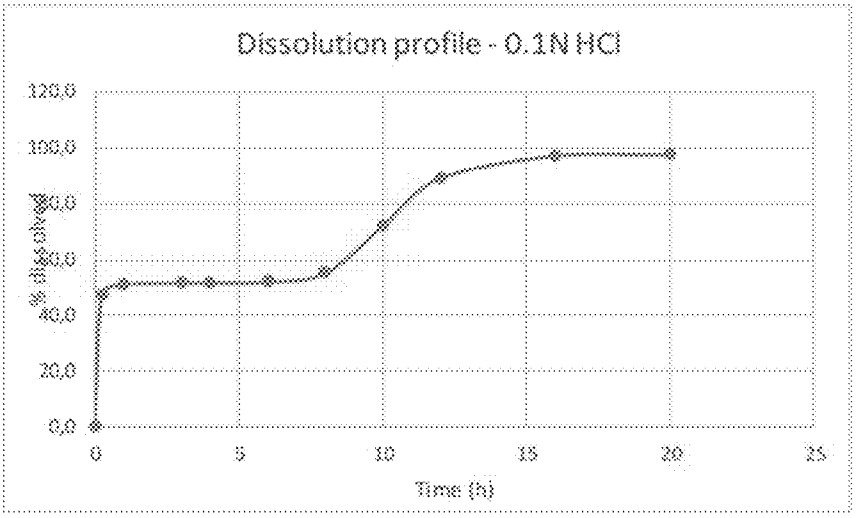


Figure 70

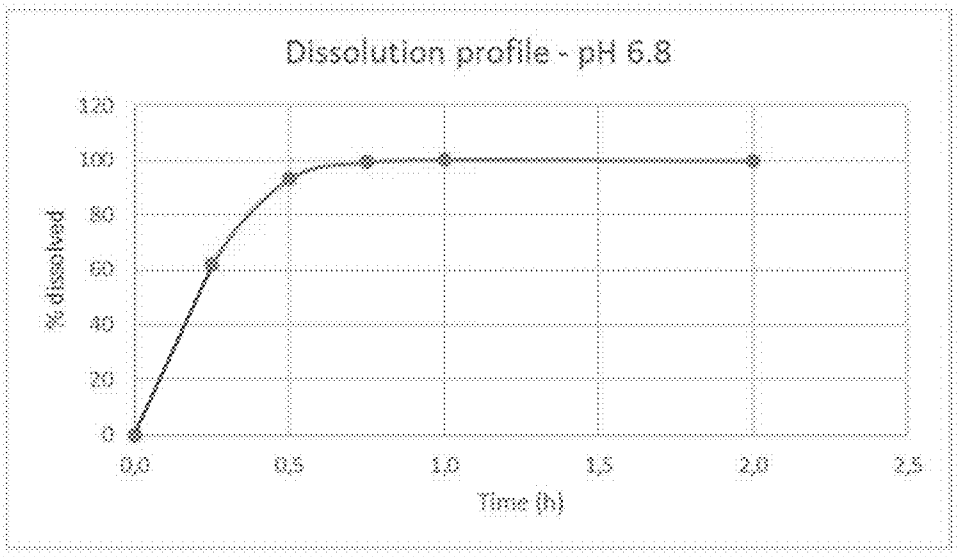


Figure 71

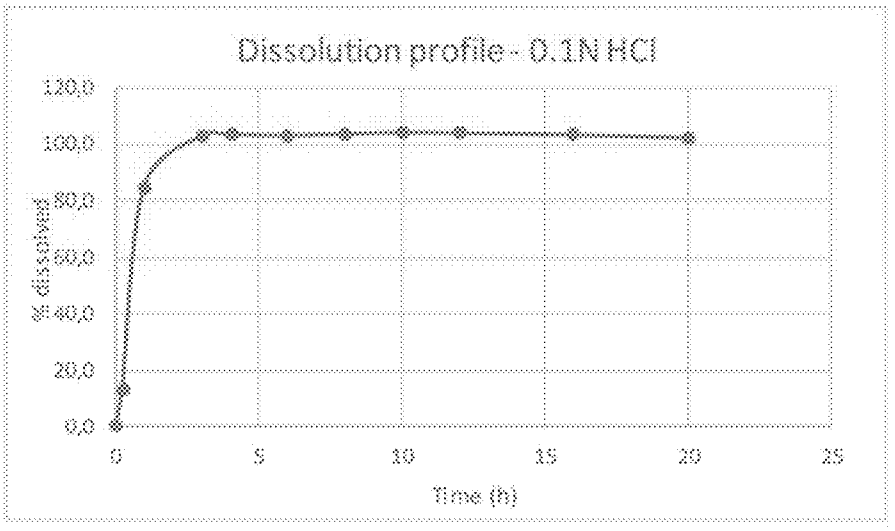


Figure 72

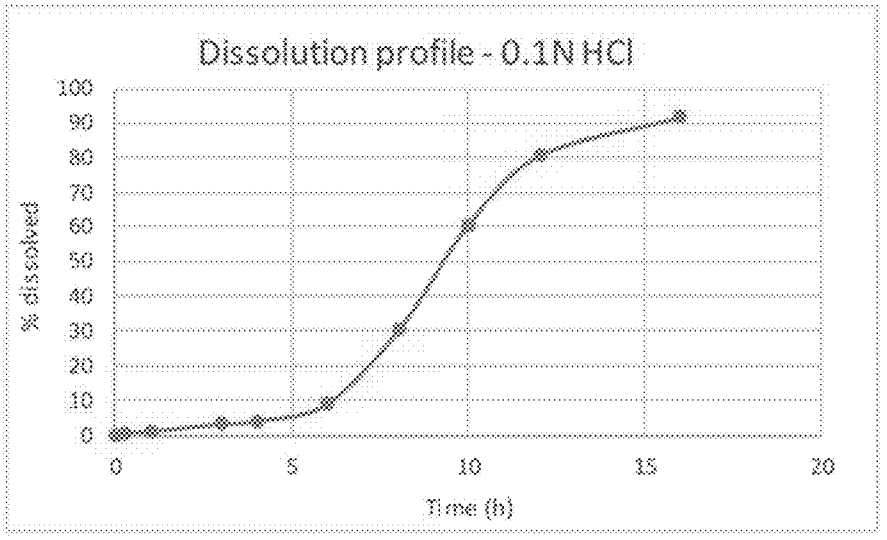


Figure 73

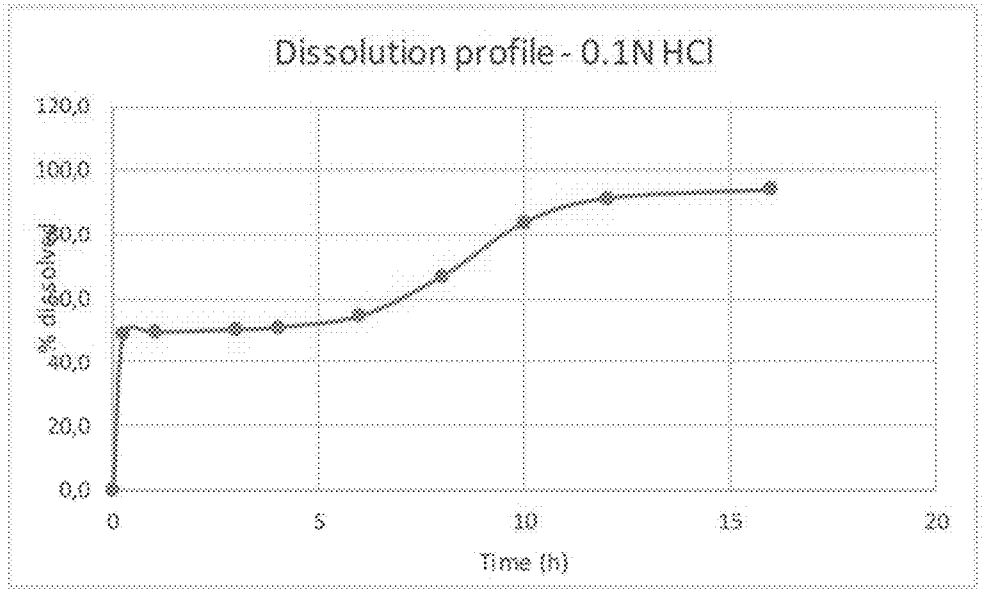


Figure 74

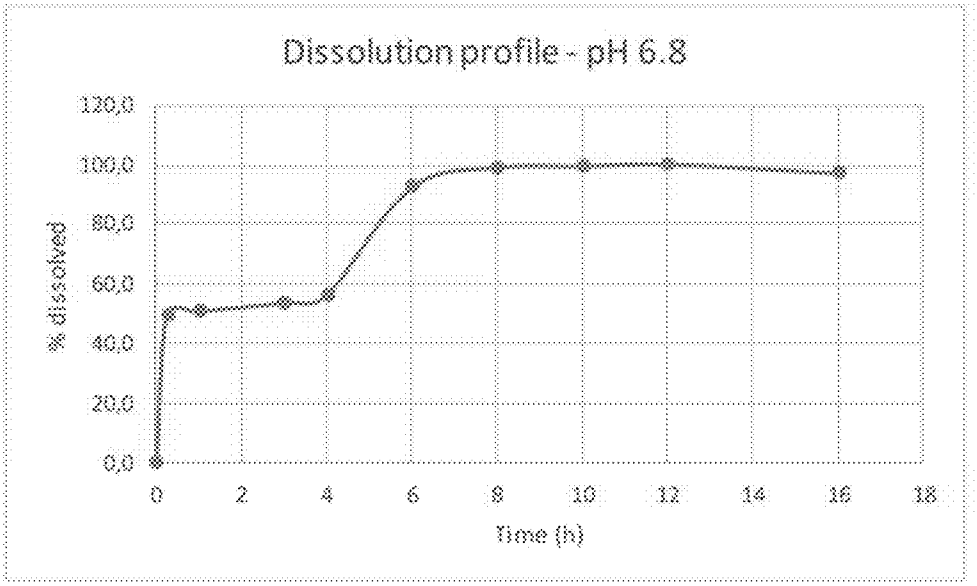


Figure 75

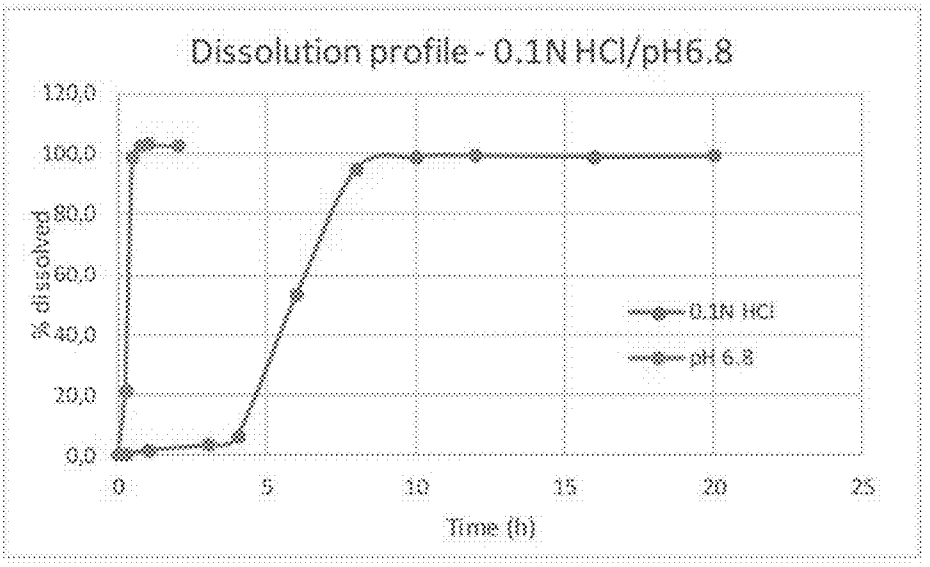


Figure 76

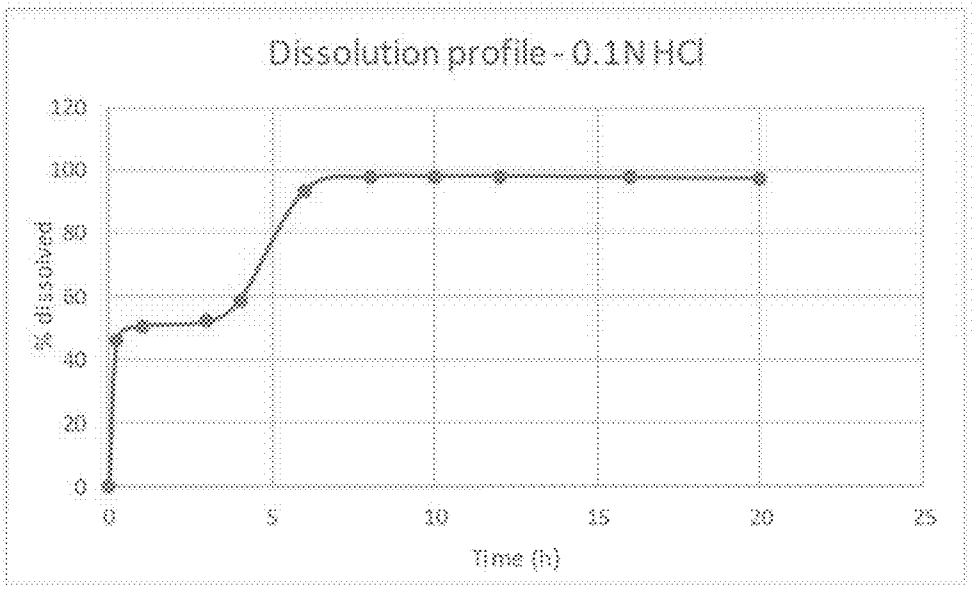


Figure 77

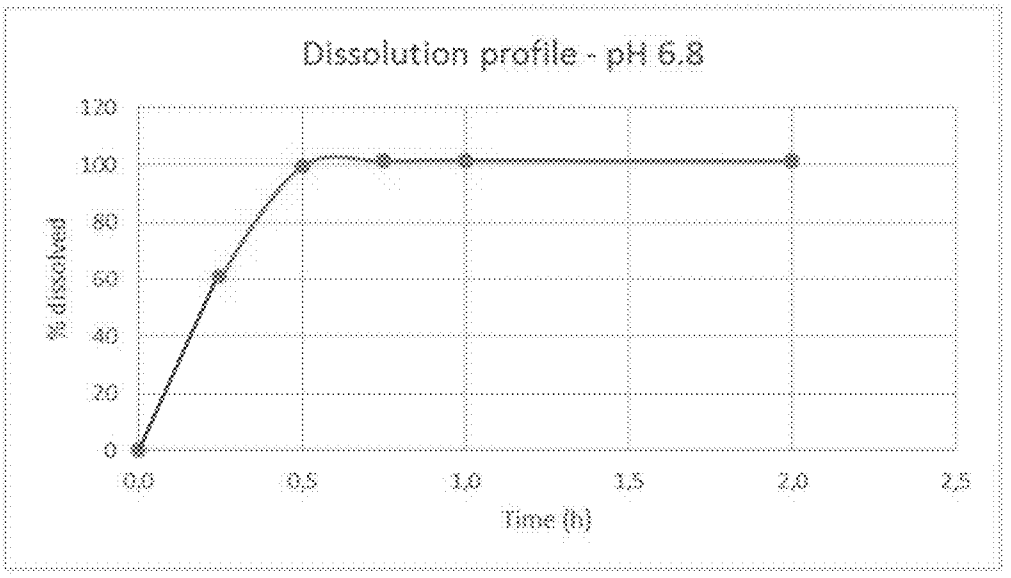


Figure 78

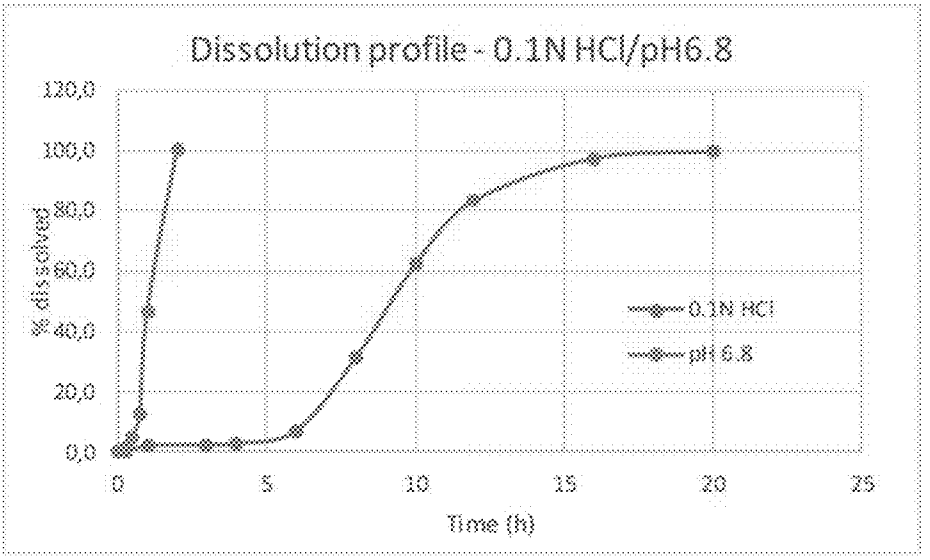


Figure 79

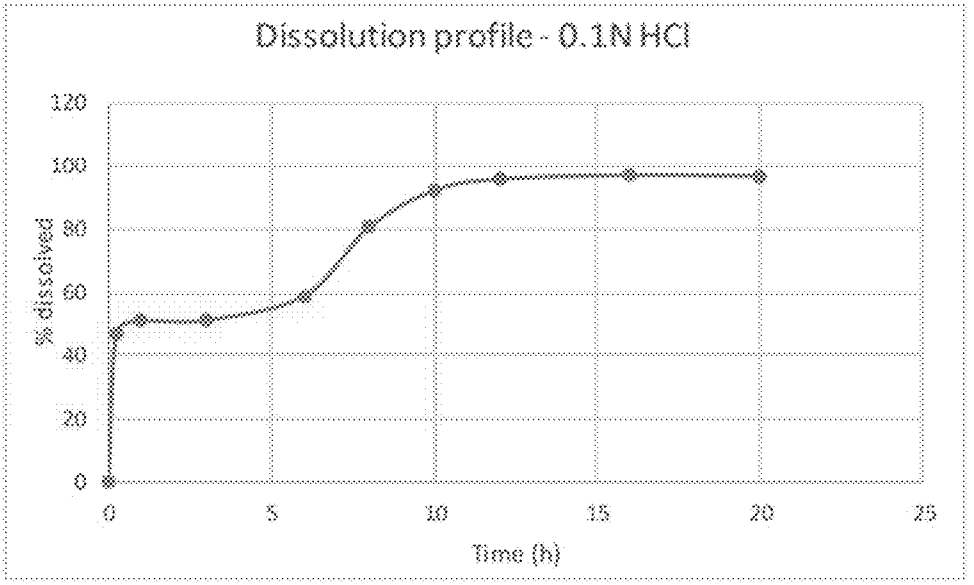


Figure 80

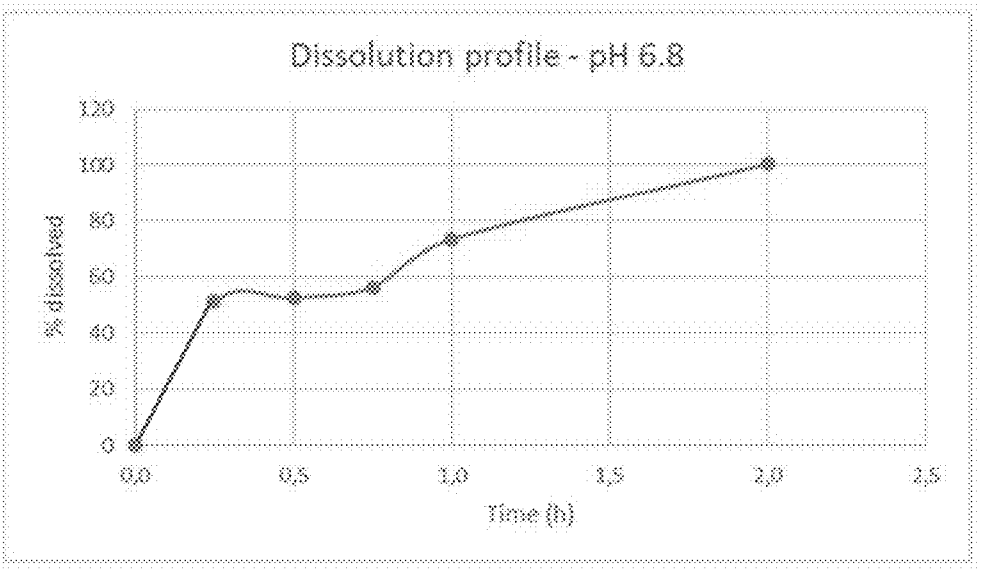


Figure 81

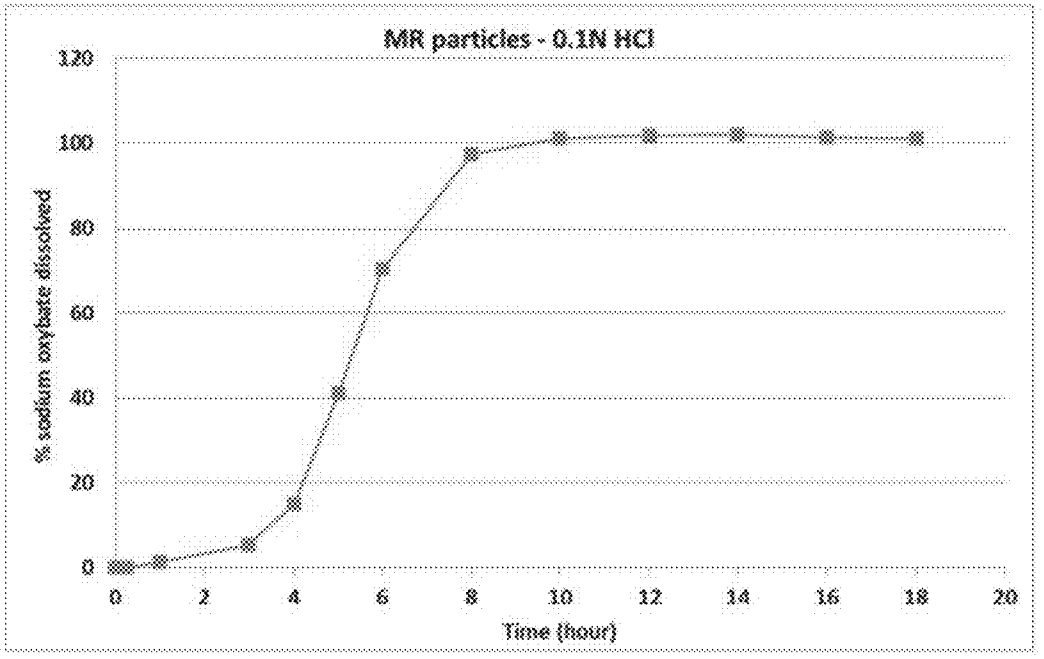


Figure 82

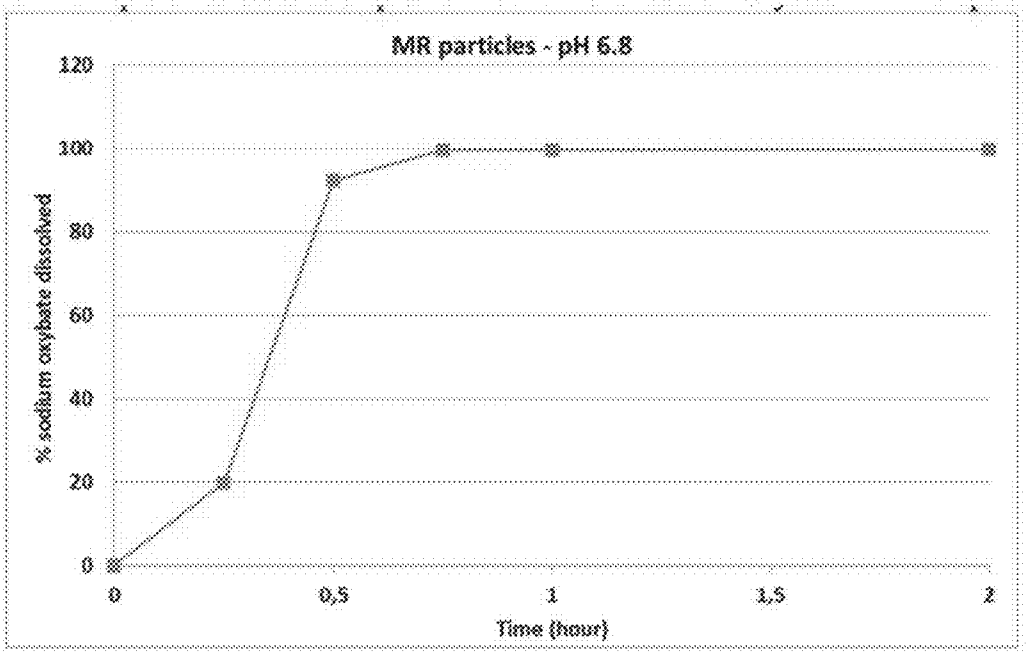


Figure 83

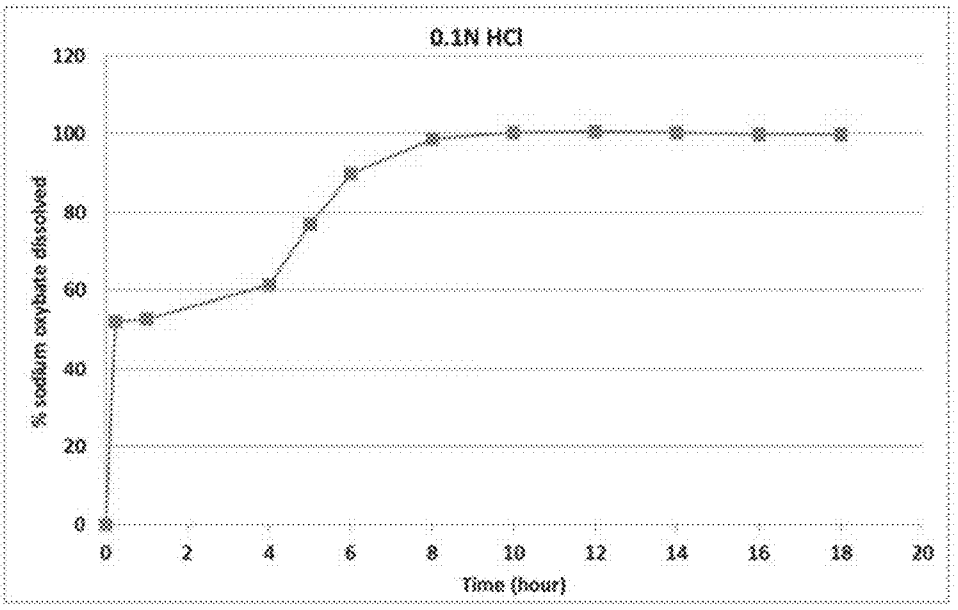


Figure 84

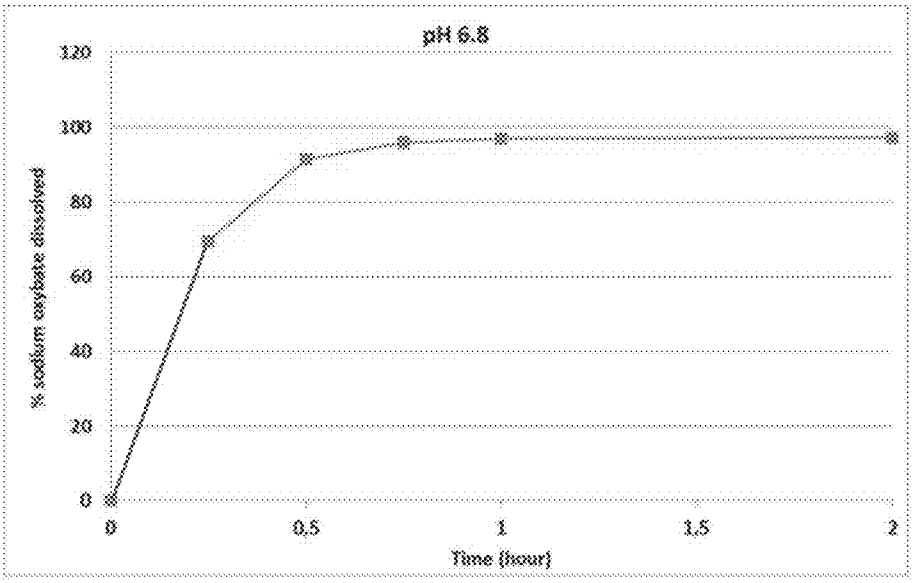


Figure 85

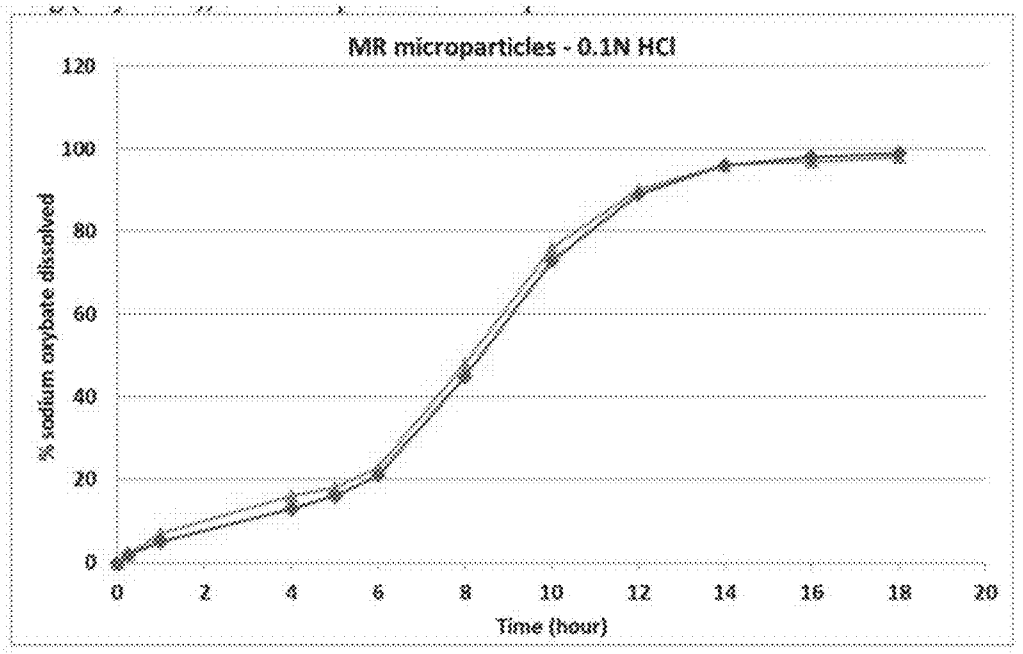


Figure 86

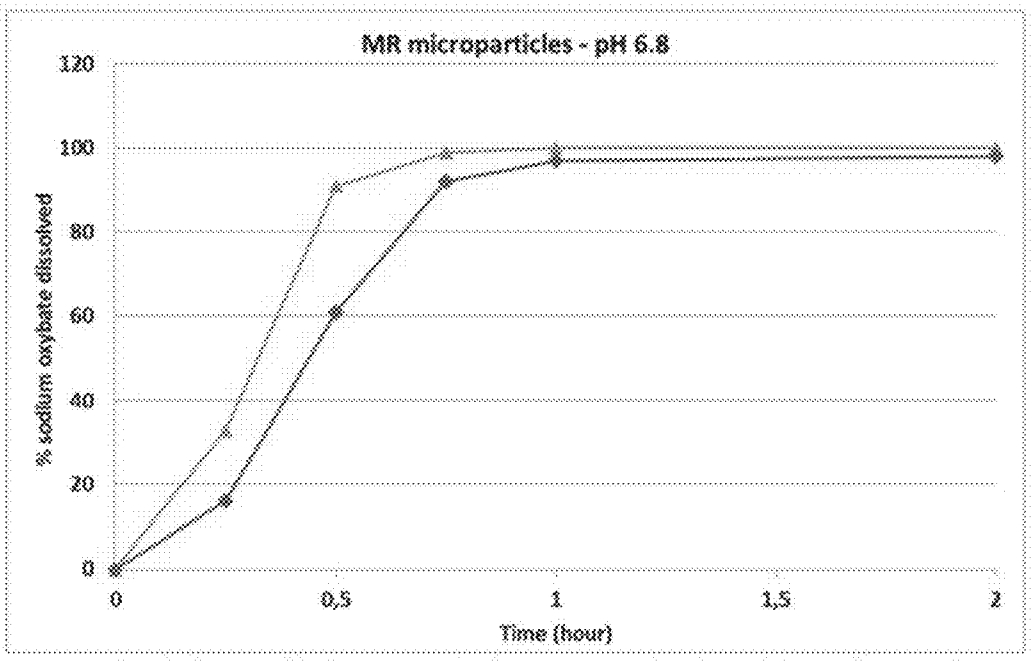


Figure 87

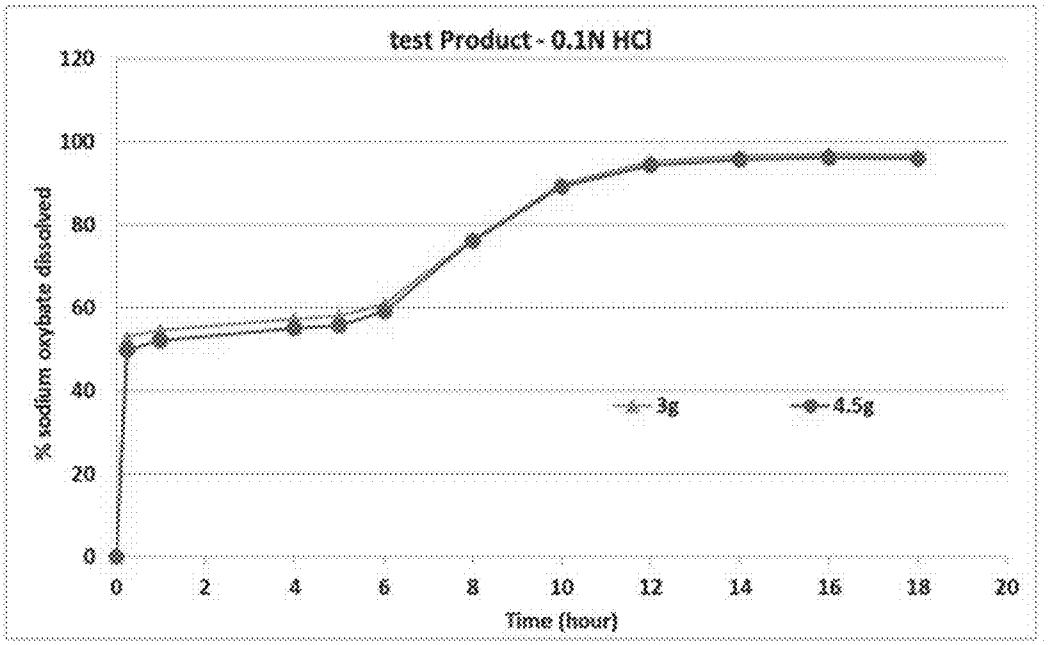


Figure 88

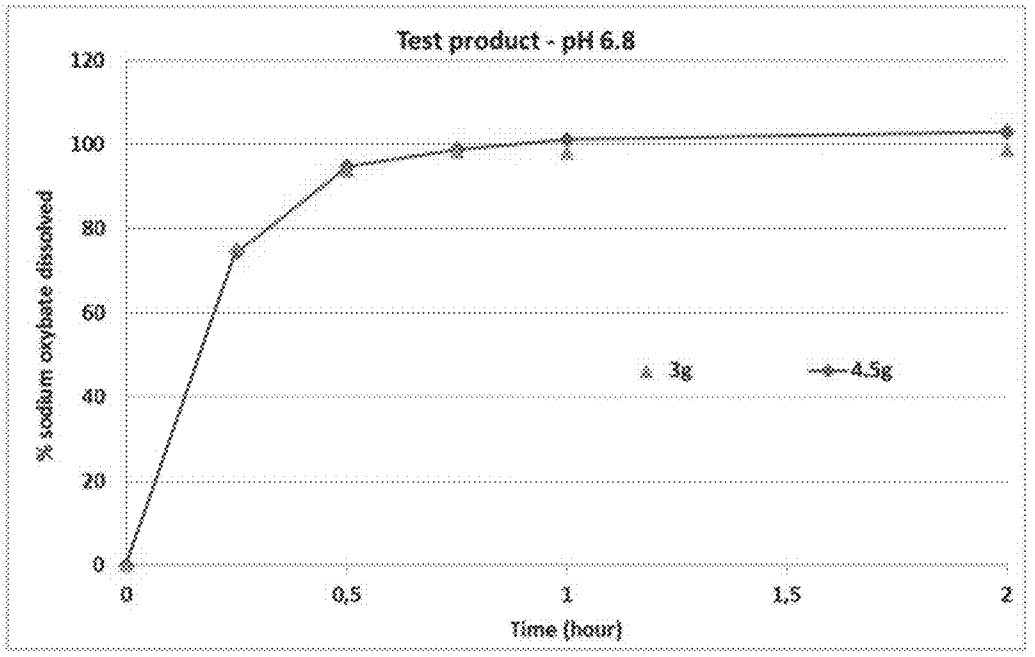

Test product - pH 6.8
% sodium oxybate dissolved
120
100
80
60
40
20
0
0
0,5
1
1,5
2
Time (hour)
3g
4,5g

Figure 89

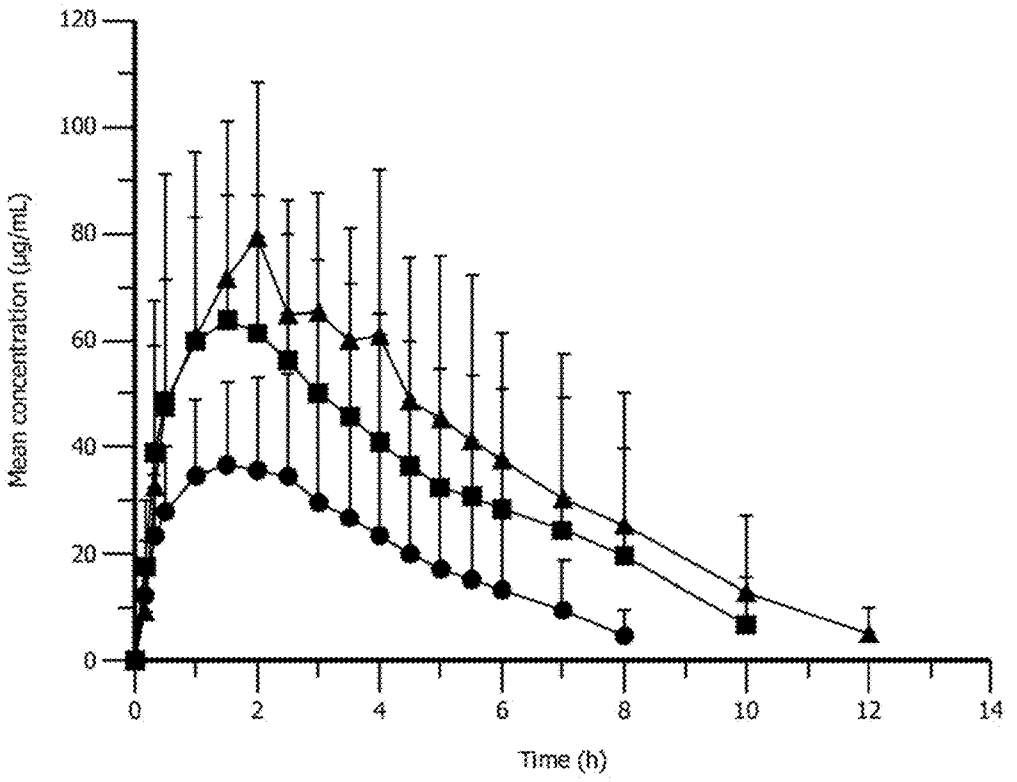

120
100
80
60
40
20
0
Mean concentration (µg/mL)
0
2
4
6
8
10
12
14
Time (h)

Figure 90

MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. application Ser. No. 16/281,235, filed Feb. 21, 2019, which is a continuation of U.S. application Ser. No. 15/655,924, filed Jul. 21, 2017, now U.S. Pat. No. 10,272,062, which claims priority to U.S. Provisional Application No. 62/365,812, filed Jul. 22, 2016, U.S. Provisional Application No. 62/399,413, filed Sep. 25, 2016, and U.S. Provisional Application No. 62/474,330, filed Mar. 21, 2017.

FIELD OF THE INVENTION

[0002] The present invention relates to modified release formulations of gamma-hydroxybutyrate having improved pharmacokinetic (PK) properties, and to therapeutic uses thereof.

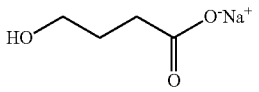
BACKGROUND

[0003] Narcolepsy is a devastating disabling condition. The cardinal symptoms are excessive daytime sleepiness (EDS), cataplexy (a sudden loss of muscle tone triggered by strong emotions, seen in approximately 60% of patients), hypnogogic hallucination (HH), sleep paralysis (SP), and disturbed nocturnal sleep (DNS). Other than EDS, DNS is the most common symptom seen among narcolepsy patients.

[0004] The diagnosis of narcolepsy rests in part on clinical grounds. When narcolepsy is suspected, it is standard practice to administer an overnight polysomnogram (PSG) followed by a multiple sleep latency test (MSLT) to document the rapid eye movement (REM) abnormality that characterizes the disorder. On the MSLT a mean sleep latency less than or equal to 8 minutes and two or more sleep onset REM periods (SOREMPs) are required to confirm a diagnosis of Type 1 or Type 2 narcolepsy. It is also possible, but infrequently preferred, that narcolepsy be diagnosed by measuring hypocretin in the cerebrospinal fluid (CSF) in cases where the PSG and/or MSLT is not completed. For these cases, a hypocretin concentration of less than 110 pg/nL confirms a narcolepsy Type 1 diagnosis.

[0005] One of the major treatments for narcolepsy is sodium oxybate, a neuroactive agent with a variety of Central Nervous System (CNS) pharmacological properties. The species is present endogenously in many tissues, where it acts as a neurotransmitter on a gamma-hydroxybutyrate (GHB) receptor (GHBR), and possesses neuromodulatory properties with significant effects on dopamine and gamma-Aminobutyric Acid (GABA). Studies have suggested that sodium oxybate improves Rapid Eye Movement Sleep (REM sleep, REMS) of narcoleptics in contrast to antidepressant drugs.

[0006] Sodium oxybate is also known as sodium 4-hydroxybutanoate, or gamma-hydroxybutyric acid sodium salt, and has the following chemical structure:



[0007] Sodium oxybate is marketed commercially in the United States as Xyrem®. The product is formulated as an immediate release liquid solution that is taken once immediately before bed, and a second time approximately 2.5 to 4 hours later, in equal doses. Sleep-onset can be dramatic and fast, and patients are advised to be sitting in bed when consuming the dose. The most commonly reported side effects are confusion, depressive syndrome, incontinence and sleepwalking.

[0008] When initiating treatment with sodium oxybate, careful titration up to an adequate level is essential both to obtain positive results and avoid adverse effects. The recommended starting dose is 4.5 g divided into 2 equal doses of 2.25 g, the first taken at bedtime and the second taken 2.5 to 4 hours later. The starting dosage can be decreased to 3.0 g/day or increased to as high as 9.0 g/day in increments of 1.5 g/day (0.75 g per dose). Two weeks are recommended between dosage adjustments to optimize reduction of daytime symptoms and minimize side effects. The ideal dose will provide an effective eight hours of sleep but, at the end of eight hours, very little of the drug will remain in the patient's bloodstream to affect the patient's wakefulness.

[0009] The requirement to take Xyrem® twice each night is a substantial inconvenience to narcolepsy patients. The patient must typically set an alarm to take the second dose, which can interrupt ongoing productive sleep. Several efforts have been made to provide a once-nightly modified release dosage form of sodium oxybate, but none has yet received approval from the United States Food and Drug Administration ("FDA") or proven effective in the clinic.

[0010] One of the biggest drawbacks of these once-nightly formulations is the reduction in bioavailability that occurs when sodium oxybate is formulated in a modified release dosage form, as measured by the blood concentration/time area under the curve ("AUC"). U.S. 2012/0076865 A1 by Allphin et al. ("Allphin"), for example, conducted two separate crossover bioavailability trials involving three separate modified release formulations and an immediate release solution, and reported the following bioavailability results:

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	0.6	4.50 (0.5, 4.75)	130.79	350.84	351.2
SD	0.27	0.13		31.52	116.74	116.74
CV %	21.93	22.61		24.1	33.27	33.24
Mean	1.19	0.58		127.3	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

-continued

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

Summary of OK 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		24.10	61.31	62.55
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

Treatment A: Two 3 g IR doses administered four hours apart
Treatment B: One 6 g CR dose administered at time zero (no IR component)
Treatment C: One 6 g CR dose administered at time zero (no IR component)
Treatment D: One 4 g dose including IR and CR fractions administered at time zero
Treatment E: One 8 g dose including IR and CR fractions administered at time zero

[0011] As can be seen, mean AUC_{inf}, which measures the total exposure of the body to sodium oxybate for a given dose, was significantly less for the doses having a modified release component when compared to the immediate release doses. Mean AUC_{inf} for Treatment B, which included the exact same dose of sodium oxybate as Treatment A, was only 56% of the mean AUC_{inf} for Treatment A; mean AUC_{inf} for Treatment C, which also included the same dose of sodium oxybate as Treatment A, was only 63% of the mean AUC_{inf} for Treatment A; mean AUC_{inf} for Treatment E was only 81% of the mean AUC_{inf} of Treatment A, even though Treatment E dosed 2 g more of sodium oxybate than Treatment A, which, compared to same dose, represented only 61% of the mean AUC_{inf} of Treatment A. Mean AUC_{inf} for Treatment D was only 22% of the mean AUC_{inf} of Treatment A, although Treatment D dosed 2 g less of sodium oxybate than Treatment A, which, compared to same dose, represented only 33% of the mean AUC_{inf} of Treatment A. As shown in FIGS. 12 and 14 of U.S. 2012/0076865 A1, Allphin's formulations also suffered from an excess of sodium oxybate remaining in the bloodstream at 8 hours.

[0012] U.S. Pat. No. 8,193,211 to Liang et al. ("Liang") reports even lower bioavailability from his once-nightly formulations. Liang developed several enterically coated delayed release formulations of sodium oxybate, and tested these formulations in dogs alongside an immediate release formulation to compare the relative pharmacokinetics (PK) of these formulations. The results of Liang's testing are reported below:

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%

DR1-w/ Acid: Two 1 g DR capsules administered at time zero
DR1-No Acid: Two 1 g DR capsules administered at time zero
IR: Two 1 g IR capsules administered at time zero
DR2: Two 1 g DR capsules administered at time zero

[0013] As can be seen, by encapsulating the sodium oxybate in an enteric/delayed release coating, Liang decreased the AUC of the sodium oxybate significantly. One of the formulations, DR1-w/ Acid, had a relative bioavailability of only 22% compared to the immediate release dosage form. DR2 had the greatest relative bioavailability, but still only 53% compared to the immediate release dosage form. One can easily calculate that any of the envisioned combinations of immediate release (IR) components and delayed release (DR) components as described in col. 5 lines 3 to 28 of U.S. Pat. No. 8,193,211 will not give a relative bioavailability greater than 78%.

[0014] All of these formulations are inconvenient for at least two reasons: (1) the low relative bioavailability necessitates an increase in the dose compared to current IR treatments which already require a large dose (4.5 to 9 g a day), and (2) when provided in the form of pills, a patient must swallow around 4 to 9 pills per dose, which is a serious inconvenience for the patient and potential drawback for patient compliance.

[0015] Various other techniques are known for formulating modified release dosage forms including, for example, the techniques described in U.S. Pat. No. 8,101,209 to Legrand et al. ("Legrand"). Legrand provides a system ensuring that the active ingredient is released with certainty from the modified release dosage form by means of a dual mechanism of "time-dependent" and "pH-dependent" release. Legrand did not describe any dosage forms for delivering sodium oxybate or other forms of gamma-hydroxybutyrate.

[0016] Another drawback of Xyrem® is the high level of the daily dose, generally 7.5 g or 9 g of sodium oxybate taken daily over long periods of time. This represents a very high sodium intake which is not recommended in persons with high blood pressure, risk of cardiovascular disease, stroke or coronary heart disease (See WHO. Guideline: Sodium intake for adults and children. Geneva, World Health Organization (WHO), 2012.).

[0017] Accordingly, one object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that are administered only once at bed-time with improved dissolution and pharmacokinetic profiles.

[0018] Another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that optimize the bioavailability of the gamma-hydroxybutyrate, and roughly approximate the bioavailability of an equal dose of an immediate release liquid solution of sodium oxybate administered twice nightly.

[0019] Still another object of the present invention is to provide once-nightly modified release formulations of gamma-hydroxybutyrate that roughly approximate or exceed the bioavailability of an equal dose of an immediate release solution of sodium oxybate administered twice nightly, across the entire therapeutic range of sodium oxybate doses.

[0020] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate which, 8 hours after administration, produce very little residual drug content in the bloodstream of most patients but still similar to the one observed after administration of an equal dose of an immediate release liquid solution of sodium oxybate administered twice nightly.

[0021] Yet another object of the present invention is to improve the therapeutic effectiveness and safety profile of gamma-hydroxybutyrate based on novel dissolution and pharmacokinetic profiles.

[0022] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that yield a similar pharmacokinetic profile compared to an immediate release liquid solution of sodium oxybate administered twice nightly while potentially giving a reduced dose.

[0023] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that allow once daily administration and reduced dose compared to the commercial treatment Xyrem®.

[0024] Yet another object of the present invention is to provide a convenient dosage form of gamma-hydroxybutyrate that can be easily swallowed.

[0025] Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that are administered only once at bed-time with improved dissolution and pharmacokinetic profiles and reduced sodium content compared to an immediate release liquid solution of sodium oxybate administered twice nightly.

SUMMARY OF INVENTION

[0026] As the prior art demonstrates, it is extremely difficult to find a modified release formulation of gamma-hydroxybutyrate which, when administered only once nightly, has a comparable bioavailability to an immediate release liquid solution of sodium oxybate administered twice nightly. Even if such a formulation could be found, it probably still would not be satisfactory because the dose of gamma-hydroxybutyrate differs among individuals, and the size of the dose affects the amount of drug absorbed through the GI tract. I.e., even if the prior art formulations achieved comparable bioavailability at one dose—which they do not—they would not be comparable at other doses.

[0027] The inventors have discovered a novel relationship between the in vitro release profile of gamma-hydroxybutyrate modified release formulations and in vivo absorption which permits, for the first time, a modified release formulation of gamma-hydroxybutyrate that approximates the bioavailability of a twice-nightly equipotent immediate release liquid solution of sodium oxybate, and that does so across a range of therapeutic doses. In particular, the inventors have discovered that a modified release formulation of gamma-hydroxybutyrate that rapidly releases half of its gamma-hydroxybutyrate in 0.1N hydrochloric acid dissolution medium, and rapidly releases the other half of its gamma-hydroxybutyrate in phosphate buffer pH 6.8 dissolution medium, approximates or exceeds the in vivo bioavailability of an equipotent immediate release liquid solution of sodium oxybate administered twice nightly. This can be seen by comparing the formulations of Examples 1 and 4, which satisfy the dissolution requirements of the present invention and achieve the necessary bioavailability for a commercial formulation, with the Comparative formulation of Example 7, which exhibited a dissolution profile similar to prior art dissolution profiles, and did not achieve the necessary bioavailability for a commercial formulation.

[0028] This phenomenon is observed especially with higher doses of gamma-hydroxybutyrate. For example, the inventors have discovered that a modified release composition of gamma-hydroxybutyrate according to the invention administered once approximately two hours after a standardized evening meal at the dose equivalent to 7.5 g of sodium oxybate results in a similar pharmacokinetic profile as an immediate release liquid solution of sodium oxybate given in two separate equal doses of 4.5 g of sodium oxybate each administered at t_0 and t_{4h}.

[0029] The modified release formulations of gamma-hydroxybutyrate preferably have both immediate release and modified release portions. The release of gamma-hydroxybutyrate from the immediate release portion is practically uninhibited, and occurs almost immediately in 0.1N hydrochloric acid dissolution medium. In contrast, while the modified release portion also preferably releases its gamma-hydroxybutyrate almost immediately when fully triggered, the release is not triggered until a predetermined lag-time or the drug is subjected to a suitable dissolution medium such as a phosphate buffer pH 6.8 dissolution medium. Without wishing to be bound by any theory, it is believed that this rapid release in two dissolution media compresses the blood concentration vs. time curve in vivo, resulting in a relative bioavailability of gamma-hydroxybutyrate comparable to or greater than an equipotent dose of an immediate-release liquid solution of sodium oxybate administered twice nightly.

[0030] Formulations that achieve this improved bioavailability can be described using several different pharmacokinetic and in vitro dissolution parameters. In a first principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL.

[0031] In a second principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL, and a mean C_{8h} that is

from 50% to 130% of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0032] In a third principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0033] In a fourth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0034] In a fifth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0035] In a sixth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and (b) the formulation releases (i) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (ii) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0036] In a seventh principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0037] In an eighth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and (d) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0038] In a ninth principal embodiment, the invention provides a modified release formulation of gamma-hydroxy-

butyrate, preferably comprising immediate release and modified release portions, wherein 4.5 g, 6 g, 7.5 g, and 9 g doses of the formulation have been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0039] In a tenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein 4.5 g and 9 g doses of the formulation have been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0040] In an eleventh principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 6.0 g or 7.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **12** or FIG. **13** for the corresponding strength.

[0041] In a twelfth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **22**.

[0042] In a thirteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **7** and FIG. **8**.

[0043] In a fourteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **20** and FIG. **21**.

[0044] In a fifteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein said modified release portion yields a dissolution profile substantially as depicted in FIG. **3** or FIG. **16**.

[0045] In a sixteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **25** and FIG. **26**.

[0046] In a seventeenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **27** and FIG. **28**.

[0047] In an eighteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate yielding a dissolution profile substantially as shown in any one of FIGS. **29** through **89**.

[0048] A nineteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 7.5 g or 9.0 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **90** for the corresponding strength.

[0049] A twentieth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **26** and FIG. **28**.

[0050] Still further embodiments relate to methods of using the formulations of the present invention to treat narcolepsy and associated disorders and symptoms, and to physical aspects of the formulations of the present invention. Additional principal embodiments and sub-embodiments thereto will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION OF THE FIGURES

[0051] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0052] FIG. **1** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 1.

[0053] FIG. **2** plots a time release dissolution profile of IR microparticles of gamma-hydroxybutyrate of Example 1 (♦) and 1bis (■) in a 0.1N HCl dissolution medium.

[0054] FIG. **3** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 1 in two sequential dissolution media (0.1 N HCl/phosphate buffer pH 6.8).

[0055] FIG. **4** plots a time release dissolution profile of MR microparticles (▲ symbols) of Example 1 in two sequential dissolution media (0.1 N HCl/phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (• symbols).

[0056] FIG. **5** plots a time release dissolution profile of the finished formulation of Example 1 in deionized water.

[0057] FIG. **6** plots a time release dissolution profile of the finished composition of Example 1 in deionized water (▲ symbols), overlaid against dissolution profile described in FIG. 2 of USP 2012/0076865 (• symbols).

[0058] FIG. **7** plots time release dissolution profiles in 0.1N HCl of four separate batches of finished compositions produced in accordance with Example 1 or Example 1bis.

[0059] FIG. **8** plots time release dissolution profiles in phosphate buffer pH 6.8 of four separate batches of finished compositions produced in accordance with Example 1 or Example 1bis.

[0060] FIG. **9** plots time release dissolution profiles in 0.1N HCl of MR microparticles of gamma-hydroxybutyrate produced in accordance with Example 1 at 75 rpm (■ symbols) and 100 rpm (▲ symbols).

[0061] FIG. **10** plots time release dissolution profiles in 0.1N HCl of finished composition produced in accordance with Example 1 performed with paddle rotation speed set at 75 rpm (■ symbols) and 100 rpm (▲ symbols).

[0062] FIG. **11** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time for two different modified release formulations of gamma-hydroxybutyrate tested in vivo according to the methods of Example 3. Time profiles are given for a 4.5 g dose of the finished composition of Example 1bis administered once (• symbols) (N=26) and a 4.5 g dose of Xyrem® administered in two divided doses (– symbols) (N=15).

[0063] FIG. **12** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time after a Single Oral Administration of 4.5 g (• symbols) and 6 g (▲ symbols) of finished composition of Example 1bis in the same 7 subjects tested in vivo according to the methods of Example 3.

[0064] FIG. **13** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time of three separate doses of finished composition prepared according to Example 1bis tested in vivo according to the methods of Example 3. Mean time profiles are given for a single oral administration of 4.5 g (N=26) (•), 6.0 g (N=19) (▲) or 7.5 g (■) doses (N=11).

[0065] FIG. **14** plots the mean plasma gamma-hydroxybutyrate Concentrations (microgram/mL) of a Single dose of 7.5 g (■) of finished composition prepared according to Example 1bis compared to 2×4.5 g Xyrem® post-fed (Source NDA 21-196 review).

[0066] FIG. **15** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 4.

[0067] FIG. **16** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 4 in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8).

[0068] FIG. **17** plots a time release dissolution profile of MR microparticles (▲ symbols) of Example 4 in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (• symbols).

[0069] FIG. **18** plots a time release dissolution profile of the finished composition of Example 4 in deionized water.

[0070] FIG. **19** plots a time release dissolution profile of the finished composition of Example 4 in deionized water (• symbols), overlaid against dissolution profile described in FIG. 2 of USP 2012/0076865 (▲ symbols).

[0071] FIG. **20** plots time release dissolution profiles in 0.1N HCl of three separate batches of finished compositions produced in accordance with Example 4 or 4bis.

[0072] FIG. **21** plots a time release dissolution profile in phosphate buffer pH 6.8 of a finished composition produced in accordance with Example 4.

[0073] FIG. **22** plots mean plasma gamma-hydroxybutyrate concentration (microgram/mL) time profiles after a Single Dose of 4.5 g (■) of finished composition of Example 4bis, N=15 compared to 2×2.25 g Xyrem® post fed, N=15.

[0074] FIG. **23** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 7.

[0075] FIG. **24** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 7 (▲ symbols) in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (• symbols).

[0076] FIG. **25** plots the Min (■) and Max (▲) values of a preferred dissolution profile in 0.1N HCl of finished composition according to the invention.

[0077] FIG. **26** plots the Min (■) and Max (▲) values of a preferred dissolution profile in phosphate buffer pH 6.8 of finished composition according to the invention.

[0078] FIG. **27** plots the Min (■) and Max (▲) values of another preferred dissolution profile in phosphate buffer pH 6.8 of finished composition according to the invention.

[0079] FIG. **28** plots the Min (■) and Max (▲) values of another preferred dissolution profile in 0.1N HCl of finished composition according to the invention.

[0080] FIG. **29** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus 2 for the formulation of Example 9.1 5 minutes and 15 minutes after reconstitution in water.

[0081] FIG. **30** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus 2 for the formulation of Example 9.2 5 minutes and 15 minutes after reconstitution in water.

[0082] FIG. **31** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus 2 for the formulation of Example 9.3 5 minutes and 15 minutes after reconstitution in water.

[0083] FIG. **32** depicts the dissolution profile determined in 0.1N HCl using a USP apparatus 2 of a 9 g dose of the formulation of Example 10 with and without rinsing.

[0084] FIG. **33** depicts the dissolution profile of the MR portion of the formulation of Example 11a in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0085] FIG. **34** depicts the dissolution profile of the formulation of Example 11a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0086] FIG. **35** depicts the dissolution profile of the formulation of Example 11a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0087] FIG. **36** depicts the dissolution profile of the MR portion of the formulation of Example 11b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0088] FIG. **37** depicts the dissolution profile of the formulation of Example 11b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0089] FIG. **38** depicts the dissolution profile of the formulation of Example 11b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0090] FIG. **39** depicts the dissolution profile of the formulation of Example 11c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0091] FIG. **40** depicts the dissolution profile of the formulation of Example 11c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0092] FIG. **41** depicts the dissolution profile of the MR portion of the formulation of Example 12a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0093] FIG. **42** depicts the dissolution profile of the formulation of Example 12a using a USP apparatus 2 in 0.1N HCl.

[0094] FIG. **43** depicts the dissolution profile of the formulation of Example 12b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0095] FIG. **44** depicts the dissolution profile of the formulation of Example 12b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0096] FIG. **45** depicts the dissolution profile of the MR portion of the formulation of Example 13 in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0097] FIG. **46** depicts the dissolution profile of the formulation of Example 13 in 900 ml of 0.1N HCl using a USP apparatus 2.

[0098] FIG. **47** depicts the dissolution profile of the formulation of Example 13 in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0099] FIG. **48** depicts the dissolution profile of the MR portion of the formulation of Example 14 in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0100] FIG. **49** depicts the dissolution profile of the formulation of Example 14 in 900 ml of 0.1N HCl using a USP apparatus 2.

[0101] FIG. **50** depicts the dissolution profile of the formulation of Example 14 in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0102] FIG. **51** depicts the dissolution profile of the MR portion of the formulation of Example 15a (coating weight 35%) in 900 ml of 0.1N HCl using a USP apparatus 2.

[0103] FIG. **52** depicts the dissolution profile of the MR portion of the formulation of Example 15a (coating weight 50%) in 900 ml of 0.1N HCl using a USP apparatus 2.

[0104] FIG. **53** depicts the dissolution profile of the formulation of Example 15a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0105] FIG. **54** depicts the dissolution profile of the MR portion of the formulation of Example 15b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0106] FIG. **55** depicts the dissolution profile of the formulation of Example 15b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0107] FIG. **56** depicts the dissolution profile of the formulation of Example 15b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0108] FIG. **57** depicts the dissolution profile of the MR portion of the formulation of Example 15c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0109] FIG. **58** depicts the dissolution profile of the formulation of Example 15c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0110] FIG. **59** depicts the dissolution profile of the formulation of Example 15c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0111] FIG. **60** depicts the dissolution profile of the MR portion of the formulation of Example 15d in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0112] FIG. **61** depicts the dissolution profile of the formulation of Example 15d in 900 ml of 0.1N HCl using a USP apparatus 2.

[0113] FIG. **62** depicts the dissolution profile of the formulation of Example 15d in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0114] FIG. **63** depicts the dissolution profile of the MR portion of the formulation of Example 16a in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0115] FIG. **64** depicts the dissolution profile of the formulation of Example 16a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0116] FIG. **65** depicts the dissolution profile of the formulation of Example 16a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0117] FIG. **66** depicts the dissolution profile of the MR portion of the formulation of Example 16b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0118] FIG. **67** depicts the dissolution profile of the formulation of Example 16b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0119] FIG. **68** depicts the dissolution profile of the formulation of Example 16b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0120] FIG. **69** depicts the dissolution profile of the MR portion of the formulation of Example 16c in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0121] FIG. **70** depicts the dissolution profile of the formulation of Example 16c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0122] FIG. **71** depicts the dissolution profile of the formulation of Example 16c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0123] FIG. **72** depicts the dissolution profile of the MR portion of the formulation of Example 16d in 900 ml of 0.1N HCl using a USP apparatus 2.

[0124] FIG. **73** depicts the dissolution profile of the MR portion of the formulation of Example 17a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0125] FIG. **74** depicts the dissolution profile of the formulation of Example 17a in 900 ml of 0.1N HCl using a USP apparatus 2.

[0126] FIG. **75** depicts the dissolution profile of the formulation of Example 17a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0127] FIG. **76** depicts the dissolution profile of the MR portion of the formulation of Example 17b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0128] FIG. **77** depicts the dissolution profile of the formulation of Example 17b in 900 ml of 0.1N HCl using a USP apparatus 2.

[0129] FIG. **78** depicts the dissolution profile of the formulation of Example 17b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0130] FIG. **79** depicts the dissolution profile of the MR portion of the formulation of Example 17c in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0131] FIG. **80** depicts the dissolution profile of the formulation of Example 17c in 900 ml of 0.1N HCl using a USP apparatus 2.

[0132] FIG. **81** depicts the dissolution profile of the formulation of Example 17c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2.

[0133] FIG. **82** depicts a preferred dissolution profile of sodium oxybate MR microparticles in 900 ml 0.1N HCl using a USP apparatus 2 at 75 rpm.

[0134] FIG. **83** depicts a preferred dissolution profile of sodium oxybate MR microparticles in 900 ml pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2 at 75 rpm.

[0135] FIG. **84** depicts a preferred dissolution profile of a sodium oxybate finished formulation comprising IR and MR microparticles in 900 ml 0.1N HCl using a USP apparatus 2 at 75 rpm.

[0136] FIG. **85** depicts a preferred dissolution profile of a sodium oxybate finished formulation comprising IR and MR microparticles in 900 ml pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2 at 75 rpm.

[0137] FIG. **86** is a dissolution profile in 0.1N HCl of two separate batches of the sodium oxybate MR microparticles present in the finished composition of Example 18.

[0138] FIG. **87** is a dissolution profile in phosphate buffer pH 6.8 of two separate batches of the sodium oxybate MR microparticles present in the finished composition of Example 18.

[0139] FIG. **88** is a dissolution profile in 0.1N HCl of two unit doses of 3 g (▲ symbols) and 4.5 g (• symbols) of the finished composition of Example 18.

[0140] FIG. **89** is a dissolution profile in phosphate buffer pH 6.8 of two unit doses of 3 g (▲ symbols) and 4.5 g (• symbols) of the finished composition of Example 18.

[0141] FIG. **90** plots mean plasma gamma-hydroxybutyrate concentrations (microgram/mL)+SD—time profiles after a single oral administration of 4.5 g (• symbols), 7.5 g (■ symbols) and 9 g (▲ symbols) of the finished composition of Example 18.

DETAILED DESCRIPTION OF THE INVENTION

[0142] The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein.

Definitions and Use of Terms

[0143] Wherever an analysis or test is required to understand a given property or characteristic recited herein, it will be understood that the analysis or test is performed in accordance with applicable guidances, draft guidances, regulations and monographs of the United States Food and Drug Administration ("FDA") and United States Pharmacopoeia ("USP") applicable to drug products in the United States in force as of Nov. 1, 2015 unless otherwise specified. Clinical endpoints can be judged with reference to standards adopted by the American Academy of Sleep Medicine, including standards published at C Iber, S Ancoli-Israel, A Chesson, SF Quan. The AASM Manual for the Scoring of Sleep and Associated Events. Westchester, Ill.: American Academy of Sleep Medicine; 2007.

[0144] When a pharmacokinetic comparison is made between a formulation described or claimed herein and a reference product, it will be understood that the comparison is preferably performed in a suitable designed cross-over trial, although it will also be understood that a cross-over trial is not required unless specifically stated. It will also be understood that the comparison can be made either directly or indirectly. For example, even if a formulation has not been tested directly against a reference formulation, it can still satisfy a comparison to the reference formulation if it has been tested against a different formulation, and the comparison with the reference formulation can be deduced therefrom.

[0145] As used in this specification and in the claims which follow, the singular forms "a," "an" and "the" include plural referents unless the context dictates otherwise. Thus, for example, reference to "an ingredient" includes mixtures of ingredients, reference to "an active pharmaceutical agent" includes more than one active pharmaceutical agent, and the like.

[0146] "Bioavailability" means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

[0147] "Relative bioavailability" or "Rel BA" or "RBA" means the percentage of mean AUC_{inf} of the tested product relative to the mean AUC_{inf} of the reference product. Unless otherwise specified, relative bioavailability refers to the percentage of the mean AUC_{inf} observed for a full dose of the test product relative to the mean AUC_{inf} observed for two ½-doses of an immediate release liquid solution administered four hours apart.

[0148] "Bioequivalence" means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or

pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

[0149] When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically and physically possible. Thus, for example, if a formulation may contain from 1 to 10 weight parts of a particular ingredient, or 2 to 8 parts of a particular ingredient, it will be understood that the formulation may also contain from 2 to 10 parts of the ingredient. In like manner, if a formulation may contain greater than 1 or 2 weight parts of an ingredient and up to or 9 weight parts of the ingredient, it will be understood that the formulation may contain 1-10 weight parts of the ingredient, 2-9 weight parts of the ingredient, etc. unless otherwise specified, the boundaries of the range (lower and upper ends of the range) are included in the claimed range.

[0150] In like manner, when various sub-embodiments of a senior (i.e. principal) embodiment are described herein, it will be understood that the sub-embodiments for the senior embodiment can be combined to define another sub-embodiment. Thus, for example, when a principal embodiment includes sub-embodiments 1, 2 and 3, it will be understood that the principal embodiment can be further limited by any one of sub-embodiments 1, 2 and 3, or any combination of sub-embodiments 1, 2 and 3 that is mathematically and physically possible. In like manner, it will be understood that the principal embodiments described herein can be combined in any manner that is mathematically and physically possible, and that the invention extends to such combinations.

[0151] When used herein the term "about" or "substantially" or "approximately" will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength due to manufacturing variation and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered bioequivalent to the recited strength, as described in FDA's March 2003 Guidance for Industry on Bioavalability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations.

[0152] When used herein the term "gamma-hydroxybutyrate" or GHB, unless otherwise specified, refers to the free base of gamma hydroxy-butyrate, a pharmaceutically acceptable salt of gamma-hydroxybutyric acid, and combinations thereof, their hydrates, solvates, complexes or tautomers forms. Gamma-hydroxybutyric acid salts can be selected from the sodium salt of gamma-hydroxybutyric acid or sodium oxybate, the potassium salt of gamma-hydroxybutyric acid, the magnesium salt of gamma-hydroxybutyric acid, the calcium salt of gamma-hydroxybutyric acid, the lithium salt of gamma-hydroxybutyric, the tetra ammonium salt of gamma-hydroxybutyric acid or any other pharmaceutically acceptable salt forms of gamma-hydroxybutyric acid.

[0153] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. The term "formulation" or "composition" refers to the quantitative and qualitative characteristics of a drug product or dosage form prepared in accordance with the current invention.

[0154] As used herein the doses and strengths of gamma-hydroxybutyrate are expressed in equivalent-gram (g) weights of sodium oxybate unless stated expressly to the contrary. Thus, when considering a dose of gamma-hydroxybutyrate other than the sodium salt of gamma-hydroxybutyrate, one must convert the recited dose or strength from sodium oxybate to the gamma-hydroxybutyrate under evaluation. Thus, if an embodiment is said to provide a 4.5 g dose of gamma-hydroxybutyrate, because the form of gamma-hydroxybutyrate is not specified, it will be understood that the dose encompasses a 4.5 g dose of sodium oxybate, a 5.1 g dose of potassium gamma-hydroxybutyrate (assuming a 126.09 g/mol MW for sodium oxybate and a 142.20 g/mol MW for potassium gamma-hydroxybutyrate), and a 3.7 g dose of the free base (assuming a 126.09 g/mol MW for sodium oxybate and a 104.1 g/mol MW for the free base of gamma-hydroxybutyrate), or by the weight of any mixture of salts of gamma-hydroxybutyric acid that provides the same amount of GHB as 4.5 g of sodium oxybate.

[0155] As used herein "microparticle" means any discreet particle of solid material. The particle can be made of a single material or have a complex structure with core and shells and be made of several materials. The terms "microparticle", "particle", "microspheres" or "pellet" are interchangeable and have the same meaning. Unless otherwise specified, the microparticle has no particular particle size or diameter and is not limited to particles with volume mean diameter D(4,3) below 1 mm.

[0156] As used herein, the "volume mean diameter D(4,3)" is calculated according to the following formula:

$$D(4,3)=\Sigma(d^4_i \cdot n_i)/\Sigma(d^3_i \cdot n_i)$$

wherein the diameter d of a given particle is the diameter of a hard sphere having the same volume as the volume of that particle.

[0157] As used herein, the terms "finished composition", "finished formulation" or "formulation" are interchangeable and designate the modified release formulation of gamma-hydroxybutyrate preferably comprising modified release microparticles of gamma-hydroxybutyrate, immediate release microparticles of gamma-hydroxybutyrate, and any other excipients.

[0158] As used herein and in the claims that follow, an "immediate release (IR) portion" of a formulation includes physically discreet portions of a formulation, mechanistically discreet portions of a formulation, and pharmacokinetically discreet portions of a formulation that lend to or support a defined IR pharmacokinetic characteristic. Thus, for example, any formulation that releases active ingredient at the rate and extent required of the immediate release portion of the formulations of the present invention includes an "immediate release portion," even if the immediate release portion is physically integrated in what might otherwise be considered an extended release formulation. Thus, the IR portion can be structurally discreet or structurally indiscreet from (i.e. integrated with) the MR portion. In a preferred embodiment, the IR portion and MR portion are provided as particles, and in an even more preferred sub-embodiment the IR portion and MR portion are provided as particles discreet from each other.

[0159] As used here in, "immediate release formulation" or "immediate release portion" refers to a composition that releases at least 80% of its gamma-hydroxybutyrate in 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in a 0.1N HCl dissolution medium at a temperature of 37° C. and a paddle speed of 75 rpm.

[0160] In like manner, a "modified-release (MR) portion" includes that portion of a formulation or dosage form that lends to or supports a particular MR pharmacokinetic characteristic, regardless of the physical formulation in which the MR portion is integrated. The modified release drug delivery systems are designed to deliver drugs at a specific time or over a period of time after administration, or at a specific location in the body. The USP defines a modified release system as one in which the time course or location of drug release or both, are chosen to accomplish objectives of therapeutic effectiveness or convenience not fulfilled by conventional IR dosage forms. More specifically, MR solid oral dosage forms include extended release (ER) and delayed-release (DR) products. A DR product is one that releases a drug all at once at a time other than promptly after administration. Typically, coatings (e.g., enteric coatings) are used to delay the release of the drug substance until the dosage form has passed through the acidic medium of the stomach. An ER product is formulated to make the drug available over an extended period after ingestion, thus allowing a reduction in dosing frequency compared to a drug presented as a conventional dosage form, e.g. a solution or an immediate release dosage form. For oral applications, the term "extended-release" is usually interchangeable with "sustained-release", "prolonged-release" or "controlled-release".

[0161] Traditionally, extended-release systems provided constant drug release to maintain a steady concentration of drug. For some drugs, however, zero-order delivery may not be optimal and more complex and sophisticated systems have been developed to provide multi-phase delivery. One can distinguish among four categories of oral MR delivery systems: (1) delayed-release using enteric coatings, (2) site-specific or timed release (e.g. for colonic delivery), (3) extended-release (e.g., zero-order, first-order, biphasic release, etc.), and (4), programmed release (e.g., pulsatile, delayed extended release, etc.) See *Modified Oral Drug Delivery Systems* at page 34 in Gibaldi's DRUG DELIVERY SYSTEMS IN PHARMACEUTICAL CARE, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, 2007 and *Rational Design of Oral Modified-release Drug Delivery Systems* at page 469 in DEVELOPING SOLID ORAL DOSAGE FORMS: PHARMACEUTICAL THEORY AND PRACTICE, Academic Press, Elsevier, 2009. As used herein, "modified release formulation" or "modified release portion" in one embodiment refers to a composition that releases its gamma-hydroxybutyrate according a multiphase delivery that is comprised in the fourth class of MR products, e.g. delayed extended release. As such it differs from the delayed release products that are classified in the first class of MR products.

[0162] As used herein the terms "coating", "coating layer," "coating film," "film coating" and like terms are interchangeable and have the same meaning. The terms refer to the coating applied to a particle comprising the gamma-hydroxybutyrate that controls the modified release of the gamma-hydroxybutyrate.

[0163] In all pharmacokinetic testing described herein, unless otherwise stated, the dosage form, or the initial dosage form if the dosing regimen calls for more than one administration, is administered approximately two hours after consumption of a standardized dinner consisting of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

[0164] A "similar PK profile" or "comparable bioavailability" means that the mean AUC_{inf} of a test product is from 80% to 125% of the mean AUC_{inf} of a reference product in a suitably designed cross-over trial, and that the mean plasma concentration at 8 hours (C_{8h}) of the test product is from 50% to 130% of the mean plasma concentration at 8 hours (C_{8h}) of the reference product.

[0165] Type 1 Narcolepsy (NT1) refers to narcolepsy characterized by excessive daytime sleepiness ("EDS") and cataplexy. Type 2 Narcolepsy (NT2) refers to narcolepsy characterized by excessive daytime sleepiness without cataplexy. A diagnosis of narcolepsy (with or without cataplexy) can be confirmed by one or a combination of (i) an overnight polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) performed within the last 2 years, (ii) a full documentary evidence confirming diagnosis from the PSG and MSLT from a sleep laboratory must be made available, (iii) current symptoms of narcolepsy including: current complaint of EDS for the last 3 months (ESS greater than 10), (iv) mean MWT less than 8 minutes, (v) mean number of cataplexy events of 8 per week on baseline Sleep/Cataplexy Diary, and/or (vi) presence of cataplexy for the last 3 months and 28 events per week during screening period.

[0166] Unless otherwise specified herein, percentages, ratios and numeric values recited herein are based on weight; averages and means are arithmetic means; all pharmacokinetic measurements based on the measurement of bodily fluids are based on plasma concentrations.

[0167] It will be understood, when defining a composition by its pharmacokinetic or dissolution properties herein, that the formulation can in the alternative be defined as "means for" achieving the recited pharmacokinetic or dissolution properties. Thus, a formulation in which the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour can instead be defined as a formulation comprising "means for" or "modified release means for" releasing less than 20% of its gamma-hydroxybutyrate at one hour. It will be further understood that the preferred structures for achieving the recited pharmacokinetic or dissolution properties are the structures described in the examples hereof that accomplish the recited pharmacokinetic or dissolution properties.

Discussion of Principal Embodiments

[0168] The invention can be described in terms of principal embodiments, which in turn can be recombined to make other principal embodiments, and limited by sub-embodiments to make other principal embodiments.

[0169] A first principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 300, 325, 340, 375, 400, 425, or 450 hr×microgram/mL, most preferably greater than 340 hr×microgram/mL.

[0170] A second principal embodiment of the present invention provides a modified release formulation of

gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 265, 285, 300, 315, 325, 340, 350, 375, 400, 425, or 450 hr×microgram/mL, most preferably greater than 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70% to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, from 90% to 110%, from 50% to 95%, from 60% to 90%, most preferably from 60% to 90% or 60% to 130% of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate (e.g. Xyrem®) administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0171] A third principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0172] A fourth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion preferably releases greater than 80% or 90% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0173] A fifth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60%, 70%, or 80%, preferably greater than 80%, of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0174] A sixth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 300, 325, 340, 375, 400, 425, or 450 hr×microgram/mL, preferably 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70% to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, from 90% to 110%, from 50% to 95%, or from 60% to 90%, preferably from 60% to 90% or from 60% to 130%, of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of gamma-hydroxybutyrate (e.g. Xyrem®) administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and (b) the formulation releases (i) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (ii) from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0175] A seventh principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% or 10% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2

according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at three hours, two hours or one hour, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0176] An eighth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at one hour, two hours, or three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% or 10% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (c) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at three hours, two hours, or one hour, when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and (d) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0177] A ninth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 4.5 g, 6 g, 7.5 g, and 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85% or 90% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal. The relative bioavailability is even higher with larger doses, and with a 6.0 g or 7.5 g or 9.0 g dose is preferably greater than 90, 95 or 100% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0178] A tenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, wherein a 4.5 g and a 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0179] An eleventh principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **12** or FIG. **13** for the corresponding strength.

[0180] A twelfth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **22**.

[0181] A thirteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **7** and FIG. **8**.

[0182] A fourteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **20** and FIG. **21**.

[0183] A fifteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions that yields a dissolution profile substantially as depicted in FIG. **3** or **16**.

[0184] In a sixteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **25** and FIG. **26**.

[0185] In a seventeenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **27** and FIG. **28**.

[0186] In an eighteenth principal embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate yielding a dissolution profile substantially as shown in any one of FIGS. **29** through **89**. It will be understood that this seventeenth principal embodiment can be limited only to one of these dissolution profiles.

[0187] A nineteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 7.5 g or 9.0 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **90** for the corresponding strength.

[0188] In any of these principal embodiments, the formulation is preferably effective to treat narcolepsy Type 1 or Type 2. The formulation is also preferably effective to induce sleep for six to eight, most preferably eight consecutive hours.

[0189] In any of these principal embodiments, the formulation preferably comprises immediate release and modified release portions, wherein the modified release portion comprises gamma hydroxybutyrate particles coated by a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C., and the ratio of gamma-hydroxybutyrate in the imme-

diate release portion and the modified release portion is from 10/90 to 65/35. The polymers comprising free carboxylic groups preferably have a pH dissolution trigger of from 5.5 to 6.97 and are preferably methacrylic acid copolymers having a pH dissolution trigger of from 5.5 to 6.97.

Principal Structural Embodiments

[0190] In a first principal structural embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

[0191] In a second principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, a suspending or viscosifying agent, and an acidifying agent, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

[0192] In a third principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

[0193] In a fourth principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

[0194] In a fifth principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a methacrylic acid copolymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

Discussion of Pharmacokinetic and Dissolution Sub-Embodiments

[0195] As mentioned in the definitions section of this document, each of the sub-embodiments can be used to further characterize and limit each of the foregoing principal embodiments. In addition, more than one of the following sub-embodiments can be combined and used to further characterize and limit each of the foregoing principal embodiments, in any manner that is mathematically and physically possible.

[0196] In various sub-embodiments of the foregoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean AUC_{inf} of greater than 245, 265, 285, 300, 315, 325, 340, 350, 375, 400, 425, or 450 hr×microgram/mL when administered once approximately two hours after a standardized evening meal. An upper limit on mean AUC_{inf} for such 7.5 g dose can be set at 500 or 550 hr×microgram/mL.

[0197] In additional sub-embodiments of the foregoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean C_{max} of greater than 65, 70, 75, 80, 85, or 90 microgram/mL when administered once approximately two hours after a standardized evening meal. An upper limit on mean C_{max} for such 7.5 g dose can be set at 125 or 100 microgram/mL.

[0198] In additional sub-embodiments of the forgoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70 to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, or from 90% to 110% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of gamma-hydroxybutyrate administered at t_0 and t_{4h} in two equally divided doses, when administered approximately two hours after a standardized evening meal.

[0199] In one sub-embodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr*microgram/mL, and a mean C_{8h} that is from 50% to 130% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0200] Further sub-embodiments can be characterized based on the dissolution properties of the entire (or finished) modified release formulation of gamma-hydroxybutyrate in 0.1N hydrochloric acid dissolution medium. Thus, in additional sub-embodiments the entire modified release formulation of gamma-hydroxybutyrate releases greater than 30%, 35%, 40%, or 45%, and less than 70%, 65%, 60%, or 55%, of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0201] Further sub-embodiments can be defined based on the dissolution properties of the modified release portion of the formulation of gamma-hydroxybutyrate in a phosphate buffer pH 6.8 dissolution medium. Thus, in additional sub-embodiments the modified release portion releases greater than 80%, 85%, 90%, 95%, 98% or even 99% of its gamma-hydroxybutyrate at 3, 2, 1, 0.5 or 0.25 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0202] Still further embodiments can be defined based on the dissolution properties of the modified release portion of the modified release formulation of gamma-hydroxybutyrate in a 0.1N HCl dissolution medium. Thus, in additional sub-embodiments the modified release portion releases less than 20%, 15%, 10%, 5%, or even 2% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0203] In additional embodiments, the modified release portion releases less than 20%, 15%, 10%, 5%, or even 2% of its gamma-hydroxybutyrate at one hour and at three hours and more than 30%, 35%, 40%, 45% of its gamma-hydroxybutyrate at ten hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0204] Further embodiments can be defined based on the dissolution properties of the immediate release portion of the modified release formulation of gamma-hydroxybutyrate in a 0.1N HCl dissolution medium. Thus, in additional sub-embodiments the immediate release portion releases greater than 80%, 85%, 90%, 95%, 98% or even 99% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0205] In another sub-embodiment, the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0206] In another subembodiment, the formulation comprises immediate release and modified release portions, and (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0207] In another sub-embodiment, the formulation comprises immediate release and modified release portions, and (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65% of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0208] Still further sub-embodiments can be defined based on a pharmacokinetic comparison of the modified release formulation of gamma-hydroxybutyrate to an immediate release solution of gamma-hydroxybutyrate. Therefore, in additional sub-embodiments the modified release formulation of gamma-hydroxybutyrate, preferably in a 4.5 g, 6.0 g, 7.5 g, and 9.0 g dose, has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85%, 90%, or 95% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0209] In additional sub-embodiments of the forgoing principal embodiments the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 4.5 g and 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85% or 90% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal

[0210] In additional sub-embodiments, a 6.0 g or 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85%, 90%, 95% or 100% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

[0211] The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined by comparing the area under the concentration/time curve for eight hours to the area under the concentration/time curve calculated to infinity. Thus, in still further sub-embodiments a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate of the present invention has been shown to achieve a ratio of AUC_{8h} to

AUC_{inf} of greater than 0.80, 0.85, 0.90, 0.95 or 0.98 when administered once approximately two hours after a standardized evening meal.

[0212] In still further sub-embodiments, the modified release formulations of gamma-hydroxybutyrate are defined based on the concentration of gamma-hydroxybutyrate in the blood stream 8 hours after administration. Therefore, in other sub-embodiments the formulation can be characterized by a 4.5 g dose of the modified release formulation of gamma-hydroxybutyrate that has been shown to achieve a mean C_{8h} of from 4.7 to 9.0, from 5.4 to 8.3, from 6.1 to 7.6, from 3.5 to 7.0, or from 4.0 to 5.5 microgram/mL, a 6.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{8h} of from 6.3 to 16.7, from 7.3 to 15.4, from 8.2 to 14.1, from 8.9 to 16.7, from 10.2 to 15.4, or from 11.5 to 14.1 microgram/mL; or a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{8h} of from 13.0 to 40.3, from 16.0 to 26.0, 15.0 to 25.0, from 17.5 to 22.0, from 21.6 to 40.3, from 24.7 to 37.2, or from 27.8 to 34.1 microgram/mL, when administered once approximately two hours after a standardized evening meal.

[0213] The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined by the concentration/time and dissolution curves that they produce when tested according to the examples of the present invention. Therefore, in other sub-embodiments, a 4.5 g, 6.0 g, or 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate of the present invention has been shown to achieve a time/concentration curve substantially as shown in FIGS. **13** (*a*), (*b*) and (*c*) respectively herein. In another principal embodiment or sub-embodiment, the formulation has been shown to achieve a dissolution curve substantially as shown in FIGS. **7** and **8** or FIGS. **20** and **21** herein.

[0214] The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined based on the time required to reach maximum blood concentration of gamma-hydroxybutyrate. Thus, in additional sub-embodiments, the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a median T_{max} of 1.25 to 3.25 hours, preferably of about 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, or 3.25 hours when administered once approximately two hours after a standardized evening meal. A lower limit on the median T_{max} in any of the foregoing ranges can alternatively be set at 0.5 or 1.0 hours.

[0215] Additional embodiments can be defined by comparing a dose of the modified release formulation of gamma-hydroxybutyrate, administered once nightly, to the same dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a median T_{max} within one hundred fifty, one hundred twenty, ninety, sixty or thirty minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

[0216] In still another sub-embodiment a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

[0217] Additional embodiments can be defined by comparing the pharmacokinetic profile of a dose of the modified release formulation of gamma-hydroxybutyrate administered once nightly to the same dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{3h} to the mean C_{max} of the first half dose of the immediate release liquid solution of sodium oxybate from 0.6 to 1.2, preferably from 0.7 to 1.1 and most preferably from 0.8 to 1. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{4h} to the mean C_{max} of the first half dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1.1, preferably from 0.6 to 1 and most preferably from 0.7 to 0.9. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean $C_{4.5h}$ to the mean C_{max} of the first half dose of the immediate release liquid solution of gamma-hydroxybutyrate from 0.5 to 1, preferably from 0.5 to 0.9 and most preferably from 0.6 to 0.8.

[0218] Additional sub-embodiments can be defined by the range of mean blood concentrations of gamma-hydroxybutyrate achieved 3, 4, 4.5 or 5 hours after administration once nightly by a modified release formulation of gamma-hydroxybutyrate according to the invention at the dose of 7.5 g. Thus, in another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{3h} of 43 to 81 microgram/mL, preferably 49 to 75 microgram/mL and more preferably 55 to 69 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{4h} of 40 to 75 microgram/mL, preferably 45 to 69 microgram/mL and more preferably 51 to 64 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean $C_{4.5h}$ of 35 to 67 microgram/mL, preferably 40 to 62 microgram/mL and more preferably 45 to 56 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{5h} of 31 to 59 microgram/mL, preferably 36 to 55 microgram/mL and more preferably 40 to 50 microgram/mL.

[0219] In another subembodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 300 hr·microgram/mL and a mean C_{max} of greater than 70 microgram/mL when administered once approximately two hours after a standardized evening meal.

[0220] In still another subembodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 350 hr·microgram/mL and a mean C_{max} of greater than 80 microgram/mL when administered once approximately two hours after a standardized evening meal.

[0221] In another subembodiment, a 4.5, 6.0, 7.5 and 9.0 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses

approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95%, 90 or 85% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

[0222] Additional embodiments can be defined by comparing the pharmacokinetic profile of a dose of the modified release formulation of gamma-hydroxybutyrate administered once nightly to another dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a similar pharmacokinetic profile to the pharmacokinetic profile provided by a 2×4.5 g dose of sodium oxybate as an immediate release liquid solution administered for the first 4.5 g two hours after a standardized evening meal and for the second 4.5 g dose, 4 hours after the first dose. Thus, in another sub-embodiment a modified release formulation of gamma-hydroxybutyrate according to the invention administered at the dose of 7.5 g has been shown to achieve a ratio of its mean C_{3h} to the mean C_{max} of the first 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1.1, preferably from 0.6 to 1 and most preferably from 0.7 to 0.9. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{4h} to the mean C_{max} of the first 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1, preferably from 0.6 to 0.9 and most preferably from 0.7 to 0.8. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean $C_{4.5h}$ to the mean C_{max} of the 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.4 to 0.9, preferably from 0.5 to 0.8 and most preferably from 0.6 to 0.7.

[0223] In another subembodiment, the modified release formulation of gamma-hydroxybutyrate comprises immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0224] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0225] (a) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0226] (i) from 40% to 65% at 1 hour,

[0227] (ii) from 40% to 65% at 3 hours,

[0228] (iii) from 47% to 85% at 8 hours,

[0229] (iv) greater or equal to 60% at 10 hours,

[0230] (v) greater or equal to 80% at 16 hours, and

[0231] (b) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0232] (i) from 43% to 94% at 0.25 hour,

[0233] (ii) greater or equal to 65% at 0.35 hour, and

[0234] (iii) greater or equal to 88% at 1 hour.

[0235] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0236] (a) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0237] (i) from 40% to 65% at 1 hour,

[0238] (ii) from 40% to 65% at 3 hours,

[0239] (iii) greater or equal to 47% at 8 hours,

[0240] (iv) greater or equal to 60% at 10 hours,

[0241] (v) greater or equal to 80% at 16 hours, and

[0242] (b) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0243] (i) from 43% to 94% at 0.25 hour,

[0244] (ii) greater or equal to 65% at 0.35 hour, and

[0245] (iii) greater or equal to 88% at 1 hour.

[0246] In another preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0247] (a) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0248] (i) from 40% to 65% at 1 hour,

[0249] (ii) from 40% to 65% at 3 hours,

[0250] (iii) from 47% to 85% at 8 hours,

[0251] (iv) greater or equal to 60% at 10 hours,

[0252] (v) greater or equal to 80% at 16 hours, and

[0253] (b) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0254] (i) from 45% to 67% at 1 hour, and

[0255] (ii) greater or equal to 65% at 3 hours.

[0256] In another preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

[0257] (a) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0258] (i) from 40% to 65% at 1 hour,

[0259] (ii) from 40% to 65% at 3 hours,

[0260] (iii) greater or equal to 47% at 8 hours,

[0261] (iv) greater or equal to 60% at 10 hours,

[0262] (v) greater or equal to 80% at 16 hours, and

[0263] (b) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

[0264] (i) from 45% to 67% at 1 hour, and

[0265] (ii) greater or equal to 65% at 3 hours.

[0266] In still another subembodiment, the formulation achieves an in vitro dissolution profile: (a) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) from 40% to 65% at 1 hour, (ii) from 40% to 65% at 3 hours, (iii) greater than 45% at 8 hours, and (b) measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) greater than 40% at 0.5 hour, and (ii) greater than 85% at 1 hour.

[0267] Alternatively, the formulation can be described as achieving an in vitro dissolution profile measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) from 40% to 65% at 1 hour, (ii) from 40% to 65% at 3 hours, and (iii) greater than 45% at 8 hours.

[0268] In another alternative, the formulation can be described as achieving an in vitro dissolution profile measured in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) greater than 40% at 0.5 hour, and (ii) greater than 85% at 1 hour.

Structural Sub-Embodiments

[0269] The modified release formulations of gamma-hydroxybutyrate of the present invention can be provided in any dosage form that is suitable for oral administration, including tablets, capsules, liquids, orally dissolving tablets, and the like, but they are preferably provided as dry particulate formulations (i.e. granules, powders, coated particles, microparticles, pellets, microspheres, etc.), in a sachet or other suitable discreet packaging units. A preferred particulate formulation will be mixed with tap water shortly before administration, preferably 50 mL.

[0270] In one subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; and (b) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

[0271] In one subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; and (b) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 40/60 to 60/40.

[0272] In another subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40.

[0273] In another subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40; and (e) the film coating is from 10 to 50% of the weight of the microparticles.

[0274] In another subembodiment the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40; and (e) the coating is from 10 to 50% of the weight of the particles.

[0275] In a particularly preferred sub-embodiment of the immediately preceding sub-embodiments, the polymer carrying free carboxylic groups comprises from 100% poly (methacrylic acid, ethyl acrylate) 1:1 and 0% poly (methacrylic acid, methylmethacrylate) 1:2 to 2% poly (methacrylic acid, ethyl acrylate) 1:1 and 98% poly (methacrylic acid, methylmethacrylate) 1:2; and the hydrophobic compound comprises hydrogenated vegetable oil.

[0276] In a preferred embodiment, the formulation includes excipients to improve the viscosity and the pourability of the mixture of the particulate formulation with tap water. As such, the particulate formulation comprises, besides the immediate release and modified release particles of gamma-hydroxybutyrate, one or more suspending or viscosifying agents or lubricants.

[0277] Preferred suspending or viscosifying agents are chosen from the group consisting of xanthan gum, medium viscosity sodium carboxymethyl cellulose, mixtures of microcrystalline cellulose and sodium carboxymethyl cellulose, mixtures of microcrystalline cellulose and guar gum, medium viscosity hydroxyethyl cellulose, agar, sodium alginate, mixtures of sodium alginate and calcium alginate, gellan gum, carrageenan gum grade iota, kappa or lambda, and medium viscosity hydroxypropylmethyl cellulose.

[0278] Medium viscosity sodium carboxymethyl cellulose corresponds to grade of sodium carboxymethyl cellulose

whose viscosity, for a 2% solution in water at 25° C., is greater than 200 mPa·s and lower than 3100 mPa·s.

[0279] Medium viscosity hydroxyethyl cellulose corresponds to a grade of hydroxyethyl cellulose whose viscosity, for a 2% solution in water at 25° C., is greater than 250 mPa·s and lower than 6500 mPa·s. Medium viscosity hydroxypropylmethyl cellulose corresponds to a grade of hydroxypropylmethyl cellulose whose viscosity, for a 2% solution in water at 20° C., is greater than 80 mPa·s. and lower than 3800 mPa·s.

[0280] Preferred suspending or viscosifying agents are xanthan gum, especially Xantural 75™ from Kelco, hydroxyethylcellulose, especially Natrosol 250M™ from Ashland, Kappa carrageenan gum, especially Gelcarin PH812™ from FMC Biopolymer, and lambda carrageenan gum, especially Viscarin PH209™ from FMC Biopolymer.

[0281] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate comprises from 1 to 15% of viscosifying or suspending agents, preferably from 2 to 10%, more preferably from 2 to 5%, and most preferably from 2 to 3% of the formulation.

[0282] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate is in the form of a powder that is intended to be dispersed in water prior to administration and further comprises from 1 to 15% of a suspending or viscosifying agent selected from a mixture of xanthan gum, carrageenan gum and hydroxyethylcellulose or xanthan gum and carrageenan gum.

[0283] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate is in the form of a powder that is intended to be dispersed in water prior to administration and further comprises: from 1.2 to 15% of an acidifying agent selected from malic acid and tartaric acid; and from 1 to 15% of a suspending or viscosifying agent selected from a mixture of xanthan gum, carrageenan gum and hydroxyethylcellulose or xanthan gum and carrageenan gum.

[0284] In a most preferred embodiment, the modified release formulation of gamma-hydroxybutyrate comprises about 1% of lambda carrageenan gum or Viscarin PH209™, about 1% of medium viscosity grade of hydroxyethyl cellulose or Natrosol 250M™, and about 0.7% of xanthan gum or Xantural 75™. For a 4.5 g dose unit, these percentages will typically equate to about 50 mg xanthan gum (Xantural 75™), about 75 mg carrageenan gum (Viscarin PH209™), and about 75 mg hydroxyethylcellulose (Natrasol 250M™).

[0285] Alternative packages of viscosifying or suspending agents, for a 4.5 g dose, include about 50 mg xanthan gum (Xantural 75™) and about 100 mg carrageenan gum (Gelcarin PH812™), or about 50 mg xanthan gum (Xantural 75™), about 75 mg hydroxyethylcellulose (Natrasol 250M™), and about 75 mg carrageenan gum (Viscarin PH109™).

[0286] In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate further comprises a lubricant or a glidant, besides the immediate release and modified release particles of gamma-hydroxybutyrate. Preferred lubricants and glidants are chosen from the group consisting of salts of stearic acid, in particular magnesium stearate, calcium stearate or zinc stearate, esters of stearic acid, in particular glyceryl monostearate or glyceryl palmitostearate, stearic acid, glycerol behenate, sodium stearyl fumarate, talc, and colloidal silicon dioxide.

[0287] The preferred lubricant or glidant is magnesium stearate.

[0288] The lubricant or glidant can be used in the particulate formulation in an amount of from 0.1 to 5%. The preferred amount is about 0.5%.

[0289] Most preferably, the modified release formulation of gamma-hydroxybutyrate comprises about 0.5% of magnesium stearate.

[0290] A preferred modified release formulation of gamma-hydroxybutyrate further comprises an acidifying agent. The acidifying agent helps to ensure that the release profile of the formulation in 0.1N HCl will remain substantially unchanged for at least 15 minutes after mixing, which is approximately the maximum length of time a patient might require before consuming the dose after mixing the formulation with tap water.

[0291] In one particular subembodiment the formulation is a powder, and further comprising an acidifying agent and a suspending or viscosifying agent, preferably in the weight percentages recited herein.

[0292] The preferred acidifying agents are chosen from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid. In a preferred embodiment, the acidifying agent is present in the formulation from 1.2 to 15%, preferably from 1.2 to 10%, preferably from 1.2 to 5%. Preferred acidifying agents are tartaric acid and malic acid, with malic acid being most preferred.

[0293] When tartaric acid is employed, it is preferably employed in an amount of from 1 to 10%, from 2.5 to 7.5%, or about 5%. In a most preferred embodiment, the amount of malic acid in the modified release formulation of gamma-hydroxybutyrate is from 1.2 to 15%, preferably from 1.2 to 10%, preferably from 1.2 to 5%, and most preferably 1.6% or 3.2%.

[0294] In a most preferred embodiment, the amount of malic acid in the modified release formulation of gamma hydroxybutyrate is about 1.6%.

[0295] The modified release formulation of gamma-hydroxybutyrate preferably includes an immediate release portion and a modified release portion of gamma-hydroxybutyrate, and in a particularly preferred embodiment, the formulation is a particulate formulation that includes a plurality of immediate release gamma-hydroxybutyrate particles and a plurality of modified release gamma-hydroxybutyrate particles. The molar ratio of gamma-hydroxybutyrate in the immediate release and modified release portions preferably ranges from 0.11:1 to 1.86:1, from 0.17:1 to 1.5:1, from 0.25:1 to 1.22:1, from 0.33:1 to 1.22:1, from 0.42:1 to 1.22:1, from 0.53:1 to 1.22:1, from 0.66:1 to 1.22:1, from 0.66:1 to 1.5:1, from 0.8:1 to 1.22:1, and preferably is about 1:1. The molar percentage of gamma-hydroxybutyrate in the immediate release portion relative to the total of gamma-hydroxybutyrate in the formulation preferably ranges from 10% to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%. In a preferred embodiment, the molar percentage of the gamma-hydroxybutyrate in the immediate release portion relative to the total of gamma-hydroxybutyrate in the formulation is about 50%. The molar percentage of gamma-hydroxybutyrate in the modified release portion relative to the total of gamma-hydroxybu-

tyrate in the formulation preferably ranges from 90% to 35%, from 85 to 40%, from 80 to 45%, from 75 to 45%, from 70 to 45%, from 65 to 45%, from 60 to 45%, from 60 to 40%, or from 55 to 45%, preferably from 60% to 40%. In a preferred embodiment, the molar ratio of the gamma-hydroxybutyrate in the modified release portion relative to the total of gamma-hydroxybutyrate in the formulation is about 50%. The weight percentage of the IR microparticles relative to the total weight of IR microparticles and MR microparticles, preferably ranges from 7.2% to 58.2%, from 11.0% to 52.9%, from 14.9% to 47.8%, from 18.9% to 47.8%, from 23.1% to 47.8%, from 27.4% to 47.8%, from 31.8% to 47.8%, from 31.8% to 52.9%, or from 36.4% to 47.8%. In other embodiments, the weight percentage of the IR microparticles relative to the total weight of IR microparticles and MR microparticles preferably ranges from 5.9% to 63.2%, from 9.1% to 58.1%, from 12.4% to 53.1%, from 19.9% to 53.1%, from 19.6% to 53.1%, from 23.4% to 53.1%, from 27.4% to 53.1% from 27.4% to 58.1%, preferably from 31.7% to 53.1%.

[0296] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to 450 microns and 50% of its sodium oxybate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0297] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to 170 microns and 50% of its sodium oxybate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0298] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its sodium oxybate content in modified release particles consisting of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0299] In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its sodium oxybate content in modified release particles consisting of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0300] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0301] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0302] In a preferred embodiment, the finished formulation comprises 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline

cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0303] In a preferred embodiment, the finished formulation comprises 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0304] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of calcium salt of gamma-hydroxybutyric acid mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0305] In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of calcium salt of gamma-hydroxybutyric acid mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

Other Characteristics of Immediate Release Portion

[0306] The immediate release portion of the formulation can take any form capable of achieving an immediate release of the gamma-hydroxybutyrate when ingested. For example, when the formulation is a particulate formulation, the formulation can include unmodified "raw" gamma-hydroxybutyrate, rapidly dissolving gamma-hydroxybutyrate granules, particles or microparticles comprised of a core covered by a gamma-hydroxybutyrate loaded layer containing a binder such as povidone.

[0307] The IR granules or particles of gamma-hydroxybutyrate can be made using any manufacturing process suitable to produce the required particles, including:

[0308] agglomeration of the gamma-hydroxybutyrate sprayed preferably in the molten state, such as the Glatt ProCell™ technique,

[0309] extrusion and spheronization of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,

[0310] wet granulation of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,

[0311] compacting of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,

[0312] granulation and spheronization of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, the spheronization being carried out for example in a fluidized bed apparatus equipped with a rotor, in particular using the Glatt CPS™ technique,

[0313] spraying of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, for example in a fluidized bed type apparatus equipped with zig-zag filter, in particular using the Glatt MicroPx™ technique, or

[0314] spraying, for example in a fluidized bed apparatus optionally equipped with a partition tube or Wurster tube, the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, in dispersion or in solution in an aqueous or organic solvent on a core.

[0315] Preferably, the immediate release portion of the formulation is in the form of microparticles comprising the immediate release gamma-hydroxybutyrate and optional pharmaceutically acceptable excipients. In a preferred embodiment, the immediate release microparticles of gamma-hydroxybutyrate have a volume mean diameter D(4, 3) of from 10 to 1000 microns, preferably from 95 to 600

microns, more preferably from 150 to 400 microns. Most preferably their volume mean diameter is about 270 microns.

[0316] The preferred immediate release particles of gamma-hydroxybutyrate of the present invention comprises a core and a layer deposited on the core that contains the gamma-hydroxybutyrate. The core can be any particle chosen from the group consisting of:

[0317] crystals or spheres of lactose, sucrose (such as Compressuc™ PS from Tereos), microcrystalline cellulose (such as Avicel™ from FMC Biopolymer, Cellet™ from Pharmatrans or Celphere™ from Asahi Kasei), sodium chloride, calcium carbonate (such as Omyapure™ 35 from Omya), sodium hydrogen carbonate, dicalcium phosphate (such as Dicafos™ AC 92-12 from Budenheim) or tricalcium phosphate (such as Tricafos™ SC93-15 from Budenheim);

[0318] composite spheres or granules, for example sugar spheres comprising sucrose and starch (such as Suglets™ from NP Pharm), spheres of calcium carbonate and starch (such as Destab™ 90 S Ultra 250 from Particle Dynamics) or spheres of calcium carbonate and maltodextrin (such as Hubercal™ CCG4100 from Huber).

[0319] The core can also comprise other particles of pharmaceutically acceptable excipients such as particles of hydroxypropyl cellulose (such as Klucel™ from Aqualon Hercules), guar gum particles (such as Grinsted™ Guar from Danisco), xanthan particles (such as Xantural™ 180 from CP Kelco).

[0320] According to a particular embodiment of the invention, the cores are sugar spheres or microcrystalline cellulose spheres, such as Cellets™ 90, Cellets™ 100 or Cellets™ 127 marketed by Pharmatrans, or also Celphere™ CP 203, Celphere™ CP305, Celphere™ SCP 100. Preferably the core is a microcrystalline cellulose sphere. Most preferably the core is a Cellets™ 127 from Pharmatrans.

[0321] The core preferably has a mean volume diameter of about 95 to about 450 microns, preferably about 95 to about 170 microns, most preferably about 140 microns.

[0322] The layer deposited onto the core comprises the immediate release gamma-hydroxybutyrate. Preferably the layer also comprises a binder, which can be chosen from the group consisting of:

[0323] low molecular weight hydroxypropyl cellulose (such as Klucel™ EF from Aqualon-Hercules), low molecular weight hydroxypropyl methylcellulose (or hypromellose) (such as Methocel™ E3 or E5 from Dow), or low molecular weight methylcellulose (such as Methocel™ A15 from Dow);

[0324] low molecular weight polyvinyl pyrrolidone (or povidone) (such as Plasdone K29/32 from ISP or Kollidon™ 30 from BASF), vinyl pyrrolidone and vinyl acetate copolymer (or copovidone) (such as Plasdone™: S630 from ISP or Kollidon™ VA 64 from BASF);

[0325] dextrose, pregelatinized starch, maltodextrin; and mixtures thereof.

[0326] Low molecular weight hydroxypropyl cellulose corresponds to grades of hydroxypropyl cellulose having a molecular weight of less than 800,000 g/mol, preferably less than or equal to 400,000 g/mol, and in particular less than or equal to 100,000 g/mol. Low molecular weight hydroxypropyl methylcellulose (or hypromellose) corresponds to grades of hydroxypropyl methylcellulose the solution viscosity of which, for a 2% solution in water and at 20° C., is less than or equal to 1,000 mPa·s, preferably less than or equal to 100 mPa·s and in particular less than or equal to 15 mPa·s. Low molecular weight polyvinyl pyrrolidone (or povidone) corresponds to grades of polyvinyl pyrrolidone having a molecular weight of less than or equal to 1,000,000 g/mol, preferably less than or equal to 800,000 g/mol, and in particular less than or equal to 100,000 g/mol.

[0327] Preferably, the binding agent is chosen from low molecular weight polyvinylpyrrolidone or povidone (for example, Plasdone™ K29/32 from ISP), low molecular weight hydroxypropyl cellulose (for example, Klucel™ EF from Aqualon-Hercules), low molecular weight hydroxypropyl methylcellulose or hypromellose (for example, Methocel™ E3 or E5 from Dow) and mixtures thereof.

[0328] The preferred binder is povidone K30 or K29/32, especially Plasdone™ K29/32 from ISP. The binder can be present in an amount of 0 to 80%, 0 to 70%, 0 to 60%, 0 to 50%, 0 to 40%, 0 to 30%, 0 to 25%, 0 to 20%, 0 to 15%, 0 to 10%, or from 1 to 9%, most preferably 5% of binder based on the total weight of the immediate release coating.

[0329] The preferred amount of binder is 5% of binder over the total mass of gamma-hydroxybutyrate and binder.

[0330] The layer deposited on the core can represent at least 10% by weight, and even greater than 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85 or 90% by weight of the total weight of the immediate release particle of gamma-hydroxybutyrate. Most preferably, the layer deposited on the core represents about 85% of the weight of the immediate release particle of gamma-hydroxybutyrate.

[0331] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0332] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns.

[0333] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns.

[0334] According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0335] According to another preferred embodiment, the immediate-release particles comprise 80,75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0336] According to another preferred embodiment, the immediate-release particles comprise 80,75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0337] According to another preferred embodiment, the immediate-release particles comprise 80,75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

[0338] According to another embodiment, the immediate-release particles are manufactured by dissolving the gamma-hydroxybutyrate and the Povidone K30 in a mixture of water/ethanol 40/60 w/w and spraying the resulting solution onto the surface of the microcrystalline cellulose spheres.

Other Characteristics of Modified Release Portion

[0339] The modified release portion can be any formulation that provides the desired in vitro dissolution profile of gamma-hydroxybutyrate. The modified release portion is preferably comprised of modified release particles, obtained by coating immediate release particles of gamma-hydroxybutyrate with a coating (or coating film) that inhibits the immediate release of the gamma-hydroxybutyrate. In one sub-embodiment the modified release portion comprises particles comprising: (a) an inert core; (b) a coating; and (c) a layer comprising the gamma hydroxybutyrate interposed between the core and the coating.

[0340] In a preferred embodiment, the modified release portion comprises a time-dependent release mechanism and a pH-dependent release mechanism.

[0341] In a preferred embodiment, the coating film comprises at least one polymer carrying free carboxylic groups, and at least one hydrophobic compound preferably characterized by a melting point equal or greater than 40° C.

[0342] The polymer carrying free carboxylic groups is preferably selected from: (meth)acrylic acid/alkyl (meth) acrylate copolymers or methacrylic acid and methylmethacrylate copolymers or methacrylic acid and ethyl acrylate copolymers or methacrylic acid copolymers type A, B or C, cellulose derivatives carrying free carboxylic groups, preferably cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethylethyl cellulose, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, zein, shellac, alginate and mixtures thereof.

[0343] In a preferred embodiment, the methacrylic acid copolymers are chosen from the group consisting of poly (methacrylic acid, methyl methacrylate) 1:1 or Eudragit™ L100 or equivalent, poly (methacrylic acid, ethyl acrylate) 1:1 or Eudragit™ L100-55 or equivalent and poly (methacrylic acid, methyl methacrylate) 1:2 or Eudragit™ S100 or equivalent.

[0344] In another subembodiment the coating comprises a polymer carrying free carboxylic groups wherein the free carboxylic groups are substantially ionized at pH 7.5.

[0345] The hydrophobic compound with a melting point equal or greater than 40° C. can be selected from the group consisting of hydrogenated vegetable oils, vegetable waxes, wax yellow, wax white, wax microcrystalline, lanolin, anhydrous milk fat, hard fat suppository base, lauroyl macrogol glycerides, polyglyceryl diisostearate, diesters or triesters of glycerol with a fatty acid, and mixtures thereof.

[0346] Even more preferably, the hydrophobic compound with a melting point equal or greater than 40° C. is chosen from the group of following products: hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candellila wax, tristearin, tripalmitin, trimyristin, yellow wax, hard fat or fat that is useful as suppository bases, anhydrous dairy fats, lanolin, glyceryl palmitostearate, glyceryl stearate, lauryl macrogol glycerides, polyglyceryl diisostearate, diethylene glycol monostearate, ethylene glycol monostearate, omega 3 fatty acids, and mixtures thereof. A particularly preferred subgroup of products comprises hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candelilla wax, tristearin, tripalmitin, trimyristin, beeswax, hydrogenated poly-1 decene, carnauba wax, and mixtures thereof.

[0347] In practice, and without this being limiting, it is preferable the hydrophobic compound with a melting point equal or greater than 40° C. to be chosen from the group of products sold under the following trademarks: Dynasan™, Cutina™, Hydrobase™, Dub™, Castorwax™, Croduret™, Compritol™, Sterotex™, Lubritab™, Apifil™, Akofine™, Softisan™, Hydrocote™, Livopol™, Super Hartolan™, MGLA™, Corona™, Protalan™, Akosoft™, Akosol™, Cremao™, Massupol™, Novata™, Suppocire™, Wecobee™, Witepsol™, Lanolin™, Incromega™, Estaram™, Suppoweiss™, Gelucire™, Precirol™, Emulcire™, Plurol Diisostéarique™, Geleol™, Hydrine™, Monthyle™, Kahlwax™ and mixtures thereof; and, preferably, from the group of products sold under the following trademarks: Dynasan™ P60, Dynasan™114, Dynasan™116, Dynasan™118, Cutina™ HR, Hydrobase™ 66-68, Dub™ HPH, Compritol™ 888, Sterotex™ NF, Sterotex™ K, Lubritab™, and mixtures thereof.

[0348] A particularly suitable coating is composed of a mixture of hydrogenated vegetable oil and a methacrylic acid copolymer. The exact structure and amount of each component, and the amount of coating applied to the particle, controls the release rate and release triggers. Eudragit® methacrylic acid copolymers, namely the methacrylic acid—methyl methacrylate copolymers and the methacrylic acid—ethyl acrylate copolymers, have a pH-dependent solubility: typically, the pH triggering the release of the active ingredient from the microparticles is set by the choice and mixture of appropriate Eudragit® polymers. In the case of gamma hydroxybutyrate modified release microparticles, the theoretical pH triggering the release is preferably from 5.5 to 6.97 or 6.9, more preferably 6.5 up to 6.9. By "pH trigger" is meant the minimum pH above which dissolution of the polymer occurs.

[0349] In a particular embodiment, the coating comprises a hydrophobic compound with a melting point equal or greater than 40° C. and a polymer carrying free carboxylic groups are present in a weight ratio from 0.4 or 0.5 to 4, preferably from 0.6 or 0.67 to 2.5, most preferably from 0.6 or 0.67 to 2.33; most preferably about 1.5.

[0350] A particularly suitable coating is composed of a mixture of hydrogenated vegetable oil and a methacrylic acid copolymer with a theoretical pH triggering the release from 6.5 up to 6.97 in a weight ratio from 0.4 or 0.5 to 4, preferably from 0.6 or 0.67 to 2.5, most preferably from 0.6 or 0.67 to 2.33; most preferably of about 1.5.

[0351] The modified release particles of gamma-hydroxybutyrate preferably have a volume mean diameter of from 100 to 1200 microns, from 100 to 500 microns, from 200 to 800 microns, and preferably of about 320 microns.

[0352] The coating can preferably represent 10 to 50%, 15 to 45%, 20 to 40%, or 25 to 35% by weight of the total weight of the coated modified release particles. Preferably, the coating represents 25-30% by weight of the total weight of the modified release particles of gamma-hydroxybutyrate.

[0353] In a preferred embodiment, the coating layer of the modified release particles of gamma-hydroxybutyrate is obtained by spraying, in particular in a fluidized bed appa-

ratus, a solution, suspension or dispersion comprising the coating composition as defined previously onto the immediate release particles of gamma-hydroxybutyrate, in particular the immediate release particles of gamma-hydroxybutyrate as previously described. Preferably, the coating is formed by spraying in a fluidized bed equipped with a Wurster or partition tube and according to an upward spray orientation or bottom spray a solution of the coating excipients in hot isopropyl alcohol.

[0354] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of gamma-hydroxybutyrate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of gamma-hydroxybutyrate.

[0355] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of gamma-hydroxybutyrate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of gamma-hydroxybutyrate.

[0356] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of sodium oxybate.

[0357] According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of sodium oxybate.

[0358] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of gamma-hydroxybutyrate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0359] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of gamma-hydroxybutyrate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0360] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

[0361] According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

Packaging

[0362] The modified release formulation of gamma-hydroxybutyrate is preferably supplied in sachets or stick-packs comprising a particulate formulation. The sachets are preferably available in several different doses, comprising gamma-hydroxybutyrate in amounts equivalents to 0.5 g, 1.0 g, 1.5 g, 3.0 g, 4.5 g, 6.0 g, 7.5 g, 9.0 g, 10.5 g and/or 12 g of sodium oxybate. Depending on the dose required, one or more of these sachets can be opened, and its contents mixed with tap water to provide the nightly dose of gamma-hydroxybutyrate.

Methods of Treatment

[0363] The invention further provides a method of treating a disorder treatable with gamma-hydroxybutyrate in a human subject in need thereof comprising orally administering a single bedtime daily dose to said human amounts of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate in the formulation of the present invention. The invention further provides methods of treating narcolepsy, types 1 and/or 2, by orally administering at bedtime a

therapeutically effective amount of a gamma-hydroxybutyrate formulation characterized by the novel gamma-hydroxybutyrate pharmacokinetics or dissolution properties of the present invention. The modified release formulation of the present invention is effective to treat narcolepsy Type 1 or Type 2, wherein said treatment of narcolepsy is defined as reducing excessive daytime sleepiness or reducing the frequency of cataplectic attacks. The therapeutically effective amount preferably comprises equivalents from 3.0 to 12.0 g of sodium oxybate, more preferably from to 9.0 g of sodium oxybate, and most preferably 4.5, 6.0, 7.5 or 9.0 g of sodium oxybate. The effectiveness of the treatment can be measured by one or any combination of the following criteria:

[0364] Increase the mean sleep latency, preferably as determined on the Maintenance of Wakefulness Test (MWT)

[0365] Improve the Clinical Global Impression (CGI) rating of sleepiness

[0366] Decrease the number of cataplexy attacks (NCA) preferably determined from the cataplexy frequency item in the Sleep and Symptoms Daily Diary

[0367] Decrease the disturbed nocturnal sleep (DNS), the disturbed nocturnal events or the adverse respiratory events preferably as determined by polysomnographic (PSG) measures of sleep fragmentation

[0368] Decrease the excessive daytime sleepiness (EDS) preferably as measured by patient report via the Epworth Sleepiness Scale (ESS)

[0369] Decrease the daytime sleepiness as measured by the Maintenance of Wakefulness Test based on EEG measures of wakefulness

[0370] Decrease PSG transitions from N/2 to N/3 and REM sleep to wake and N1 sleep (as determined by C Iber, S Ancoli-Israel, A Chesson, SF Quan. *The AASM Manual for the Scoring of Sleep and Associated Events*. Westchester, Ill.: American Academy of Sleep Medicine; 2007).

[0371] Decrease the number of arousals or wakenings, preferably obtained from a PSG as defined by the American Academy of Sleep Medicine

[0372] Improve the sleep quality, preferably obtained from one or more of (i) the Sleep and Symptom Daily Diary, (ii) Visual Analog Scale (VAS) for sleep quality and sleep diary, and (iii) VAS for the refreshing nature of sleep

[0373] Decrease the Hypnagogic Hallucinations (HH) or sleep paralysis (SP) symptoms in NT1 narcolepsy patients, preferably as measured by the Sleep and Symptom Daily Diary

[0374] In a preferred embodiment, the treatment of the present invention is superior, as measured by any one or combination of the foregoing criteria, to an equal dose administered twice nightly of an immediate release liquid solution of sodium oxybate, with the second dose administered 4 hours after the first dose.

[0375] The invention further provides a method of treatment of narcolepsy Type 1 or Type 2 wherein, compared to a dosing regimen consisting of administering half the dose at t_0 and another half of the dose at t_{4h} of an immediate release liquid solution of sodium oxybate, a single bedtime daily dose administration of a therapeutically effective amount of the formulation of the invention has been shown to produce less confusion, less depressive syndrome, less incontinence, less nausea or less sleepwalking.

Additional Embodiments

[0376] In one additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0377] In a second additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0378] In a third additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0379] In a fourth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle

speed of 75 rpm, and (b) from 40% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0380] In a fifth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hour 3 when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 40% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0381] In a sixth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 40% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0382] In a seventh additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 40% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

[0383] In an eighth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 40% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

[0384] In a ninth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 40 to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus 2 according to USP 38<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

EXAMPLES

Example 1. Formulations

[0385] Tables 1a-1d provide the qualitative and quantitative compositions of sodium oxybate IR microparticles, MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **1**.

[0386] Briefly, sodium oxybate immediate release (IR) microparticles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of polyvinylpyrrolidone (Povidone K30-Plasdone™ K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 270 microns were obtained.

[0387] Sodium oxybate modified release (MR) microparticles were prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), were dissolved in 1542.9 g of isopropanol at 78° C. The solution was sprayed entirely onto 400.0 g of the sodium oxybate IR

microparticles described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR microparticles with mean volume diameter of about 320 microns were obtained.

[0388] The finished composition, which contains a 50:50 mixture of MR and IR microparticles calculated on their sodium oxybate content, was prepared as follows: 353.36 g of the above IR microparticles, 504.80 g of the above MR microparticles, 14.27 g of malic acid (D/L malic acid), 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.51 g of magnesium stearate were mixed. Individual samples of 7.11 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 1a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		2.786

TABLE 1b

Composition of MR Microparticles

Component	Function	Quantity per 4.5 g dose (g)
IR Microparticles	Core of MR microparticles	2.786
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.981

TABLE 1c

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

TABLE 1c-continued

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

TABLE 1d

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

Example 1Bis: Alternative Formulation

[0389] An alternative formulation to the formulation described in example 1 is described in Example 1bis.

[0390] Sodium oxybate immediate release (IR) microparticles were prepared by coating the IR microparticles described in example 1 with a top coat layer. Microparticles were prepared as follows: 170.0 of hydroxypropyl cellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the IR microparticles of Example 1 in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 298 microns were obtained (see Table 1bis-a).

[0391] Sodium oxybate modified release (MR) microparticles were prepared as described in example 1 (see Table 1b).

[0392] The finished composition, which contains a 50:50 mixture of MR and IR microparticles based on their sodium oxybate content, was prepared as follows: 412.22 g of the above IR microparticles, 530.00 g of the above MR microparticles, 29.96 g of malic acid (D/L malic acid), 4.96 g of xanthan gum (Xantural™ 75 from Kelco), 4.96 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 9.92 g of magnesium stearate were mixed. Individual samples of 7.45 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose in an immediate-release fraction and half of the dose in a modified release fraction) were weighed (see Table 1bis-b and 1bis-c).

TABLE 1bis-a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Hydroxypropyl cellulose	Top coat	0.310
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Total		3.096

TABLE 1bis-b

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of sodium oxybate	3.096
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.037
Colloidal silicon dioxide	Gliding agent	0.037
Magnesium stearate	Lubricant	0.075
Total		7.451

TABLE 1bis-c

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydroxypropyl cellulose	Top coat	0.310
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.037
Colloidal silicon dioxide	Gliding agent	0.037
Magnesium stearate	Lubricant	0.075
Total		7.451

[0393] Compared to the finished composition described in example 1, this alternative composition has the following characteristics: same MR microparticles, same IR microparticles but with a top coat, increased amount of malic acid, only one suspending agent (xanthan gum) and presence of a glidant.

[0394] Finished compositions from Example 1 and 1bis exhibit substantially the same in-vitro dissolution profiles (see FIGS. **7** and **8**).

Example 2: In Vitro Release Profiles of IR, MR and Finished Compositions of Formulations of Examples 1 and 1Bis

Dissolution Testing of IR Microparticles

[0395] The dissolution profile of 2786 mg of IR microparticles of Example 1, corresponding to 2250 mg of sodium oxybate per vessel, was determined in 0.1N HCl dissolution medium using a USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile of the IR microparticles is shown in FIG. **2** and Table 2a. All the sodium oxybate was released at 1 hour.

TABLE 2a

Percent Sodium Oxybate Released in 0.1N HCl for IR microparticles of sodium oxybate prepared according to Example 1

Time (min)	% released
0	0
5	94
10	97
15	97
30	98
60	98

Dissolution Testing of IR Microparticles from Example 1bis

[0396] The dissolution profile of 3096 mg of IR microparticles of Example 1bis, corresponding to 2250 mg of sodium oxybate per vessel, was determined in 0.1N HCl dissolution medium using a USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile of the IR microparticles is shown in FIG. **2** and Table 2b. All the sodium oxybate was released at 1 hour.

TABLE 2b

Percent Sodium Oxybate Released in 0.1N HCl for IR microparticles of sodium oxybate prepared according Example 1bis

Time (min)	% Released
0	0
5	91
10	99
15	100
30	101
60	100

Dissolution Testing of MR Microparticles from Example 1—Protocol (2 h 0.1N HC/Phosphate Buffer pH 6.8)

[0397] 49.1 g of MR microparticles from Example 1 were mixed with 0.5 g of magnesium stearate (from Peter Graven) and 0.25 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4040 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

[0398] After 2 hours in 750 mL of 0.1N HCl medium, 6.5 g of monobasic potassium phosphate was added to the dissolution vessel. pH and volume were then respectively adjusted to 6.8 and 950 mL, as needed by the addition of

NaOH and water. The potassium phosphate concentration was equal to 0.05 M in the dissolution medium after pH and volume adjustment.

[0399] The release profile of the MR microparticles is shown in FIG. **3** and Table 2c. The sodium oxybate was not released in the 0.1N HCl dissolution medium during two hours. After the switch to pH 6.8 dissolution medium, all the sodium oxybate was released within 30 minutes.

TABLE 2c

Percent Sodium Oxybate Released in two sequential dissolution media (0.1HCl for 2 hours, then phosphate buffer pH 6.8) for MR microparticles of sodium oxybate prepared according to Example 1

Time (h)	% released
0	0
1	1
2	2
2.25	33
2.5	97
3	103
4	104
6	103

[0400] FIG. **4** overlays the dissolution profile of the MR microparticles of Example 1 with the dissolution profile for MR microparticles reported in Supernus U.S. Pat. No. 8,193,211, FIG. 3. It shows that the dissolution profiles are different and that the MR microparticles according to the present invention release greater than 80% of their sodium oxybate at 3 hours, whereas the MR microparticles described in Supernus U.S. Pat. No. 8,193,211, FIG. 3 do not and exhibit a much slower release profile.

Dissolution Testing of Finished Composition According to Example 1 in Deionized Water

[0401] The dissolution profile of the quantity equivalent to 4.5 g sodium oxybate of the finished composition according Example 1 was determined in 900 mL of deionized water using the USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 50 rpm. The release profile is shown in FIG. **5** and Table 2d. The IR fraction of sodium oxybate was solubilized in 15 minutes. The release of sodium oxybate from the modified-release fraction started after approximately 4 hours with 90% of the total dose released at 6 hours.

TABLE 2d

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 1

Time (h)	% released
0	0
0.25	53
1	52
2	54
3	55
4	58
5	69
6	92
7	96
8	97

[0402] An overlay of the release profile of the finished formulation of Example 1 versus that reported in USP 2012/0076865 FIG. **2** is shown in FIG. **6**. It shows that the dissolution profiles are different. The formulation described in USP 2012/0076865 FIG. **2** does not exhibit a lag phase after the dissolution of the immediate release part.

Release Testing of Different Batches of MR Microparticles and Finished Dosage Forms

[0403] In vitro release profiles obtained in 900 mL of 0.1N HCl dissolution medium for different batches of modified release (MR) microparticles prepared according to Example 1 are described below in Table 2e. The dissolution profile of 4040 mg of microparticles corresponding to 2250 mg of sodium oxybate per vessel is determined using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 2e

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium from different manufacturing lots of MR Particles of Example 1

Time	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5	Lot 6	Lot 7	Lot 8
0.25	2.22	0.62	0.42	0.86	0.56	1.03	0.69	0.26
1.0	2.59	1.14	1.23	1.48	0.96	2.15	1.43	0.97
2.00	3.07	1.71	2.09	1.94	1.36	3.16	2.17	1.39
3	3.55	2.31	2.75	2.29	1.76	4.08	2.82	1.80
4.0	4.23	3.03	3.53	2.75	2.18	4.92	3.50	2.31
6	7.99	7.68	8.69	5.33	3.78	7.52	5.70	8.10
8.0	37.44	33.84	33.84	26.20	17.00	21.59	21.02	37.27
10	77.09	69.85	65.51	61.77	49.89	50.98	53.48	67.64
12	91.26	85.72	84.25	83.55	77.65	75.68	78.00	82.66
16	96.15	90.48	95.35	97.34	96.94	95.19	96.17	90.35

[0404] In vitro release profiles obtained in 0.1N HCl for three batches of finished composition comprising IR (50% w/w sodium oxybate dose) and MR microparticles (50% w/w sodium oxybate dose), prepared as described in Example 1, are provided in Table 2f. The sodium oxybate dose per vessel was 4.5 g, 6 g and 7.5 g respectively and dissolution was determined in 900 mL of 0.1N HCl dissolution medium using the USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 2f

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for three batches of finished composition prepared according to Example 1

Time (hour)	Batch 1	Batch 2	Batch 3
0.5	50	49	50
1	50	50	50
3	50	50	50
6	52	52	53
8	61	64	63
12	90	93	97
16	26	24	25

[0405] FIG. **7** and Table 2 g depict dissolution profiles determined using a USP apparatus 2 in a 900 mL in 0.1N HCl dissolution medium of four finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases from 10 to 65% of its sodium oxybate at 1 and 3 hours and releases greater than 60% at 10 hours.

TABLE 2g

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for four batches of finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis

Time (hour)	Example 1bis	Example 1bis	Example 1	Example 1
0	0	0	0	0
0.25	Nd	Nd	52	50
0.5	51	50	Nd	Nd
1	51	50	54	51
3	51	50	54	52
6	55	52	55	53
8	72	61	60	57
10	Nd	Nd	73	70
12	86	90	85	83
16	88	96	96	94
20	Nd	Nd	99	98

Nd: not determined

[0406] FIG. **8** and Table 2h depict dissolution profiles determined using a USP apparatus 2 in a 900 mL phosphate buffer pH 6.8 dissolution medium for four finished compositions prepared according to Example 1 or 1bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases more than 80% of its sodium oxybate at 3 hours.

TABLE 2h

Percent Sodium Oxybate Released in phosphate buffer pH 6.8 Dissolution Medium for four batches of finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis

Time (hour)	Example 1bis	Example 1bis	Example 1	Example 1
0	0	0	0	0
0.25	Nd	Nd	75	84
0.5	99	98	Nd	Nd
1	101	101	100	102
1.5	101	101	106	108
2	100	100	Nd	Nd
3	103	100	Nd	Nd
4	103	100	Nd	Nd
6	102	99	101	102
8	103	99	101	105
10	103	99	101	Nd
12	101	99	101	102
16	Nd	Nd	100	101
20	Nd	Nd	99	98

Nd: not determined

Release Testing of MR Microparticles and Finished Compositions—Effect of Paddle Speed:

[0407] FIG. **9** and Table 2i depict dissolution profiles in 0.1N HCl of a batch of MR microparticles prepared according to Example 1. The dissolution profile of 4040 mg of microparticles corresponding to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2. The dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 or 100 rpm.

TABLE 2i

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for MR microparticles prepared according to Example 1

Time (hour)	75 rpm	100 rpm
0	0	0
0.25	1	1
1	2	1
2	2	2
3	3	2
4	3	3
6	6	5
8	28	26
10	65	62
12	86	84
16	97	97

[0408] FIG. **10** and Table 2j depict dissolution profiles in 0.1N HCl of a finished composition prepared according to Example 1. The dose per vessel was 4.5 g and dissolution was determined in 900 mL of dissolution medium using the USP apparatus 2. The dissolution medium temperature was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 75 or 100 rpm.

[0409] Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 2j

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for finished composition prepared according to Example 1

Time (hour)	75 rpm	100 rpm
0	0	0
0.25	48	47
1	53	52
3	54	53
6	56	56
8	65	65
10	82	79
12	92	89
16	97	96
20	98	98

Example 3. In Vivo Pharmacokinetic Study of Finished Composition According to Example 1Bis

[0410] Pharmacokinetic testing was undertaken in vivo in healthy human volunteers according to the principles described in FDA's March 2003 Guidance for Industry on BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS. All testing was performed in subjects two hours after eating a standardized dinner. Xyrem® doses were administered in two equipotent doses four hours apart. All other tested doses were manufactured as described in Example 1bis. The standardized dinner consisted of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

[0411] The finished composition of Example 1bis given as a 4.5 g once-nightly dose rather than a standard Xyrem® dosing twice (2×2.25 g) nightly 4 hours apart, produced a dramatically different pharmacokinetic profile than Xyrem® as shown in FIG. **11**. As summarized below (Tables 3a and 3b), 4.5 g nighttime doses of finished composition of the invention equivalent to twice-nightly doses of Xyrem® (2×2.25 g) provided somewhat less total exposure to sodium oxybate with a later median T_{max} than the initial Xyrem® dose. The relative bioavailability was about 88%. Composition according to the invention avoids the high second-dose peak concentration of Xyrem® and therefore does not exhibit the substantial between-dose fluctuations in concentration, while achieving a comparable mean C_{8h}.

TABLE 3a

Pharmacokinetic Parameters of finished composition of Example 1bis vs. Xyrem ®

	Mean Cmax (μg/mL) (% CV)	Mean AUCinf (h*μg/mL)	Median Tmax (hour) (min-max)
Finished composition of Example 1bis 4.5 g	44.35 (38)	188.88 (44)	1.5 (0.5-4)
Xyrem ® 2 × 2.25 g	1st dose: 33.41 (41) 2nd dose: 65.91 (40)	214.32 (48)	1st dose: 1.00 (0.5-2) 2nd dose: 4.50 (4.33-6.5)

TABLE 3b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 1bis and Xyrem ®

Time (hour)	Finished composition Example 1bis 4.5 g (2 h after meal) pooled mean (N = 26)	Finished composition Example 1bis 6.0 g (2 h after meal) pooled mean (N = 19)	Finished composition Example 1bis 7.5 g (2 h after meal) (N = 11)	Xyrem ® (2 × 2.25 g) part I (N = 15)
0	0.00	0.00	0.00	0.00
0.5	29.31	36.44	43.19	27.44
1	34.93	49.97	63.32	28.97
1.5	36.63	54.66	73.40	26.12

TABLE 3b-continued

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 1bis and Xyrem ®

Time (hour)	Finished composition Example 1bis 4.5 g (2 h after meal) pooled mean (N = 26)	Finished composition Example 1bis 6.0 g (2 h after meal) pooled mean (N = 19)	Finished composition Example 1bis 7.5 g (2 h after meal) (N = 11)	Xyrem ® (2 × 2.25 g) part I (N = 15)
2	36.78	54.82	67.96	21.11
2.5	33.35	53.05	66.59	NA
3	30.28	50.25	62.13	13.93
3.5	27.30	47.22	59.45	10.25
4	23.66	43.06	57.40	6.92
4.5	19.89	39.13	50.85	57.33
5	16.55	34.28	45.09	52.27
5.5	13.62	32.11	44.94	43.55
6	12.40	25.84	42.36	35.20
6.5	11.25	22.36	41.02	27.44
7	11.27	18.07	40.76	19.36
7.5	9.65	15.41	35.83	13.88
8	6.86	12.80	30.94	9.24
10	1.08	2.38	7.99	2.64
12	NC	0.52	1.47	NC

NC: Not Calculated

[0412] The pharmacokinetic profile of a single 6 g dose of finished composition produced according to Example 1bis was also tested and found to have a similar pharmacokinetic profile as the 4.5 g dose. FIG. **12** provides a pharmacokinetic profile comparison of a single 4.5 g or 6 g dose of finished composition according to Example 1bis in the same 7 subjects. The pharmacokinetic profile for a 7.5 g dose of finished formulation produced according to Example 1bis was also obtained. FIG. **13** and Table 3c provide data on a single 4.5 g, 6 g and 7.5 g dose, showing effects on T_{max}, C_{max}, C_{8h}, AUC_{8h} and AUC_{inf} related to dose strength. The 7.5 g dose achieved a mean C_{8h} equal to about 31 microgram/mL which represents approximately 128.5% of the C_{8h} obtained for Xyrem® dosed 2×3.75 g which was extrapolated to be approximately 24.07 microgram/mL from published data. The 7.5 g dose achieved a ratio of AUC_{8h} to AUC_{inf} of about 0.89, whereas the ratio was 0.83 and 0.93 for the 4.5 g and 6 g doses respectively.

TABLE 3c

Pharmacokinetic Parameters of 4.5 g, 6 g, and 7.5 g of finished composition produced according to Example 1bis

Finished composition according to Example 1bis	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h*μg/mL) (% CV)	Mean $AUC_{8\,h}$ (h*μg/mL) (% CV)	Median T_{max} (h) (min-max)	Mean $C_{8\,h}$ (μg/mL) (% CV)
4.5 g	44.35 (38)	188.88 (47)	174.68 (48)	1.5 (0.5-4)	6.86 (84)
6 g	65.46 (35)	307.34 (48)	290.97 (47)	3 (0.5-5.5)	12.8 (82)
7.5 g	88.21 (30)	454.99 (34)	404.88 (31)	2 (0.5-6)	30.94 (34)

[0413] FIG. **14** and table 3d compare the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g of a finished composition according to Example 1bis to the same parameters calculated for 2×4.5 g, i.e. 9 g total dose of Xyrem®. The data show that a 7.5 g dose of a formulation according to the invention given once nightly exhibits a similar PK profile to 9 g of Xyrem® given in two separate equal doses.

TABLE 3d

Pharmacokinetic Parameters of 7.5 g of finished composition produced according to Example 1bis compared to 2 × 4.5 g of Xyrem ®

	Mean $C_{8\ h}$ (μg/mL)	Mean AUC_{inf} (μg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®	Ratio (%) $C_{8\ h}$ composition to $C_{8\ h}$ Xyrem ®
Xyrem ® 2 × 4.5 g	28.9	518	NA	NA
Finished composition according to Example 1bis 7.5 g	30.9	455	88%	107%

Example 4. Alternative Formulation

[0414] Tables 4a-4d provide the qualitative and quantitative compositions of IR microparticles, MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **15**.

[0415] Briefly, sodium oxybate immediate release (IR) microparticle were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of polyvinylpyrrolidone (Povidone K30-Plasdone™ K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus. IR microparticles with volume mean diameter of about 270 microns were obtained.

[0416] Sodium oxybate modified release (MR) microparticles were prepared as follows: 4.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55), 49.3 g of Methacrylic acid copolymer Type B (Eudragit™ S100), 80 g of Hydrogenated cottonseed oil (Lubritab™), were dissolved in 1200.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR microparticles prepared above in a fluid bed spray coater apparatus with an inlet temperature 48° C., spraying rate around 11 g per min and atomization pressure 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR microparticles with volume mean diameter of about 330 microns were obtained.

[0417] The finished composition, which contained a 50:50 mixture of MR and IR microparticles calculated on their sodium oxybate content, was prepared as follows: 27.86 g of IR microparticles, 37.15 g of MR microparticles, 1.13 g of malic acid (D/L malic acid), 0.50 g of xanthan gum (Xantural™ 75 from Kelco), 0.75 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 0.75 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.34 g of magnesium stearate were mixed. Individual samples of 6.85 g (corresponding to a 4.5 g sodium oxybate dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 4a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		2.786

TABLE 4b

Composition of MR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
IR Microparticles	Core of MR Microparticles	2.786
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.715

TABLE 4c

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.715

TABLE 4c-continued

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.848

TABLE 4d

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.848

Example 4Bis

[0418] An alternative formulation to example 4 is described in example 4bis. Sodium oxybate immediate release (IR) microparticles were prepared by coating the IR microparticles described in example 4 with a top coat layer. IR Microparticles were prepared as follows: 170.0 of hydroxypropyl cellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the IR microparticles of Example 4 in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 298 microns were obtained (see Table 4bis-a).

[0419] Sodium oxybate modified release (MR) microparticles were prepared as described in example 4 (see Table 4b).

[0420] The finished composition, which contains a 50:50 mixture of MR and IR microparticles calculated based on sodium oxybate content, was prepared as follows: 424.99 g of the above IR microparticles, 509.98 g of the above MR microparticles, 30.89 g of malic acid (D/L malic acid), 4.93 g of xanthan gum (Xantural™ 75 from Kelco), 4.93 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 9.86 g of magnesium stearate were mixed. Individual samples of 7.18 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose as an immediate-release fraction and half of the dose as a modified release fraction) were weighed. (see Tables 4bis-b and 4bis-c).

TABLE 4bis-a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Hydroxypropyl cellulose	Top coat	0.310
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Total		3.096

TABLE 4bis-b

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.715
IR microparticles	Immediate release fraction of sodium oxybate	3.096
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.036
Colloidal silicon dioxide	Gliding agent	0.036
Magnesium stearate	Lubricant	0.072
Total		7.180

TABLE 4bis-c

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydroxypropyl cellulose	Top coat	0.310
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.036
Colloidal silicon dioxide	Gliding agent	0.036
Magnesium stearate	Lubricant	0.072
Total		7.180

[0421] Compared to the finished composition described in example 4, this alternative composition has the following characteristics: same MR microparticles, same IR microparticles but with a top coat, increased amount of malic acid, only one suspending agent (xanthan gum) and presence of a glidant.

Example 5 In Vitro Release Profiles of IR, MR and Finished Compositions of Formulation of Example 4 and 4Bis

[0422] Dissolution Testing of MR Microparticles from Example 4—Protocol (2 h 0.1N HCl/Phosphate Buffer pH 6.8)

[0423] 49.1 g of MR microparticles from Example 4 were mixed with 0.5 g of magnesium stearate (from Peter Greven) and 0.25 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik).

[0424] The dissolution profile of 3770 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

[0425] After 2 hours in 750 mL of 0.1N HCl dissolution medium, 6.5 g of monobasic potassium phosphate was added in the dissolution vessel. pH and volume were then respectively adjusted to 6.8 and 950 mL. The potassium phosphate concentration was equal to 0.05 M in the dissolution medium after pH and volume adjustment. The release profile is shown in FIG. **16** and Table 5a.

TABLE 5a

Percent Sodium Oxybate Released in two sequential dissolution media (0.1N HCl for two hours, then phosphate buffer pH 6.8) for MR microparticles of sodium oxybate prepared according to Example 4

Time (h)	% sodium oxybate dissolved
0	0
1	1
2	2
2.25	9
2.5	40
3	89
4	102
6	103

[0426] The sodium oxybate was not released in the 0.1N HCl medium during two hours. After the switch at pH 6.8, 40% of the API was released after 30 minutes and 90% of API after 1 hour. FIG. **17** overlays the dissolution profile of the MR microparticles of Example 4 with the dissolution profile for MR microparticles reported in Supernus U.S. Pat. No. 8,193,211, FIG. 3. It shows that the dissolution profiles are different and especially that the MR microparticles according to the invention release greater than 80% of its sodium oxybate at 3 hours, whereas the MR microparticles described in Supernus U.S. Pat. No. 8,193,211, FIG. 3 do not and exhibit a much slower releasing profile.

Dissolution Testing of Finished Composition According to Example 4 in Deionized Water:

[0427] The dissolution profile of the quantity equivalent to 4.5 g of sodium oxybate of the finished composition of the Example 4 was determined in 900 mL of deionized water using the USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 50 rpm. The release profile of is shown in FIG. **18** and Table 5b.

TABLE 5b

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 4

Time (hour)	Example 4
0	0
0.25	52
1	55
2	53
3	54
4	52
5	54
6	60
7	78
8	90

[0428] The IR fraction of sodium oxybate was solubilized in 15 minutes. The release of sodium oxybate from the modified release fraction started after 5 hours with 90% of the total dose released at 8 hours.

[0429] An overlay of the release profile of the finished composition of the Example 4 versus that reported in USP 2012/0076865 FIG. **2** is shown in FIG. **19**. It shows that the dissolution profiles are different. The formulation described in USP 2012/0076865 FIG. **2** does not exhibit a lag phase after the dissolution of the immediate release part.

[0430] FIG. **20** and Table 5c depict dissolution profiles determined using a USP apparatus 2 in a 900 mL in 0.1N HCl dissolution medium of three finished compositions prepared according to Example 4bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases from 10 to 65% of its sodium oxybate at 1 and 3 hours and releases greater than 60% at 10 hours.

TABLE 5c

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for three batches of finished composition prepared according to Example 4bis

Time (Hour)	Batch 1	Batch 2	Batch 3
0	0	0	0
0.25	50	Nd	Nd
0.5	51	50	49
0.75	51	Nd	Nd
1	51	51	51
1.5	51	Nd	Nd
2	51	Nd	Nd
3	51	52	53
4	51	Nd	Nd
6	55	57	57
8	74	70	71
10	89	Nd	Nd
12	93	90	92
16	94	95	97

Nd = not determined

[0431] FIG. **21** and Table 5d depict dissolution profile determined using a USP apparatus 2 in a 900 mL phosphate buffer pH 6.8 dissolution medium for a finished composition prepared according to Example 4bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 100 rpm. It shows that the composition according to the invention releases more than 80% of its sodium oxybate at 3 hours.

TABLE 5d

Percent Sodium Oxybate Released in phosphate buffer pH 6.8 Dissolution Medium for finished composition prepared according to Example 4bis

Time (Hour)	Example 4bis
0	0
0.25	54
0.5	54
0.75	55
1.0	56
1.5	63
2	77
3	103
4	105
6	105
8	102
10	101
12	104
16	100

Example 6. In Vivo Pharmacokinetic Study of Finished Composition According to Example 4Bis

[0432] Pharmacokinetic testing was undertaken in vivo in healthy human volunteers according to the principles described in FDA's March 2003 Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Product—General Considerations. All testing was performed in subjects two hours after eating a standardized dinner. Xyrem® doses were administered in two equipotent doses four hours apart. All other tested doses were manufactured as described in Example 4bis. The standardized dinner consisted of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

[0433] The finished composition of Example 4bis given as a 4.5 g once-nightly dose rather than a standard Xyrem® dosing twice (2×2.25 g) nightly 4 hours apart, produced a dramatically different pharmacokinetic profile than Xyrem® as shown in FIG. **22**. As summarized below (Tables 6a and 6b), 4.5 g nighttime doses of finished composition of the invention equivalent to twice-nightly doses of Xyrem® (2×2.25 g) provided somewhat less total exposure to sodium oxybate with a later median T_{max} than the initial Xyrem® dose. The relative bioavailability was about 88%. Composition according to the invention avoids the high second-dose peak concentration of Xyrem® and therefore does not exhibit the substantial between-dose fluctuations in concentration, while achieving a comparable mean C_{8h}.

TABLE 6b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 4bis and Xyrem ®

Time (hour)	Finished composition Example 4bis 4.5 g (2 h after meal) (N = 15)	Xyrem ® (2 × 2.25 g) (N = 15)
0	0.00	0.00
0.5	23.80	27.44
1	33.26	28.97
1.5	35.60	26.12
2	35.57	21.11
2.5	33.81	13.93
3	30.96	10.25
3.5	28.73	6.92
4	26.06	42.32
4.5	23.27	57.33
5	18.68	52.27
5.5	16.67	43.55
6	15.55	35.20
6.5	13.07	27.44
7	11.75	19.36
7.5	9.20	13.88
8	6.85	9.24
10	1.94	2.64
12	NC	NC

NC: Not Calculated

[0434] The 4.5 g dose achieved a mean C_{8h} equal to about 6.85 microgram/mL which represents approximately 74.1% of the C_{8h} obtained for Xyrem® dosed 2×2.25 g. The ratio of AUC_{8h} to AUC_{inf} was about 0.89.

Example 7. In Vitro and In Vivo Pharmacokinetic Study of a Comparative Formulation

[0435] A formulation having an in vitro dissolution profile comparable to the formulation reported in FIG. 3 of U.S. Pat. No. 8,193,211 was prepared to confirm the in vitro/in vivo correlations reported herein. Tables 7a-7c provide the qualitative and quantitative compositions of the MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **23**.

[0436] Briefly, sodium oxybate immediate release (IR) microparticles were prepared according to Example 1bis. Sodium oxybate modified release (MR) microparticles were prepared in two steps:

TABLE 6a

Pharmacokinetic Parameters of finished composition of Example 4bis vs. Xyrem ®

	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h*μg/mL) (% CV)	Mean $AUC_{8\ h}$ (h*μg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (μg/mL) (% CV)
Finished composition of Example 4bis 4.5 g	43.47 (49)	188.96 (57)	179.69 (57)	2 (0.5-7)	6.85 (118)
Xyrem ® 2 × 2.25 g	1^{st} dose: 33.41 (41) 2^{nd} dose: 65.91 (40)	214.32 (48)	202.78 (46)	1^{st} dose: 1.0 (0.5-2) 2^{nd} dose: 4.5 (4.33-6.5)	9.24 (127)

[0437] Step 1: 106.7 g of water insoluble polymer Ethylcellulose (Ethocel™ 20 Premium), 10.7 g of polyvinylpyrrolidone (Plasdone™ K30 from ISP), 10.7 g of castor oil (from Olvea) and 5.3 g of Polyoxyl 40 Hydrogenated Castor Oil (Kolliphor RH40 from BASF), were dissolved in a mixture of 828.0 g of acetone, 552.0 g of isopropanol and 153.3 g of water. The solution was sprayed entirely on 400.0 g of immediate release microparticles of sodium oxybate prepared above in a fluid bed spray coater apparatus Glatt G.P.C.G. 1.1 with inlet temperature 57° C., spraying rate around 14.5 g per min and atomization pressure 2.5 bar. Microparticles with volume mean diameter of about 310 microns were obtained.

[0438] Step 2: 15.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 30.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 67.5 g of Hydrogenated cottonseed oil (Lubritab™), were dissolved in 1012.5 g of isopropanol at 78° C. The solution was sprayed entirely on 450.0 g of the above prepared microparticles in a fluid bed spray coater apparatus with an inlet temperature 47° C., spraying rate around 10.5 g per min and atomization pressure 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR Microparticles with volume mean diameter of 335 microns were obtained.

[0439] The finished composition, which contains a 60:40 mixture of MR and IR microparticles calculated based on their sodium oxybate content, was prepared as follows: 326.69 g of the above IR microparticles, 735.04 g of the above MR microparticles, 23.74 g of malic acid (D/L malic acid), 5.54 g of xanthan gum (Xantural™ 75 from Kelco), 5.54 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 11.08 g of magnesium stearate were mixed. Individual samples of 8.40 g (corresponding to a 4.5 g dose of sodium oxybate with 40% of the dose as immediate-release fraction and 60% of the dose as modified release fraction) were weighed.

TABLE 7a

Composition of MR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
IR Microparticles	Core of MR Microparticles	2.786
Ethylcellulose 20	Coating excipient	0.743
Povidone K30	Coating excipient	0.074
Polyoxyl 40 Hydrogenated Castor Oil	Coating excipient	0.037
Castor oil	Coating excipient	0.074
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.124
Methacrylic acid Copolymer Type B	Coating excipient	0.248
Ethyl alcohol	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Water	Solvent	Eliminated during processing
Isopropyl alcohol	Solvent	Eliminated during processing
Total		4.644

TABLE 7b

Qualitative Composition of Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	5.573
IR microparticles	Immediate release fraction of sodium oxybate	2.477
Malic acid	Acidifying agent	0.180
Xanthan gum	Suspending agent	0.042
Colloidal silicon dioxide	Gliding agent	0.042
Magnesium stearate	Lubricant	0.084
Total		8.398

TABLE 7c

Quantitative Composition of Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder and coating excipient	0.326
Hydroxypropyl cellulose	Top coat	0.248
Ethylcellulose 20	Coating excipient	0.892
Polyoxyl 40 Hydrogenated Castor Oil	Coating excipient	0.045
Castor oil	Coating excipient	0.089
Hydrogenated Vegetable Oil	Coating excipient	0.669
Methacrylic acid Copolymer Type C	Coating excipient	0.149
Methacrylic acid Copolymer Type B	Coating excipient	0.297
Malic acid	Acidifying agent	0.180
Xanthan gum	Suspending agent	0.042
Colloidal silicon dioxide	Gliding agent	0.042
Magnesium stearate	Lubricant	0.084
Total		8.398

[0440] The dissolution profile obtained for the MR microparticles in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8) is shown in FIG. **24** and Table 7d. These data show that the dissolution profile of the MR microparticles produced according the comparative Example 7 was quite similar to the dissolution profile of FIG. **3** from U.S. Pat. No. 8,193,211. In particular, the MR microparticles according to the comparative Example 7 do not release more than 80% of its sodium oxybate at 3 hours.

TABLE 7d

Dissolution profile obtained for the MR microparticles of Example 7 in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8)

Time (hour)	Example 7
0	0
1	0
2	1
2.25	5
2.5	44
3	74

TABLE 7d-continued

Dissolution profile obtained for the MR microparticles of Example 7 in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8)	
Time (hour)	Example 7
64	89
6	96

[0441] The finished composition of Comparative Example 7 was tested in the same pharmacokinetic study than the finished composition of Example 1 and 4. As summarized below (Tables 7e), 4.5 g nighttime dose of finished composition of the comparative Example 7 compared to twice-nightly doses of Xyrem® (2×2.25 g) provided much less total exposure to sodium oxybate with a relative bioavailability of 67%.

TABLE 7e

Pharmacokinetic Parameters of finished composition of Comparative Example 7 vs. Xyrem ®				
	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h*μg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (μg/mL) (% CV)
Finished composition of Comparative Example 7 4.5 g	28.99 (45)	143.90 (53)	1.5 (0.5-8)	7.79 (82)
Xyrem ® 2 × 2.25 g	1st dose: 33.41 (41) 2nd dose: 65.91 (40)	214.32 (48)	1st dose: 1.0 (0.5-2) 2nd dose: 4.5 (4.33-6.5)	9.24 (127)

TABLE 7f

Mean plasma concentration (microgram/mL) of gamma-hydroxybutyrate versus time of finished composition of Comparative Example 7 and Xyrem ®				
Time (hour)	Comparative Example 7 @ 4.5 g (2 h after meal) pooled mean (N = 27)	Comparative Example 7 @ 6.0 g (2 h after meal) pooled mean (N = 18)	Comparative Example 7 @ 7.5 g (2 h after meal) (N = 12)	Xyrem ® (2 × 2.25 g) part I (N = 15)
0	0.00	0.00	0.00	0.00
0.5	18.84	25.54	31.40	27.44
1	23.93	35.80	46.78	28.97
1.5	24.31	38.59	58.29	26.12
2	24.32	40.78	57.47	21.11
2.5	23.10	38.03	52.25	13.93
3	20.05	35.76	49.00	10.25
3.5	17.47	33.99	45.66	6.92
4	16.48	30.47	40.52	0.00
4.5	15.44	26.87	37.70	57.33
5	14.10	25.59	36.82	52.27
5.5	12.60	24.63	35.93	43.55
6	11.68	23.90	34.47	35.20
6.5	11.45	23.98	31.60	27.44
7	10.64	20.94	31.89	19.36
7.5	9.35	17.93	29.69	13.88
8	7.79	14.36	25.80	9.24
10	1.98	3.71	11.00	2.64
12	0.59	0.78	3.63	NC

NC: not calculated

[0442] The pharmacokinetic profiles of single 6 g and 7.5 g doses of the finished composition produced according to comparative Example 7 were also generated. Table 7 g provides data on a single 4.5 g, 6 g and 7.5 g dose, showing effects on C_{max}, C_{8h}, AUC_{8h} and AUC_{inf} related to dose strength.

TABLE 7g

Pharmacokinetic Parameters of 4.5 g, 6 g, and 7.5 g of finished composition produced according Comparative Example 7

Finished composition Comparative of Example 7	Mean C_{max} (µg/mL) (% CV)	Mean AUC_{inf} (h*µg/mL) (% CV)	Mean $AUC_{8\ h}$ (h*µg/mL) (% CV)	Median T_{max} (min-max) (h) (% CV)	Mean $C_{8\ h}$ (µg/mL) (% CV)
4.5 g	28.98 (45)	143.90 (53)	128.83 (55)	1.5 (0.5-8)	7.79 (82)
6 g	45.64 (35)	248.24 (47)	225.00 (47)	2 (0.5-6.5)	14.36 (77)
7.5 g	63.31 (33)	379.83 (54)	316.18 (48)	1.75 (1-4.5)	25.80 (74)

Example 8. Alternative Formulations

Example 8.1: Modified Release Formulation of Gamma-Hydroxybutyrate

[0443] comprising immediate release microparticles of potassium salt of gamma-hydroxybutyric acid and modified release microparticles of sodium salt of gamma-hydroxybutyric acid (sodium oxybate).

[0444] Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid can be prepared as follows: 1615.0 g of potassium salt of gamma-hydroxybutyric acid and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone™ K29/32 from ISP) are solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution is entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus.

[0445] Immediate release (IR) microparticles of sodium salt of gamma-hydroxybutyric acid were prepared as follows: 1615.0 g of sodium salt of gamma-hydroxybutyric acid and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans Sanaq) in a fluid bed spray coater apparatus.

[0446] Sodium oxybate modified release (MR) microparticles are prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), are dissolved in 1542.9 g of isopropanol at 78° C. The solution is sprayed entirely onto 400.0 g of the sodium oxybate IR microparticles described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles are dried for two hours with inlet temperature set to 56° C. MR microparticles with mean volume diameter of about 320 microns were obtained.

[0447] The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 398.51 g of the above IR microparticles, 504.80 g of the above MR microparticles, 16.09 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.75 g of magnesium stearate were mixed. Individual samples of 7.49 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8a

Composition of IR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Potassium salt of hydroxybutyric acid	Drug substance	2.537
Microcrystalline cellulose spheres	Core	0.471
Povidone K30	Binder and excipient in diffusion coating	0.134
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		3.142

TABLE 8b

Composition of MR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Povidone K30	Binder	0.118
Microcrystalline cellulose spheres	Core	0.419
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Ethyl alcohol	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing

TABLE 8b-continued

Composition of MR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Water	Solvent	Eliminated during processing
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.981

TABLE 8c

Qualitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid	3.142
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.487

TABLE 8d

Quantitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	2.25
Potassium salt of gamma-hydroxybutyric acid	Drug substance	2.537
Microcrystalline cellulose spheres	Core	0.890
Povidone K30	Binder	0.252
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.487

Example 8.2

[0448] Modified release formulation of gamma-hydroxybutyrate comprising immediate release microparticles of potassium salt of gamma-hydroxybutyric acid, immediate release microparticles of magnesium salt of gamma-hydroxybutyric acid, immediate release microparticles of calcium salt of gamma-hydroxybutyric acid and modified release microparticles of sodium salt of gamma-hydroxybutyric acid (sodium oxybate).

[0449] Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid are prepared according to example 8.1.

[0450] Immediate release (IR) microparticles of magnesium salt of gamma-hydroxybutyric acid or calcium salt of gamma-hydroxybutyric acid can be prepared using the same manufacturing process by replacing the potassium salt of gamma-hydroxybutyric acid by the same weight of respectively magnesium salt of gamma-hydroxybutyric acid or calcium salt of gamma-hydroxybutyric acid.

[0451] Sodium oxybate modified release (MR) microparticles are prepared according to example 8.1.

[0452] The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 132.84 g of the IR microparticles of potassium salt of gamma-hydroxybutyric acid, 215.32 g of the IR microparticles of magnesium salt of gamma-hydroxybutyric acid, 230.05 g of the IR microparticles of calcium salt of gamma-hydroxybutyric acid, 504.80 g of the MR microparticles of sodium oxybate, 23.35 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 5.69 g of magnesium stearate were mixed. Individual samples of 8.96 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8e

Qualitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid + immediate release fraction of magnesium salt of gamma-hydroxybutyric acid + immediate release fraction of calcium salt of gamma-hydroxybutyric acid	4.559
Malic acid	Acidifying agent	0.184
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.97

TABLE 8f

Quantitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	2.25
Potassium salt of gamma-hydroxybutyric acid	Drug substance	0.84
Magnesium salt of gamma-hydroxybutyric acid	Drug substance	1.37

TABLE 8f-continued

Quantitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
Calcium salt of gamma-hydroxybutyric acid	Drug substance	1.46
Microcrystalline cellulose spheres	Core	1.102
Povidone K30	Binder	0.312
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.184
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.96

Example 8.3: Modified Release Formulation of Gamma-Hydroxybutyrate Comprising Immediate Release Microparticles of Potassium Salt of Gamma-Hydroxybutyric Acid and Modified Release Microparticles of Calcium Salt of Gamma-Hydroxybutyric Acid

[0453] Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid are prepared according to example 8.1.

[0454] Immediate release (IR) microparticles of calcium salt of gamma-hydroxybutyric acid can be prepared using the manufacturing process described in example 8.1 for immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid by replacing the potassium salt of gamma-hydroxybutyric acid by the same weight of calcium salt of gamma-hydroxybutyric acid. These Immediate release (IR) microparticles of calcium salt of gamma-hydroxybutyric acid are used to manufacture modified release (MR) microparticles of calcium salt of gamma-hydroxybutyric acid as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), are dissolved in 1542.9 g of isopropanol at 78° C. The solution is sprayed entirely onto 400.0 g of the immediate release microparticles of calcium salt of gamma-hydroxybutyric acid described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles are dried for two hours with inlet temperature set to 56° C.

[0455] The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 398.53 g of the IR microparticles of potassium salt of gamma-hydroxybutyric acid, 492.87 g of the MR microparticles of sodium oxybate, 16.10 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.69 g of magnesium stearate were mixed. Individual samples of 7.39 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8g

Qualitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of calcium salt of gamma-hydroxybutyric acid	3.887
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid	3.143
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydro xyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

TABLE 8h

Quantitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
Potassium salt of gamma-hydroxybutyric acid	Drug substance	2.54
Calcium salt of gamma-hydroxybutyric acid	Drug substance	2.19
Microcrystalline cellulose spheres	Core	0.880
Povidone K30	Binder	0.249
Hydrogenated Vegetable Oil	Coating excipient	0.700
Methacrylic acid Copolymer Type C	Coating excipient	0.155
Methacrylic acid Copolymer Type B	Coating excipient	0.311
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

Example 9: Alternative Formulations with Differing Concentrations of Acidic Agents

[0456] Different prototypes were developed to evaluate the effect of acidic agent on the dissolution stability of the formulation dispersed in water. Experimental data with 0.8%, 1.6% and 15% malic acid are detailed below.

Example 9.1: 1.6% Malic Acid

[0457] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0458] MR coated particles were prepared as follows: 39.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 180.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 49° C., spraying rate around 11.6 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 324 microns were obtained.

[0459] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 655.1 g of the above IR particles, 936.4 g of the above MR particles, 26.5 g of Malic acid (D/L malic acid regular from Bartek), 11.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 17.6 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 17.6 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 8.2 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.11 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0460] FIG. **29** and Table 9a below depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9a

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	47	48
1	53	52
3	53	53
6	55	54
8	59	60
10	74	77
12	87	88
16	96	97
20	97	98

Example 9.2: 0.8% Malic Acid

[0461] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 273 microns were obtained.

[0462] MR coated particles were prepared as follows: 39.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 180.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 47° C., spraying rate around 10.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 60° C. Sodium oxybate MR coated particles with mean diameter of 309 microns were obtained.

[0463] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 100.0 g of the above IR particles, 142.9 g of the above MR particles, 2.0 g of Malic acid (D/L malic acid regular from Bartek), 1.2 g of xanthan gum (Xantural™ 75 from CP Kelco), 1.2 g of hydrophilic fumed silica (Aerosil™ 200 from Degussa) and 2.5 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.93 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0464] FIG. **30** and Table 9b below depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9b

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	51	51
1	51	52
3	51	53
6	52	62
8	60	86
10	77	96
12	90	98
16	98	98

Example 9.3: 15% Malic Acid

[0465] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 255 microns were obtained.

[0466] MR coated particles were prepared as follows: 22.8 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1544.8 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet tem-

perature 49° C., spraying rate around 12.0 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 298 microns were obtained.

[0467] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 36.2 g of the above IR particles, 51.8 g of the above MR particles, 16.1 g of Malic acid (D/L malic acid regular from Bartek), 0.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 1.0 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 1.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.6 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 8.25 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0468] FIG. **31** and Table 9c below depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9c

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	48	49
1	51	51
3	51	51
4	51	51
6	52	51
8	56	56
10	71	71
12	86	85
16	97	96
20	99	98

Example 10. Alternative Formulations

[0469] Suspending agents are present in the formulation to limit microparticles settling after reconstitution. Without suspending agents, microparticles starts settling as soon as shaking stops. In presence of the suspending agents, full microparticles settling does not occur in less than 1 minute. The following data illustrates the good pourability of the suspension assessed by the high recovery of sodium oxybate content in the dissolution test:

[0470] IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 271 microns were obtained.

[0471] MR coated particles were prepared as follows: 39.9 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 80.1 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 180.0 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of sodium oxybate IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.5 g per min and atomization pressure 1.6 bar. MR coated particles were dried for 2 hours with inlet temperature set to 56° C. MR particles of sodium oxybate with mean diameter of 321 microns were obtained.

[0472] The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 634.0 g of the above IR particles, 907.6 g of the above MR particles, 25.7 g of malic acid (D/L malic acid regular from Bartek), 11.4 g of xanthan gum (Xantural™ 75 from CP Kelco), 17.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 17.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 8.1 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 14.20 g (corresponding to a 9 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0473] FIG. **32** and Table 10a below depict dissolution profiles of 9 g doses determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel. Dissolution profile was determined with and without rinsing step.

TABLE 10a

Time (h)	with rinsing	without rinsing
0	0	0
0.25	47	46
1	51	51
3	53	52
6.0	54	53
8	61	60
10	77	74
12	91	88
16	98	95
20	98	96

Example 11. Alternative Formulations with a Different Ratio of IR and MR Fractions

[0474] Different prototypes were prepared and evaluated to determine the effect of IR/MR ratio.

Example 11A: 15% IR/85% IR with MR pH*6.5 Microparticles

[0475] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1896.2 g of absolute ethyl alcohol and 1264.4 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus

GPCG1.1. Sodium oxybate IR particles with mean diameter of 275 microns were obtained.

[0476] MR coated particles were prepared as follows: 22.8 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.1 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 47° C., spraying rate around 10.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 330 microns were obtained.

[0477] 17.1 g of MR microparticles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown in FIG. **33**, Table 11a, and Table 11b.

TABLE 11a

Dissolution data - 0.1N HCl	
Time (hour)	% dissolved
0	0.0
0.25	1
1	1
3	2
4	3
6	6
8	24
10	59
12	83
16	95
20	97

TABLE 11b

Dissolution data - 50 mM phosphate buffer pH 6.8	
Time (hour)	% dissolved
0	0
0.25	18
0.5	80
0.75	97
1	97
2	97

[0478] The qualitative composition of 4.5 g dose units comprising 15% of the dose as IR fraction and 85% of the dose as MR fraction is described in Table 11c.

TABLE 11c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	6.767
IR microparticles	Immediate release fraction of sodium oxybate	0.836
Malic acid	Acidifying agent	0.034
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.039
Total		7.876

[0479] The finished composition, which contains a 85:15 mixture of MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 100.0 g of the above IR particles, 809.5 g of the above MR particles, 4.0 g of malic acid (D/L malic acid regular from Bartek), 6.0 g of xanthan gum (Xantural™ 75 from CP Kelco), 9.0 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.7 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.88 g (corresponding to a 4.5 g dose with 15% of the dose as immediate-release fraction and 85% of the dose as modified release fraction) were weighed.

[0480] After reconstitution with 50 ml of tap water and a rinsing volume of 10 ml of tap water, the finished composition will display the dissolution profiles in FIGS. **34** and **35** and Tables 11d and 11e in 840 ml of 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 11d

Time (hour)	% dissolved
0	0.0
0.25	16
1	16
3	17
4	17
6	20
8	35
10	65
12	85
16	96

TABLE 11e

Time (hour)	% dissolved
0	0
0.25	30
0.5	83
0.75	97
1	98
2	98

Example 11B: 30% IR/70% MR with MR pH*6.2 Microparticles

[0481] IR particles were prepared as follows: 1615.1 g of sodium oxybate and 85.0 g of water soluble polymer poly-

vinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0482] MR coated particles were prepared as follows: 36.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 32.1 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 103.0 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.5 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 12.0 g per min and atomization pressure 1.3 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 323 microns were obtained.

[0483] 17.0 g of sodium oxybate MR particles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile of 4050 mg of the mixture which correspond to 2280 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl dissolution medium using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile in 0.1N HCl is shown in FIG. **36** and Table 1 f.

TABLE 11f

Time (hour)	% dissolved
0.0	0
0.3	1
1.0	3
3.0	4
4.0	4
6.0	8
8.0	40
10.0	81
12.0	95
16.0	100
20.0	99

[0484] The finished composition, which contains a 70:30 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 92.1 g of the above IR particles, 306.5 g of the above MR particles, 7.5 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.0 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.62 g (corresponding to a 4.5 g dose with 30% of the dose as immediate-release fraction and 70% of the dose as modified release fraction) were weighed.

[0485] FIGS. **37** and **38** and Tables 11g and 11h below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 11g

Time (hour)	% dissolved in 0.1N HCl
0.0	0.0
0.3	29
1.0	31
3.0	32
4.0	32
6.0	35
8.0	70
10.0	94
12.0	99
16.0	99

TABLE 11h

Time (h)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	64
0.5	87
1	100
2	100
3	102

Example 11C: 65% IR/35% MR with MR pH*6.5 Microparticles

[0486] IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 270 microns were obtained.

[0487] MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 45.8 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.1 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 47° C., spraying rate around 10.8 g per min and atomization pressure 1.3 bar. MR coated particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 330 microns were obtained.

[0488] Refer to the Example 11a for the dissolution profile of the MR microparticles. The qualitative composition of 4.5 g dose units comprising 65% of the dose as IR fraction and 35% of the dose as MR fraction is described in Table 11i.

TABLE 11i

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	2.786

TABLE 11i-continued

Component	Function	Quantity per 4.5 g dose (g)
IR microparticles	Immediate release fraction of sodium oxybate	3.622
Malic acid	Acidifying agent	0.110
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.752

[0489] The finished composition, which contains a 85:15 mixture of sodium oxybate MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 100.0 g of the above IR particles, 76.9 g of the above MR coated particles, 3.0 g of Malic acid (D/L malic acid regular from Bartek), 1.4 g of xanthan gum (Xantural™ 75 from CP Kelco), 2.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 2.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.75 g (corresponding to a 4.5 g dose with 65% of the dose as immediate-release fraction and 35% of the dose as modified release fraction) were weighed.

[0490] Dissolution profile: After reconstitution with 50 ml tap water and rinsing with 10 ml of tap water, the finished composition will display the dissolution profiles in FIGS. **39** and **40** and Tables 11j and 11k in 840 ml of 0.1N HCl and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 11j

Time (hour)	% dissolved in 0.1N HCl
0	0.0
0.25	65
1	65
3	66
4	66
6	67
8	73
10	86
12	94
16	98
20	99

TABLE 11k

Time (hour)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	71
0.5	93
0.75	99
1	99
2	99

Example 12: Alternative Formulations with IR Fraction Obtained Using Different Manufacturing Processes

[0491] Prototype formulations were developed to test the impact of different manufacturing processes on the dissolution of the formulations.

Example 12A: IR Portion=Raw Sodium Oxybate

[0492] IR particles to serve as cores of the MR coated microparticles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 256 microns were obtained.

[0493] MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 45.8 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1542.9 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 10 g per min and atomization pressure 1.3 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 308 microns were obtained.

[0494] 25.2 g of MR microparticles were mixed with 0.26 g of magnesium stearate (from Peter Greven) and 0.13 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl dissolution medium using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile in 0.1N HCl is shown in FIG. **41** and Table 12a.

TABLE 12a

Time (hour)	% dissolved
0	0
0.25	1
1	1
3	2
4	3
6	14
8	40
10	65
12	78
16	89

[0495] The finished composition, which contains a 50:50 mixture of sodium oxybate MR coated particles and raw sodium oxybate as IR fraction calculated on their sodium oxybate content, was prepared as follows: 36 g of raw sodium oxybate, 63.7 g of the above MR coated particles, 1.8 g of malic acid (D/L malic acid regular from Bartek), 1.6 g of xanthan gum (Xantural™ 75 from CP Kelco), 2.4 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 0.047 g of an apple aroma and 0.3 g of hydrophilic fumed silica (Aerosil 200 from Degussa) were mixed in a Roue-Roehn mixer. Individual doses of 6.66 g (corresponding to a 4.5 g dose with half of the dose as raw sodium oxybate as IR fraction and half of the dose as modified release fraction) were weighed.

[0496] FIG. **42** and Table 12b below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and

the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 12b

Time (hour)	% dissolved
0	0
0.25	50
1	52
4	55
6	57
8	70
10	82
12	87
16	93

[0497] Considering that the 0.1N HCl dissolution profile of the MR coated particles is similar to the MR microparticles from examples 1 and 1bis, the dissolution profile in pH 6.8 phosphate buffer of the finished composition is expected to be similar to the profile depicted in FIG. **8**, insofar as the MR particles are similar and only the nature of the immediate-release fraction was changed.

Example 12B: IR=Microparticles Obtained by Extrusion-Spheronization

[0498] IR particles were prepared as follows: 97 g of sodium oxybate and 3 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were mixed with 7.5 g of water. The mixture was extruded through a 400 micron mesh and spheronized at 1500 rpm for 1.5 min in an extruder-spheronizer Fuji-Paudal MG-55. After drying for 4 hours at 45° C. in a ventilated oven, microparticles were sieved between 150 microns and 500 microns.

[0499] MR coated particles were prepared as described in Example 14.

[0500] The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 67.4 g of the above IR particles obtained by extrusion-spheronization, 115.6 g of the above MR coated particles, 3.3 g of malic acid (D/L malic acid regular from Bartek), 0.9 g of xanthan gum (Xantural™ 75 from CP Kelco), 0.9 g of hydrophilic fumed silica (Aerosil 200 from Degussa) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.54 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0501] FIG. **43** and Table 12c below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 12c

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	51
1	53
4	54
6	54
8	56
10	65
12	79
16	92

[0502] Based on the dissolution profile of the MR coated particles in pH 6.8 phosphate buffer, finished compositions are expected to have the dissolution profile in pH 6.8 phosphate buffer given in Table 12d and FIG. **44**.

TABLE 12d

Time (h)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	55
0.50	97
1	101
1.5	102
2	101
3	101

Example 13. Alternative Formulation without Binder

[0503] IR particles were prepared as follows: 1700.0 g of Sodium Oxybate are solubilized in 1899.4 g of absolute ethyl alcohol and 1261.3 g of water. The solution is entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 244 microns are obtained.

[0504] MR coated particles were prepared as follows: 17.1 g of methacrylic acid copolymer type C (Eudragit L100-55 from Evonik), 34.3 g of methacrylic acid copolymer type B (Eudragit S 100 from Evonik), 77.1 g of hydrogenated cottonseed oil (Lubritab from JRS), are dissolved in 1157.9 g of isopropanol at 78° C. The solution is sprayed entirely on 300.0 g of IR particles prepared above in a fluid bed spray coater apparatus Glatt G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.7 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 289 microns are obtained.

[0505] 25.3 g of MR coated microparticles were mixed with 0.12 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which correspond to 2368 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using the USP apparatus 2. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown below in FIG. **45** and Tables 13a and 13b.

TABLE 13a

Dissolution data - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	0
3	1
4	3
6	29
8	50
10	69
12	82
16	97
20	102

TABLE 13b

Dissolution data - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	5
1	102
3	106

[0506] The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 13c.

TABLE 13c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.841
IR microparticles	Immediate release fraction of sodium oxybate	2.647
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.835

[0507] After reconstitution with 50 ml of tap water and rinsing with 10 ml of tap water, the finished composition is expected to provide the following dissolution profiles in FIGS. **46** and **47** and Tables 13d and 13e in 840 ml of 0.1N HCl and pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 13d

Time (h)	% dissolved in 0.1N HCl
0.0	0
0.3	50
1.0	50
3.0	50
4.0	52
6.0	64
8.0	75
10.0	84
12.0	91
16.0	98
20.0	101

TABLE 13e

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	53
1.0	101
3	103

Example 14: MR Particles with Larger Core Size (160 Microns)

[0508] Different prototypes were also developed to evaluate the impact of the core size on the dissolution of the formulation.

[0509] IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 100 from Pharmatrans) (D[4,3]=160 microns) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 310 microns were obtained.

[0510] MR coated particles were prepared as follows: 25.7 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 51.5 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 115.7 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1735.7 g of isopropanol at 78° C. The solution was sprayed entirely on 450.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 47° C., spraying rate around 9.6 g per min and atomization pressure 1.6 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 370 microns were obtained.

[0511] 49.3 g of sodium oxybate MR particles were mixed with 0.52 g of magnesium stearate (from Peter Greven) and 0.26 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile in 0.1N HCl and pH 6.8 phosphate buffer is shown below in FIG. **48** and Tables 14a and 14b.

TABLE 14a

Dissolution data - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	1

TABLE 14a-continued

Dissolution data - 0.1N HCl	
Time (h)	% dissolved
3	2
6	3
8	7
10	18
12	37
16	75

TABLE 14b

Dissolution data - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	9
0.5	95
1	101
3	101

[0512] The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 14c.

TABLE 14c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	2.786
IR microparticles	Immediate release fraction of sodium oxybate	3.981
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.115

[0513] After reconstitution with 50 ml of tap water and rinsing with 10 ml of tap water, the finished composition is expected to provide the dissolution profiles in FIGS. **49** and **50** and Table 14d and 14e in 840 ml of 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 14d

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	51
4	51
6	52
8	53
10	59
12	69
16	87

TABLE 14e

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	55
1	101
3	101

Example 15. MR Microparticles with Different Ratios of Lubritab™ and Eudragit™

[0514] Different prototypes were developed to evaluate the effect of the ratio between Lubritab™ and Eudragit™ on the formulation.

Example 15A: 30% Lubritab™; Cellets™ 127; Coating Level=35%

[0515] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 100 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

[0516] MR coated particles were prepared as follows: 50.2 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 100.6 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 64.6 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1943.5 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.0 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 403 microns were obtained.

[0517] 17.9 g of sodium oxybate MR microparticles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4308 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **51** and Table 15a.

TABLE 15a

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	3
1	5
3	69
4	96
6	101
8	102
10	102

[0518] Alternative MR coated particles of sodium oxybate were prepared according to the above manufacturing protocol with the coating level adjusted to 50% instead of 35%.

The dissolution profile of the alternative sodium oxybate MR particles was determined using the same protocol as above. The 0.1N HCl dissolution profile is shown in FIG. **52** and Table 15b.

TABLE 15b

Time (h)	% dissolved
0	0
0.25	1
1	1
3	36
4	67
6	95
8	98
10	98

[0519] The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR microparticles, 235.8 g of the above sodium oxybate MR microparticles with a coating level of 30%, 6.2 g of malic acid (D/L malic acid regular from Bartek), 2.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH109 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.0 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.42 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0520] FIG. **53** and Table 15c below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15c

Time (hour)	% dissolved
0	0
0.25	45
1	52
2	92
3	94
4	97
6	97
8	97
10	96

Example 15B: Celphere™ CP203 as Neutral Cores and Coating Level=35%

[0521] IR particles were prepared as follows: 665.0 g of Sodium Oxybate and 35.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 781.2 g of absolute ethyl alcohol and 521.6 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Celphere™ CP203 from Asahi Kasei—mean diameter D[4,3]=250 microns) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 398 microns were obtained.

[0522] MR coated particles were prepared as follows: 37.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 75.4 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 48.5 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1458.0 g of isopropanol at 78° C. The solution was sprayed entirely on 300.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 491 microns were obtained.

[0523] 17.0 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 5210 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **54** and Tables 15d and 15e.

TABLE 15d

Dissolution data - 0.1N HCl	
Time (hour)	% dissolved
0	0
0.25	3
1	3
3	45
4	77
6	96
8	98
10	98

TABLE 15e

Dissolution data - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	1
0.5	22
0.75	87
1	98
2	97

[0524] The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 15f.

TABLE 15f

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	5.205
IR microparticles	Immediate release fraction of sodium oxybate	3.383

TABLE 15f-continued

Component	Function	Quantity per 4.5 g dose (g)
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulo	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.946

[0525] After reconstitution, the finished composition is expected to exhibit the dissolution profiles in FIGS. **55** and **56** and Tables 15g and 15h in 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 15g

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	51
1	51
3	73
4	88
6	98
8	99
10	99

TABLE 15h

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	50
0.5	61
0.75	93
1	99
2	99

Example 15C: 40% Lubritab™ (Coating Level=40%)

[0526] IR pellets were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0527] MR coated particles were prepared as follows: 40.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 80.5 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1799.4 g of isopropanol at 78° C. The solution was sprayed entirely on 300.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.5 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 348 microns were obtained.

[0528] 20.0 g of MR coated particles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4700 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **57** and Table 15i.

TABLE 15i

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	0
1	0
3	1
4	8
6	52
8	84
10	95
12	97
16	98

[0529] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 156.0 g of the above IR particles, 260.0 g of the above MR coated particles, 6.3 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.2 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.2 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.2 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.78 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0530] FIGS. **58** and **59** and Tables 15j and 15k below depict dissolution profiles determined in 0.1N HCl and pH 6.8 buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15j

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	48
1	52
3	52
4	62
6	89
8	96
10	97
12	98
16	98
20	97

TABLE 15k

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	49
0.5	85
1	91
2	96
3	104

Example 15D: 70% Lubritab™ (Coating Level 25%)

[0531] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

[0532] MR coated particles were prepared as follows: 13.3 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 26.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 93.3 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1200.3 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.6 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 313 microns were obtained.

[0533] 17.0 g of MR coated particles were mixed with 0.06 g of magnesium stearate (from Peter Greven). The dissolution profile of 3750 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **60** and Tables 15l and 15m.

TABLE 15l

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0.0
0.25	5
1	4
3	5
4	5
6	8
8	33
10	78
12	98
16	103

TABLE 15M

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0.0
0.25	1
0.5	45
1	97
2	108
3	114

[0534] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR particles, 204.3 g of the above MR coated particles, 6.2 g of Malic acid (D/L malic acid regular from Bartek), 2.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.85 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0535] FIG. **61** and Table 15n depict the dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15n

Time (h)	% dissolved
0	0
0.25	48
1	52
3	52
4	52
6	55
8	76
10	95
12	100
16	100
20	100

[0536] Based on the dissolution profile of the MR coated particles in pH 6.8 phosphate buffer, single dose units are expected to have the dissolution profile in pH6.8 buffer shown in FIG. **62** and in Table 15o.

TABLE 15o

Time (h)	% dissolved in pH 6.8 buffer
0	0.0
0.25	51
0.5	72
1	99
2	104
3	107

Example 16. Evaluation of Different Hydrophobic Compounds in the Coating

[0537] Prototypes with different hydrophobic coatings were prepared and evaluated to determine the effect of coating type on the dissolution of the formulations.

Example 16A: Glyceryl Dibehenate (Compritol™ ATO888)

[0538] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0539] MR coated particles were prepared as follows: 22.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102; 9 g of glyceryl dibehenate (Compritol™ ATO 888 from Gattefossé), were dissolved in 1371.8 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 322 microns were obtained.

[0540] 17.0 g of MR coated particles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **63** and Tables 16a and 16b.

TABLE 16a

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	1
3	3
4	6
6	31
8	67
10	90
12	98
16	100

TABLE 16b

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	1
1	102
3	105

[0541] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 181.1 g of the above IR particles, 258.7 g of the above MR coated particles, 7.3 g of Malic acid (D/L malic acid regular from Bartek), 3.3 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.9 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.9 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.3 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.12 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0542] FIG. **64** and Table 16c depict dissolution profiles determined in 0.1N HCl using a USP apparatus 2. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 16c

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	46
1	50
3	51
4	56
6	78
8	92
10	96
12	97
16	96

[0543] Based on the dissolution profile of the MR microparticles alone in pH 6.8 phosphate buffer, single dose units are expected to have the dissolution profile at pH6.8 shown in FIG. **65** and in Table 16d.

TABLE 16d

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	50
1	101
3	102

Example 16B: 60% Candelilla Wax with Coating Level of 20%

[0544] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from

ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 255 microns were obtained.

[0545] MR coated particles were prepared as follows: 13.3 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 26.7 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 60.0 g of candelilla wax (Kahlwax™ 2039L from Brenntag), were dissolved in 902.2 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 12.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 289 microns were obtained.

[0546] 21.2 g of MR microparticles were mixed with 0.11 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2570 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown below in FIG. **66** and Tables 16e and 16f.

TABLE 16e

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	0
3	0
4	1
6	2
8	2
10	2
12	2
16	3
20	4

TABLE 16f

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	0
0.5	10
0.75	62
1	89
2	101

[0547] The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 16 g.

TABLE 16g

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.483
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.033
Total		6.615

[0548] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 200.0 g of the above IR particles, 250.0 g of the above MR coated particles, 8.1 g of Malic acid (D/L malic acid regular from Bartek), 3.6 g of xanthan gum (Xantural™ 75 from CP Kelco), 5.4 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 5.4 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.4 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.61 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0549] After reconstitution, the finished composition is expected to provide the dissolution profiles in FIGS. **67** and **68** and Tables 16h and 16i in 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus 2, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 16h

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	50
3	50
4	50
6	51
8	51
10	51
12	51
16	52
20	52

TABLE 16i

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	50
0.5	55
0.75	81
1	94
2	100

Example 16C: 40% Candelilla Wax (Coating Level=20%)

[0550] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer

polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 270 microns were obtained.

[0551] MR coated particles were prepared as follows: 20.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 40.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 40.0 g of candelilla wax (Kahlwax™ 2039L from Brenntag), were dissolved in 904.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.9 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 302 microns were obtained.

[0552] 17.0 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 3500 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **69** and Tables 16j and 16k. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

TABLE 16j

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	3
3	6
4	8
6	9
8	15
10	37
12	70
16	97
20	100

TABLE 16k

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	24
0.5	86
0.75	99
1	100
2	100

[0553] The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 16l.

TABLE 16l

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.483
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.033
Total		6.615

[0554] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 122.7 g of the above IR particles, 153.2 g of the above MR coated particles, 5.0 g of malic acid (D/L malic acid regular from Bartek), 2.2 g of xanthan gum (Xantural™ 75 from CP Kelco), 3.3 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 3.3 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.5 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.62 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0555] FIG. **70** and Table 16m depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 16m

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	47
1	51
3	51
4	52
6	52
8	55
10	72
12	89
16	97

[0556] Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished compositions are expected to provide the dissolution profile in pH 6.8 phosphate buffer shown in FIG. **71** and in Table 16n.

TABLE 16n

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	62
0.5	93

TABLE 16n-continued

Time (h)	% dissolved in pH 6.8 buffer
0.75	99
1	100
2	100

Example 16D—60% Cetyl Alcohol (Kolliwax™ CA)

[0557] IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1898.7 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

[0558] MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of cetyl alcohol (Kolliwax™ CA from BASF), were dissolved in 1472.5 g of isopropanol and 77.7 g of water at room temperature. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 14.5 g per min and atomization pressure 2.5 bar. Sodium oxybate MR coated particles with mean diameter of 315 microns were obtained.

[0559] 16.4 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium is given in FIG. **72** and Table 16o. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

TABLE 16o

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	13
1	84
3	103
4	103
6	103
8	103
10	104
12	104
16	103
20	102

Example 17. Effect of Eudragit™ Selection in the Coating of the MR Microparticles

[0560] Further prototypes were developed and evaluate to determine the effect of the Eudragit™ selected on the dissolution of the MR microparticles.

Example 17A: 100% Eudragit™ S100

[0561] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 285 microns were obtained.

[0562] Sodium oxybate IR seal-coated particles were prepared by coating the IR particles described above with a seal-coat layer: 170.0 g of hydroxypropylcellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the above IR particles in a fluid bed spray coater apparatus. Sodium oxybate IR particles with volume mean diameter of about 298 microns were obtained.

[0563] MR coated particles were prepared as follows: 100.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 150.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2250.0 g of isopropanol at 78° C. The solution was sprayed entirely on 750.0 g of the above IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 12.0 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 307 microns were obtained.

[0564] The dissolution profile of 2100 mg of the mixture which corresponds to 1253 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 500 ml of 0.1N HCl medium is reported in FIG. **73** and Table 17a. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17a

Time (h)	% dissolved
0	0
0.25	0
1	1
3	3
4	4
6	9
8	30
10	60
12	81
16	92

[0565] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 425.0 g of the above IR seal-coated particles, 510.0 g of the above MR coated particles, 30.9 g of malic acid (D/L malic acid regular from Bartek), 4.9 g of xanthan gum (Xantural™ 180 from CP Kelco), 4.9 g of Aerosil™ 200 (amorphous anhydrous colloidal silicon dioxide from Evonik) and 9.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.18 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0566] FIG. **74** and Table 17b below depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose

units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17b

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	50
3	50
4	51
6	55
8	67
10	84
12	91
16	94

[0567] FIG. **75** and Table 17c depict the dissolution profile determined using a USP apparatus 2 in phosphate buffer pH 6.8 (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of pH 6.8 dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17c

Time (hour)	% dissolved
0	0
0.25	50
1	51
3	54
4	56
6	93
8	99
10	100
12	100
16	97

Example 17B: 100% Eudragit™ L100-55

[0568] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.1 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1896.2 g of absolute ethyl alcohol and 1264.4 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 275 microns were obtained.

[0569] MR coated particles were prepared as follows: 68.7 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.2 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 46° C., spraying rate around 12.7 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 328 microns were obtained.

[0570] 17.0 g of MR microparticles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile in of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **76** and Tables 17d and 17e. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17d

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	2
3	3
4	6
6	53
8	95
10	99
12	99
16	99
20	99

TABLE 17e

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	21
0.5	99
0.75	103
1	103
2	103

[0571] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR particles, 219.0 g of the above MR coated particles, 6.2 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.12 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0572] FIG. **77** and Table 17f depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17f

Time (hour)	% dissolved
0	0
0.25	46
1	51
3	52
4	59
6	94
8	98
10	98
12	98
16	98

[0573] Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished compositions are expected to provide the dissolution profile in pH 6.8 phosphate buffer in FIG. **78** and Table 17 g.

TABLE 17g

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	61
0.5	99
0.75	101
1	101
2	101

Example 17C: Mixture Eudragit™ L100-S100 (50-50)

[0574] IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

[0575] MR coated particles were prepared as follows: 34.3 g of Methacrylic acid copolymer Type A (Eudragit™ L100 from Evonik), 34.3 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G. 1.1 with inlet temperature 48° C., spraying rate around 11.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 316 microns were obtained.

[0576] 24.0 g of MR microparticles were mixed with 0.12 g of magnesium stearate (from Peter Greven). The dissolution profile of 4050 mg of the mixture which corresponds to 2280 mg of sodium oxybate per vessel was determined using the USP apparatus 2 in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **79** and Tables 17h and 17i. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17h

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	2
3	2
4	3
6	7
8	31
10	62
12	83
16	98
20	100

TABLE 17i

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	2
0.5	5
0.75	13
1	47
2	101

[0577] The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 223.0 g of the above IR particles, 318.4 g of the above MR coated particles, 11.2 g of malic acid (D/L malic acid regular from Bartek), 4.0 g of xanthan gum (Xantural™ 75 from CP Kelco), 6.0 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 6.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.14 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

[0578] FIG. **80** and Table 17j depict dissolution profiles determined using a USP apparatus 2 in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17j

Time (hour)	% dissolved
0	0
0.25	47
1	51
3	51
6	59
8	80
10	92
12	96
16	97

[0579] Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units

of the finished composition are expected to have the dissolution profile in pH 6.8 phosphate buffer given in FIG. **81** and Table 17k.

TABLE 17k

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	51
0.5	53
0.75	56
1	73
2	100

Example 18: In Vivo Pharmacokinetic Study of Finished Composition According to Example 1 (Dose Escalating Study)

[0580] Pharmacokinetic testing was undertaken in vivo in healthy human volunteers. Pharmacokinetic parameters were normalized by the dose. To assess the dose-proportionality, log-transformed dose-normalized PK parameters were pairwise compared according to the statistical methodology described in FDA's 2013 Draft Guidance entitled BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS FOR DRUGS SUBMITTED UNDER AN ANDA (2013). All testing was performed in subjects two hours after eating a standardized dinner. A test product with finished composition of Example 1 and manufactured at larger scale was administered in sequential ascending doses, 4.5 g, 7.5 g and 9 g, one week apart. The tested samples were manufactured as described in Table 1c for 4.5 g and quantities were homothetically adjusted for the other strengths. The dissolution profiles of the MR portions of the test product are presented in FIGS. **86** and **87**. The dissolution profiles of the test product are presented in FIGS. **88** and **89**. The individual concentrations of gamma-hydroxybutyrate and derived PK parameters are summarized below (Tables 18a and 18b) and in FIG. **90**.

TABLE 18a

Pharmacokinetic Parameters of 4.5 g, 7.5 g, and 9 g

Finished composition of test product	Mean C_{max} (µg/mL) (% CV)	Mean AUC_{inf} (µg/mL*h) (% CV)	Mean $AUC_{8\ h}$ (µg/mL*h) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (µg/mL) (% CV)
4.5 g	42.9 (37)	191 (50)	174 (55)	1.71 (0.333-4)	4.76 (105)
7.5 g	72.0 (32)	357 (48)	320 (46)	1.5 (0.333-7)	19.7 (101)
9.0 g	84.5 (34)	443 (46)	379 (41)	2 (0.5-4)	25.5 (97)

[0581] AUC and C_{max} values increased more than dose-proportionally with increasing doses of gamma-hydroxybutyrate formulated as the test product.

TABLE 18b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of test product

Time (hr)	Test product 4.5 g (2 h after meal) (N = 20)	Test product 7.5 g (2 h after meal) (N = 20)	Test product 9 g (2 h after meal) (N = 12)
0	0.00	0.00	0.00
0.167	12.5	17.7	9.34

TABLE 18b-continued

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of test product

Time (hr)	Test product 4.5 g (2 h after meal) (N = 20)	Test product 7.5 g (2 h after meal) (N = 20)	Test product 9 g (2 h after meal) (N = 12)
0.333	23.4	39.0	32.7
0.5	28.1	48.4	47.5
1	34.7	59.8	60.9
1.5	36.7	63.8	71.6
2	35.7	61.6	79.3
2.5	34.7	56.0	64.9
3	29.8	50.1	65.3
3.5	26.9	46.0	60.0
4	23.5	40.9	60.8
4.5	20.1	36.6	48.8
5	17.3	32.7	45.3
5.5	15.4	30.8	41.3
6	13.4	28.7	37.6
7	9.66	24.7	30.5
8	4.76	19.7	25.5
10	0.727	6.97	13.0
12	0.211	1.35	5.13
14	NC	0.392	0.820

NC: Not Calculated

[0582] Table 18c compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 4.5 g of the test product to the same parameters calculated 2×2.25 g, i.e. 4.5 g total dose of Xyrem®.

TABLE 18c

Comparison to 4.5 g divided dose of Xyrem ®

	Mean $C_{8\ h}$ (µg/mL)	Ratio (%) $C_{8\ h}$ composition to $C_{8\ h}$ Xyrem ®	Mean AUC_{inf} (µg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 2.25 g *	9.24	NA	214	NA

TABLE 18c-continued

Comparison to 4.5 g divided dose of Xyrem ®

	Mean $C_{8\ h}$ (µg/mL)	Ratio (%) $C_{8\ h}$ composition to $C_{8\ h}$ Xyrem ®	Mean AUC_{inf} (µg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Test product 4.5 g	4.76	52%	191	89%

* data from the pilot PK study of example 3

[0583] Table 18d compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g of the test product to the same parameters calculated 2×3.75 g, i.e. 7.5 g total dose of Xyrem®.

TABLE 18d

Comparison to 7.5 g divided dose of Xyrem ®

	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 3.75 g (extrapolation from 2 × 4.5 g *)	24.1	NA	432	NA
Test product 7.5 g	19.7	82%	357	83%

* based on data from NDA #21-196

[0584] Table 18e compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g and 9 g of the test product to the same parameters calculated for 2×4.5 g, i.e. 9 g total dose of Xyrem®.

TABLE 18e

Comparison to 9 g divided dose of Xyrem ®

	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL*h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 4.5 g *	28.9	NA	518	NA
Test product 7.5 g	19.7	68%	357	69%
Test product 9 g	25.5	88%	443	86%

* data from NDA #21-196

[0585] For the finished composition administered at 4.5 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max}(Xyrem®) is 1.03. The ratio C_{4h}/C_{max}(Xyrem®) is 0.81. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.69.

[0586] For the finished composition administered at 7.5 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max}(Xyrem®) is 0.77. The ratio C_{4h}/C_{max}(Xyrem®) is 0.63. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.57.

[0587] For the finished composition administered at 9 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max}(Xyrem®) is 0.84. The ratio C_{4h}/C_{max}(Xyrem®) is 0.78. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.63.

[0588] For the finished composition administered at 7.5 g compared to Xyrem® at 2×4.5 g, i.e. total dose of 9 g, the ratio C_{3h}/C_{max}(Xyrem®) is 0.65. The ratio C_{4h}/C_{max}(Xyrem®) is 0.53. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.47.

[0589] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a single daily dose to said human an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises

opening a sachet containing a gamma-hydroxybutyrate formulation,

mixing the formulation with water, and

orally administering the mixture.

2. The method of claim **1**, wherein the orally administering occurs at bedtime.

3. The method of claim **1**, wherein the mixing occurs shortly before the orally administering.

4. The method of claim **1**, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.

5. The method of claim **1**, wherein said administering results in inducing said human to sleep for 6 to 8 hours.

6. The method of claim **1**, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g of sodium oxybate.

7. The method of claim **1**, wherein the mixture is a suspension.

8. The method of claim **1**, wherein the mixing comprises pouring the gamma-hydroxybutyrate formulation from the sachet into a container containing the water.

9. The method of claim **8**, wherein the container contains 50 mL of water prior to the pouring.

10. A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a 4.5 g dose of gamma-hydroxybutyrate to said human that yields a pharmacokinetic profile as shown in FIG. **11**,

wherein the dose comprises immediate release and modified release portions.

11. A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, at a dose of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized evening meal that yields a plasma concentration versus time curve substantially as depicted in FIG. **12**.

12. A method of treating a disorder treatable with gamma-hydroxybutyrate in a human in need thereof, the method comprising:

administering a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, at a dose of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized

evening meal that yields a plasma concentration versus time curve substantially as depicted in FIG. **13**.

13. A method of treating narcolepsy Type 1 or Type 2, the method comprising:

administering a single daily dose to a human in need thereof an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises

opening a sachet containing a gamma-hydroxybutyrate formulation,

mixing the formulation with water, and

orally administering the mixture.

14. The method of claim **13**, wherein the orally administering occurs at bedtime.

15. The method of claim **13**, wherein the mixing occurs shortly before the orally administering.

16. The method of claim **13**, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.

17. The method of claim **13**, wherein said administering results in inducing said human to sleep for 6 to 8 hours.

18. The method of claim **13**, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g of sodium oxybate.

19. The method of claim **13**, wherein the mixture is a suspension.

20. The method of claim **13**, wherein the mixing comprises pouring the gamma-hydroxybutyrate formulation from the sachet into a container containing the water.

21. The method of claim **20**, wherein the container contains 50 mL of water prior to the pouring.

22. A method of treatment of narcolepsy Type 1 or Type 2, the method comprising:

administering a single daily dose to a human in need thereof an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate,

wherein, compared to a dosing regimen consisting of administering half the dose at t_0 and another half of the dose at t_{4h} of an immediate release liquid solution of sodium oxybate, the method produces less confusion, less depressive syndrome, less incontinence, less nausea, or less sleepwalking.

23. A method of reducing narcolepsy-related excessive daytime sleepiness or frequency of cataplectic attacks, the method comprising:

administering a single daily dose to a human in need thereof an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate, wherein the administering comprises

opening a sachet containing a gamma-hydroxybutyrate formulation,

mixing the formulation with water, and

orally administering the mixture.

24. The method of claim **23**, wherein the orally administering occurs at bedtime.

25. The method of claim **23**, wherein the mixing occurs shortly before the orally administering.

26. The method of claim **23**, wherein the orally administering occurs approximately 2 hours after said human has eaten a meal.

27. The method of claim **23**, wherein said administering results in inducing said human to sleep for 6 to 8 hours.

28. The method of claim **23**, wherein the amount of gamma-hydroxybutyrate administered to the human is equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g of sodium oxybate.

29. The method of claim **23**, wherein the mixture is a suspension.

30. The method of claim **23**, wherein the mixing comprises pouring the gamma-hydroxybutyrate formulation from the sachet into a container containing the water.

31. The method of claim **30**, wherein the container contains 50 mL of water prior to the pouring.

* * * * *

EXHIBIT H

US010736866B2

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

(10) **Patent No.: US 10,736,866 B2**
(45) **Date of Patent: *Aug. 11, 2020**

(54) **MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS**

(71) Applicant: **Flamel Ireland Limited**, Dublin (IE)

(72) Inventors: **Claire Mégret**, Lyons (FR); **Hervé Guillard**, Villeurbanne (FR); **Jean-François Dubuisson**, Lyons (FR)

(73) Assignee: **Flamel 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.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/281,235**

(22) Filed: **Feb. 21, 2019**

(65) **Prior Publication Data**

US 2019/0183836 A1 Jun. 20, 2019

Related U.S. Application Data

(63) Continuation of application No. 15/655,924, filed on Jul. 21, 2017, now Pat. No. 10,272,062.

(60) Provisional application No. 62/474,330, filed on Mar. 21, 2017, provisional application No. 62/399,413, filed on Sep. 25, 2016, provisional application No. 62/365,812, filed on Jul. 22, 2016.

(51) **Int. Cl.**

A61K 31/22	(2006.01)
A61K 9/16	(2006.01)
A61K 9/50	(2006.01)
A61K 31/19	(2006.01)
A61K 9/14	(2006.01)

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

CPC ***A61K 31/22*** (2013.01); ***A61K 9/14*** (2013.01); ***A61K 9/1676*** (2013.01); ***A61K 9/5015*** (2013.01); ***A61K 9/5026*** (2013.01); ***A61K 9/5042*** (2013.01); ***A61K 9/5078*** (2013.01); ***A61K 9/5084*** (2013.01); ***A61K 31/19*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,426,120 A	6/1995	Crepaldi et al.
5,594,030 A	1/1997	Conte et al.
6,472,431 B2	10/2002	Cook et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	1316309 A1	6/2003
EP	3353145 A4	7/2019

(Continued)

OTHER PUBLICATIONS

Takahara et al., "Stimulatory Effects of Gamma-Hydroxybutyric Acid on Growth Hormone and Prolactin Release in Humans", J. Clin. Endocrino. Metab., 1977, pp. 1014-1017, vol. 44, No. 5.

(Continued)

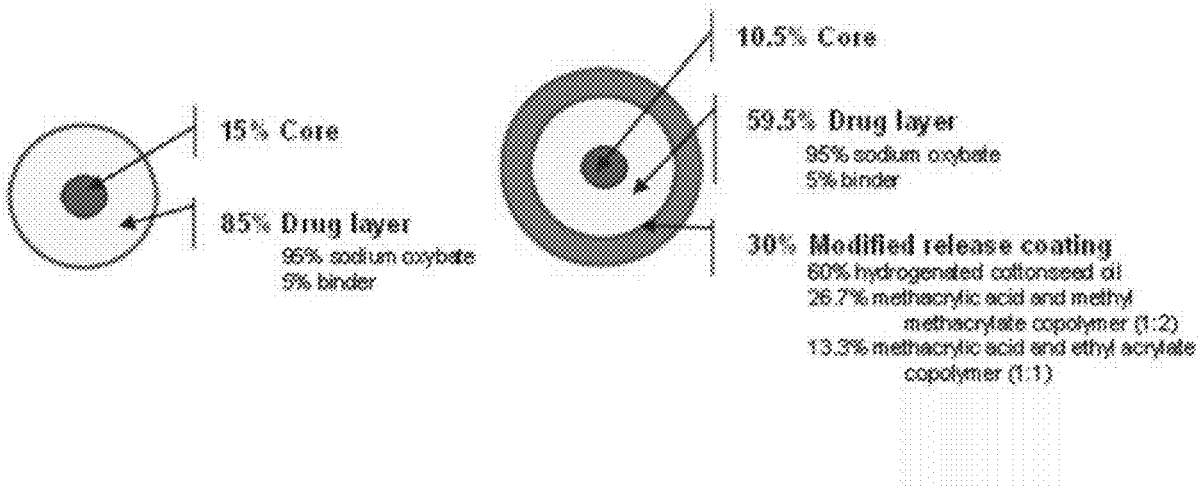
Primary Examiner — Aradhana Sasan

(74) *Attorney, Agent, or Firm* — Polsinelli PC

(57) **ABSTRACT**

Modified release formulations of gamma-hydroxybutyrate having improved dissolution and pharmacokinetic properties are provided, and therapeutic uses thereof.

52 Claims, 46 Drawing Sheets
(43 of 46 Drawing Sheet(s) Filed in Color)



(56) **References Cited**

U.S. PATENT DOCUMENTS

6,780,889	B2	8/2004	Cook et al.	
6,913,768	B2	7/2005	Couch	
7,262,219	B2	8/2007	Cook et al.	
7,668,730	B2	2/2010	Reardan et al.	
7,765,106	B2	7/2010	Reardan et al.	
7,765,107	B2	7/2010	Reardan et al.	
7,797,171	B2	9/2010	Reardon	
7,851,506	B2	12/2010	Cook et al.	
7,895,059	B2	2/2011	Reardan et al.	
8,101,209	B2	1/2012	Legrand	
8,193,211	B2	6/2012	Liang et al.	
8,263,650	B2	9/2012	Cook et al.	
8,324,275	B2	12/2012	Cook et al.	
8,457,988	B1	6/2013	Reardan et al.	
8,461,197	B2	6/2013	Tung	
8,461,203	B2	6/2013	Cook et al.	
8,529,954	B2	9/2013	Lebon et al.	
8,589,182	B1	11/2013	Reardan et al.	
8,591,922	B1	11/2013	Allphin et al.	
8,598,191	B2	12/2013	Liang et al.	
8,731,963	B1	5/2014	Reardon	
8,759,394	B2	6/2014	Tung	
8,771,735	B2	7/2014	Rourke	
8,772,306	B1	7/2014	Eller	
8,778,301	B2	7/2014	Mamelak	
8,778,398	B2	7/2014	Rourke	
8,859,619	B2	10/2014	Cook	
8,901,173	B2	12/2014	Allphin et al.	
8,999,392	B2	4/2015	Suplie et al.	
9,132,107	B2	9/2015	Allphin et al.	
9,486,426	B2	11/2016	Eller	
9,539,330	B2	1/2017	Cook et al.	
9,555,017	B2	1/2017	Allphin et al.	
10,272,062	B2 *	4/2019	Megret	A61K 9/1676
2003/0091632	A1	3/2003	Campbell	
2004/0092455	A1	5/2004	Mamelak	
2005/0158384	A1	7/2005	Couch	
2005/0181050	A1	8/2005	Hirsh	
2005/0244496	A1	11/2005	Campbell	
2006/0018933	A1	1/2006	Vaya	
2006/0204575	A1	9/2006	Feng	
2006/0210630	A1	9/2006	Liang et al.	
2007/0270491	A1	11/2007	Cook	
2009/0220611	A1	9/2009	Dargelas	
2010/0112056	A1	5/2010	Rourke et al.	
2011/0039929	A1	2/2011	Cook	
2011/0111027	A1	5/2011	Rourke et al.	
2011/0293729	A1	12/2011	Lebon et al.	
2012/0020833	A1	1/2012	Cook	
2012/0076865	A1	3/2012	Allphin et al.	
2012/0164228	A1	6/2012	Suplie et al.	
2012/0202879	A1	8/2012	Cook	
2012/0202880	A1	8/2012	Cook	
2013/0012565	A1	1/2013	Tung et al.	
2013/0143965	A1	6/2013	Cook et al.	
2013/0267595	A1	10/2013	Cook et al.	
2014/0004202	A1	1/2014	Suplie et al.	
2014/0037745	A1	2/2014	Liang et al.	
2014/0231300	A1	8/2014	Mogna	
2014/0348917	A1	11/2014	Rourke	
2015/0073052	A1	3/2015	Cook	
2016/0326086	A1	11/2016	Tung et al.	
2018/0318222	A1	11/2018	Allphin	
2019/0194120	A1	6/2019	Xiang et al.	
2019/0218168	A1	7/2019	Xiang et al.	
2020/0113840	A1	4/2020	Allphin	

FOREIGN PATENT DOCUMENTS

WO	2006/053186	A2	5/2006
WO	2010/053691		5/2010
WO	2011/119839	A1	9/2011
WO	2011/139271	A1	11/2011
WO	2012/107652	A1	8/2012
WO	2017/049470		3/2017
WO	2017/050259		3/2017
WO	2018/015563	A1	1/2018

OTHER PUBLICATIONS

Thai et al., "GHB and Ethanol Effects and Interactions in Humans", J Clin Psychopharmacol., 2006, pp. 524-529, vol. 26, No. 5.

Thorpy et al., "Reducing the Clinical and Socioeconomic Burden of Narcolepsy by Earlier Diagnosis and Effective Treatment", Sleep Med Clin., 2017, pp. 61-71, vol. 12.

Tittarelli et al., "Ultra-high-performance liquid chromatography tandem mass spectrometry determination of GHB, GHB-glucuronide in plasma and cerebrospinal fluid of narcoleptic patients under sodium oxybate treatment", Forensic Science International, 2017, pp. 70-74, vol. 274.

Van der Heide et al., "Core Body and Skin Temperature in Type 1 Narcolepsy in Daily Life; Effects of Sodium Oxybate and Prediction of Sleep Attacks", Sleep, 2016, pp. 1941-1949, vol. 39, No. 11.

Van Ginneken et al., "Linear and Nonlinear Kinetics of Drug Elimination. I. Kinetics on the Basis of a Single Capacity-Limited Pathway of Elimination with or Without Simultaneous Supply-Limited Elimination", Journal of Pharmacokinetics and Biopharmaceutics, 1974, pp. 395-415, vol. 2, No. 5.

Van Schie et al., "Improved vigilance after sodium oxybate treatment in narcolepsy: a comparison between in-field and in-laboratory measurements", Journal of Sleep Research, 2016, pp. 486-496, vol. 25.

Wang et al., "The Role of Monocarboxylate Transporter 2 and 4 in the Transport of γ-Hydroxybutyric Acid in Mammalian Cells", Drug Metabolism and Disposition, 2007, pp. 1393-1399, vol. 35, No. 8.

Wang et al., "Flavonoids Modulate Monocarboxylate Transporter-1-Mediated Transport of γ-Hydroxybutyrate in Vitro and in Vivo", Drug Metabolism and Disposition, 2007, pp. 201-208, vol. 35, No. 2.

Wang et al., "Transport of γ-Hydroxybutyrate in Rat Kidney Membrane Vesicles: Role of Monocarboxylate Transporters", J. Pharmacol. Exp. Ther., 2006, pp. 751-761, vol. 318, No. 2.

Wang et al., "Characterization of Monocarboxylate Transport in Human Kidney HK-2 Cells", Molecular Pharmaceutics, 2006, pp. 675-685, vol. 3, No. 6.

Wang et al., "Monocarboxylate Transporter (MCT) Mediates the Transport of γ-Hydroxybutyrate in Human Kidney HK-2 cells", Pharmaceutical Research, 2007, pp. 1067-1078, vol. 24, No. 6.

Wang et al., "Pharmacokinetic Interaction between the Flavonoid Luteolin and γ-Hydroxybutyrate in Rats: Potential Involvement of Monocarboxylate Transporters", The AAPS Journal, 2008, pp. 47-55, vol. 10, No. 1.

Abad et al., "New developments in the management of narcolepsy", Nature and Science of Sleep, 2017, pp. 39-57, vol. 9.

Abanades et al., "γ-Hydroxybutyrate (GHB) in Humans, Pharmacodynamics and Pharmacokinetics", Annals New York Academy of Sciences, 2006, pp. 559-576, vol. 1074.

Abanades et al., "Relative Abuse Liability of γ-Hydroxybutyric Acid, Flunitrazepam, and Ethanol in Club Drug Users", Journal of Clinical Psychopharmacology, 2007, pp. 625-638, vol. 27, No. 6.

Ahmed et al., "Narcolepsy and influenza vaccination-induced autoimmunity", Annals of Translational Medicine, 2017, pp. 1-4, vol. 5, No. 1.

Ahmed et al., "The Safety of Adjuvanted Vaccines Revisited: Vaccine-Induced Narcolepsy", Isr Med Assoc J., 2016, pp. 216-220, vol. 18.

Aldrete et al., "Does Magnesium Produce Anesthesia? Evaluation of its Effects on the Cardiovascular and Neurologic Systems", Anesthesia and Analgesia, 1968, pp. 428-433, vol. 47, No. 4.

Alshaikh et al., "Sodium Oxybate for Narcolepsy with Cataplexy: Systematic Review and Meta-Analysis", Journal of Clinical Sleep Medicine, 2012, pp. 451-458, vol. 8, No. 4.

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, pp. 356-358, vol. 69, No. 3.

(56) **References Cited**

OTHER PUBLICATIONS

Barateau et al., "Hypersomnolence, Hypersomnia, and Mood Disorders", Current Psychiatry Reports, 2017, pp. 1-11, vol. 19.
Barateau et al., "Management of Narcolepsy", Current Treatment Options in Neurology, 2016, pp. 1-13, vol. 18.
Bayram et al., "Efficiency of a Combination of Pharmacological Treatment and Nondrug Interventions in Childhood Narcolepsy", Neuropediatrics, 2016, pp. 380-387, vol. 47, No. 6.
Bhattacharya et al., "Feasibility of D-Glucuronate to Enhance γ-Hydroxybutyric Acid Metabolism During γ-Hydroxybutyric Acid Toxicity: Pharmacokinetic and Pharmacodynamic Studies", Biopharmaceutics & Drug Disposition, 2007, pp. 1-11, vol. 28.
Bhattacharya et al., "Potential γ-Hydroxybutyric acid (GHB) Drug Interactions Through Blood-Brain Barrier Transport Inhibition: A Pharmacokinetic Simulation-Based Evaluation", Journal of Pharmacokinetics and Pharmacodynamics, 2006, pp. 657-681, vol. 33, No. 5.
Black et al., "Challenges in the development of therapeutics for narcolepsy", Prog Neurobiol., 2017, pp. 89-113, vol. 152.
Black et al., "Medical Comorbidity in Narcolepsy: Findings from the Burden of Narcolepsy Disease (BOND) Study", Sleep Medicine, 2017, pp. 13-18, vol. 33.
Black et al., "The Nightly Use of Sodium Oxybate is Associated with a Reduction in Noctural Sleep Disruption: A Double-Blind, Placebo-Controlled Study in Patients with Narcolepsy", Journal of Clinical Sleep Medicine, 2010, pp. 596-602, vol. 6, No. 6.
Bogan et al., "Evaluation of Quality of Life in Patients With Narcolepsy Treated with Sodium Oxybate: Use of the 36-Item Short-Form Health Survey in a Clinical Trial", Neurology and Therapy, 2016, pp. 203-213, vol. 5.
Borgen et al., "The Influence of Gender and Food on the Pharmacokinetics of Sodium Oxybate Oral Solution in Healthy Subjects", Journal of Clinical Pharmacology, 2003, pp. 59-65, vol. 43.
Borgen et al., "The Pharmacokinetics of Sodium Oxybate Oral Solution following Acute and Chronic Administration to Narcoleptic Patients", Journal of Clinical Pharmacology, 2004, pp. 253-257, vol. 44.
Boscolo-Berto et al., "Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): A systematic review and meta-analysis of randomized controlled trials", Sleep Medicine Reviews, 2012, pp. 431-443, vol. 16.
Brailsford et al. "Increases in Serum Growth Hormone Concentrations Associated with GHB Administration", Journal of Analytical Toxicology, 2017, pp. 54-59, vol. 41.
Brenneisen et al., "Pharmacokinetics and Excretion of Gamma-Hydroxybutyrate (GHB) in Healthy Subjects", Journal of Analytical Toxicology, 2004, pp. 625-630, vol. 28.
Calik, "Update on the treatment of narcolepsy: clinical efficacy of pitolisant", Nature and Science of Sleep, 2017, pp. 127-133, vol. 9.
Carlier et al., "Gamma-hydroxybutyrate (GHB), an unusual cause of high anion gap metabolic acidosis", CJEM-JCMU, 2018, pp. S2-S5, vol. 20.
Carter et al., "Behavioral Analyses of GHB: Receptor Mechanisms", Pharmacol Ther., 2009, pp. 100-114, vol. 121, No. 1.
Carter et al., "Cognitive, psychomotor, and subjective effects of sodium oxybate and triazolam in healthy volunteers", Psychopharmacology (Berl), 2009, pp. 141-154, vol. 206, No. 1.
Ciolino et al., "The Chemical Interconversion of GHB and GBL: Forensic Issues and Implications", Journal of Forensic Sciences, 2001, pp. 1315-1323, vol. 46, No. 6.
Cook et al., "Review article: short chain fatty acids in health and disease", Aliment Pharmacol Ther, 1998, pp. 499-507, vol. 12.
Cremaschi et al., "Narcolepsy type 1 and type 2—a 10-year follow-up: body mass index and comorbidities", Sleep Medicine, 2017, pp. 285-286, vol. 32.
Dauvilliers et al., "Vitamin D deficiency in type 1 narcolepsy: a reappraisal", Sleep Medicine, 2017, pp. 1-6, vol. 29.
Dauvilliers et al., "Narcolepsy with cataplexy", The Lancet, 2007, pp. 499-511, vol. 369.
Donjacour et al., "Sodium oxybate increases prolactin secretion in narcolepsy patients and healthy controls", European Journal of Endocrinology, 2011, pp. 363-370, vol. 164.
Drakatos et al., "Sleep-stage sequencing of sleep-onset REM periods in MSLT predicts treatment response in patients with narcolepsy", J Sleep Res., 2016, pp. 203-210, vol. 25.
Dye et al., "Epidemiology and Pathophysiology of Childhood Narcolepsy", Paediatric Respiratory Reviews, 2018, pp. 14-18, vol. 25.
Felmlee et al., "Concentration-Effect Relationships for the Drug of Abuse γ-Hydroxybutyric Acid", The Journal of Pharmacology and Experimental Therapeutics, 2010, pp. 764-771, vol. 333, No. 3.
Felmlee et al., "Mechanistic Toxicokinetic Model for γ-Hydroxybutyric Acid: Inhibition of Active Renal Reabsorption as a Potential Therapeutic Strategy", The AAPS Journal, 2010, pp. 407-416, vol. 12, No. 3.
Ferrara et al., "Therapeutic gamma-hydroxybutyric acid monitoring in plasma and urine by gas chromatography-mass spectrometry", Journal of Pharmaceutical & Biomedical Analysis, 1993, pp. 483-487, vol. 11, No. 6.
Ferris et al., "Synthesis, characterisation and detection of gamma-hydroxybutyrate salts", Forensic Science International, 2012, pp. 158-162, vol. 216.
Flores et al., "The Humanistic and Economic Burden of Narcolepsy", Journal of Clinical Sleep Medicine, 2016, pp. 401-407, vol. 12, No. 3.
Franco et al., "High bicarbonate levels in narcoleptic children", J Sleep Res., 2016, pp. 194-202, vol. 25.
Fuller et al., "The Xyrem® Risk Management Program", Drug Safety, 2004, pp. 293-306, vol. 27, No. 5.
Fung et al., "Pharmacokinetics of 1,4-Butanediol in Rats: Bioactivation to γ-Hydroxybutyric Acid, Interaction with Ethanol, and Oral Bioavailability", The AAPS Journal, 2008, pp. 56-69, vol. 10, No. 1.
Gadroen et al., "Patterns of spontaneous reports on narcolepsy following administration of pandemic influenza vaccine; a case series of individual case safety reports in Eudravigilance", Vaccine, 2016, pp. 4892-4897, vol. 34.
George et al., "A 2-week, polysomnographic, safety study of sodium oxybate in obstructive sleep apnea syndrome", Sleep Breath, 2011, pp. 13-20, vol. 15.
Gill et al., "Expression and membrane localization of MCT isoforms along the length of the human intestine", Am J Physiol Cell Physiol, 2005, pp. C846-C852, vol. 289.
Grenier et al., "Enzymatic Assay for GHB Determination in Forensic Matrices", Journal of Analytical Toxicology, 2012, pp. 523-528, vol. 36.
International Search Report and Written Opinion from related Application No. PCT/EP2017/068552 dated Sep. 15, 2017, 10 pp.
Morgenthaler, Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin, Sleep. vol. 30, No. 12, 2007.
A Double-Blind, Placebo-Controlled Study Demonstrates Sodium Oxybate is Effective for the Treatment of Excessive Daytime Sleepiness in Narcolepsy, International Xyrem Study Group, Journal of clinical Sleep Medicine, vol. 1, No. 4, 2005, pp. 291-397.
Xyrem (sodum oxybate); Highlights of Prescribing Information and Full Prescribing Information, Jazz Pharmaceuticals, Inc., Revised: Apr. 2015, 31 pp.
International Search Report and Written Opinion dated Apr. 15, 2019 from related International Application No. PCT/IB2018/060278, 11 pp.
Haller et al., "GHB Urine Concentrations After Single-Dose Administration in Humans", Journal of Analytical Toxicology, 2006, pp. 360-364, vol. 30.
Helrich et al., "Correlation of Blood Levels of 4-Hydroxybutyrate with State of Consciousness", Anesthesiology, 1964, pp. 771-775, vol. 25, No. 6.
Hennessy et al., "The Reactivity of Gamma-hydroxybutyric acid (GHB) and Gamma-butyrolactone (GBL) in Alcoholic Solutions", Journal of Forensic Sciences, 2004, pp. 1-10, vol. 49, No. 6.
Jennum et al., "Morbidity of childhood onset narcolepsy: a controlled national study", Sleep Medicine, 2017, pp. 13-17, vol. 29.

(56) **References Cited**

OTHER PUBLICATIONS

Johnson et al., "Comparative Abuse Liability of GHB and Ethanol in Humans", Experimental and Clinical Psychopharmacology, 2013, pp. 112-123, vol. 21, No. 2.
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", Journal of Analytical Toxicology, 2009, pp. 332-335, vol. 33.
Kallweit et al., "Pharmacological management of narcolepsy with and without cataplexy", Expert Opinion on Pharmacotherapy, 2017, pp. 809-817, vol. 18, No. 8.
Keating, "Sodium Oxybate: A Review of its use in Alcohol Withdrawal Syndrome and in the Maintenance of Abstinence in Alcohol Dependence", Clinical Drug Investigation, 2014, pp. 63-80, vol. 34.
Khatami et al., "The European Narcolepsy Network (EU-NN) database", J Sleep Res., 2016, pp. 356-364, vol. 25.
Kollb-Sielecka et al., "The European Medicines Agency Review of pitolisant for treatment of narcolepsy: summary of the scientific assessment by the Committee for Medicinal Products for Human Use", Sleep Medicine, 2017, pp. 125-129, vol. 33.
Kornum et al., "Narcolepsy", Nature Reviews/Disease Primers, 2017, Article No. 16100, pp. 1-19, vol. 3.
Kovalska et al., "Narcolepsy with cataplexy in patients aged over 60 years: a case-control study", Sleep Medicine, 2016, pp. 79-84, vol. 26.
Kovalska et al., "Higher body mass index in narcolepsy with cataplexy: lifelong experience", Sleep Medicine, 2017, p. 277, vol. 32.
Krahn, "Understanding the needs of older patients with narcolepsy", Sleep Medicine, 2016, p. 85, vol. 26.
Kristoffersen et al., "Determination of safety margins for whole blood concentrations of alcohol and nineteen drugs in driving under the influence cases", Forensic Science International, 2016, pp. 119-126, vol. 259.
Lam et al., "Monocarboxylate Transporter-Mediated Transport of γ-Hydroxybutyric Acid in Human Intestinal Caco-2 Cells", Drug Metabolism and Disposition, 2010, pp. 441-447, vol. 38, No. 3.
Lecendreux et al., "Narcolepsy Type 1 is Associated with a Systemic Increase and Activation of Regulatory T Cells and with a Systemic Activation of Global T Cells", PLoS One, 2017, e0169836, pp. 1-14.
Lernmark, "Environmental factors in the etiology of type 1 diabetes, celiac disease and narcolepsy", Pediatric Diabetes, 2016, pp. 65-72, vol. 17 (Suppl 22).
Liakoni et al., "Presentations to an urban emergency department in Switzerland due to acute γ-hydroxybutyrate toxicity", Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine, 2016, pp. 1-9, vol. 24.
Liechti et al., "Pharmacokinetics and pharmacodynamics of γ-hydroxybutyrate in healthy subjects", British Journal of Clinical Pharmacology, 2016, pp. 980-988, vol. 81.
Lin et al., "Human Monocarboxylate Transporter 2 (MCT2) is a High Affinity Pyruvate Transporter", The Journal of Biological Chemistry, 1998, pp. 28959-28965, vol. 273, No. 44.
Lingford-Hughes et al., "Improving GHB withdrawal with baclofen: study protocol for a feasibility study for a randomised controlled trial", Trials, 2016, pp. 1-11, vol. 17.
Linselle et al., "Can drugs induce or aggravate Sleep Apneas? A case non case Study in Vigibase®, the WHO Pharmacovigilance Database", Fundamental & Clinical Pharmacology, 2017, pp. 359-366, vol. 31, No. 3.
Maitre et al., "Mechanisms for the Specific Properties of γ-Hydroxybutyrate in Brain", Medicinal Research Reviews, 2016, pp. 363-388, vol. 36.
Mamelak et al., "A Pilot Study on the Effects of Sodium Oxybate on Sleep Architecture and Daytime Alertness in Narcolepsy", Sleep, 2004, pp. 1327-1334, vol. 27, No. 7.
Maresova et al., "Treatment cost of narcolepsy with cataplexy in Central Europe", Therapeutics and Clinical Risk Management, 2016, pp. 1709-1715, vol. 12.
Martinez-Orozco et al., "Comorbidity of Narcolepsy Type 1 With Autoimmune Diseases and Other Immunopathological Disorders: A Case-Control Study", J Clin Med Res., 2016, pp. 495-505, vol. 8, No. 7.
Mason et al., "Gamma Hydroxybutyric Acid (GHB) Intoxication", Acad Emerg Med, 2002, pp. 730-739, vol. 9, No. 7.
Mazarr-Proo et al., "Distribution of GHB in Tissues and Fluids Following a Fatal Overdose", Journal of Analytical Toxicology, 2005, pp. 398-400, vol. 29.
Mesmer et al., "Determination of Gamma-Hydroxybutyrate (GHB) and Gamma-Butyrolactone (GBL) by HPLC/UV-VIS Spectrophotometry and HPLC/Thermospray Mass Spectrometry", Journal of Forensic Sciences, 1998, pp. 489-492, vol. 43, No. 3.
Moresco et al., "Pharmacogenetics and Treatment Response in Narcolepsy Type 1: Relevance of the Polymorphisms of the Drug Transporter Gene ABCB1", Clinical Neuropharmacology, 2016, pp. 18-23, vol. 39, No. 1.
Morris et al., "Renal Clearance of γ-Hydroxybutyric Acid in Rats: Increasing Renal Elimination as a Detoxification Strategy", Journal of Pharmacology and Experimental Therapeutics, 2005, pp. 1194-1202, vol. 313, No. 3.
Morris et al., "Overview of the Proton-coupled MCT (SLC16A) Family of Transporters: Characterization, Function and Role in the Transport of the Drug of Abuse γ-Hydroxybutyric Acid", The AAPS Journal, 2008, pp. 311-321, vol. 10, No. 2.
Morse et al., "Effects of Monocarboxylate Transporter Inhibition on the Oral Toxicokinetics/Toxicodynamics of γ-Hydroxybutyrate and γ-Butyrolactone", The Journal of Pharmacology and Experimental Therapeutics, 2013, pp. 102-110, vol. 345.
Nellore et al., "Narcolepsy and influenza vaccination—the inappropriate awakening of immunity", Annals of Translational Medicine, 2016, S29, pp. 1-6, vol. 4 (Suppl 1).
Okun et al., "GHB: An Important Pharmacologic and Clinical Update", J Pharm Pharmaceut Sci., 2001, pp. 167-175, vol. 4, No. 2.
Palatini et al., "Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers", European Journal of Clinical Pharmacology, 1993, pp. 353-356, vol. 45.
Pardi et al., "γ-Hydroxybutyrate/Sodium Oxybate; Neurobiology, and Impact on Sleep and Wakefulness", CNS Drugs, 2006, pp. 993-1018, vol. 20, No. 12.
Raybon et al., "Pharmacokinetics and Pharmacodynamics of γ-Hydroxybutyric Acid during Tolerance in Rats: Effects on Extracellular Dopamine", The Journal of Pharmacology and Experimental Therapeutics, 2007, pp. 1252-1260, vol. 320, No. 3.
Ritzhaupt et al., "The characterization of butyrate transport across pig and human colonic luminal membrane", Journal of Physiology, 1998, pp. 819-830, vol. 507.3.
Roth et al., "Effect of sodium oxybate on disrupted nighttime sleep in patients with narcolepsy", Journal of Sleep Research, 2017, pp. 407-414, vol. 26.
Russell et al., "Sodium Oxybate Relieves Pain and Improves Function in Fibromyalgia Syndrome. A Randomized, Double-Blind, Placebo-Controlled, Multicenter Clinical Trial", Arthritis & Rheumatism, 2009, pp. 299-309, vol. 60, No. 1.
Russell et al., "Sodium oxybate reduces pain, fatigue, and sleep disturbance and improves functionality in fibromyalgia: results from a 14-week, randomized, double-blind, placebo-controlled study", Pain, 2011, pp. 1007-1017, vol. 152, No. 5.
Scharf et al., "Pharmacokinetics of Gammahydroxybutyrate (GHB) in Narcoleptic Patients", Sleep, 1998, pp. 507-514, vol. 21, No. 5.
Strand et al., "Driving Under the Influence of Non-Alcohol Drugs—An Update. Part II: Experimental Studies", Forensic Science Review, 2016, pp. 100-101, vol. 28, No. 2.
Susta et al., "Emotion stimulus processing in narcolepsy with cataplexy", J Sleep Res., 2017, pp. 30-37, vol. 26.
Office action dated Apr. 15, 2020 from related U.S. Appl. No. 16/223,940, 22 pgs.
Office action dated Feb. 18, 2020 from related CA Application No. 3,028,878, 3 pgs.
Notice of Allowance dated Mar. 29, 2020 from related JP Application No. 2019-503463, 3 pgs.

(56) **References Cited**

OTHER PUBLICATIONS

Rowe, Raymond C. "Polymethacrylates," Handbook of Pharmaceutical Excipients, 2006, Fifth Edition, Pharmaceutical Press, London, pp. 553-560.

Haque et al., "Model Dependent and Independent Approaches to Compare in vitro Release Profiles from Ethylcellulose and Eudragit L100 Based Matrix Tablets," Dhaka Univ. J. Pharm. Sci., 2009, 8(1): 89-98.

FDA Guideline, Revised Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations; Availability, Federal Register, Mar. 19, 2003, vol. 68, No. 53, 1 pp.

Office action dated Apr. 15, 2020 from corresponding U.S. Appl. No. 16/223,940, 22 pp.

* cited by examiner

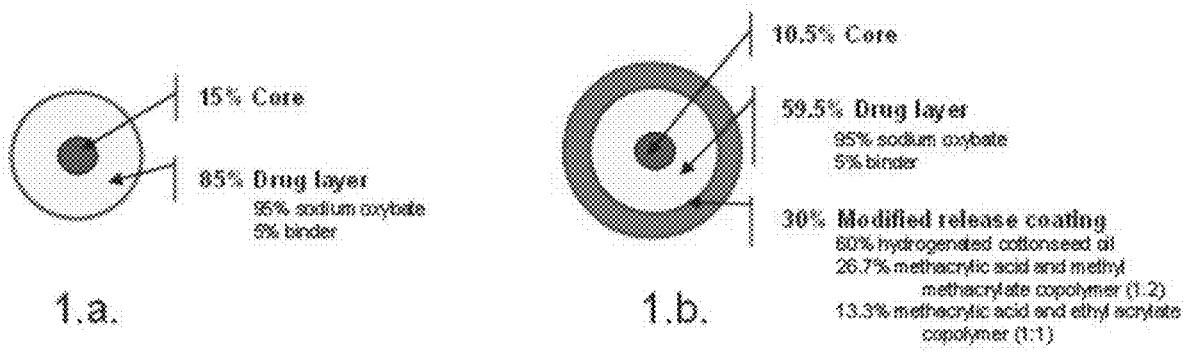


Figure 1

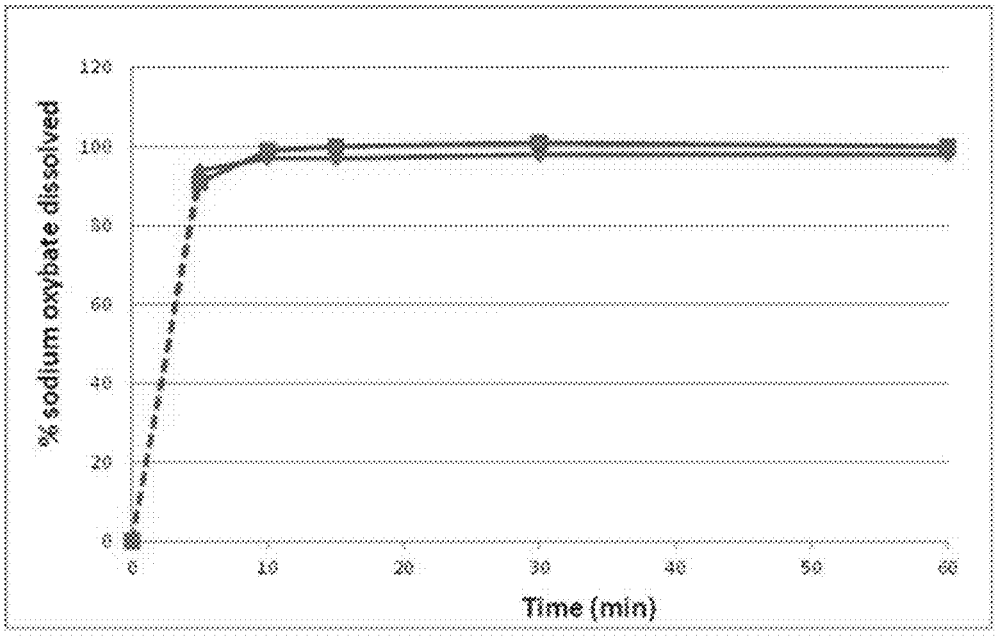


Figure 2

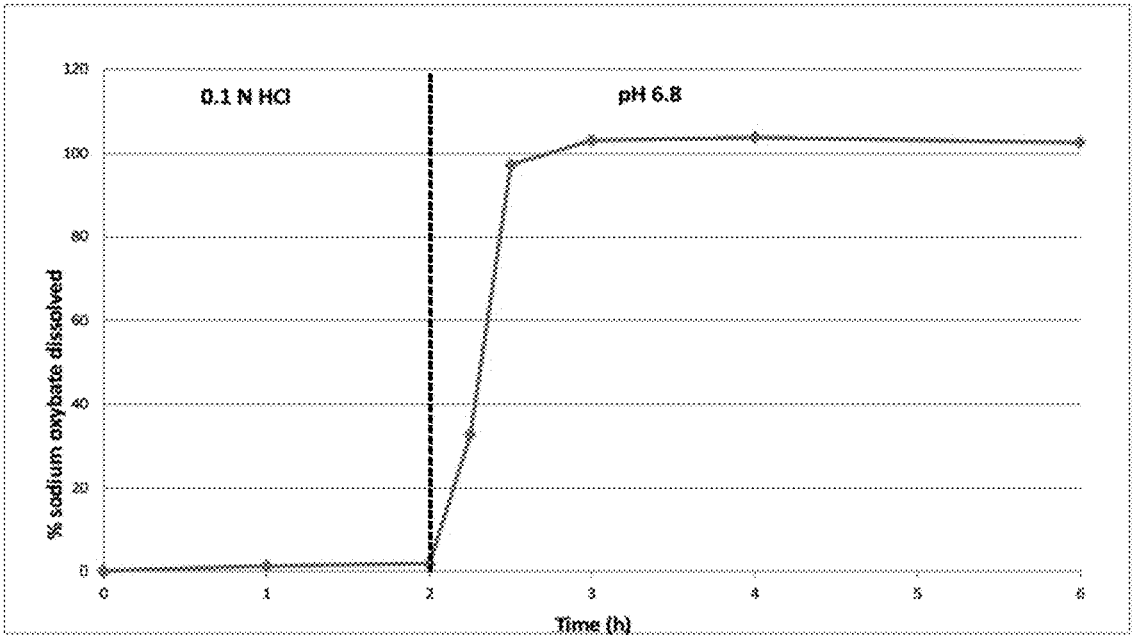


Figure 3

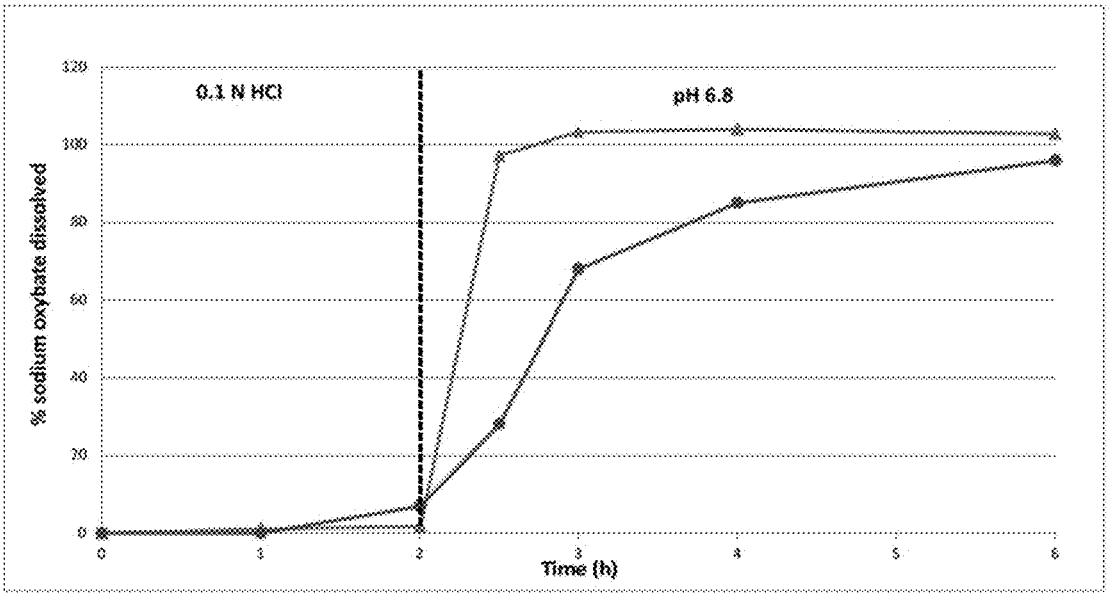


Figure 4

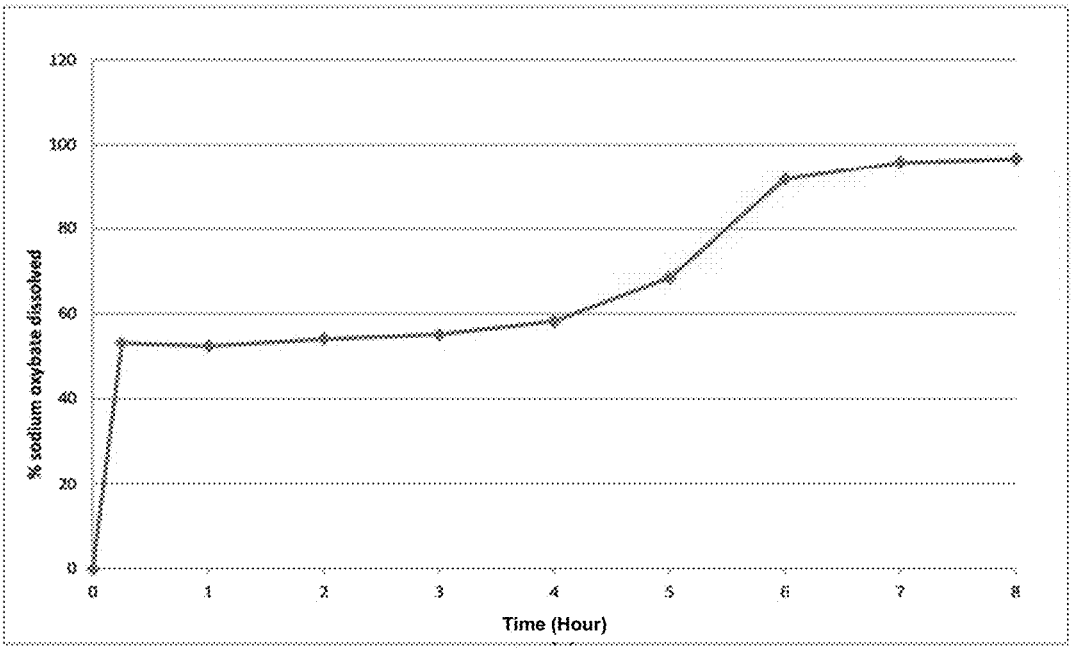


Figure 5

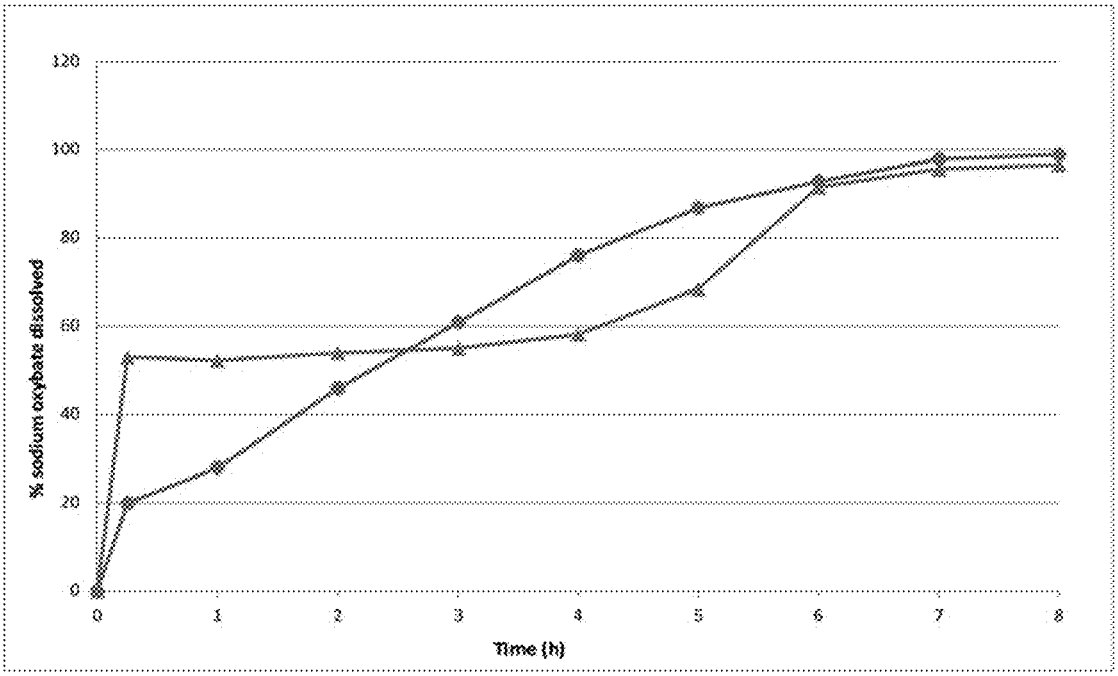


Figure 6

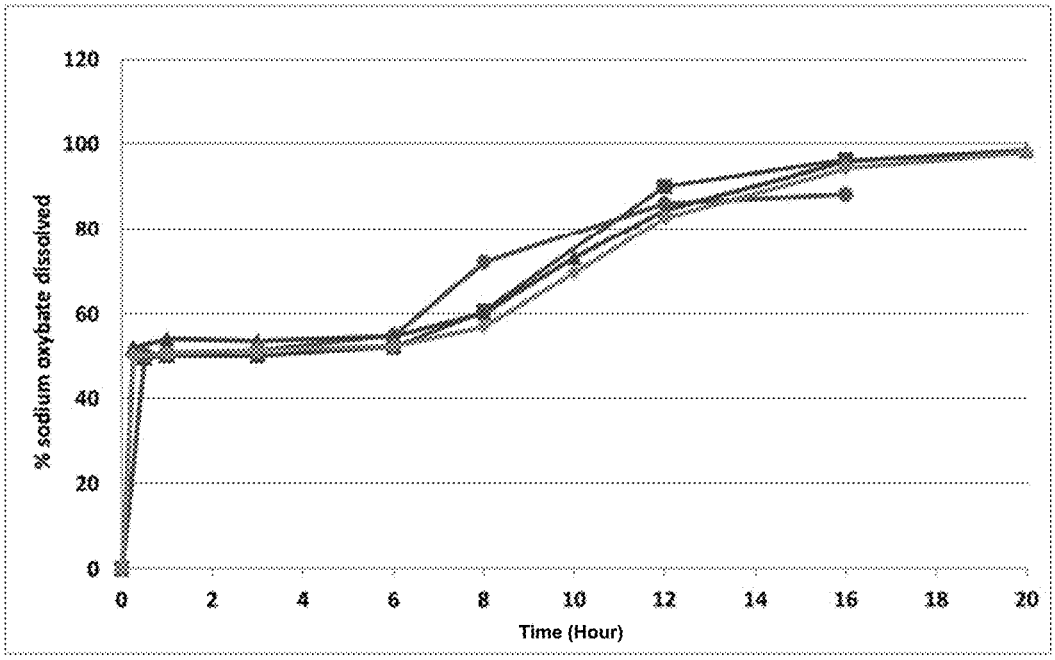


Figure 7

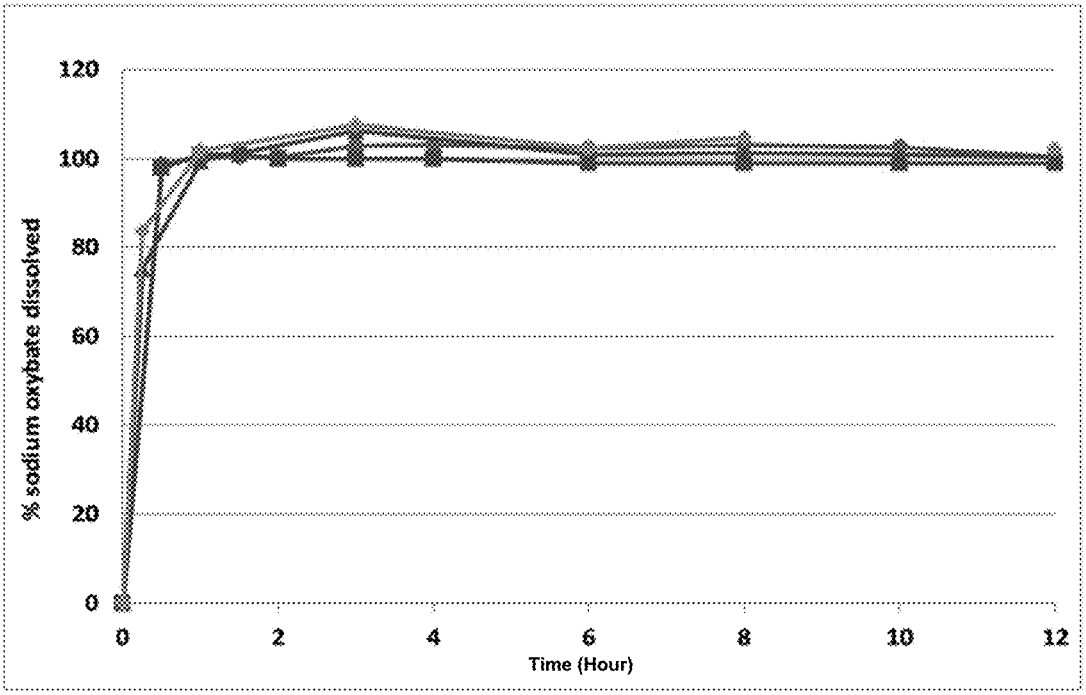


Figure 8

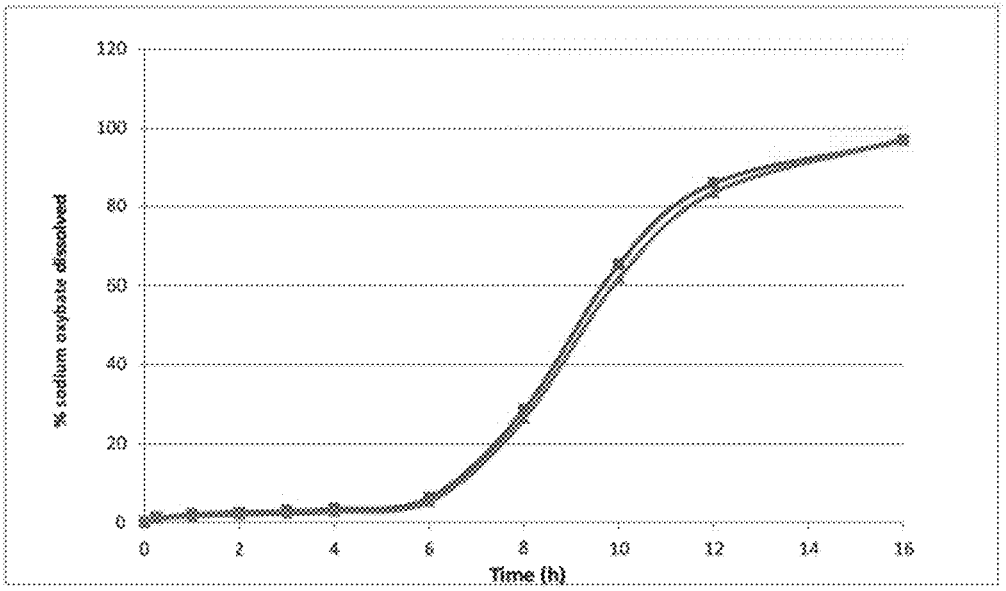


Figure 9

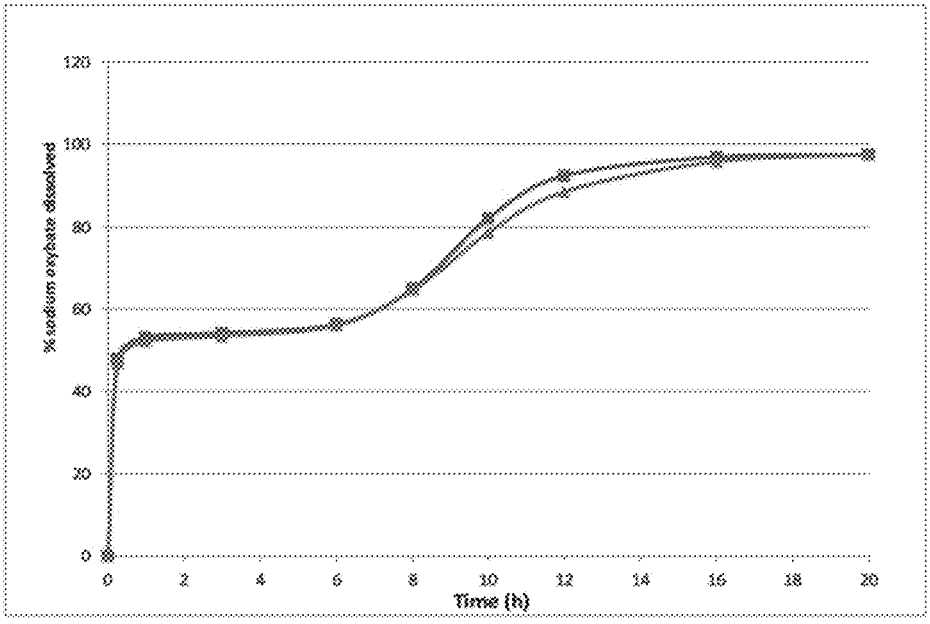


Figure 10

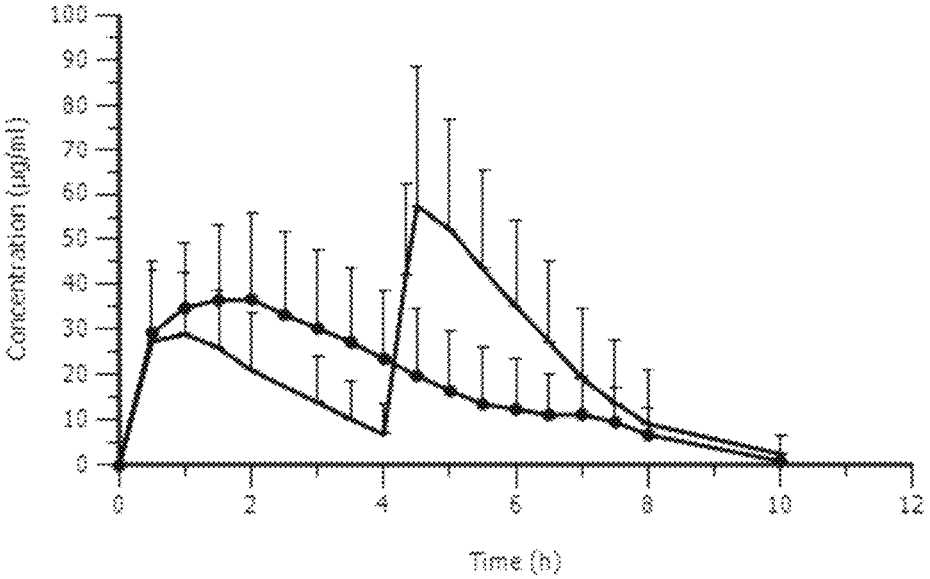


Figure 11

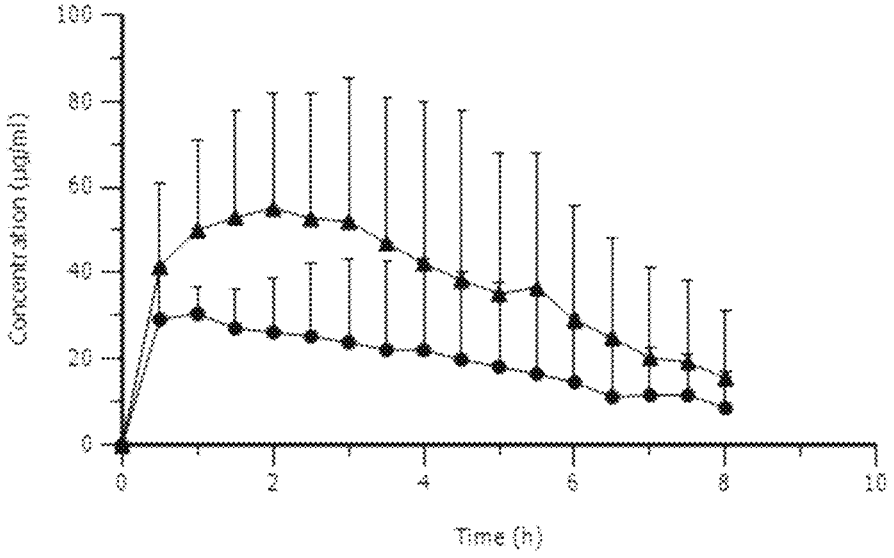


Figure 12

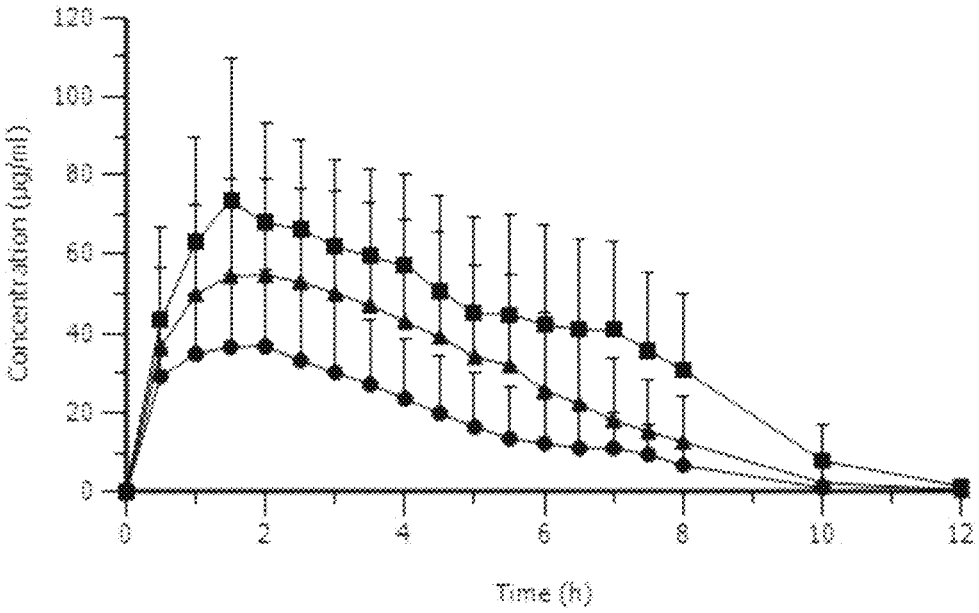


Figure 13

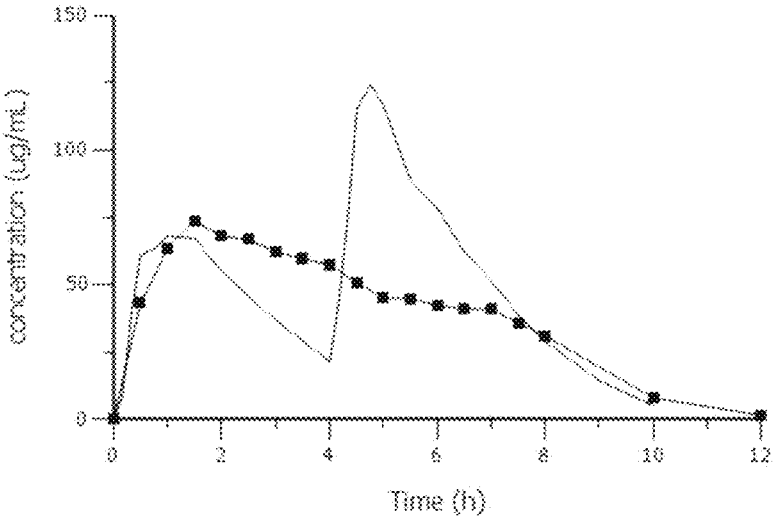


Figure 14

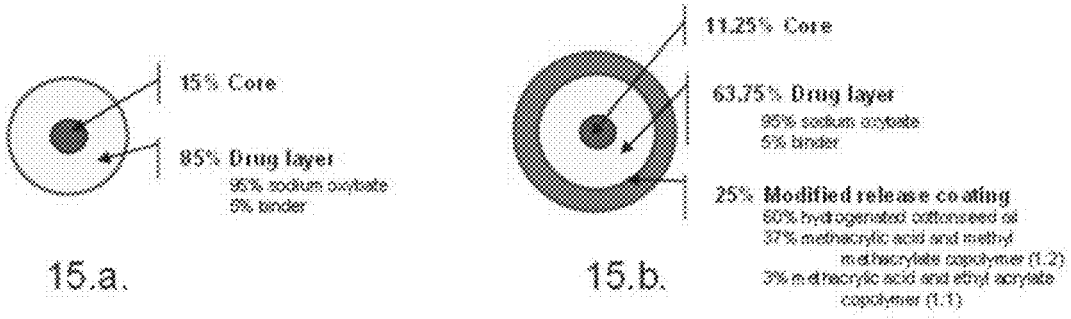


Figure 15

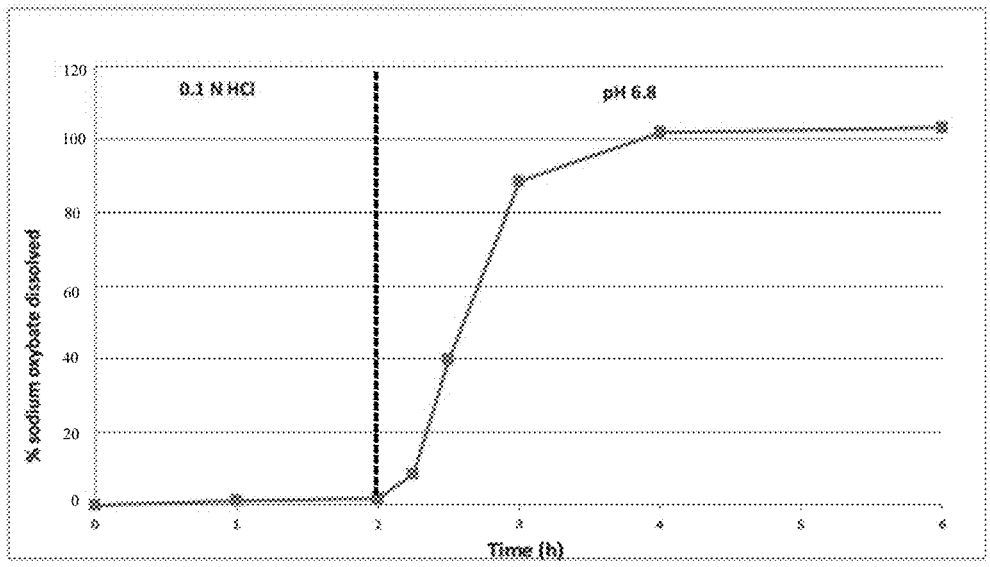


Figure 16

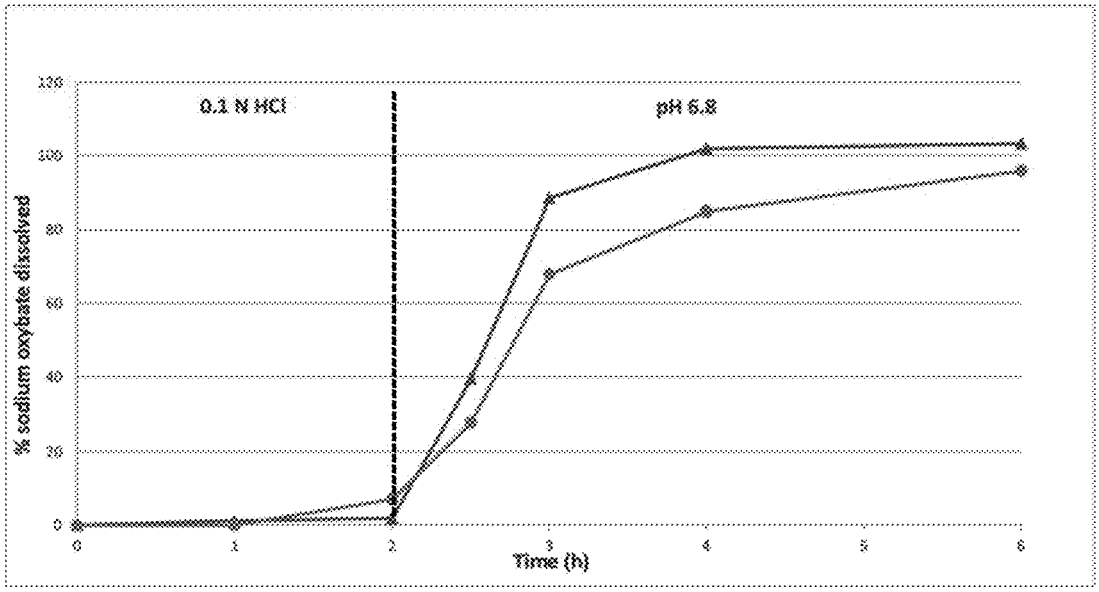


Figure 17

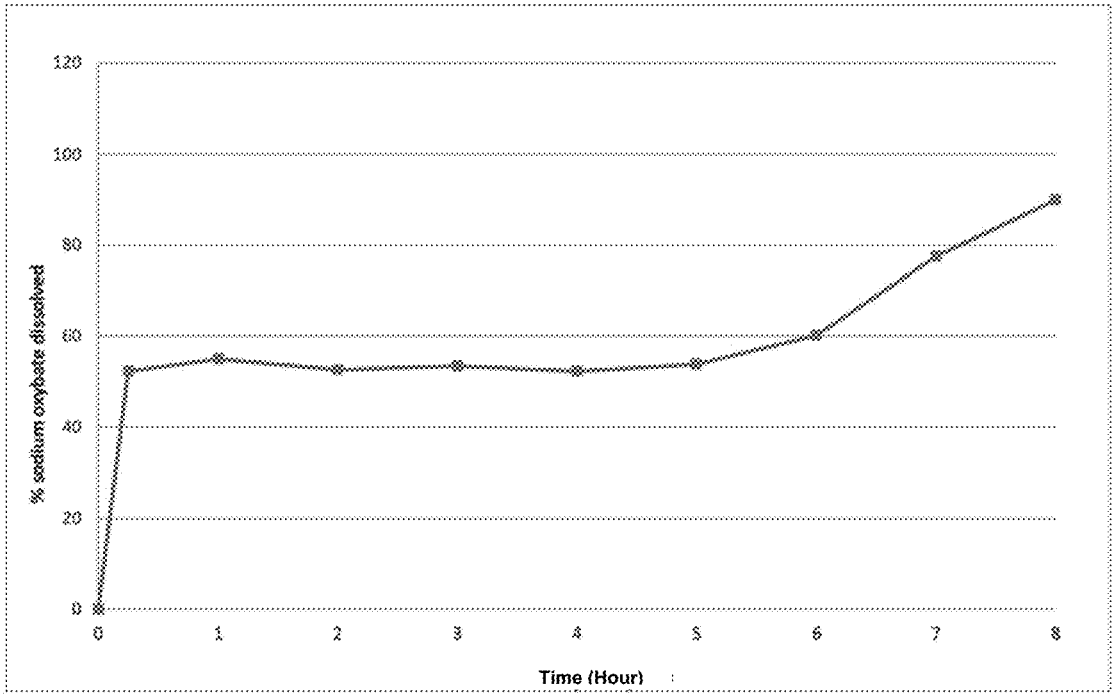


Figure 18

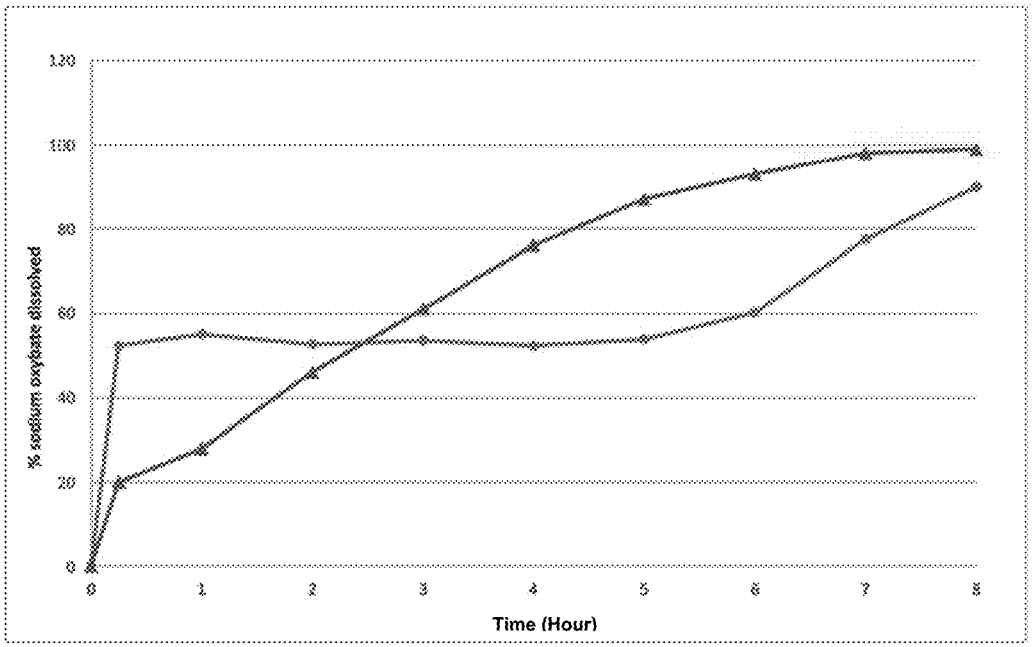


Figure 19

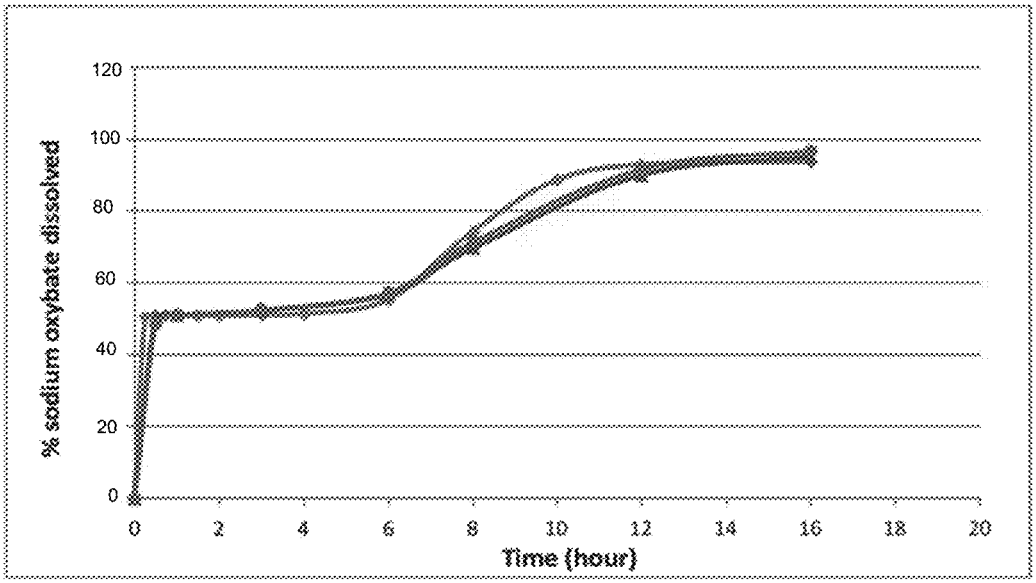


Figure 20

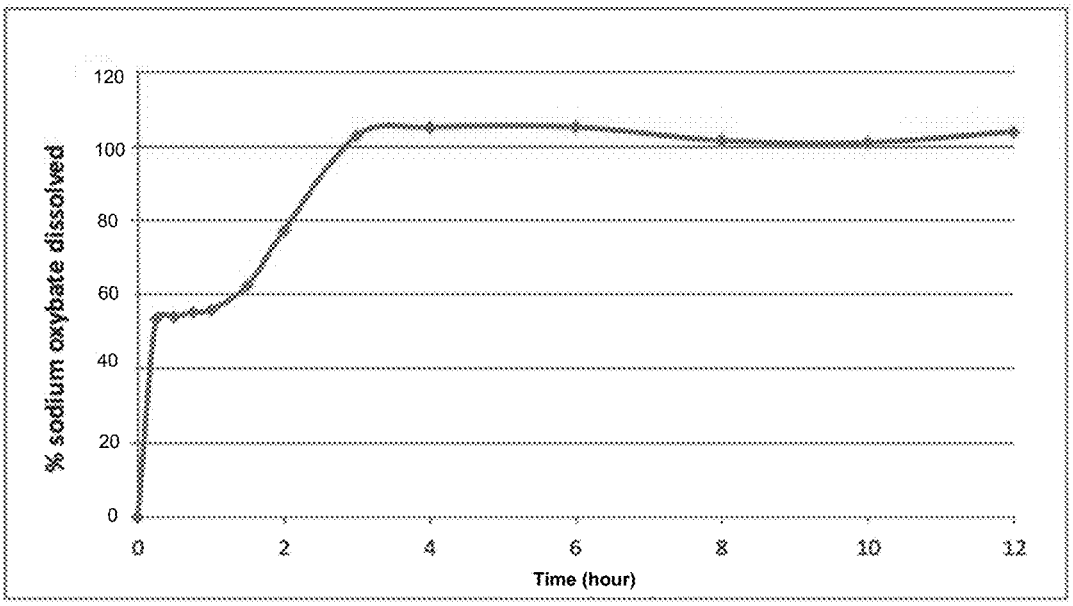


Figure 21

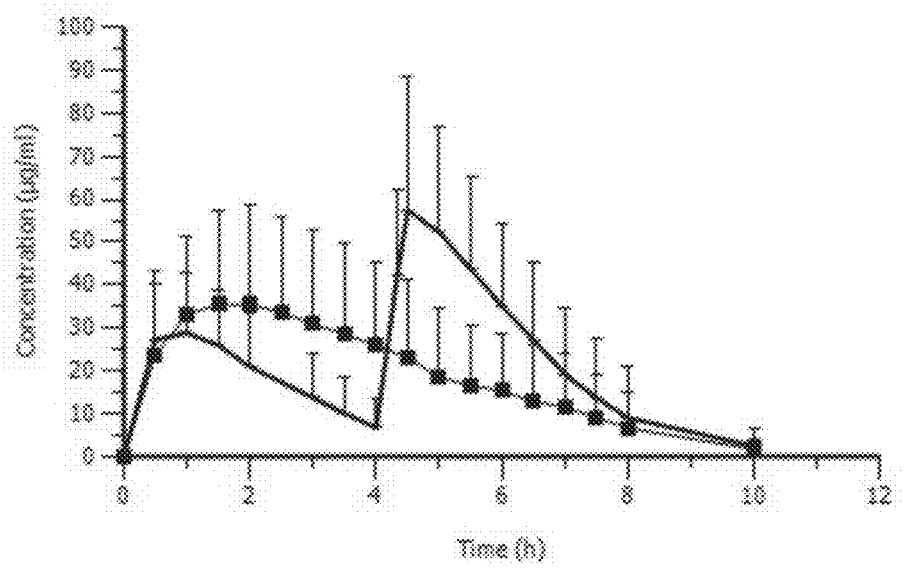
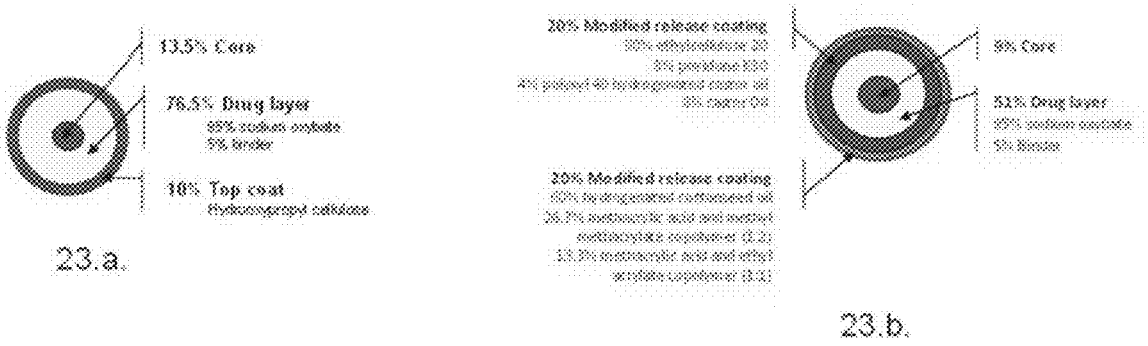


Figure 22



23.a. 23.b.

Figure 23

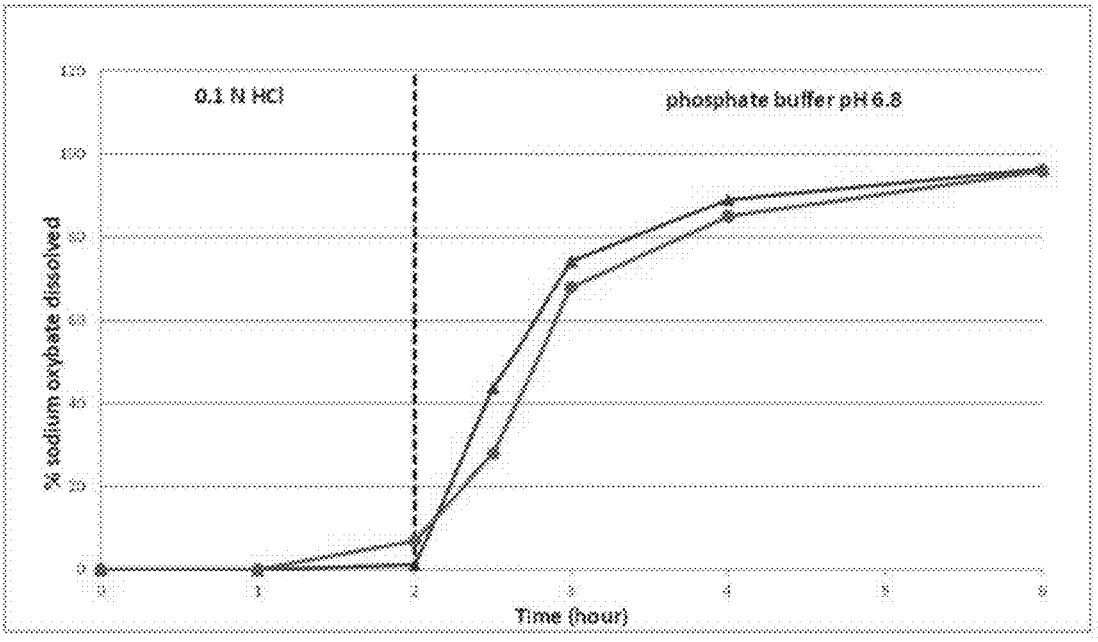


Figure 24

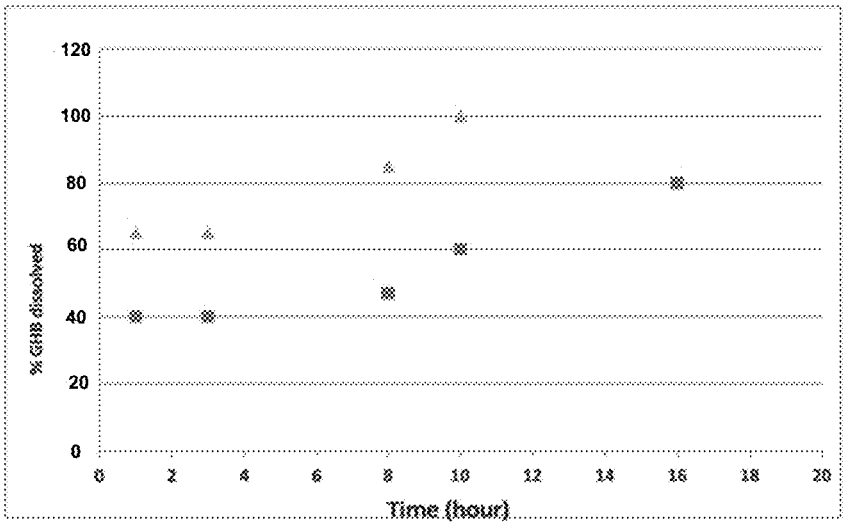


Figure 25

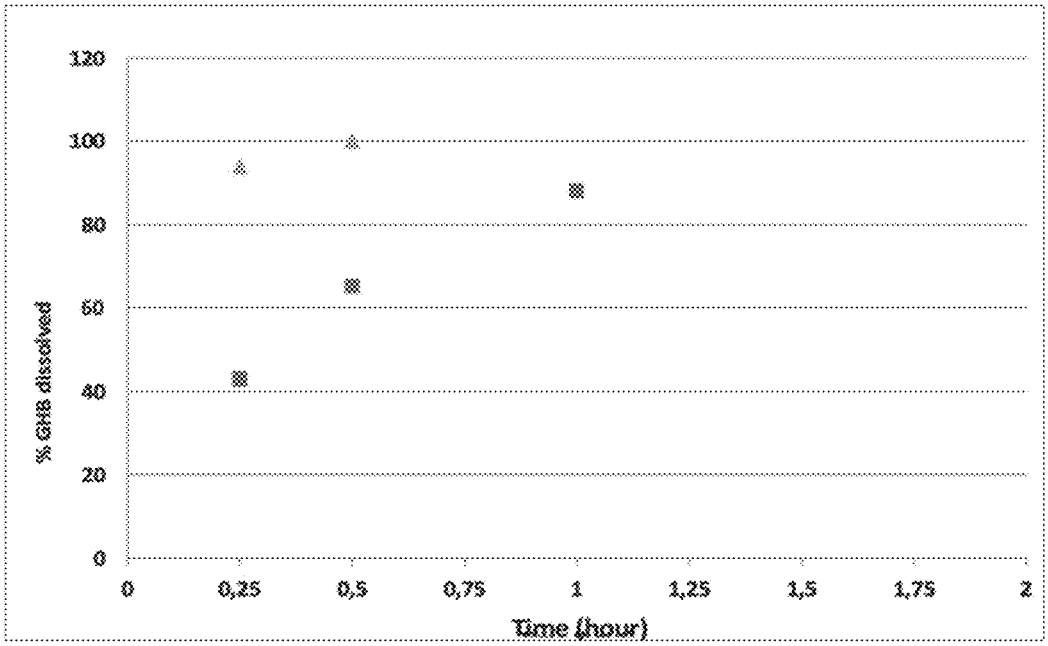


Figure 26

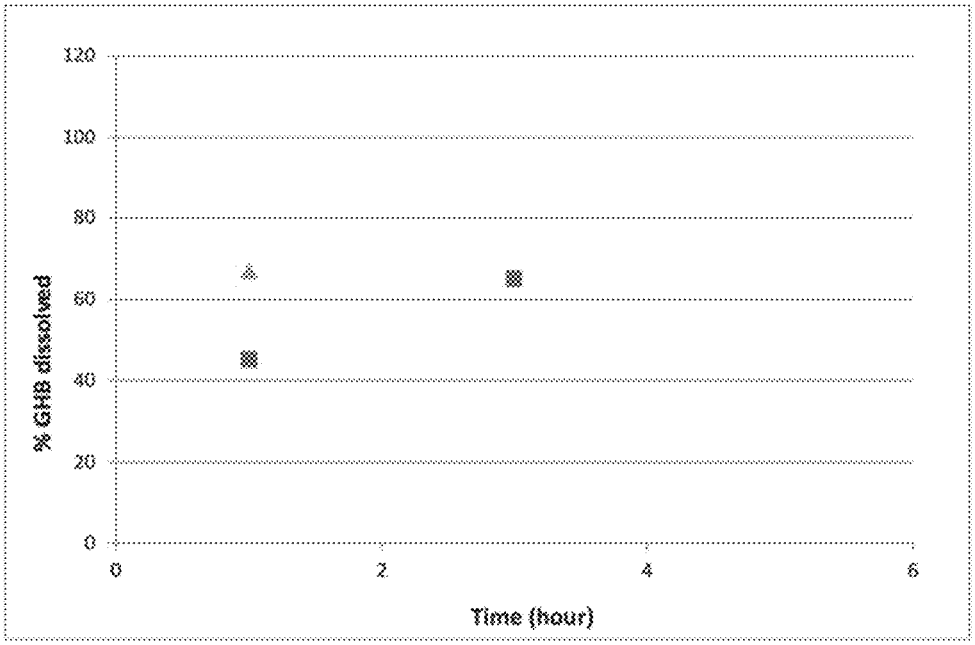


Figure 27

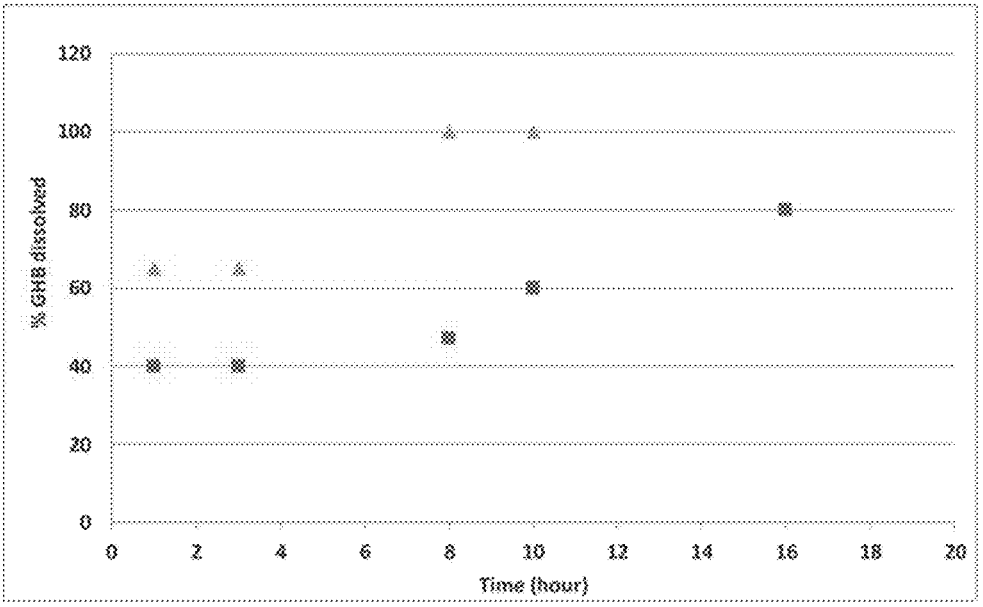


Figure 28

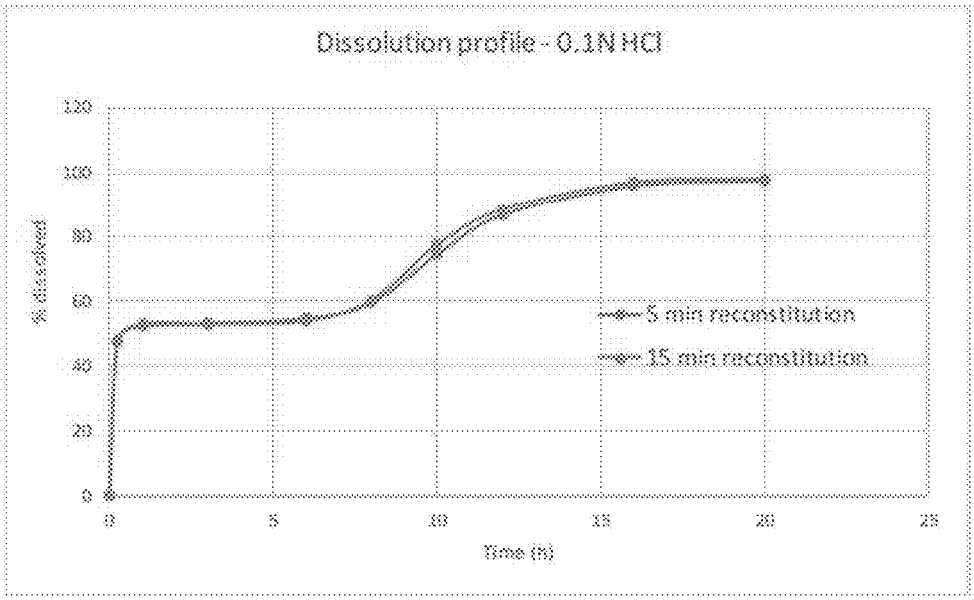


Figure 29

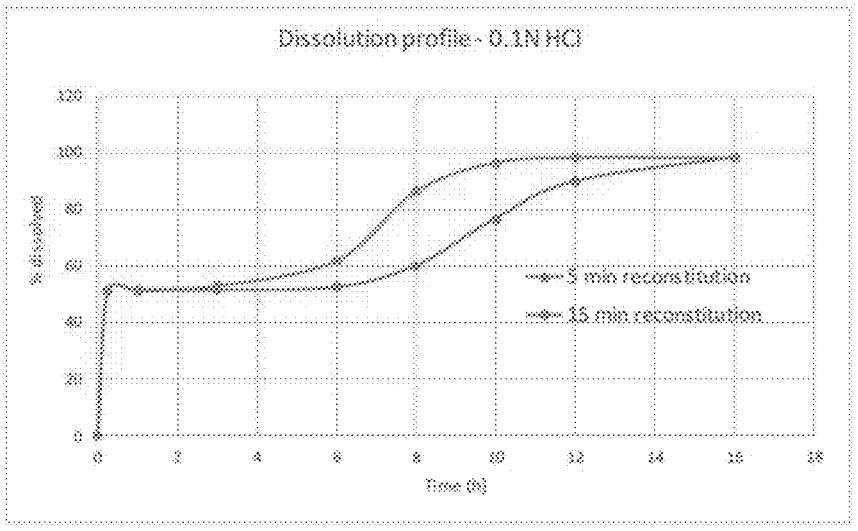


Figure 30

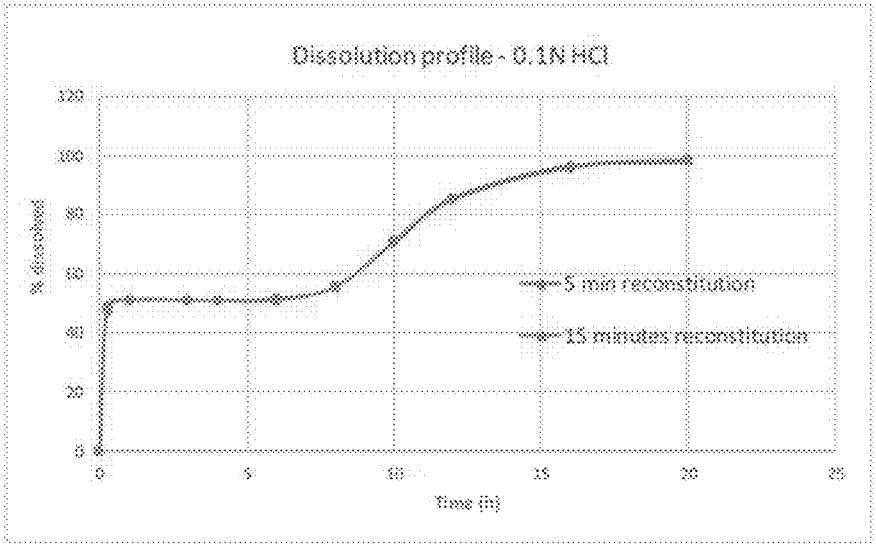


Figure 31

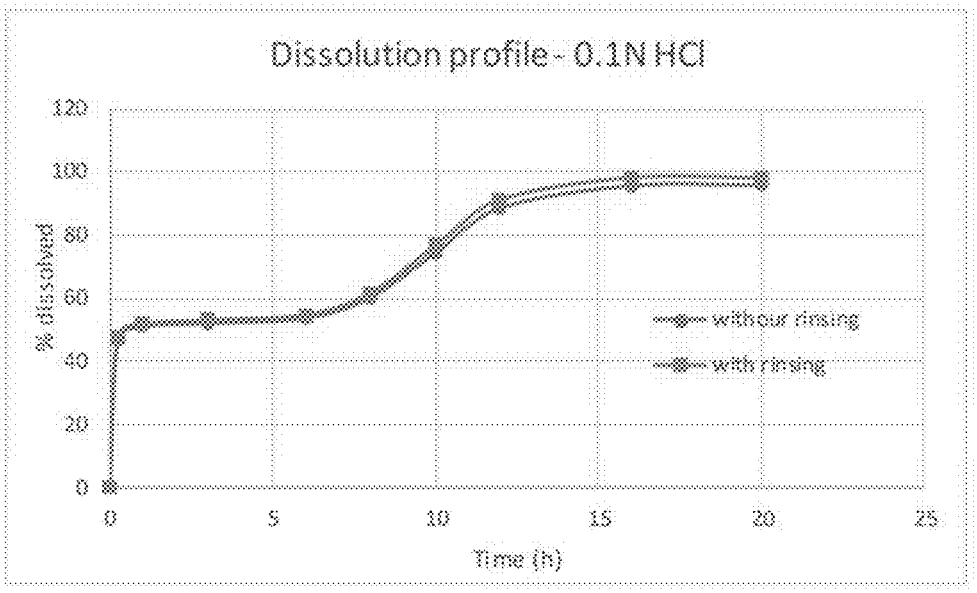


Figure 32

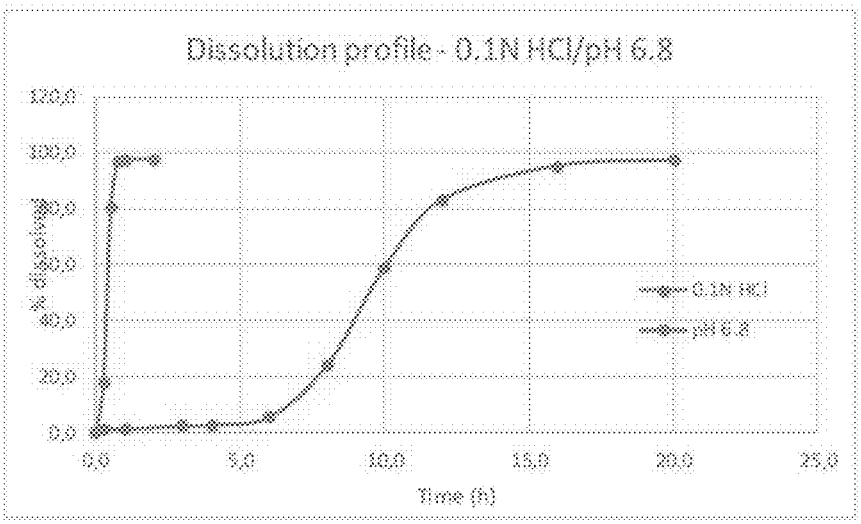


Figure 33

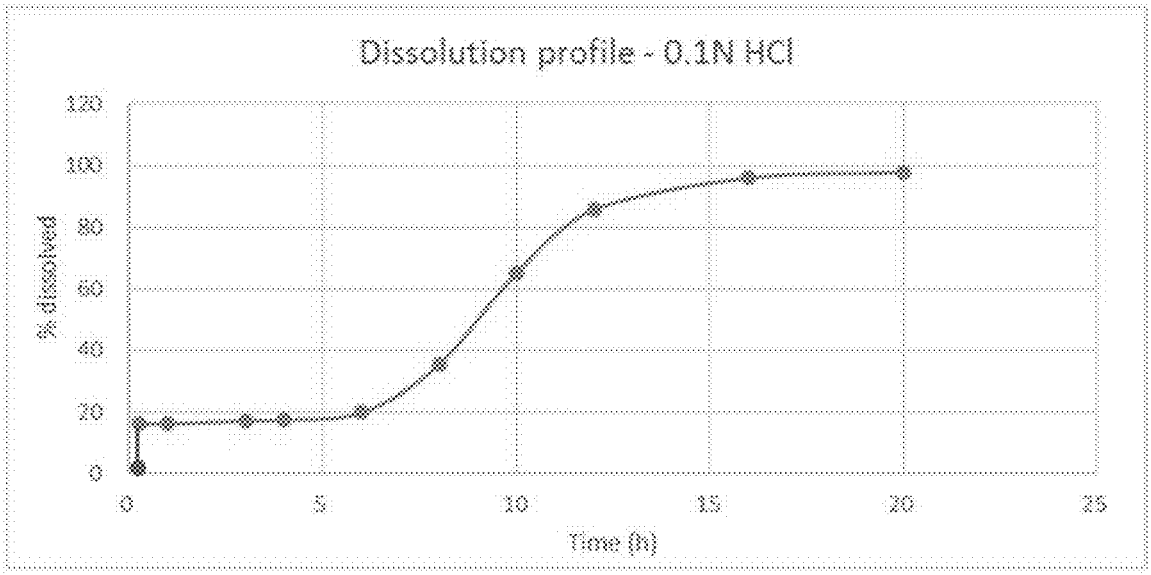


Figure 34

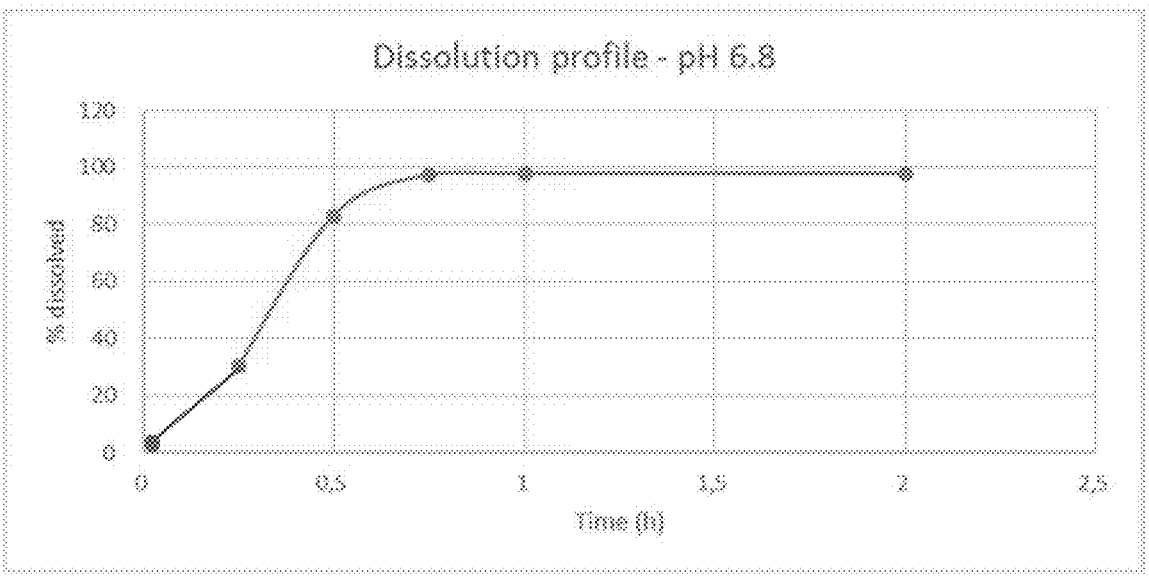


Figure 35

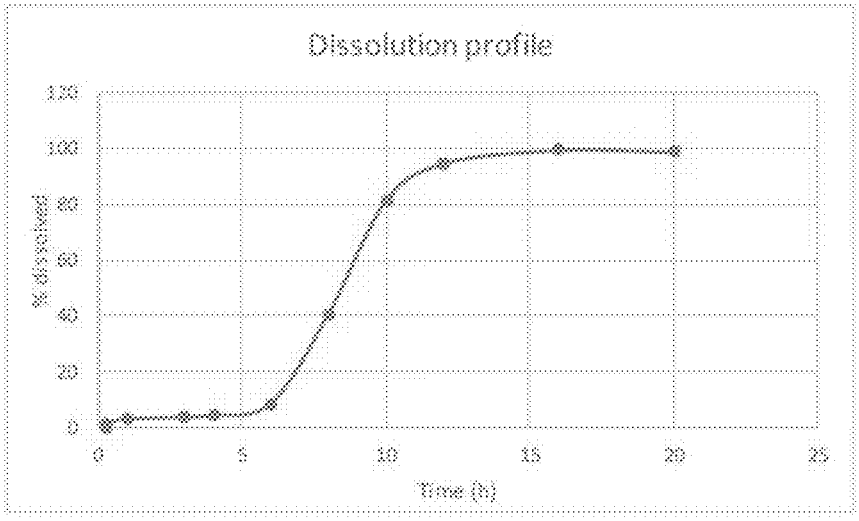


Figure 36

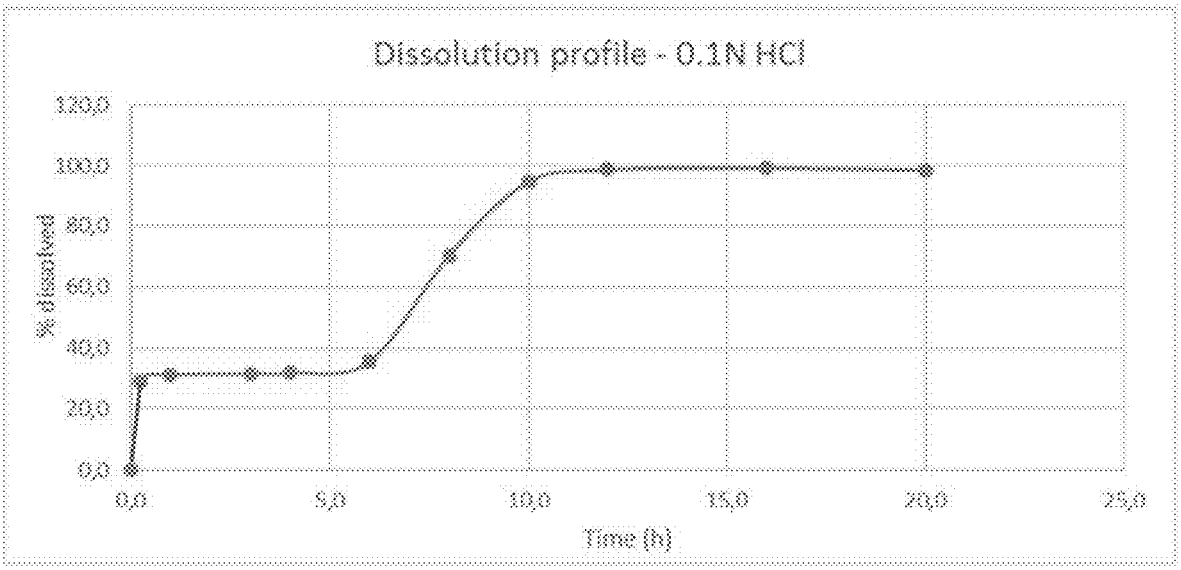


Figure 37

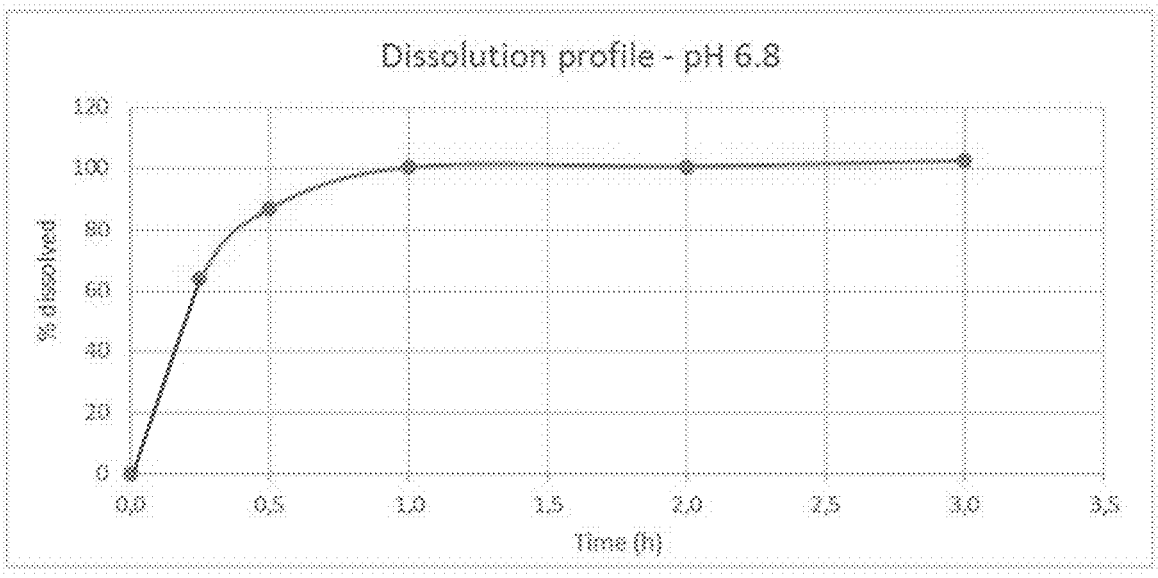


Figure 38

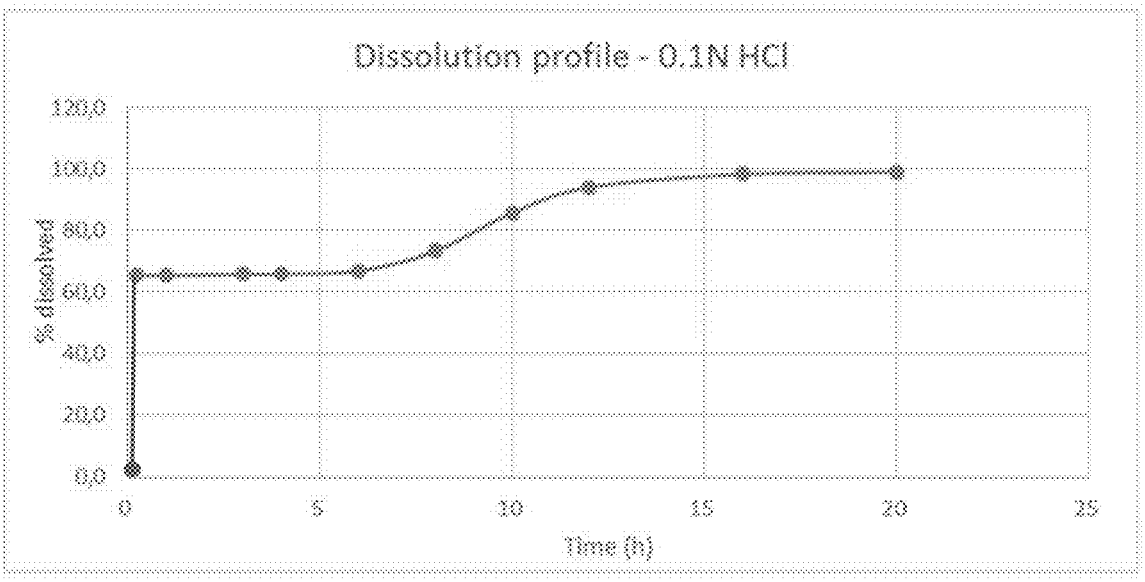


Figure 39

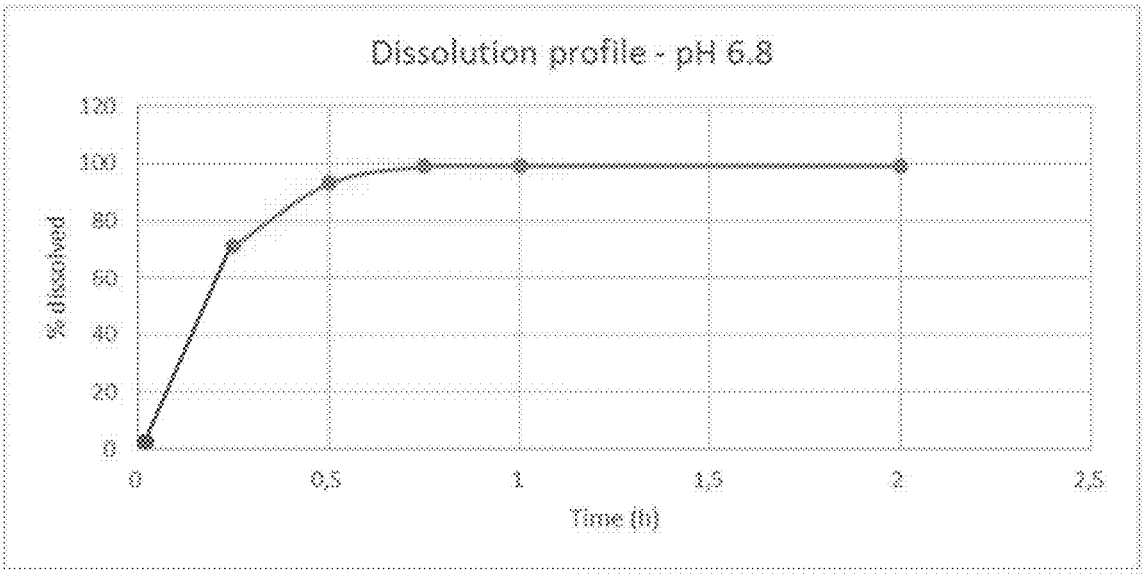


Figure 40

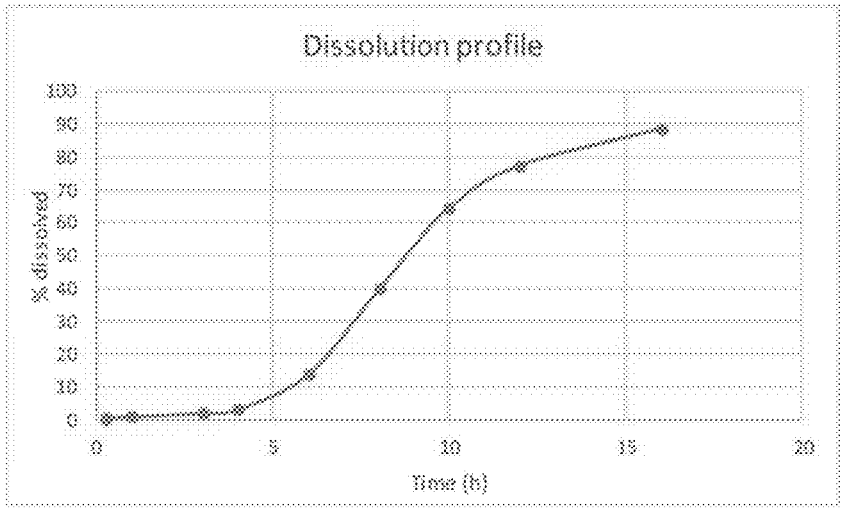


Figure 41

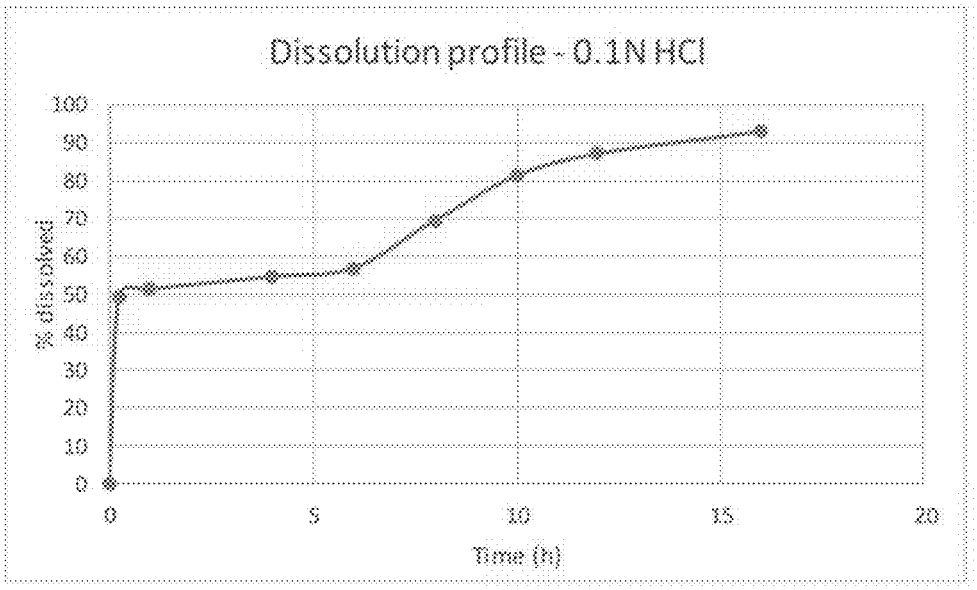


Figure 42

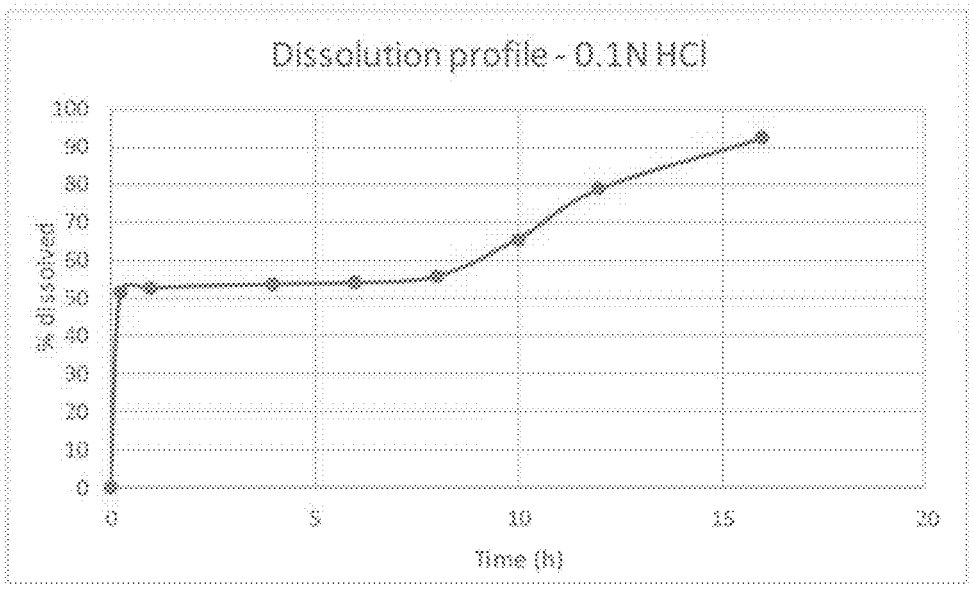


Figure 43

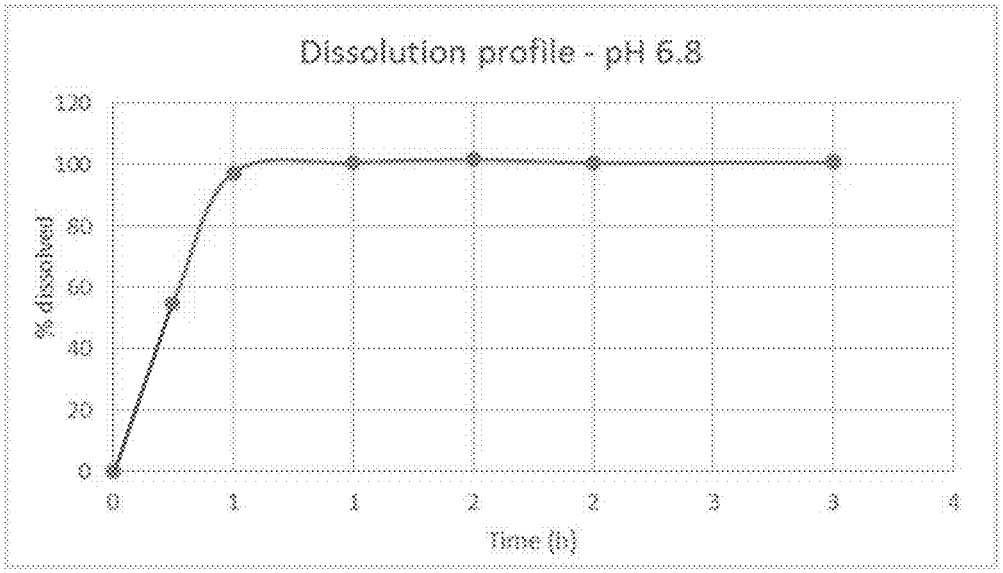


Figure 44

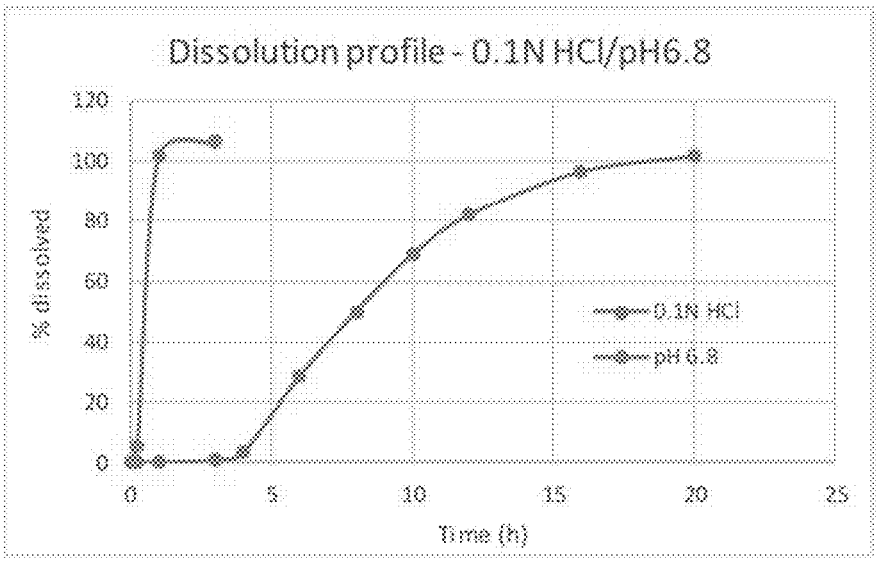


Figure 45

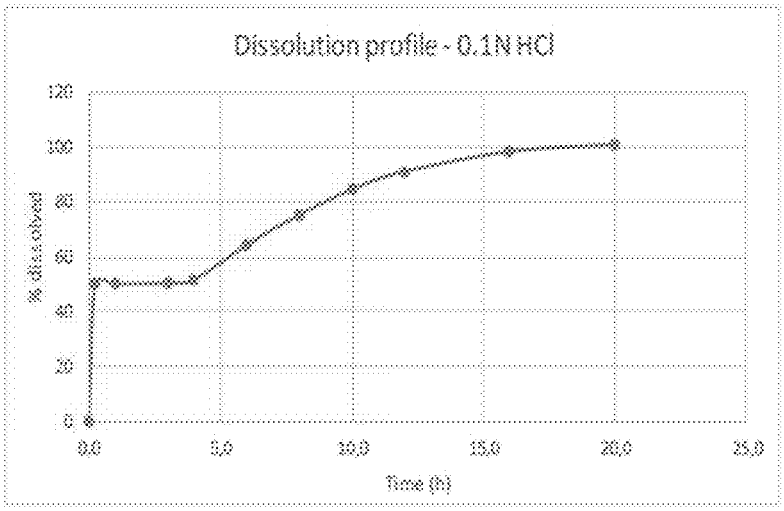


Figure 46

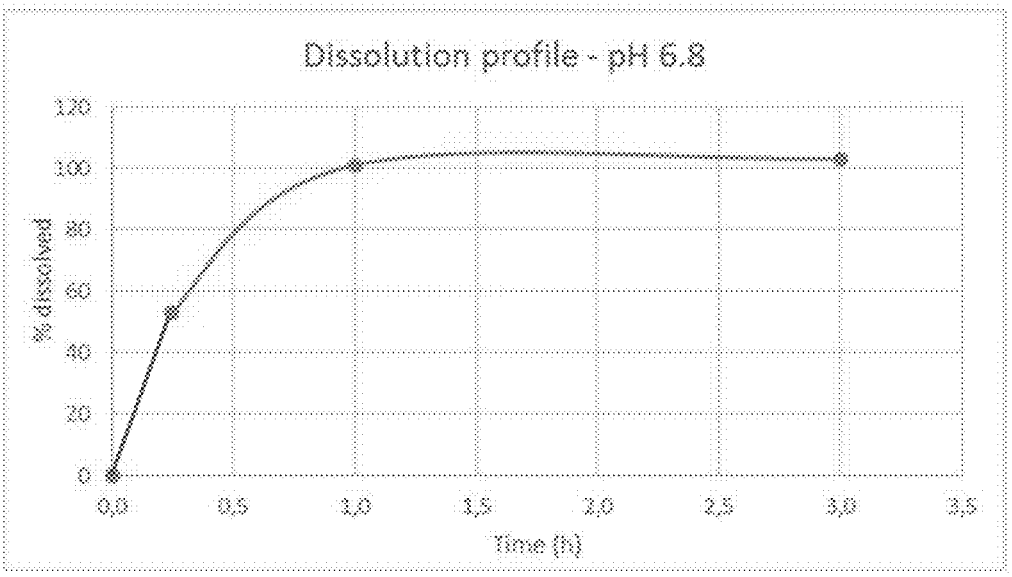


Figure 47

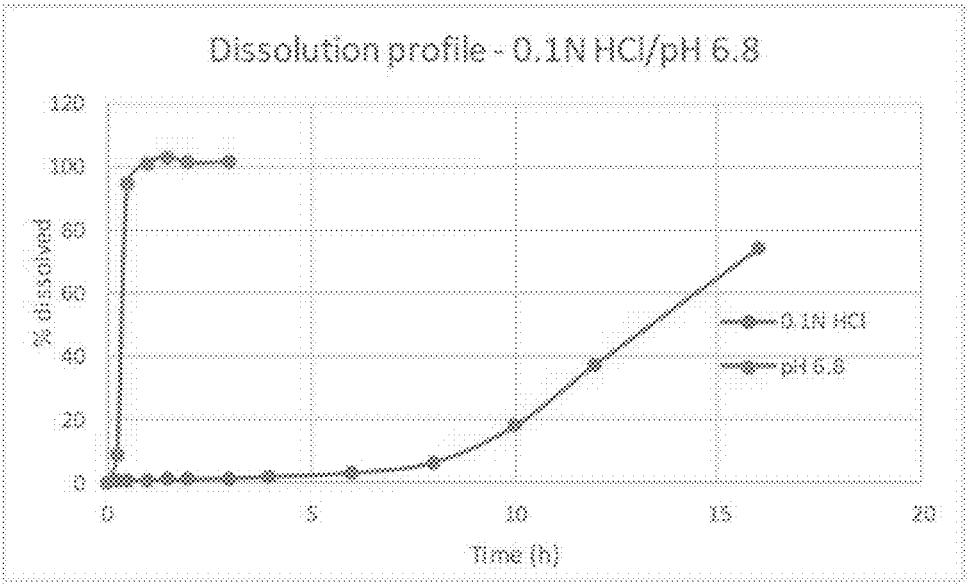


Figure 48

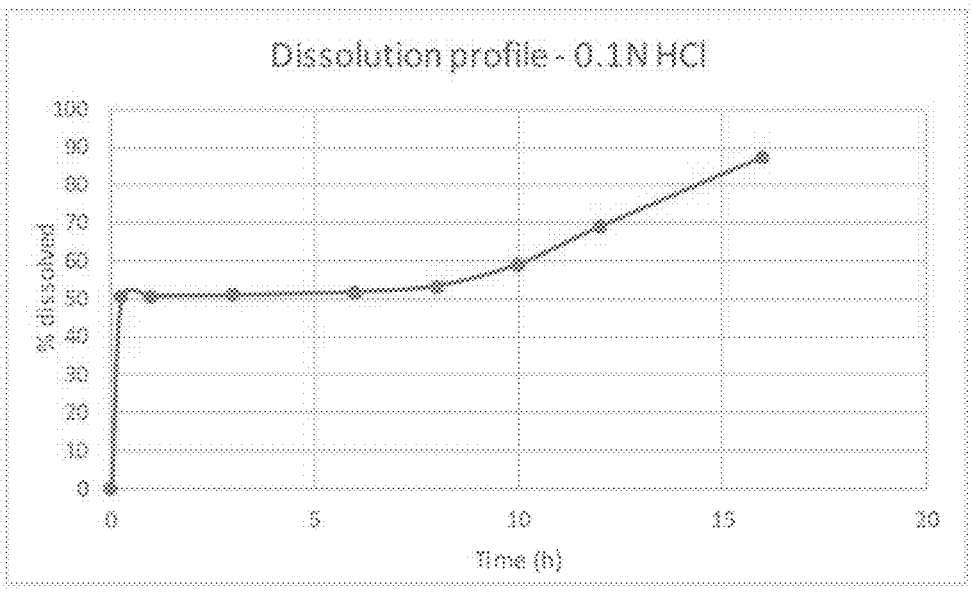


Figure 49

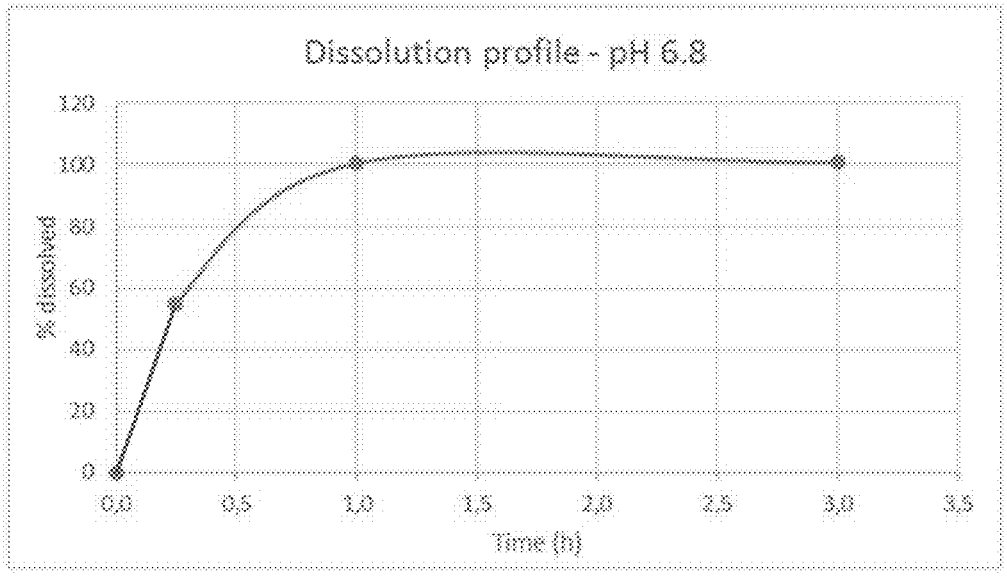


Figure 50

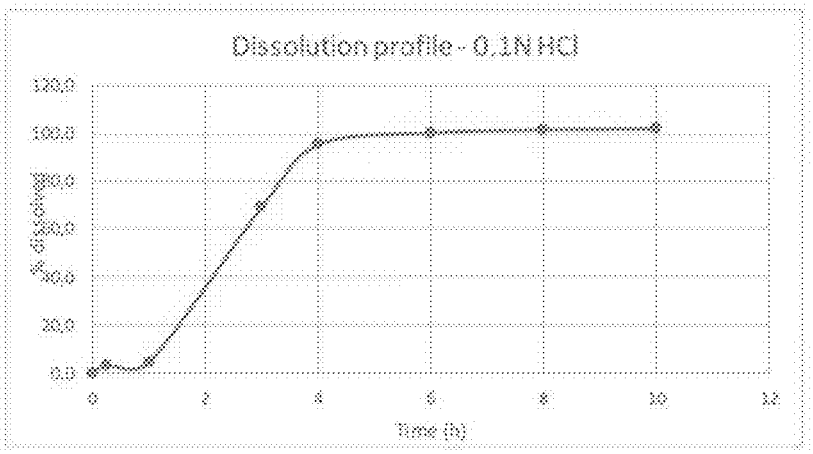


Figure 51

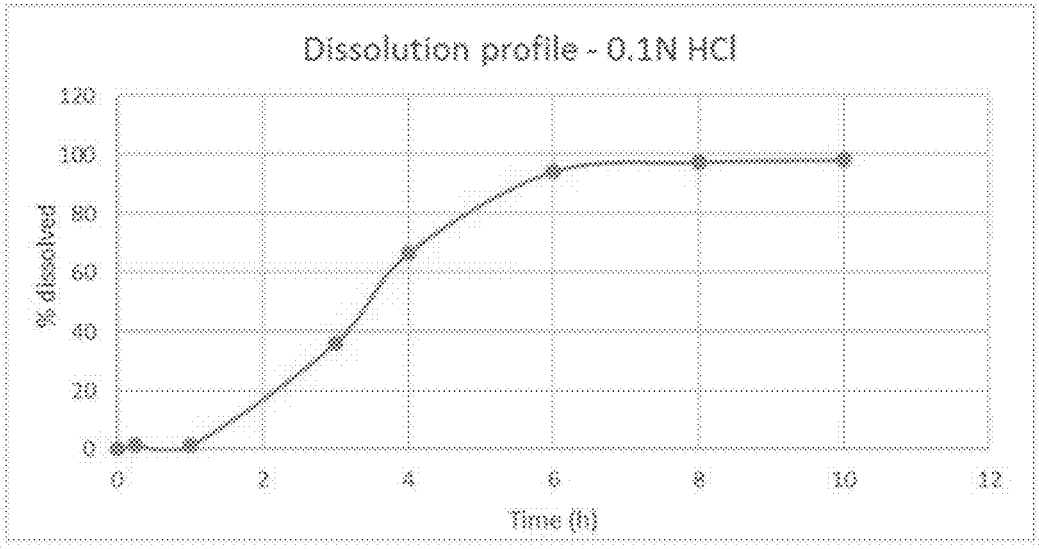


Figure 52

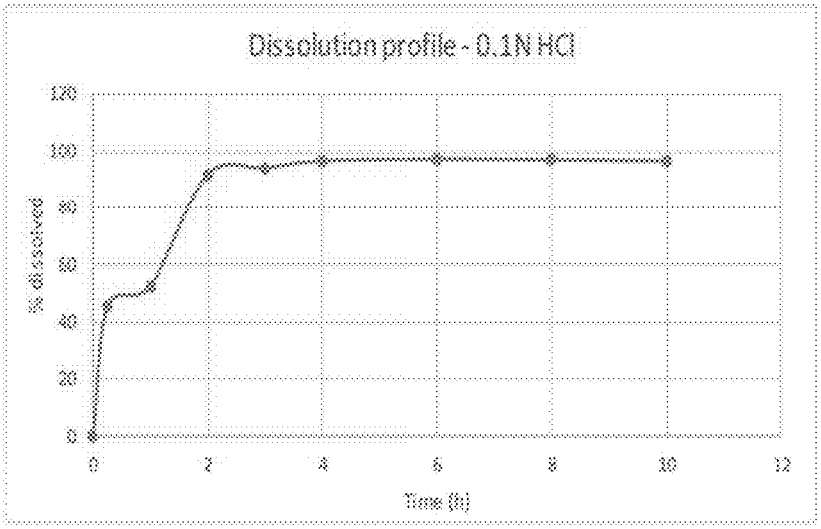


Figure 53

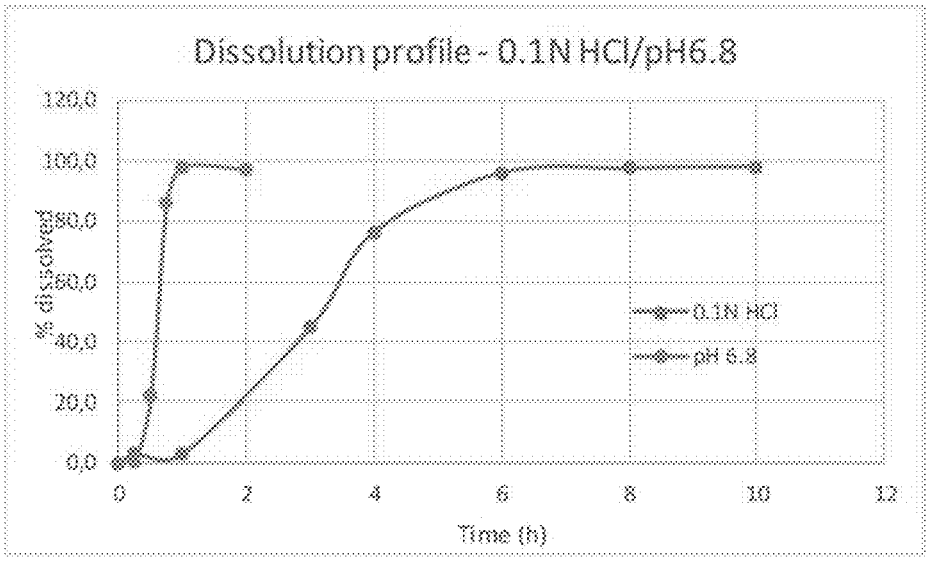


Figure 54

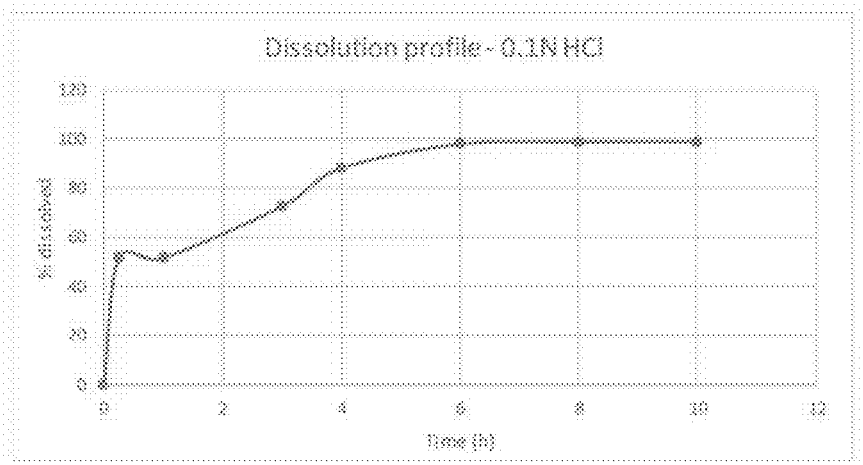


Figure 55

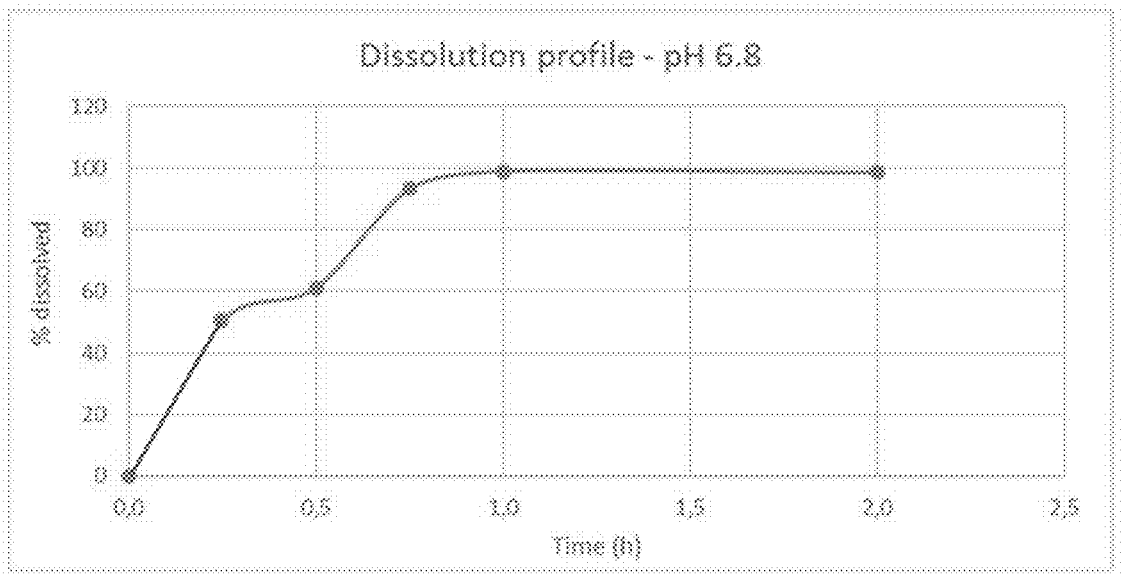


Figure 56

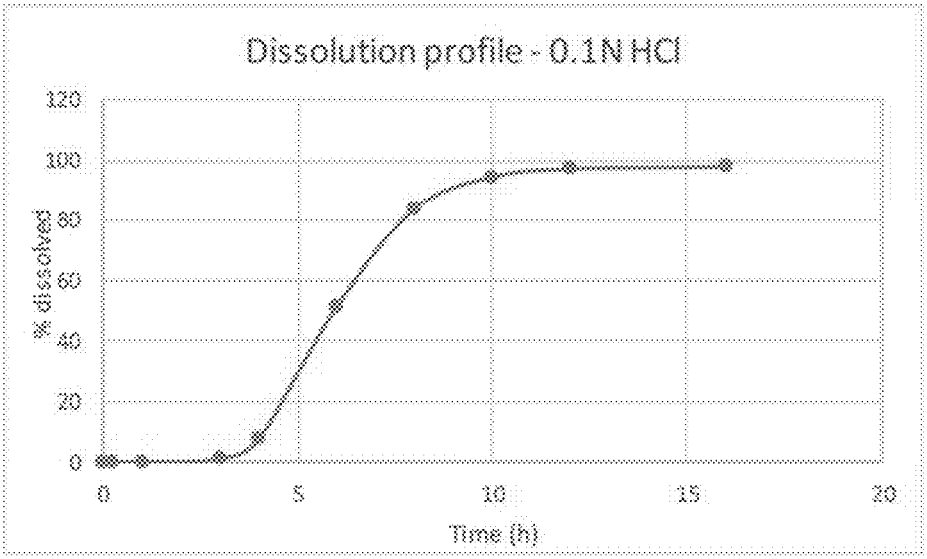


Figure 57

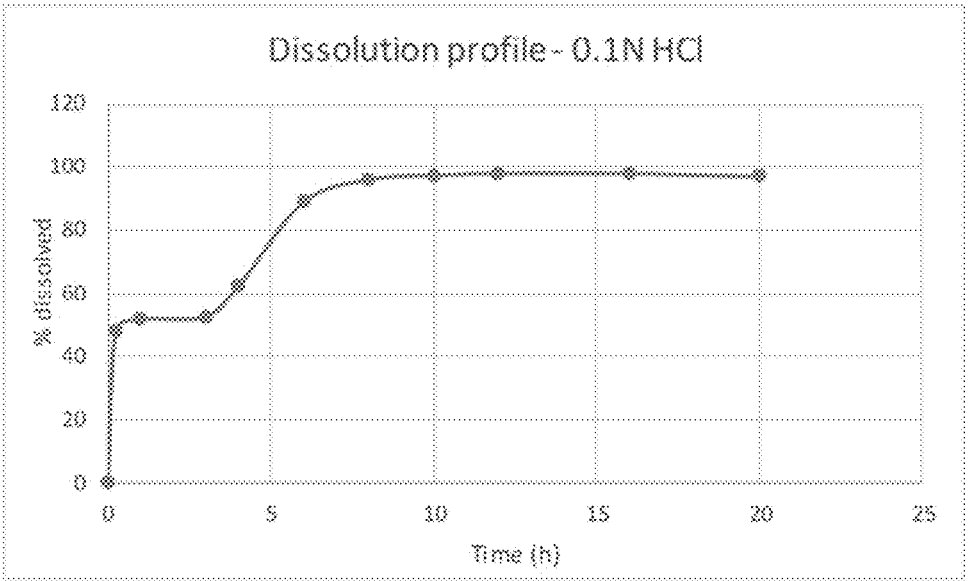


Figure 58

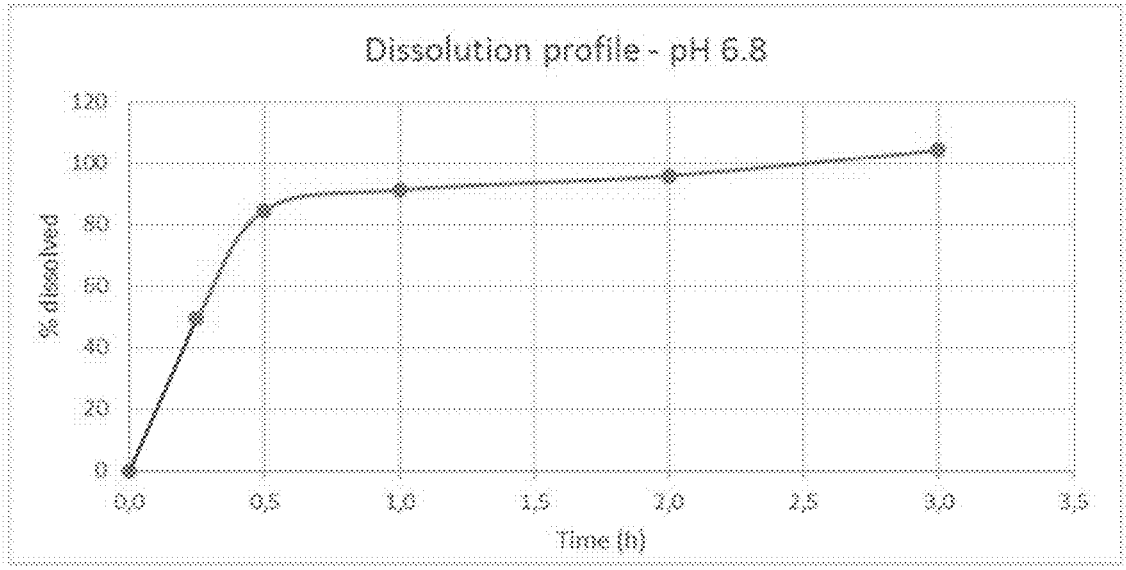


Figure 59

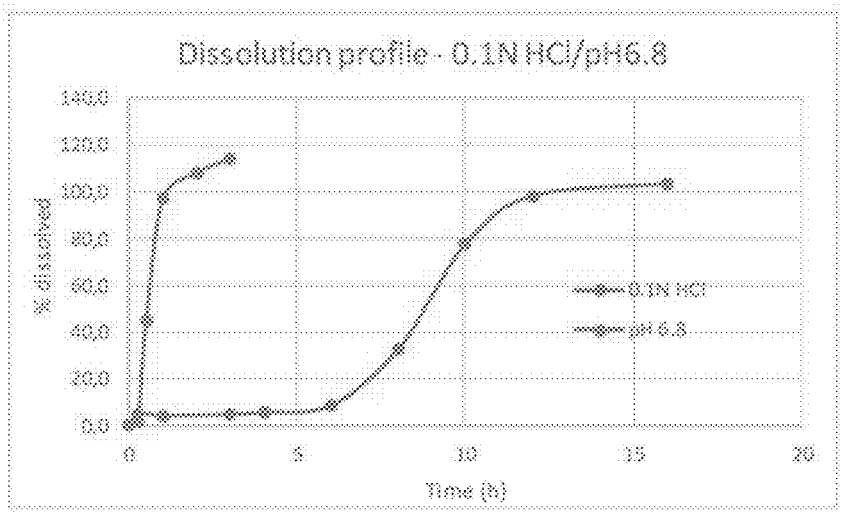


Figure 60

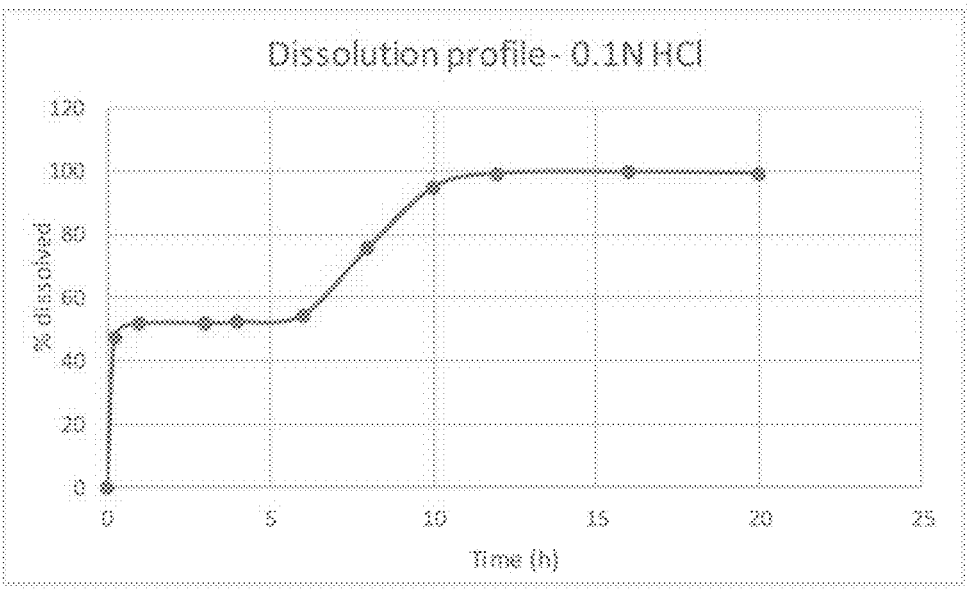


Figure 61

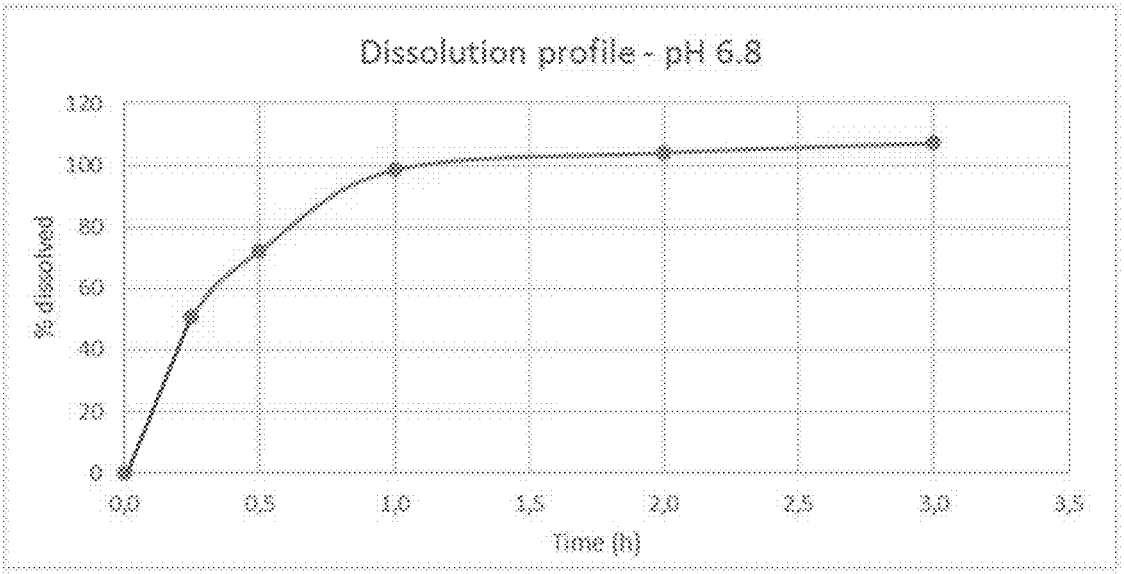


Figure 62

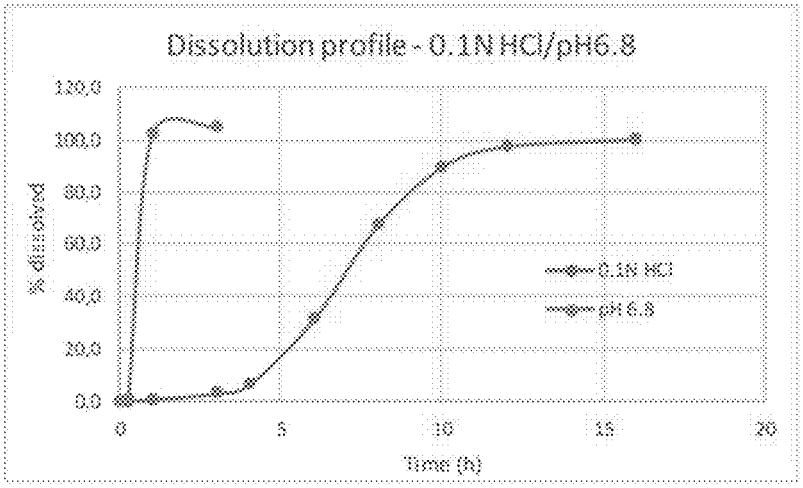


Figure 63

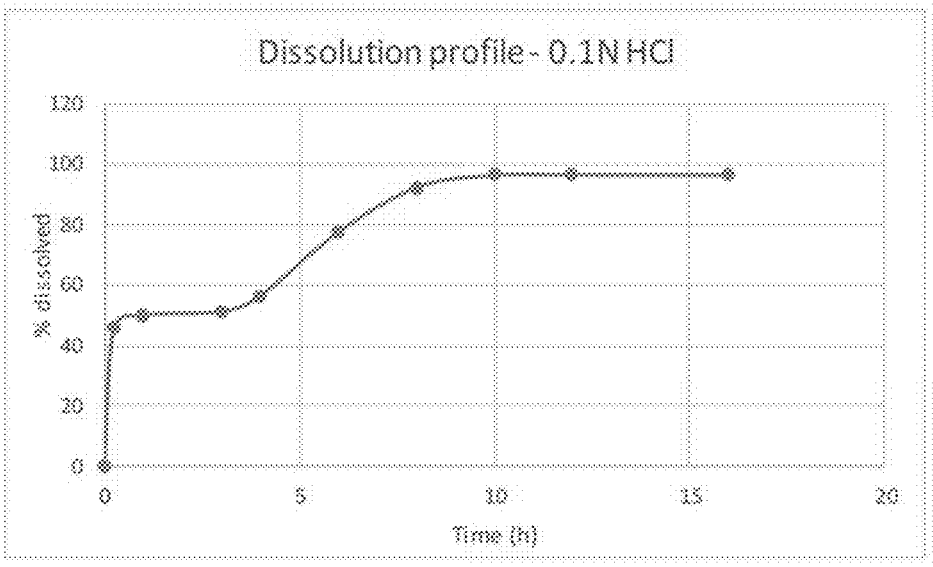


Figure 64

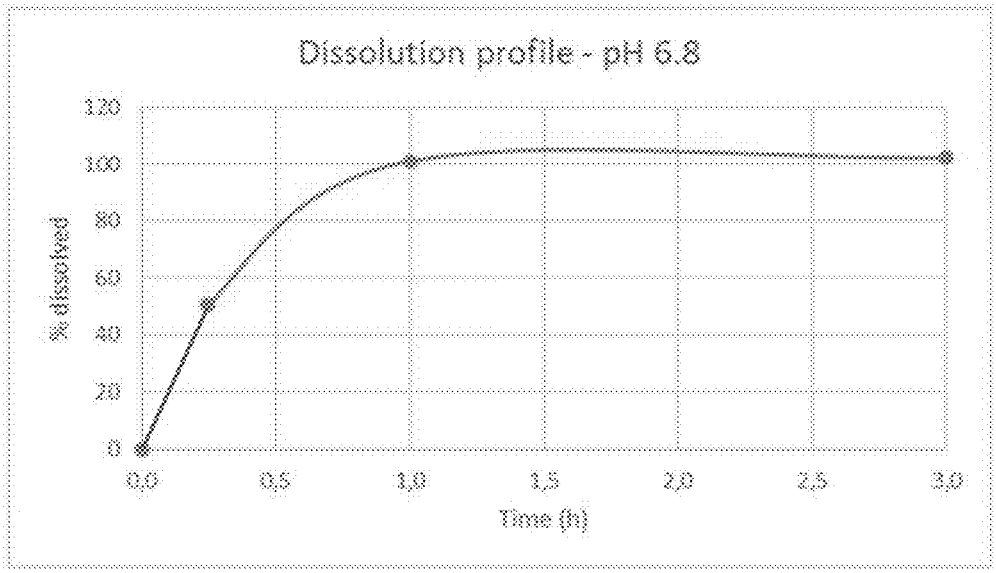


Figure 65

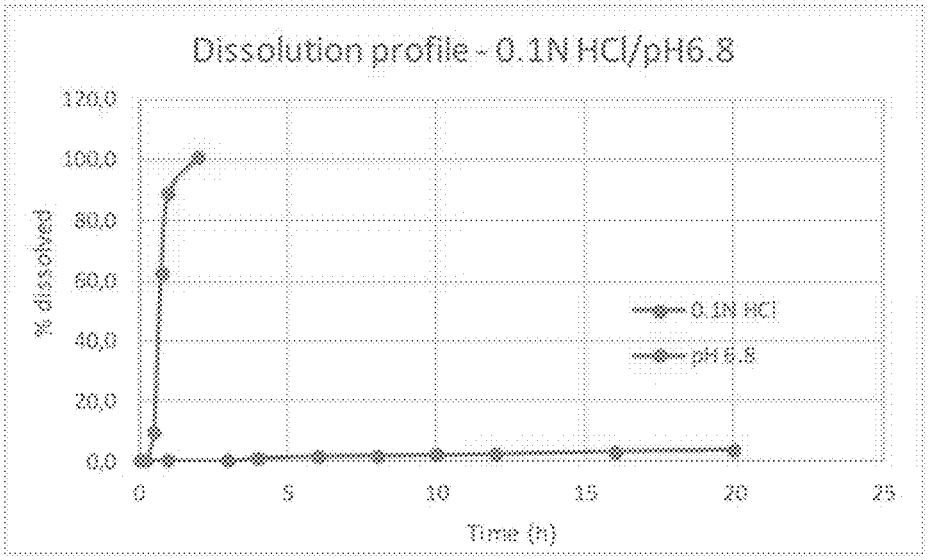


Figure 66

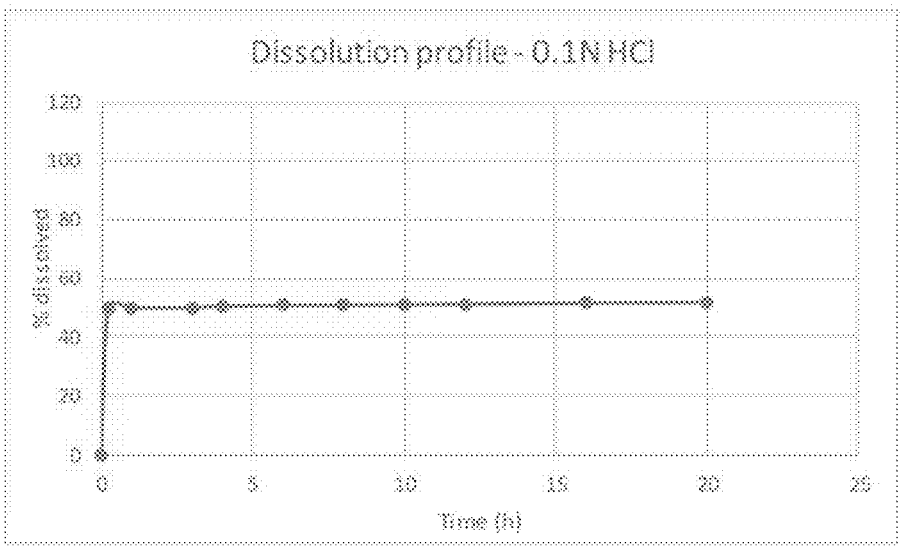


Figure 67

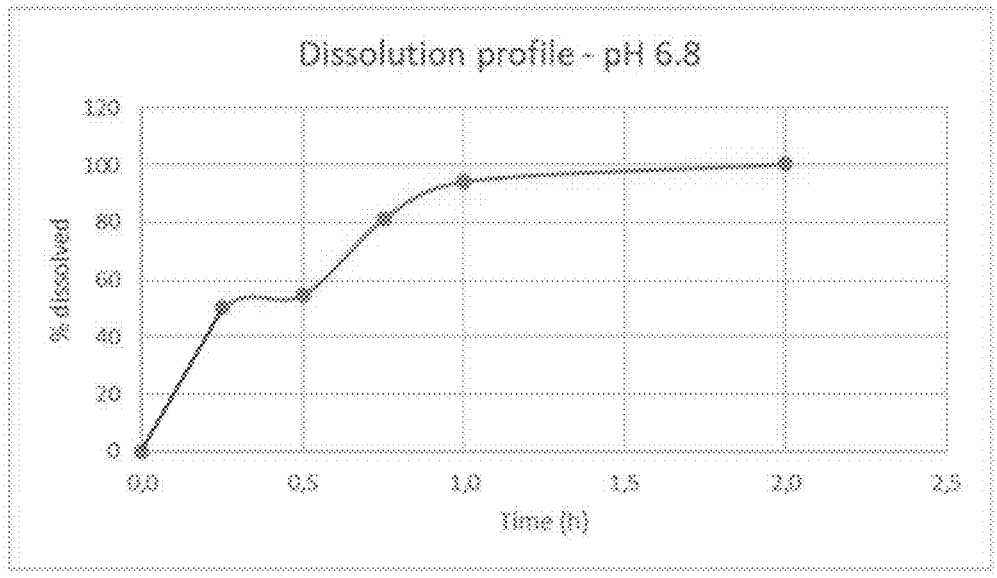


Figure 68

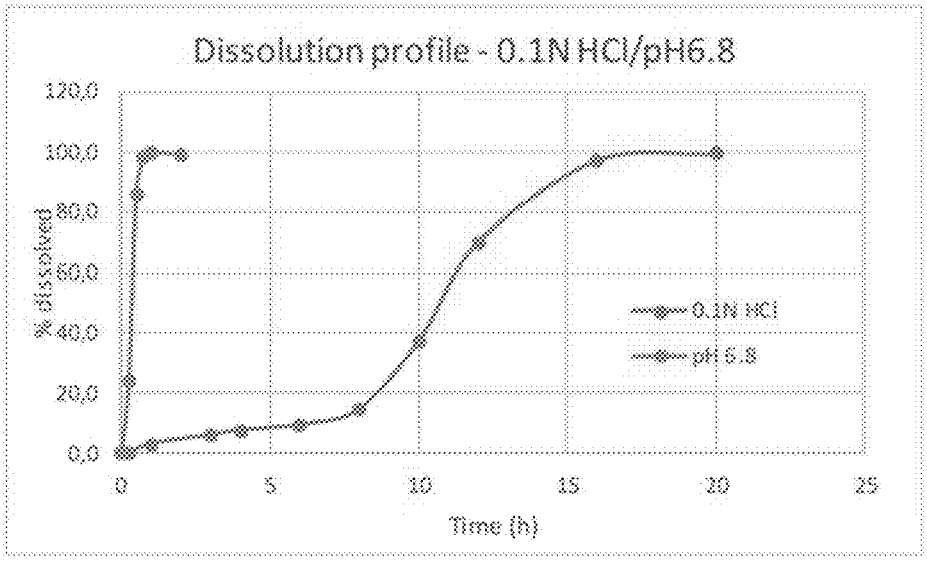


Figure 69

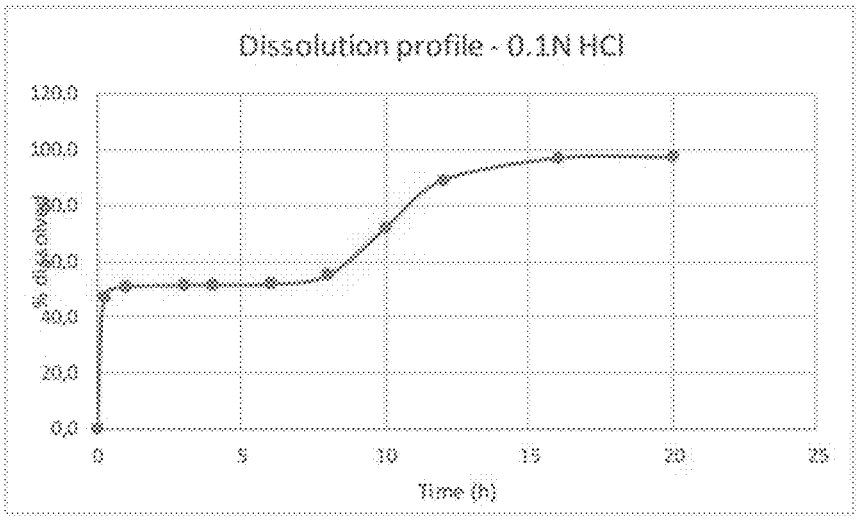


Figure 70

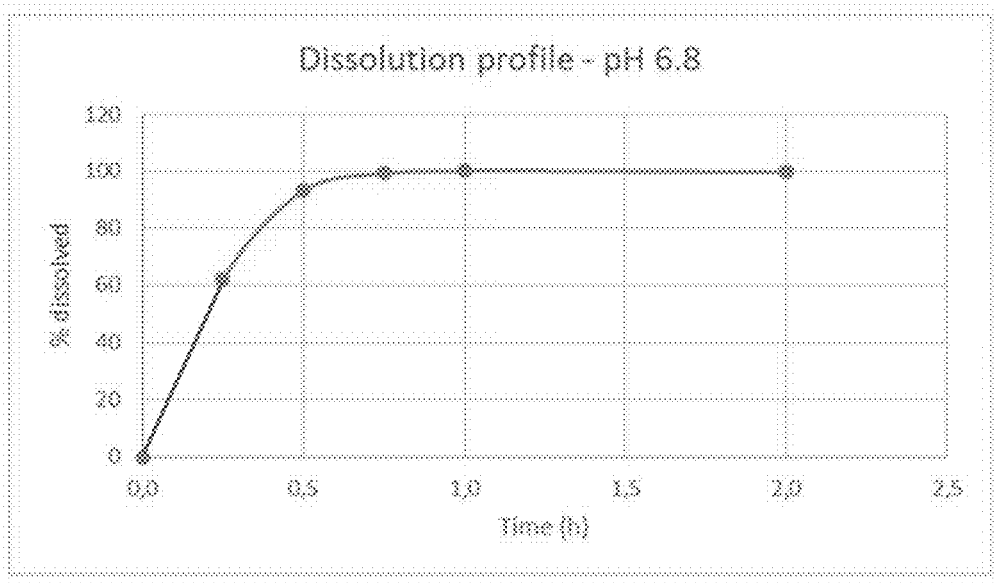


Figure 71

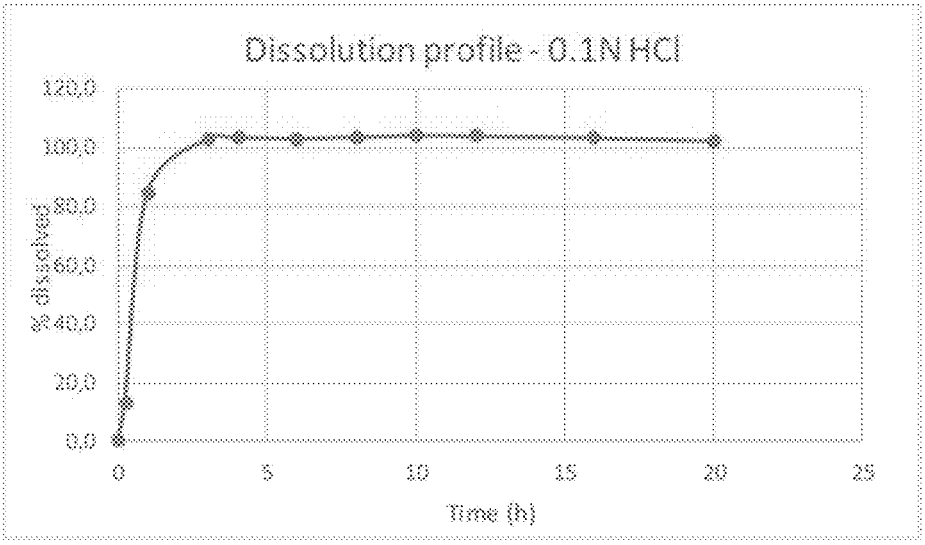


Figure 72

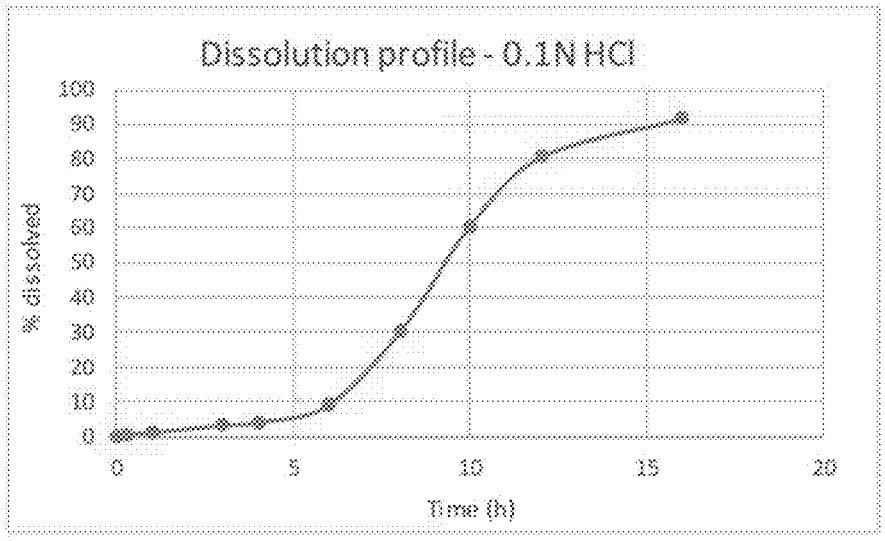


Figure 73

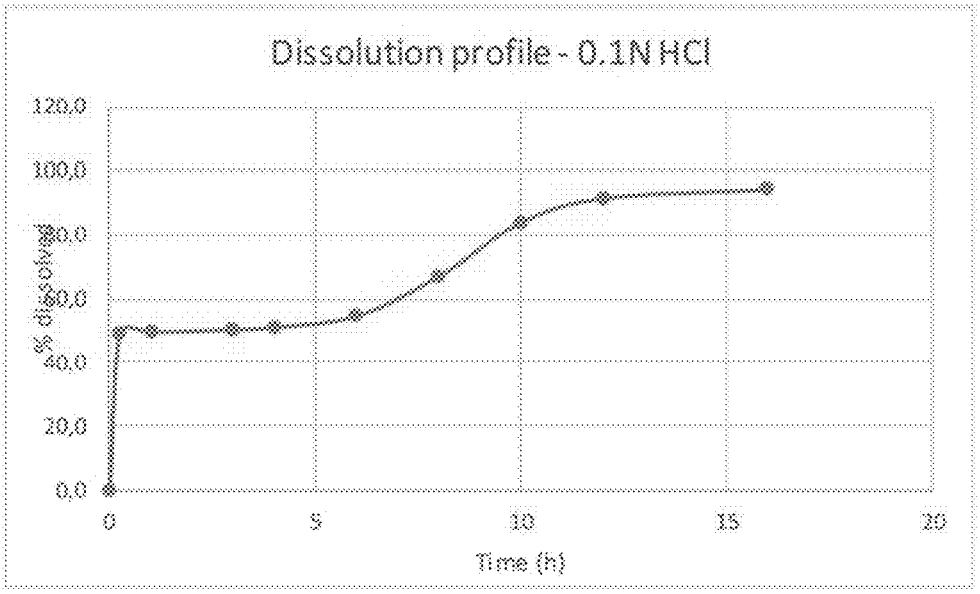


Figure 74

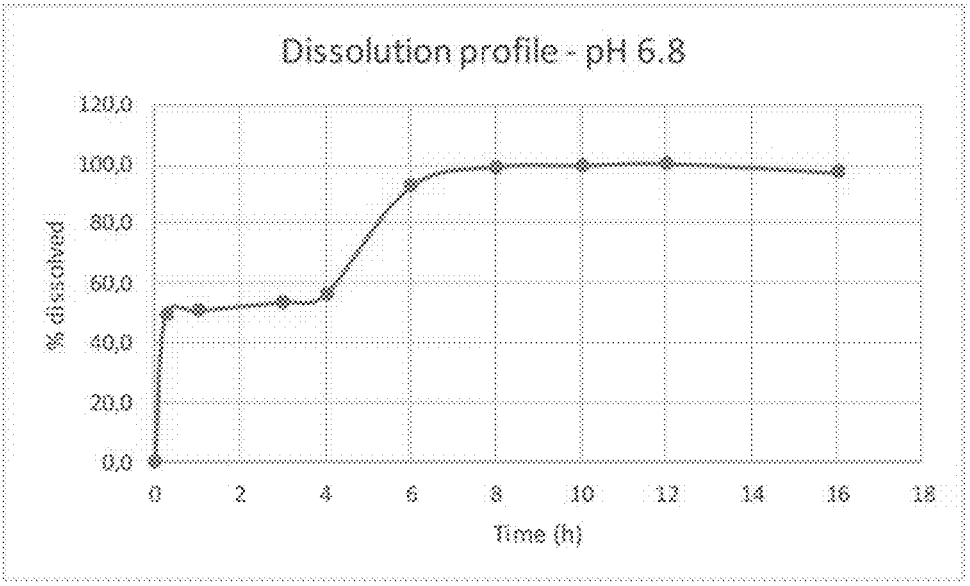


Figure 75

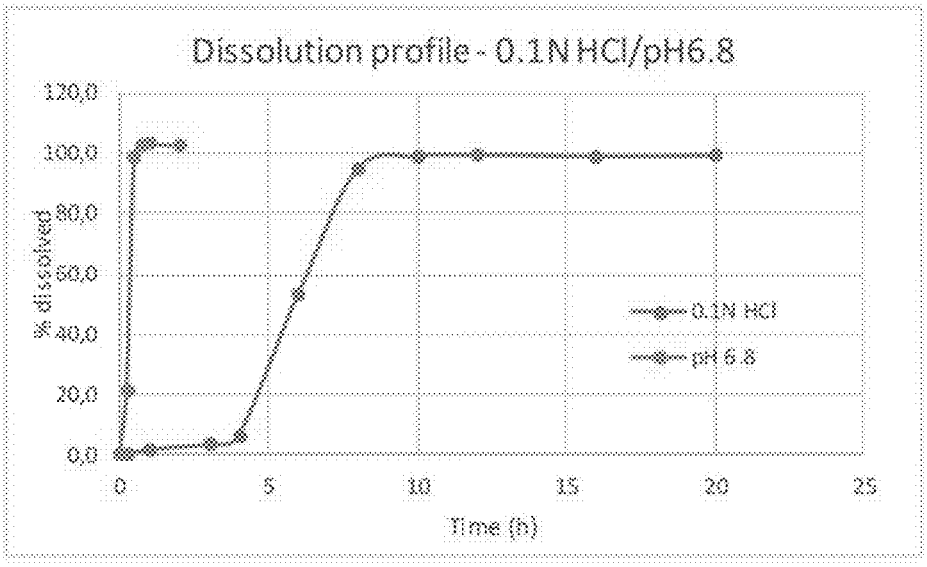


Figure 76

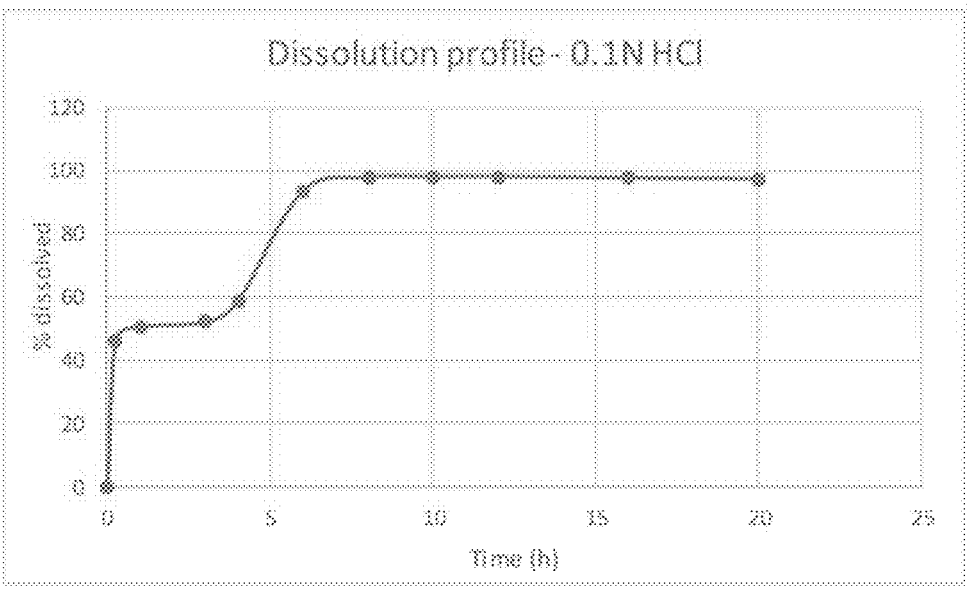


Figure 77

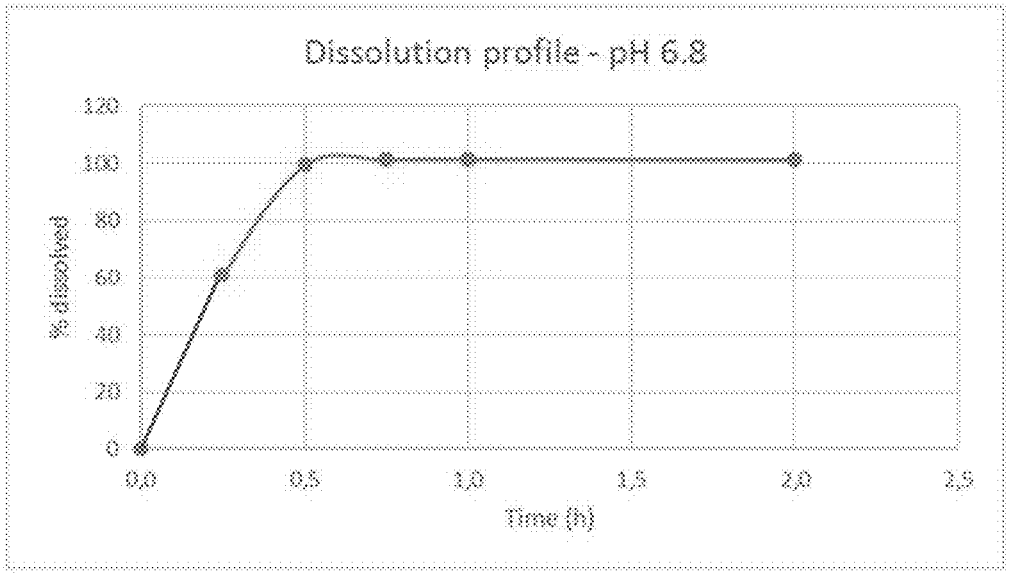


Figure 78

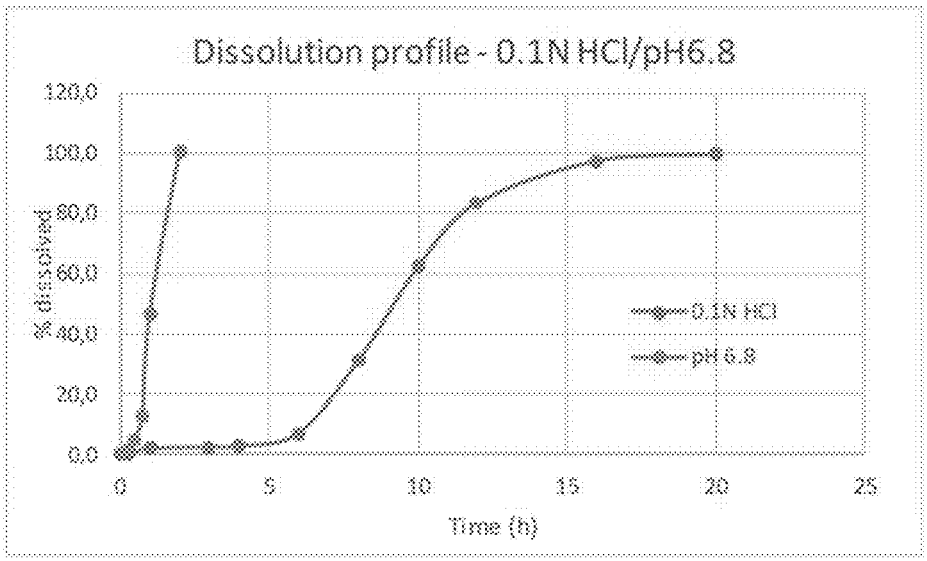


Figure 79

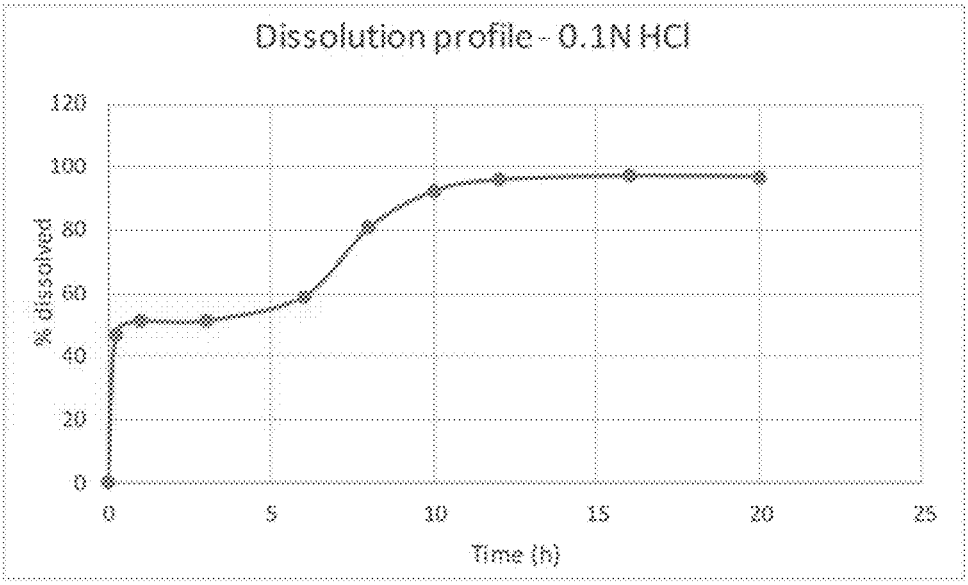


Figure 80

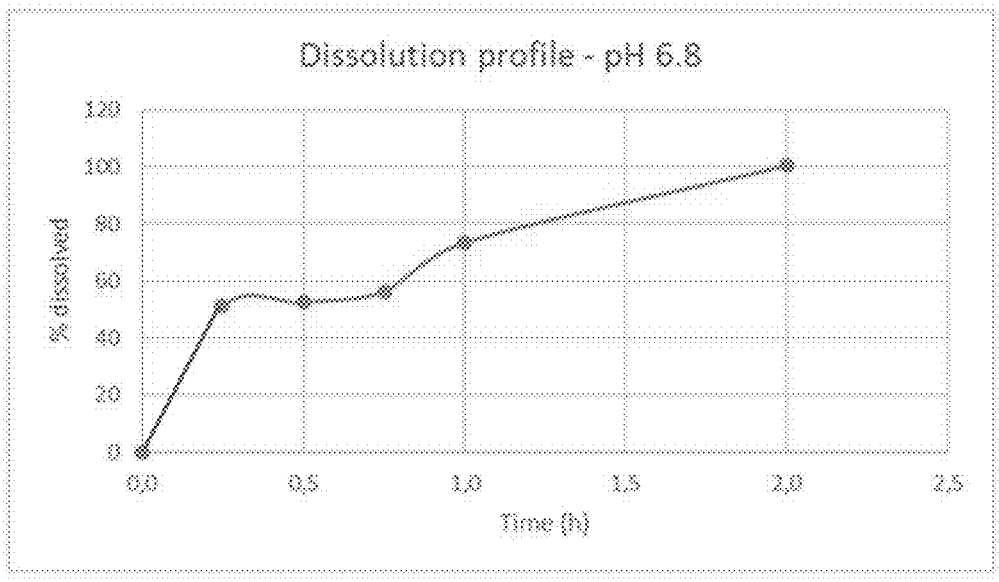


Figure 81

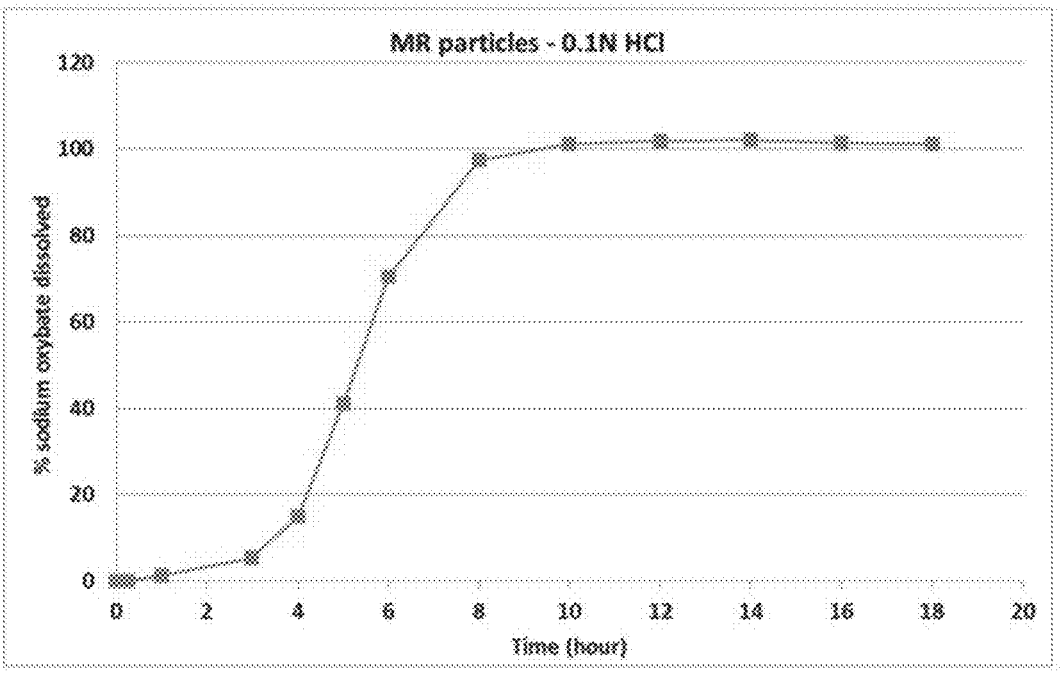


Figure 82

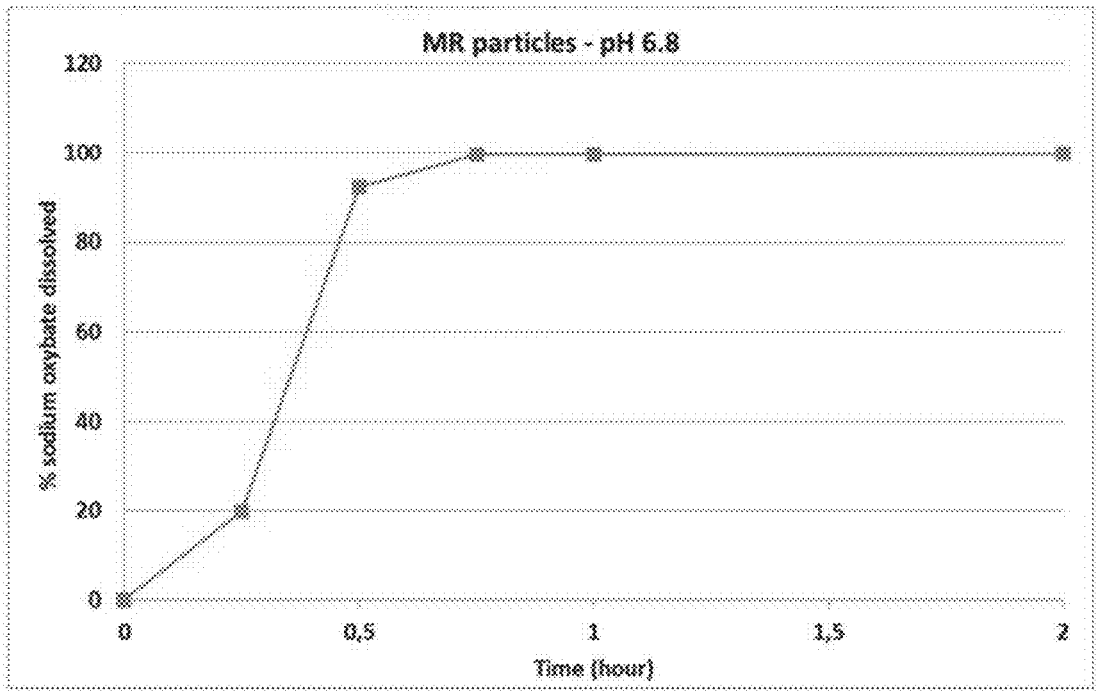


Figure 83

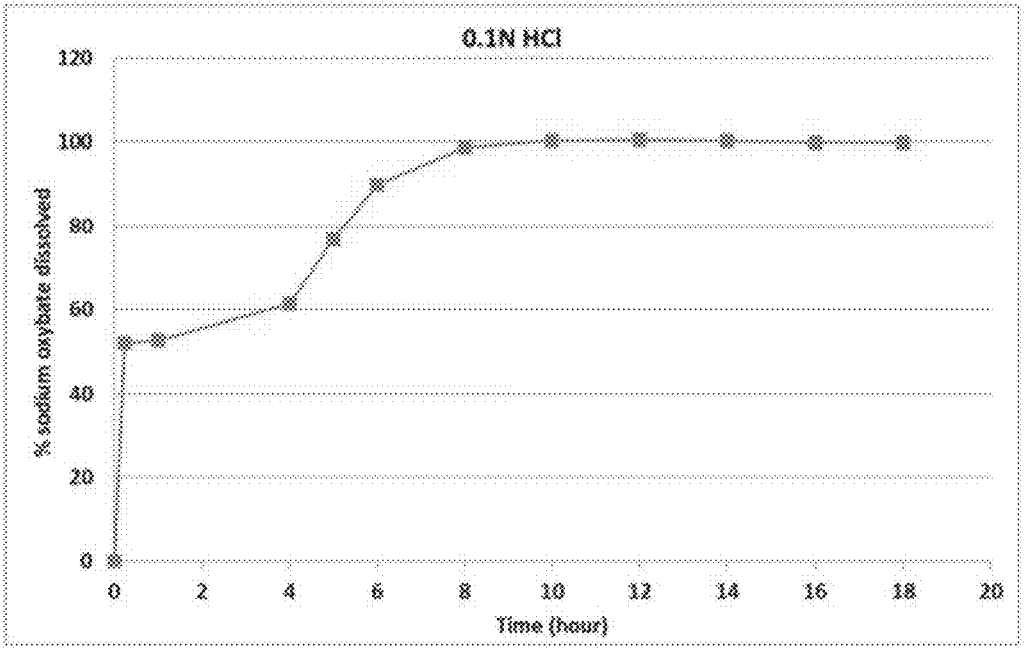


Figure 84

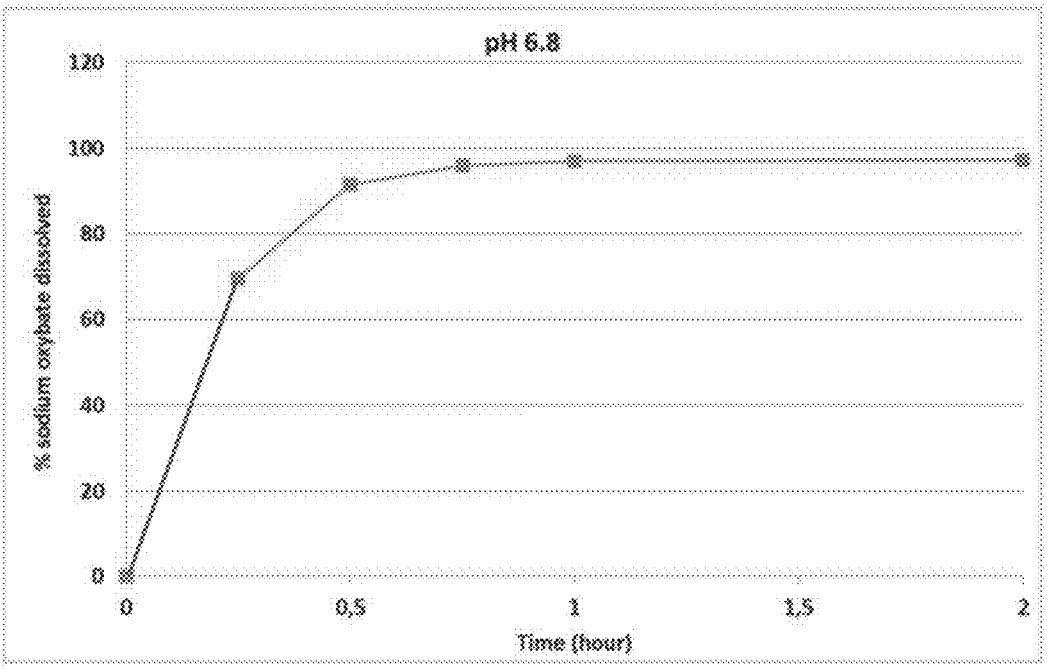


Figure 85

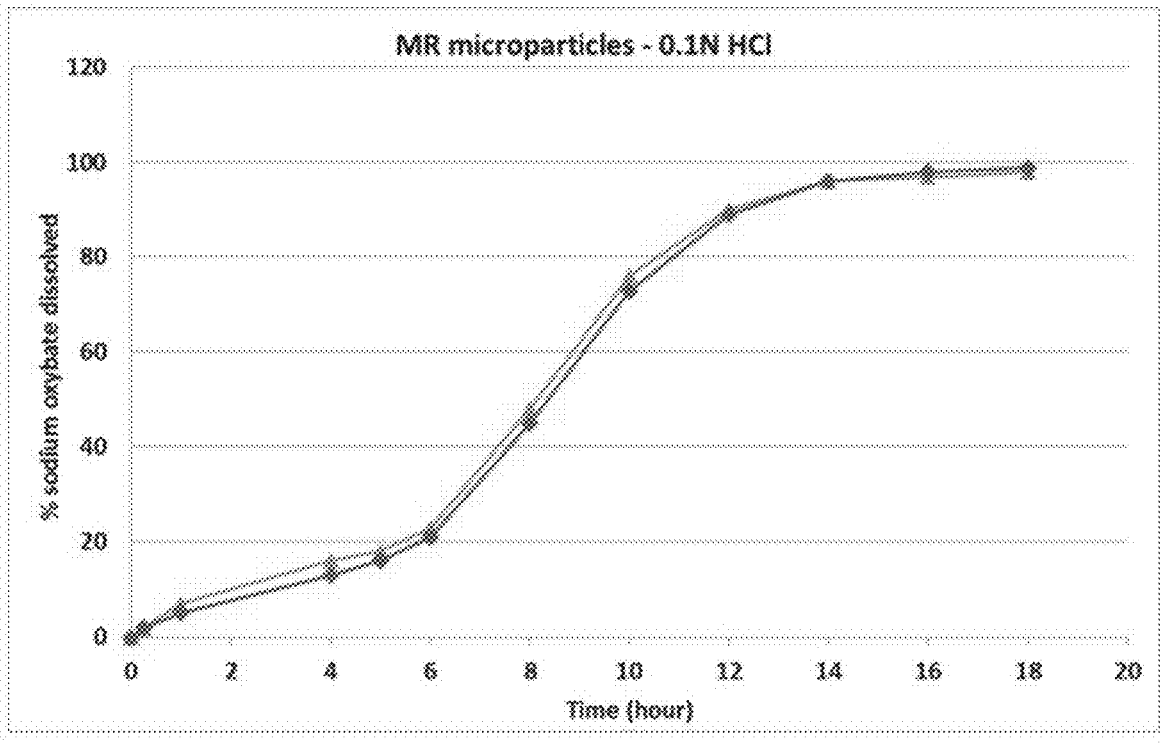


Figure 86

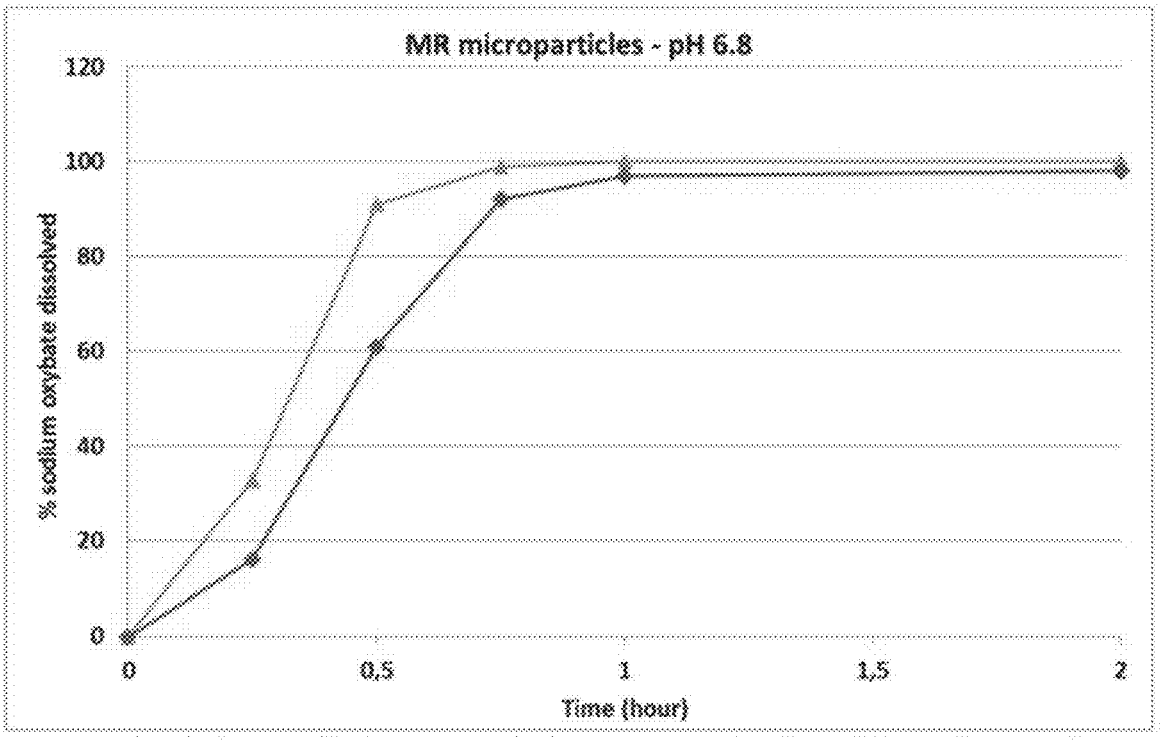


Figure 87

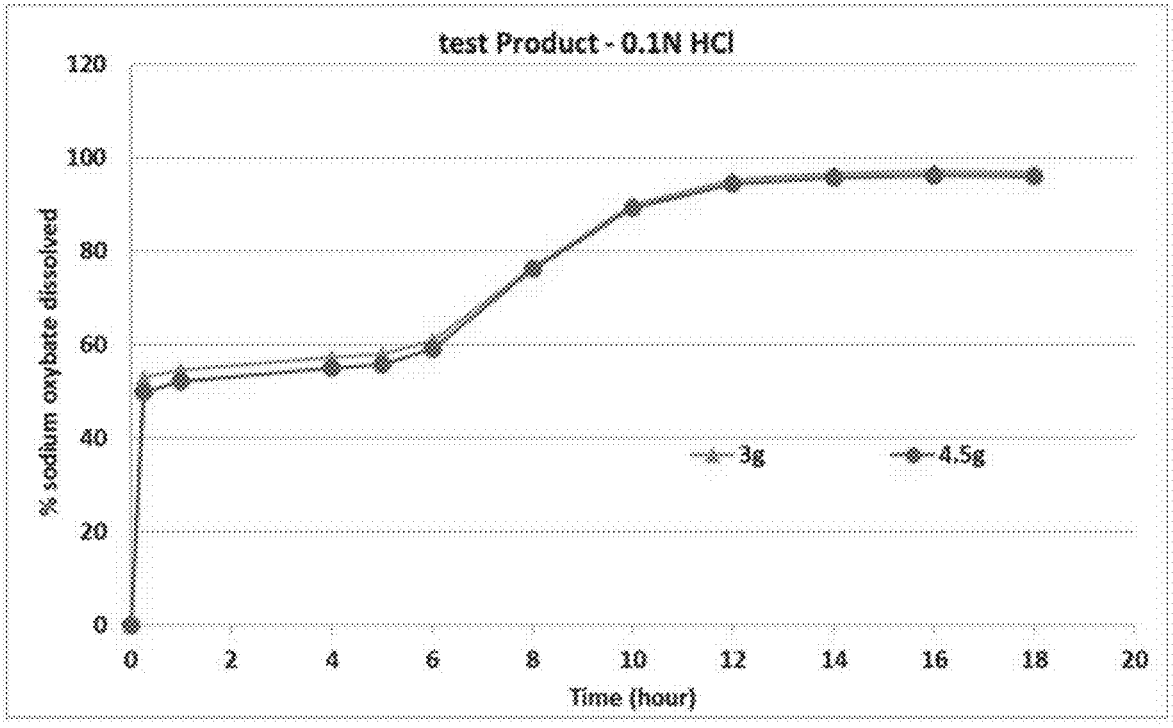


Figure 88

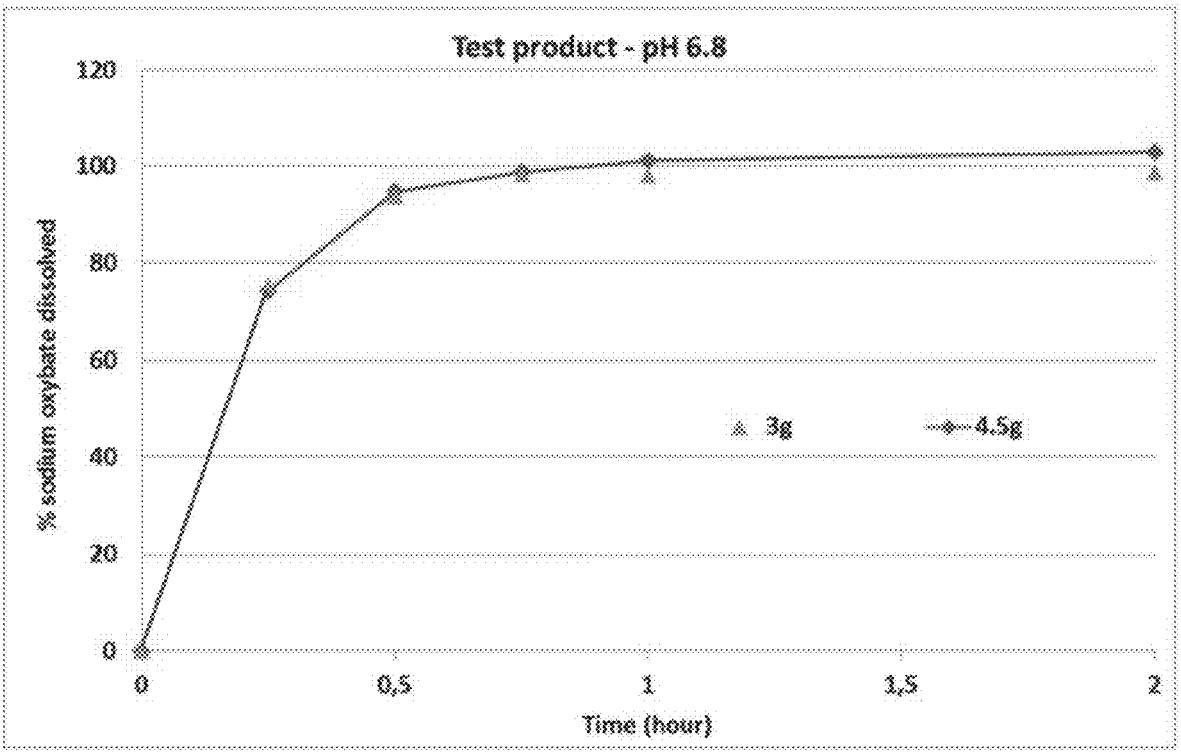

Test product - pH 6.8
% sodium oxybate dissolved
120
100
80
60
40
20
0
0
0,5
1
1,5
2
Time (hour)
3g
4.5g

Figure 89

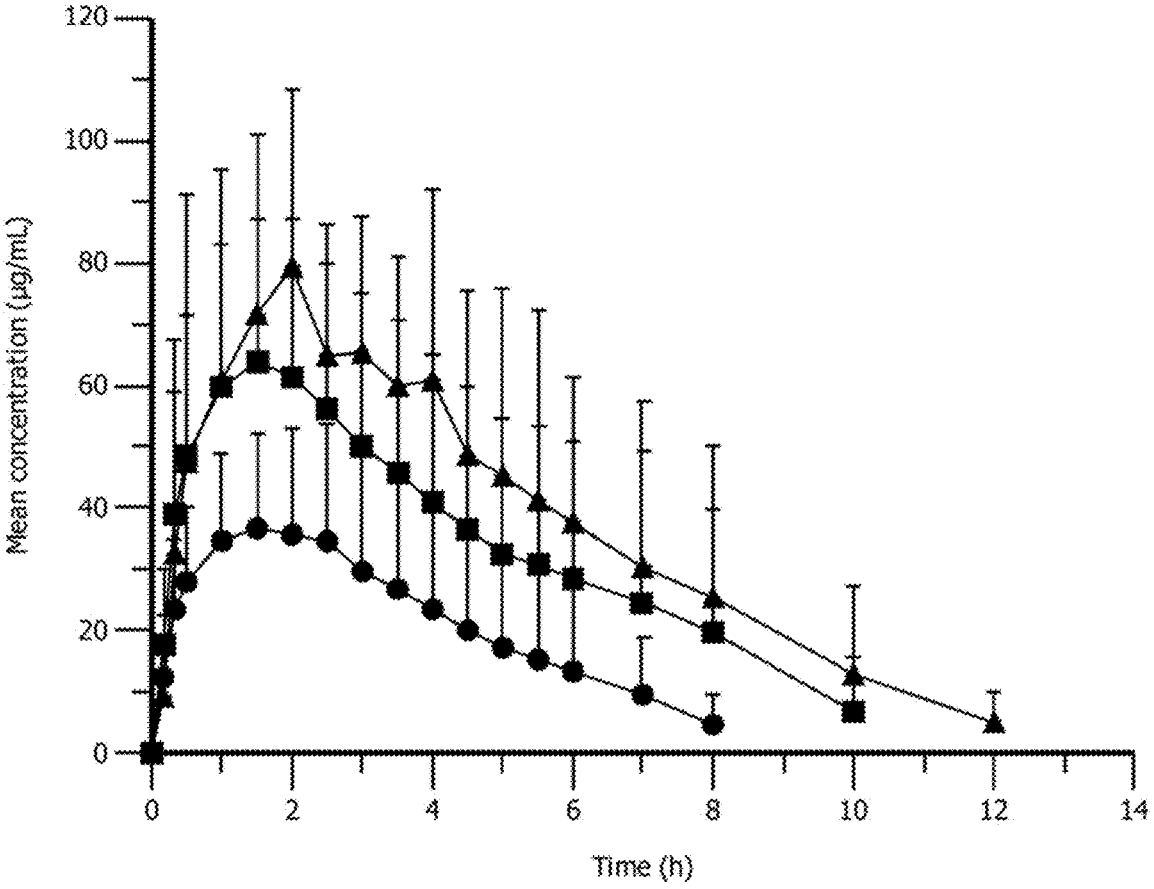

120
100
80
60
40
20
0
Mean concentration (µg/mL)
0
2
4
6
8
10
12
14
Time (h)

Figure 90

MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 15/655,924, filed Jul. 21, 2017, which claims priority to U.S. Provisional Application No. 62/365,812, filed Jul. 22, 2016, U.S. Provisional Application No. 62/399,413, filed Sep. 25, 2016, and U.S. Provisional Application No. 62/474,330, filed Mar. 21, 2017.

FIELD OF THE INVENTION

The present invention relates to modified release formulations of gamma-hydroxybutyrate having improved pharmacokinetic (PK) properties, and to therapeutic uses thereof.

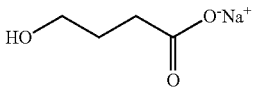
BACKGROUND

Narcolepsy is a devastating disabling condition. The cardinal symptoms are excessive daytime sleepiness (EDS), cataplexy (a sudden loss of muscle tone triggered by strong emotions, seen in approximately 60% of patients), hypnogogic hallucination (HH), sleep paralysis (SP), and disturbed nocturnal sleep (DNS). Other than EDS, DNS is the most common symptom seen among narcolepsy patients.

The diagnosis of narcolepsy rests in part on clinical grounds. When narcolepsy is suspected, it is standard practice to administer an overnight polysomnogram (PSG) followed by a multiple sleep latency test (MSLT) to document the rapid eye movement (REM) abnormality that characterizes the disorder. On the MSLT a mean sleep latency less than or equal to 8 minutes and two or more sleep onset REM periods (SOREMPs) are required to confirm a diagnosis of Type 1 or Type 2 narcolepsy. It is also possible, but infrequently preferred, that narcolepsy be diagnosed by measuring hypocretin in the cerebrospinal fluid (CSF) in cases where the PSG and/or MSLT is not completed. For these cases, a hypocretin concentration of less than 110 pg/nL confirms a narcolepsy Type 1 diagnosis.

One of the major treatments for narcolepsy is sodium oxybate, a neuroactive agent with a variety of Central Nervous System (CNS) pharmacological properties. The species is present endogenously in many tissues, where it acts as a neurotransmitter on a gamma-hydroxybutyrate (GHB) receptor (GHBR), and possesses neuromodulatory properties with significant effects on dopamine and gamma-Aminobutyric Acid (GABA). Studies have suggested that sodium oxybate improves Rapid Eye Movement Sleep (REM sleep, REMS) of narcoleptics in contrast to antidepressant drugs.

Sodium oxybate is also known as sodium 4-hydroxybutanoate, or gamma-hydroxybutyric acid sodium salt, and has the following chemical structure:



Sodium oxybate is marketed commercially in the United States as Xyrem®. The product is formulated as an immediate release liquid solution that is taken once immediately before bed, and a second time approximately 2.5 to 4 hours later, in equal doses. Sleep-onset can be dramatic and fast, and patients are advised to be sitting in bed when consuming the dose. The most commonly reported side effects are confusion, depressive syndrome, incontinence and sleep-walking.

When initiating treatment with sodium oxybate, careful titration up to an adequate level is essential both to obtain positive results and avoid adverse effects. The recommended starting dose is 4.5 g divided into 2 equal doses of 2.25 g, the first taken at bedtime and the second taken 2.5 to 4 hours later. The starting dosage can be decreased to 3.0 g/day or increased to as high as 9.0 g/day in increments of 1.5 g/day (0.75 g per dose). Two weeks are recommended between dosage adjustments to optimize reduction of daytime symptoms and minimize side effects. The ideal dose will provide an effective eight hours of sleep but, at the end of eight hours, very little of the drug will remain in the patient's bloodstream to affect the patient's wakefulness.

The requirement to take Xyrem® twice each night is a substantial inconvenience to narcolepsy patients. The patient must typically set an alarm to take the second dose, which can interrupt ongoing productive sleep. Several efforts have been made to provide a once-nightly modified release dosage form of sodium oxybate, but none has yet received approval from the United States Food and Drug Administration ("FDA") or proven effective in the clinic.

One of the biggest drawbacks of these once-nightly formulations is the reduction in bioavailability that occurs when sodium oxybate is formulated in a modified release dosage form, as measured by the blood concentration/time area under the curve ("AUC"). U.S. 2012/0076865 A1 by Allphin et al. ("Allphin"), for example, conducted two separate crossover bioavailability trials involving three separate modified release formulations and an immediate release solution, and reported the following bioavailability results:

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr)[a]	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
Summary of PK Parameters for Treatments A, B, C						
Treatment A						
N	29	29	29	29	29	29
Mean	1.22	0.6	4.50 (0.5, 4.75)	130.79	350.84	351.2
SD	0.27	0.13		31.52	116.74	116.74
CV %	21.93	22.61		24.1	33.27	33.24
Mean	1.19	0.58		127.3	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

-continued

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr)[a]	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
Summary of OK Parameters for Treatments A, D, E						
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		24.10	61.31	62.55
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

Treatment A: Two 3 g IR doses administered four hours apart
Treatment B: One 6 g CR dose administered at time zero (no IR component)
Treatment C: One 6 g CR dose administered at time zero (no IR component)
Treatment D: One 4 g dose including IR and CR fractions administered at time zero
Treatment E: One 8 g dose including IR and CR fractions administered at time zero

As can be seen, mean AUC_{inf}, which measures the total exposure of the body to sodium oxybate for a given dose, was significantly less for the doses having a modified release component when compared to the immediate release doses. Mean AUC_{inf} for Treatment B, which included the exact same dose of sodium oxybate as Treatment A, was only 56% of the mean AUC_{inf} for Treatment A; mean AUC_{inf} for Treatment C, which also included the same dose of sodium oxybate as Treatment A, was only 63% of the mean AUC_{inf} for Treatment A; mean AUC_{inf} for Treatment E was only 81% of the mean AUC_{inf} of Treatment A, even though Treatment E dosed 2 g more of sodium oxybate than Treatment A, which, compared to same dose, represented only 61% of the mean AUC_{inf} of Treatment A. Mean AUC_{inf} for Treatment D was only 22% of the mean AUC_{inf} of Treatment A, although Treatment D dosed 2 g less of sodium oxybate than Treatment A, which, compared to same dose, represented only 33% of the mean AUC_{inf} of Treatment A. As shown in FIGS. 12 and 14 of U.S. 2012/0076865 A1, Allphin's formulations also suffered from an excess of sodium oxybate remaining in the bloodstream at 8 hours.

U.S. Pat. No. 8,193,211 to Liang et al. ("Liang") reports even lower bioavailability from his once-nightly formulations. Liang developed several enterically coated delayed release formulations of sodium oxybate, and tested these formulations in dogs alongside an immediate release formulation to compare the relative pharmacokinetics (PK) of these formulations. The results of Liang's testing are reported below:

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

-continued

Mean GHB Concentrations (ug/mL)

	Period			
Time Point (Hr)	1 DR1-w/ Acid	2 DR1-No Acid	3 IR	4 DR2
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%

DR1-w/ Acid: Two 1 g DR capsules administered at time zero
DR1-No Acid: Two 1 g DR capsules administered at time zero
IR: Two 1 g IR capsules administered at time zero
DR2: Two 1 g DR capsules administered at time zero

As can be seen, by encapsulating the sodium oxybate in an enteric/delayed release coating, Liang decreased the AUC of the sodium oxybate significantly. One of the formulations, DR1-w/Acid, had a relative bioavailability of only 22% compared to the immediate release dosage form. DR2 had the greatest relative bioavailability, but still only 53% compared to the immediate release dosage form. One can easily calculate that any of the envisioned combinations of immediate release (IR) components and delayed release (DR) components as described in col. 5 lines 3 to 28 of U.S. Pat. No. 8,193,211 will not give a relative bioavailability greater than 78%.

All of these formulations are inconvenient for at least two reasons: (1) the low relative bioavailability necessitates an increase in the dose compared to current IR treatments which already require a large dose (4.5 to 9 g a day), and (2) when provided in the form of pills, a patient must swallow around 4 to 9 pills per dose, which is a serious inconvenience for the patient and potential drawback for patient compliance.

Various other techniques are known for formulating modified release dosage forms including, for example, the techniques described in U.S. Pat. No. 8,101,209 to Legrand et al. ("Legrand"). Legrand provides a system ensuring that the active ingredient is released with certainty from the modified release dosage form by means of a dual mechanism of "time-dependent" and "pH-dependent" release. Legrand did not describe any dosage forms for delivering sodium oxybate or other forms of gamma-hydroxybutyrate.

Another drawback of Xyrem® is the high level of the daily dose, generally 7.5 g or 9 g of sodium oxybate taken daily over long periods of time. This represents a very high sodium intake which is not recommended in persons with high blood pressure, risk of cardiovascular disease, stroke or coronary heart disease (See WHO. Guideline: Sodium intake for adults and children. Geneva, World Health Organization (WHO), 2012.).

Accordingly, one object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that are administered only once at bed-time with improved dissolution and pharmacokinetic profiles.

Another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that optimize the bioavailability of the gamma-hydroxybutyrate, and roughly approximate the bioavailability of an equal dose of an immediate release liquid solution of sodium oxybate administered twice nightly.

Still another object of the present invention is to provide once-nightly modified release formulations of gamma-hydroxybutyrate that roughly approximate or exceed the bioavailability of an equal dose of an immediate release solution of sodium oxybate administered twice nightly, across the entire therapeutic range of sodium oxybate doses.

Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate which, 8 hours after administration, produce very little residual drug content in the bloodstream of most patients but still similar to the one observed after administration of an equal dose of an immediate release liquid solution of sodium oxybate administered twice nightly.

Yet another object of the present invention is to improve the therapeutic effectiveness and safety profile of gamma-hydroxybutyrate based on novel dissolution and pharmacokinetic profiles.

Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that yield a similar pharmacokinetic profile compared to an immediate release liquid solution of sodium oxybate administered twice nightly while potentially giving a reduced dose.

Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that allow once daily administration and reduced dose compared to the commercial treatment Xyrem®.

Yet another object of the present invention is to provide a convenient dosage form of gamma-hydroxybutyrate that can be easily swallowed.

Yet another object of the present invention is to provide modified release formulations of gamma-hydroxybutyrate that are administered only once at bed-time with improved dissolution and pharmacokinetic profiles and reduced sodium content compared to an immediate release liquid solution of sodium oxybate administered twice nightly.

SUMMARY OF INVENTION

As the prior art demonstrates, it is extremely difficult to find a modified release formulation of gamma-hydroxybutyrate which, when administered only once nightly, has a comparable bioavailability to an immediate release liquid solution of sodium oxybate administered twice nightly. Even if such a formulation could be found, it probably still would not be satisfactory because the dose of gamma-hydroxybutyrate differs among individuals, and the size of the dose affects the amount of drug absorbed through the GI tract. I.e., even if the prior art formulations achieved comparable bioavailability at one dose—which they do not—they would not be comparable at other doses.

The inventors have discovered a novel relationship between the in vitro release profile of gamma-hydroxybutyrate modified release formulations and in vivo absorption which permits, for the first time, a modified release formulation of gamma-hydroxybutyrate that approximates the bioavailability of a twice-nightly equipotent immediate release liquid solution of sodium oxybate, and that does so across a range of therapeutic doses. In particular, the inventors have discovered that a modified release formulation of gamma-hydroxybutyrate that rapidly releases half of its gamma-hydroxybutyrate in 0.1N hydrochloric acid dissolution medium, and rapidly releases the other half of its gamma-hydroxybutyrate in phosphate buffer pH 6.8 dissolution medium, approximates or exceeds the in vivo bioavailability of an equipotent immediate release liquid solution of sodium oxybate administered twice nightly. This can be seen by comparing the formulations of Examples 1 and 4, which satisfy the dissolution requirements of the present invention and achieve the necessary bioavailability for a commercial formulation, with the Comparative formulation of Example 7, which exhibited a dissolution profile similar to prior art dissolution profiles, and did not achieve the necessary bioavailability for a commercial formulation.

This phenomenon is observed especially with higher doses of gamma-hydroxybutyrate. For example, the inventors have discovered that a modified release composition of gamma-hydroxybutyrate according to the invention administered once approximately two hours after a standardized evening meal at the dose equivalent to 7.5 g of sodium oxybate results in a similar pharmacokinetic profile as an immediate release liquid solution of sodium oxybate given in two separate equal doses of 4.5 g of sodium oxybate each administered at t_0 and t_{4h}.

The modified release formulations of gamma-hydroxybutyrate preferably have both immediate release and modified release portions. The release of gamma-hydroxybutyrate from the immediate release portion is practically uninhibited, and occurs almost immediately in 0.1N hydrochloric acid dissolution medium. In contrast, while the modified release portion also preferably releases its gamma-hydroxybutyrate almost immediately when fully triggered, the release is not triggered until a predetermined lag-time or the drug is subjected to a suitable dissolution medium such as a phosphate buffer pH 6.8 dissolution medium. Without wishing to be bound by any theory, it is believed that this rapid release in two dissolution media compresses the blood concentration vs. time curve in vivo, resulting in a relative bioavailability of gamma-hydroxybutyrate comparable to or greater than an equipotent dose of an immediate-release liquid solution of sodium oxybate administered twice nightly.

Formulations that achieve this improved bioavailability can be described using several different pharmacokinetic and in vitro dissolution parameters. In a first principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL.

In a second principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130% of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

In a third principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH

6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In a fourth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a fifth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a sixth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and (b) the formulation releases (i) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (ii) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a seventh principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In an eighth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and (d) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a ninth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein 4.5 g, 6 g, 7.5 g, and 9 g doses of the formulation have been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

In a tenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein 4.5 g and 9 g doses of the formulation have been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate

administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

In an eleventh principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 6.0 g or 7.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **12** or FIG. **13** for the corresponding strength.

In a twelfth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **22**.

In a thirteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **7** and FIG. **8**.

In a fourteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **20** and FIG. **21**.

In a fifteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein said modified release portion yields a dissolution profile substantially as depicted in FIG. **3** or FIG. **16**.

In a sixteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **25** and FIG. **26**.

In a seventeenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **27** and FIG. **28**.

In an eighteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate yielding a dissolution profile substantially as shown in any one of FIGS. **29** through **89**.

A nineteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 7.5 g or 9.0 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **90** for the corresponding strength.

A twentieth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **26** and FIG. **28**.

Still further embodiments relate to methods of using the formulations of the present invention to treat narcolepsy and associated disorders and symptoms, and to physical aspects of the formulations of the present invention. Additional principal embodiments and sub-embodiments thereto will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The embodiments and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIG. **1** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 1.

FIG. **2** plots a time release dissolution profile of IR microparticles of gamma-hydroxybutyrate of Example 1 (♦) and 1bis (■) in a 0.1N HCl dissolution medium. FIG. **3** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 1 in two sequential dissolution media (0.1 N HCl/phosphate buffer pH 6.8).

FIG. **4** plots a time release dissolution profile of MR microparticles (▲ symbols) of Example 1 in two sequential dissolution media (0.1 N HCl/phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (● symbols).

FIG. **5** plots a time release dissolution profile of the finished formulation of Example 1 in deionized water.

FIG. **6** plots a time release dissolution profile of the finished composition of Example 1 in deionized water (▲ symbols), overlaid against dissolution profile described in FIG. 2 of USP 2012/0076865 (● symbols).

FIG. **7** plots time release dissolution profiles in 0.1N HCl of four separate batches of finished compositions produced in accordance with Example 1 or Example 1bis.

FIG. **8** plots time release dissolution profiles in phosphate buffer pH 6.8 of four separate batches of finished compositions produced in accordance with Example 1 or Example 1bis.

FIG. **9** plots time release dissolution profiles in 0.1N HCl of MR microparticles of gamma-hydroxybutyrate produced in accordance with Example 1 at 75 rpm (■ symbols) and 100 rpm (▲ symbols).

FIG. **10** plots time release dissolution profiles in 0.1N HCl of finished composition produced in accordance with Example 1 performed with paddle rotation speed set at 75 rpm (■ symbols) and 100 rpm (▲ symbols).

FIG. **11** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time for two different modified release formulations of gamma-hydroxybutyrate tested in vivo according to the methods of Example 3. Time profiles are given for a 4.5 g dose of the finished composition of Example 1bis administered once (● symbols) (N=26) and a 4.5 g dose of Xyrem® administered in two divided doses (– symbols) (N=15).

FIG. **12** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL) versus time after a Single Oral Administration of 4.5 g (● symbols) and 6 g (▲ symbols) of finished composition of Example 1bis in the same 7 subjects tested in vivo according to the methods of Example 3.

FIG. **13** plots the mean+SD (standard deviation) plasma gamma-hydroxybutyrate concentrations (microgram/mL)

versus time of three separate doses of finished composition prepared according to Example 1bis tested in vivo according to the methods of Example 3. Mean time profiles are given for a single oral administration of 4.5 g (N=26) (●), 6.0 g (N=19) (▲) or 7.5 g (■) doses (N=11).

FIG. **14** plots the mean plasma gamma-hydroxybutyrate Concentrations (microgram/mL) of a Single dose of 7.5 g (■) of finished composition prepared according to Example 1bis compared to 2×4.5 g Xyrem® post-fed (Source NDA 21-196 review).

FIG. **15** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 4.

FIG. **16** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 4 in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8).

FIG. **17** plots a time release dissolution profile of MR microparticles (▲ symbols) of Example 4 in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (● symbols).

FIG. **18** plots a time release dissolution profile of the finished composition of Example 4 in deionized water.

FIG. **19** plots a time release dissolution profile of the finished composition of Example 4 in deionized water (● symbols), overlaid against dissolution profile described in FIG. 2 of USP 2012/0076865 (▲ symbols).

FIG. **20** plots time release dissolution profiles in 0.1N HCl of three separate batches of finished compositions produced in accordance with Example 4 or 4bis.

FIG. **21** plots a time release dissolution profile in phosphate buffer pH 6.8 of a finished composition produced in accordance with Example 4.

FIG. **22** plots mean plasma gamma-hydroxybutyrate concentration (microgram/mL) time profiles after a Single Dose of 4.5 g (■) of finished composition of Example 4bis, N=15 compared to 2×2.25 g Xyrem® post fed, N=15.

FIG. **23** depicts the qualitative and quantitative structure of the immediate release (IR) and modified release (MR) microparticles of gamma-hydroxybutyrate of Example 7.

FIG. **24** plots a time release dissolution profile of MR microparticles of gamma-hydroxybutyrate of Example 7 (▲ symbols) in two sequential dissolution media (0.1 N HCl and phosphate buffer pH 6.8), overlaid against dissolution profile described in FIG. 3 of U.S. Pat. No. 8,193,211 (● symbols).

FIG. **25** plots the Min (■) and Max (▲) values of a preferred dissolution profile in 0.1N HCl of finished composition according to the invention.

FIG. **26** plots the Min (■) and Max (▲) values of a preferred dissolution profile in phosphate buffer pH 6.8 of finished composition according to the invention.

FIG. **27** plots the Min (■) and Max (▲) values of another preferred dissolution profile in phosphate buffer pH 6.8 of finished composition according to the invention.

FIG. **28** plots the Min (■) and Max (▲) values of another preferred dissolution profile in 0.1N HCl of finished composition according to the invention.

FIG. **29** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus **2** for the formulation of Example 9.1 5 minutes and 15 minutes after reconstitution in water.

FIG. **30** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus **2** for the formulation of Example 9.2 5 minutes and 15 minutes after reconstitution in water.

FIG. **31** depicts a dissolution profile determined in 0.1N HCl using a USP apparatus **2** for the formulation of Example 9.3 5 minutes and 15 minutes after reconstitution in water.

FIG. **32** depicts the dissolution profile determined in 0.1N HCl using a USP apparatus **2** of a 9 g dose of the formulation of Example 10 with and without rinsing.

FIG. **33** depicts the dissolution profile of the MR portion of the formulation of Example 11a in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **34** depicts the dissolution profile of the formulation of Example 11a in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **35** depicts the dissolution profile of the formulation of Example 11a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **36** depicts the dissolution profile of the MR portion of the formulation of Example 11b in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **37** depicts the dissolution profile of the formulation of Example 11b in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **38** depicts the dissolution profile of the formulation of Example 11b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **39** depicts the dissolution profile of the formulation of Example 11c in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **40** depicts the dissolution profile of the formulation of Example 11c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **41** depicts the dissolution profile of the MR portion of the formulation of Example 12a in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **42** depicts the dissolution profile of the formulation of Example 12a using a USP apparatus **2** in 0.1N HCl.

FIG. **43** depicts the dissolution profile of the formulation of Example 12b in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **44** depicts the dissolution profile of the formulation of Example 12b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **45** depicts the dissolution profile of the MR portion of the formulation of Example 13 in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **46** depicts the dissolution profile of the formulation of Example 13 in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **47** depicts the dissolution profile of the formulation of Example 13 in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **48** depicts the dissolution profile of the MR portion of the formulation of Example 14 in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **49** depicts the dissolution profile of the formulation of Example 14 in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **50** depicts the dissolution profile of the formulation of Example 14 in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **51** depicts the dissolution profile of the MR portion of the formulation of Example 15a (coating weight 35%) in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **52** depicts the dissolution profile of the MR portion of the formulation of Example 15a (coating weight 50%) in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **53** depicts the dissolution profile of the formulation of Example 15a in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **54** depicts the dissolution profile of the MR portion of the formulation of Example 15b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **55** depicts the dissolution profile of the formulation of Example 15b in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **56** depicts the dissolution profile of the formulation of Example 15b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **57** depicts the dissolution profile of the MR portion of the formulation of Example 15c in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **58** depicts the dissolution profile of the formulation of Example 15c in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **59** depicts the dissolution profile of the formulation of Example 15c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **60** depicts the dissolution profile of the MR portion of the formulation of Example 15d in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **61** depicts the dissolution profile of the formulation of Example 15d in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **62** depicts the dissolution profile of the formulation of Example 15d in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **63** depicts the dissolution profile of the MR portion of the formulation of Example 16a in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **64** depicts the dissolution profile of the formulation of Example 16a in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **65** depicts the dissolution profile of the formulation of Example 16a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **66** depicts the dissolution profile of the MR portion of the formulation of Example 16b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **67** depicts the dissolution profile of the formulation of Example 16b in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **68** depicts the dissolution profile of the formulation of Example 16b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **69** depicts the dissolution profile of the MR portion of the formulation of Example 16c in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **70** depicts the dissolution profile of the formulation of Example 16c in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **71** depicts the dissolution profile of the formulation of Example 16c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **72** depicts the dissolution profile of the MR portion of the formulation of Example 16d in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **73** depicts the dissolution profile of the MR portion of the formulation of Example 17a in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **74** depicts the dissolution profile of the formulation of Example 17a in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **75** depicts the dissolution profile of the formulation of Example 17a in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **76** depicts the dissolution profile of the MR portion of the formulation of Example 17b in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **77** depicts the dissolution profile of the formulation of Example 17b in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **78** depicts the dissolution profile of the formulation of Example 17b in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **79** depicts the dissolution profile of the MR portion of the formulation of Example 17c in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **80** depicts the dissolution profile of the formulation of Example 17c in 900 ml of 0.1N HCl using a USP apparatus **2**.

FIG. **81** depicts the dissolution profile of the formulation of Example 17c in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**.

FIG. **82** depicts a preferred dissolution profile of sodium oxybate MR microparticles in 900 ml 0.1N HCl using a USP apparatus **2** at 75 rpm.

FIG. **83** depicts a preferred dissolution profile of sodium oxybate MR microparticles in 900 ml pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2** at 75 rpm.

FIG. **84** depicts a preferred dissolution profile of a sodium oxybate finished formulation comprising IR and MR microparticles in 900 ml 0.1N HCl using a USP apparatus **2** at 75 rpm.

FIG. **85** depicts a preferred dissolution profile of a sodium oxybate finished formulation comprising IR and MR

microparticles in 900 ml pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2** at 75 rpm.

FIG. **86** is a dissolution profile in 0.1N HCl of two separate batches of the sodium oxybate MR microparticles present in the finished composition of Example 18.

FIG. **87** is a dissolution profile in phosphate buffer pH 6.8 of two separate batches of the sodium oxybate MR microparticles present in the finished composition of Example 18.

FIG. **88** is a dissolution profile in 0.1N HCl of two unit doses of 3 g (▲ symbols) and 4.5 g (● symbols) of the finished composition of Example 18.

FIG. **89** is a dissolution profile in phosphate buffer pH 6.8 of two unit doses of 3 g (▲ symbols) and 4.5 g (● symbols) of the finished composition of Example 18.

FIG. **90** plots mean plasma gamma-hydroxybutyrate concentrations (microgram/mL)+SD—time profiles after a single oral administration of 4.5 g (● symbols), 7.5 g (■ symbols) and 9 g (▲ symbols) of the finished composition of Example 18.

DETAILED DESCRIPTION OF THE INVENTION

The present invention may be understood more readily by reference to the following detailed description of preferred embodiments of the invention and the Examples included therein.

Definitions and Use of Terms

Wherever an analysis or test is required to understand a given property or characteristic recited herein, it will be understood that the analysis or test is performed in accordance with applicable guidances, draft guidances, regulations and monographs of the United States Food and Drug Administration ("FDA") and United States Pharmacopoeia ("USP") applicable to drug products in the United States in force as of Nov. 1, 2015 unless otherwise specified. Clinical endpoints can be judged with reference to standards adopted by the American Academy of Sleep Medicine, including standards published at C Iber, S Ancoli-Israel, A Chesson, S F Quan. The AASM Manual for the Scoring of Sleep and Associated Events. Westchester, Ill.: American Academy of Sleep Medicine; 2007.

When a pharmacokinetic comparison is made between a formulation described or claimed herein and a reference product, it will be understood that the comparison is preferably performed in a suitable designed cross-over trial, although it will also be understood that a cross-over trial is not required unless specifically stated. It will also be understood that the comparison can be made either directly or indirectly. For example, even if a formulation has not been tested directly against a reference formulation, it can still satisfy a comparison to the reference formulation if it has been tested against a different formulation, and the comparison with the reference formulation can be deduced therefrom.

As used in this specification and in the claims which follow, the singular forms "a," "an" and "the" include plural referents unless the context dictates otherwise. Thus, for example, reference to "an ingredient" includes mixtures of ingredients, reference to "an active pharmaceutical agent" includes more than one active pharmaceutical agent, and the like.

"Bioavailability" means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

"Relative bioavailability" or "Rel BA" or "RBA" means the percentage of mean AUC_{inf} of the tested product relative to the mean AUC_{inf} of the reference product. Unless otherwise specified, relative bioavailability refers to the percentage of the mean AUC_{inf} observed for a full dose of the test product relative to the mean AUC_{inf} observed for two ½-doses of an immediate release liquid solution administered four hours apart.

"Bioequivalence" means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives become available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically and physically possible. Thus, for example, if a formulation may contain from 1 to 10 weight parts of a particular ingredient, or 2 to 8 parts of a particular ingredient, it will be understood that the formulation may also contain from 2 to 10 parts of the ingredient. In like manner, if a formulation may contain greater than 1 or 2 weight parts of an ingredient and up to 10 or 9 weight parts of the ingredient, it will be understood that the formulation may contain 1-10 weight parts of the ingredient, 2-9 weight parts of the ingredient, etc. unless otherwise specified, the boundaries of the range (lower and upper ends of the range) are included in the claimed range.

In like manner, when various sub-embodiments of a senior (i.e. principal) embodiment are described herein, it will be understood that the sub-embodiments for the senior embodiment can be combined to define another sub-embodiment. Thus, for example, when a principal embodiment includes sub-embodiments 1, 2 and 3, it will be understood that the principal embodiment can be further limited by any one of sub-embodiments 1, 2 and 3, or any combination of sub-embodiments 1, 2 and 3 that is mathematically and physically possible. In like manner, it will be understood that the principal embodiments described herein can be combined in any manner that is mathematically and physically possible, and that the invention extends to such combinations.

When used herein the term "about" or "substantially" or "approximately" will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength due to manufacturing variation and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered bioequivalent to the recited strength, as described in FDA's March 2003 Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations.

When used herein the term "gamma-hydroxybutyrate" or GHB, unless otherwise specified, refers to the free base of gamma hydroxy-butyrate, a pharmaceutically acceptable salt of gamma-hydroxybutyric acid, and combinations thereof, their hydrates, solvates, complexes or tautomers forms. Gamma-hydroxybutyric acid salts can be selected from the sodium salt of gamma-hydroxybutyric acid or sodium oxybate, the potassium salt of gamma-hydroxybutyric acid, the magnesium salt of gamma-hydroxybutyric

acid, the calcium salt of gamma-hydroxybutyric acid, the lithium salt of gamma-hydroxybutyric, the tetra ammonium salt of gamma-hydroxybutyric acid or any other pharmaceutically acceptable salt forms of gamma-hydroxybutyric acid.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use. The term "formulation" or "composition" refers to the quantitative and qualitative characteristics of a drug product or dosage form prepared in accordance with the current invention.

As used herein the doses and strengths of gamma-hydroxybutyrate are expressed in equivalent-gram (g) weights of sodium oxybate unless stated expressly to the contrary. Thus, when considering a dose of gamma-hydroxybutyrate other than the sodium salt of gamma-hydroxybutyrate, one must convert the recited dose or strength from sodium oxybate to the gamma-hydroxybutyrate under evaluation. Thus, if an embodiment is said to provide a 4.5 g dose of gamma-hydroxybutyrate, because the form of gamma-hydroxybutyrate is not specified, it will be understood that the dose encompasses a 4.5 g dose of sodium oxybate, a 5.1 g dose of potassium gamma-hydroxybutyrate (assuming a 126.09 g/mol MW for sodium oxybate and a 142.20 g/mol MW for potassium gamma-hydroxybutyrate), and a 3.7 g dose of the free base (assuming a 126.09 g/mol MW for sodium oxybate and a 104.1 g/mol MW for the free base of gamma-hydroxybutyrate), or by the weight of any mixture of salts of gamma-hydroxybutyric acid that provides the same amount of GHB as 4.5 g of sodium oxybate.

As used herein "microparticle" means any discreet particle of solid material. The particle can be made of a single material or have a complex structure with core and shells and be made of several materials. The terms "microparticle", "particle", "microspheres" or "pellet" are interchangeable and have the same meaning. Unless otherwise specified, the microparticle has no particular particle size or diameter and is not limited to particles with volume mean diameter D(4,3) below 1 mm.

As used herein, the "volume mean diameter D(4,3)" is calculated according to the following formula:

$$D(4,3)=\Sigma(d^4_i \cdot n_i)/\Sigma(d^3_i \cdot n_i)$$

wherein the diameter d of a given particle is the diameter of a hard sphere having the same volume as the volume of that particle.

As used herein, the terms "finished composition", "finished formulation" or "formulation" are interchangeable and designate the modified release formulation of gamma-hydroxybutyrate preferably comprising modified release microparticles of gamma-hydroxybutyrate, immediate release microparticles of gamma-hydroxybutyrate, and any other excipients.

As used herein and in the claims that follow, an "immediate release (IR) portion" of a formulation includes physically discreet portions of a formulation, mechanistically discreet portions of a formulation, and pharmacokinetically discreet portions of a formulation that lend to or support a defined IR pharmacokinetic characteristic. Thus, for example, any formulation that releases active ingredient at the rate and extent required of the immediate release portion of the formulations of the present invention includes an "immediate release portion," even if the immediate release portion is physically integrated in what might otherwise be considered an extended release formulation. Thus, the IR portion can be structurally discreet or structurally indiscreet from (i.e. integrated with) the MR portion. In a preferred embodiment, the IR portion and MR portion are provided as particles, and in an even more preferred subembodiment the IR portion and MR portion are provided as particles discreet from each other.

As used here in, "immediate release formulation" or "immediate release portion" refers to a composition that releases at least 80% of its gamma-hydroxybutyrate in 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in a 0.1N HCl dissolution medium at a temperature of 37° C. and a paddle speed of 75 rpm.

In like manner, a "modified-release (MR) portion" includes that portion of a formulation or dosage form that lends to or supports a particular MR pharmacokinetic characteristic, regardless of the physical formulation in which the MR portion is integrated. The modified release drug delivery systems are designed to deliver drugs at a specific time or over a period of time after administration, or at a specific location in the body. The USP defines a modified release system as one in which the time course or location of drug release or both, are chosen to accomplish objectives of therapeutic effectiveness or convenience not fulfilled by conventional IR dosage forms. More specifically, MR solid oral dosage forms include extended release (ER) and delayed-release (DR) products. A DR product is one that releases a drug all at once at a time other than promptly after administration. Typically, coatings (e.g., enteric coatings) are used to delay the release of the drug substance until the dosage form has passed through the acidic medium of the stomach. An ER product is formulated to make the drug available over an extended period after ingestion, thus allowing a reduction in dosing frequency compared to a drug presented as a conventional dosage form, e.g. a solution or an immediate release dosage form. For oral applications, the term "extended-release" is usually interchangeable with "sustained-release", "prolonged-release" or "controlled-release".

Traditionally, extended-release systems provided constant drug release to maintain a steady concentration of drug. For some drugs, however, zero-order delivery may not be optimal and more complex and sophisticated systems have been developed to provide multiphase delivery. One can distinguish among four categories of oral MR delivery systems: (1) delayed-release using enteric coatings, (2) site-specific or timed release (e.g. for colonic delivery), (3) extended-release (e.g., zero-order, first-order, biphasic release, etc.), and (4), programmed release (e.g., pulsatile, delayed extended release, etc.) See *Modified Oral Drug Delivery Systems* at page 34 in Gibaldi's DRUG DELIVERY SYSTEMS IN PHARMACEUTICAL CARE, AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS, 2007 and *Rational Design of Oral Modified-release Drug Delivery Systems* at page 469 in DEVELOPING SOLID ORAL DOSAGE FORMS: PHARMACEUTICAL THEORY AND PRACTICE, Academic Press, Elsevier, 2009. As used herein, "modified release formulation" or "modified release portion" in one embodiment refers to a composition that releases its gamma-hydroxybutyrate according a multiphase delivery that is comprised in the fourth class of MR products, e.g. delayed extended release. As such it differs from the delayed release products that are classified in the first class of MR products.

As used herein the terms "coating", "coating layer," "coating film," "film coating" and like terms are interchangeable and have the same meaning. The terms refer to

the coating applied to a particle comprising the gamma-hydroxybutyrate that controls the modified release of the gamma-hydroxybutyrate.

In all pharmacokinetic testing described herein, unless otherwise stated, the dosage form, or the initial dosage form if the dosing regimen calls for more than one administration, is administered approximately two hours after consumption of a standardized dinner consisting of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

A "similar PK profile" or "comparable bioavailability" means that the mean AUC_{inf} of a test product is from 80% to 125% of the mean AUC_{inf} of a reference product in a suitably designed cross-over trial, and that the mean plasma concentration at 8 hours (C_h) of the test product is from 50% to 130% of the mean plasma concentration at 8 hours (C_{8h}) of the reference product.

Type 1 Narcolepsy (NT1) refers to narcolepsy characterized by excessive daytime sleepiness ("EDS") and cataplexy. Type 2 Narcolepsy (NT2) refers to narcolepsy characterized by excessive daytime sleepiness without cataplexy. A diagnosis of narcolepsy (with or without cataplexy) can be confirmed by one or a combination of (i) an overnight polysomnogram (PSG) and a Multiple Sleep Latency Test (MSLT) performed within the last 2 years, (ii) a full documentary evidence confirming diagnosis from the PSG and MSLT from a sleep laboratory must be made available, (iii) current symptoms of narcolepsy including: current complaint of EDS for the last 3 months (ESS greater than 10), (iv) mean MWT less than 8 minutes, (v) mean number of cataplexy events of 8 per week on baseline Sleep/Cataplexy Diary, and/or (vi) presence of cataplexy for the last 3 months and 28 events per week during screening period.

Unless otherwise specified herein, percentages, ratios and numeric values recited herein are based on weight; averages and means are arithmetic means; all pharmacokinetic measurements based on the measurement of bodily fluids are based on plasma concentrations.

It will be understood, when defining a composition by its pharmacokinetic or dissolution properties herein, that the formulation can in the alternative be defined as "means for" achieving the recited pharmacokinetic or dissolution properties. Thus, a formulation in which the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour can instead be defined as a formulation comprising "means for" or "modified release means for" releasing less than 20% of its gamma-hydroxybutyrate at one hour. It will be further understood that the preferred structures for achieving the recited pharmacokinetic or dissolution properties are the structures described in the examples hereof that accomplish the recited pharmacokinetic or dissolution properties.

Discussion of Principal Embodiments

The invention can be described in terms of principal embodiments, which in turn can be recombined to make other principal embodiments, and limited by sub-embodiments to make other principal embodiments.

A first principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 300, 325, 340, 375, 400, 425, or 450 hr×microgram/mL, most preferably greater than 340 hr×microgram/mL.

A second principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 265, 285, 300, 315, 325, 340, 350, 375, 400, 425, or 450 hr×microgram/mL, most preferably greater than 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70% to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, from 90% to 110%, from 50% to 95%, from 60% to 90%, most preferably from 60% to 90% or 60% to 130% of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of sodium oxybate (e.g. Xyrem®) administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

A third principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

A fourth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion preferably releases greater than 80% or 90% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

A fifth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and at three hours when tested

in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60%, 70%, or 80%, preferably greater than 80%, of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

A sixth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 245, 300, 325, 340, 375, 400, 425, or 450 hr×microgram/mL, preferably 340 hr×microgram/mL, and a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70% to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, from 90% to 110%, from 50% to 95%, or from 60% to 90%, preferably from 60% to 90% or from 60% to 130%, of the mean C_{8h} provided by an equal dose of an immediate release liquid solution of gamma-hydroxybutyrate (e.g. Xyrem®) administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and (b) the formulation releases (i) at least 80% or 90% of its gamma-hydroxybutyrate at 3 hours, 2 hours, 1 hour, 0.5 hours, or 0.25 hours, preferably 1 hour, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (ii) from 10 to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

A seventh principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% or 10% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at three hours, two hours or one hour, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

An eighth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at one hour, two hours, or three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% or 10% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (c) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at three hours, two hours, or one hour, when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm; and (d) said modified release portion releases greater than 80% or 90% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

A ninth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 4.5 g, 6 g, 7.5 g, and 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85% or 90% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal. The relative bioavailability is even higher with larger doses, and with a 6.0 g or 7.5 g or 9.0 g dose is preferably greater than 90, 95 or 100% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

A tenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, wherein a 4.5 g and a 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

An eleventh principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 6.0 g, or 7.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **12** or FIG. **13** for the corresponding strength.

A twelfth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **22**.

A thirteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **7** and FIG. **8**.

A fourteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a dissolution profile substantially as depicted in FIG. **20** and FIG. **21**.

A fifteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions that yields a dissolution profile substantially as depicted in FIG. **3** or **16**.

In a sixteenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **25** and FIG. **26**.

In a seventeenth principal embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions that yields a dissolution profile between the minimum and maximum values depicted in FIG. **27** and FIG. **28**.

In an eighteenth principal embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate yielding a dissolution profile substantially as shown in any one of FIGS. **29** through **89**. It will be understood that this seventeenth principal embodiment can be limited only to one of these dissolution profiles.

A nineteenth principal embodiment of the present invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, that yields a plasma concentration versus time curve when administered once nightly at a strength of 4.5 g, 7.5 g or 9.0 g approximately two hours after a standardized evening meal substantially as depicted in FIG. **90** for the corresponding strength.

In any of these principal embodiments, the formulation is preferably effective to treat narcolepsy Type 1 or Type 2. The formulation is also preferably effective to induce sleep for six to eight, most preferably eight consecutive hours.

In any of these principal embodiments, the formulation preferably comprises immediate release and modified release portions, wherein the modified release portion comprises gamma hydroxybutyrate particles coated by a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C., and the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35. The polymers comprising free carboxylic groups preferably have a pH dissolution trigger of from 5.5 to 6.97 and are preferably methacrylic acid copolymers having a pH dissolution trigger of from 5.5 to 6.97.

Principal Structural Embodiments

In a first principal structural embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

In a second principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, a suspending or viscosifying agent, and an acidifying agent, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

In a third principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

In a fourth principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

In a fifth principal structural embodiment the invention provides a modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating comprises a methacrylic acid copolymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and (e) the coating is from 10 to 50% of the weight of the particles.

Discussion of Pharmacokinetic and Dissolution Sub-Embodiments

As mentioned in the definitions section of this document, each of the sub-embodiments can be used to further characterize and limit each of the foregoing principal embodiments. In addition, more than one of the following sub-embodiments can be combined and used to further characterize and limit each of the foregoing principal embodiments, in any manner that is mathematically and physically possible.

In various sub-embodiments of the foregoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean AUC_{inf} of greater than 245, 265, 285, 300, 315, 325, 340, 350, 375, 400, 425, or 450

hr×microgram/mL when administered once approximately two hours after a standardized evening meal. An upper limit on mean AUC_{inf} for such 7.5 g dose can be set at 500 or 550 hr×microgram/mL.

In additional sub-embodiments of the foregoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean C_{max} of greater than 65, 70, 75, 80, 85, or 90 microgram/mL when administered once approximately two hours after a standardized evening meal. An upper limit on mean C_{max} for such 7.5 g dose can be set at 125 or 100 microgram/mL.

In additional sub-embodiments of the forgoing principal embodiments a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate can be characterized as having been shown to achieve a mean C_{8h} that is from 50% to 130%, from 60% to 130%, from 70 to 130%, from 75% to 125%, from 80% to 125%, from 80 to 120%, or from 90% to 110% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of gamma-hydroxybutyrate administered at t_0 and t_{4h} in two equally divided doses, when administered approximately two hours after a standardized evening meal.

In one sub-embodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 340 hr·microgram/mL, and a mean C_{8h} that is from 50% to 130% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

Further sub-embodiments can be characterized based on the dissolution properties of the entire (or finished) modified release formulation of gamma-hydroxybutyrate in 0.1N hydrochloric acid dissolution medium. Thus, in additional sub-embodiments the entire modified release formulation of gamma-hydroxybutyrate releases greater than 30%, 35%, 40%, or 45%, and less than 70%, 65%, 60%, or 55%, of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

Further sub-embodiments can be defined based on the dissolution properties of the modified release portion of the formulation of gamma-hydroxybutyrate in a phosphate buffer pH 6.8 dissolution medium. Thus, in additional sub-embodiments the modified release portion releases greater than 80%, 85%, 90%, 95%, 98% or even 99% of its gamma-hydroxybutyrate at 3, 2, 1, 0.5 or 0.25 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

Still further embodiments can be defined based on the dissolution properties of the modified release portion of the modified release formulation of gamma-hydroxybutyrate in a 0.1N HCl dissolution medium. Thus, in additional sub-embodiments the modified release portion releases less than 20%, 15%, 10%, 5%, or even 2% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In additional embodiments, the modified release portion releases less than 20%, 15%, 10%, 5%, or even 2% of its gamma-hydroxybutyrate at one hour and at three hours and more than 30%, 35%, 40%, 45% of its gamma-hydroxybutyrate at ten hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

Further embodiments can be defined based on the dissolution properties of the immediate release portion of the modified release formulation of gamma-hydroxybutyrate in a 0.1N HCl dissolution medium. Thus, in additional sub-embodiments the immediate release portion releases greater than 80%, 85%, 90%, 95%, 98% or even 99% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In another sub-embodiment, the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In another subembodiment, the formulation comprises immediate release and modified release portions, and (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In another sub-embodiment, the formulation comprises immediate release and modified release portions, and (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65% of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

Still further sub-embodiments can be defined based on a pharmacokinetic comparison of the modified release formulation of gamma-hydroxybutyrate to an immediate release solution of gamma-hydroxybutyrate. Therefore, in additional sub-embodiments the modified release formulation of gamma-hydroxybutyrate, preferably in a 4.5 g, 6.0 g, 7.5 g,

and 9.0 g dose, has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85%, 90%, or 95% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

In additional sub-embodiments of the forgoing principal embodiments the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein a 4.5 g and 9 g dose of the formulation has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85% or 90% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal

In additional sub-embodiments, a 6.0 g or 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a relative bioavailability (RBA) of greater than 80%, 85%, 90%, 95% or 100% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined by comparing the area under the concentration/time curve for eight hours to the area under the concentration/time curve calculated to infinity. Thus, in still further sub-embodiments a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate of the present invention has been shown to achieve a ratio of AUC_{8h} to AUC_{inf} of greater than 0.80, 0.85, 0.90, 0.95 or 0.98 when administered once approximately two hours after a standardized evening meal.

In still further sub-embodiments, the modified release formulations of gamma-hydroxybutyrate are defined based on the concentration of gamma-hydroxybutyrate in the blood stream 8 hours after administration. Therefore, in other sub-embodiments the formulation can be characterized by a 4.5 g dose of the modified release formulation of gamma-hydroxybutyrate that has been shown to achieve a mean C_{8h} of from 4.7 to 9.0, from 5.4 to 8.3, from 6.1 to 7.6, from 3.5 to 7.0, or from 4.0 to 5.5 microgram/mL, a 6.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{8h} of from 6.3 to 16.7, from 7.3 to 15.4, from 8.2 to 14.1, from 8.9 to 16.7, from 10.2 to 15.4, or from 11.5 to 14.1 microgram/mL; or a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{8h} of from 13.0 to 40.3, from 16.0 to 26.0, 15.0 to 25.0, from 17.5 to 22.0, from 21.6 to 40.3, from 24.7 to 37.2, or from 27.8 to 34.1 microgram/mL, when administered once approximately two hours after a standardized evening meal.

The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined by the concentration/time and dissolution curves that they produce when tested according to the examples of the present invention. Therefore, in other sub-embodiments, a 4.5 g, 6.0 g, or 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate of the present invention has been shown to achieve a time/concentration curve substantially as shown in FIGS. **13** (*a*), (*b*) and (*c*) respectively herein. In another principal embodiment or sub-embodiment, the formulation has been shown to achieve a dissolution curve substantially as shown in FIGS. **7** and **8** or FIGS. **20** and **21** herein.

The modified release formulations of gamma-hydroxybutyrate of the present invention can also be defined based on the time required to reach maximum blood concentration of gamma-hydroxybutyrate. Thus, in additional sub-embodiments, the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a median T_{max} of 1.25 to 3.25 hours, preferably of about 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, or 3.25 hours when administered once approximately two hours after a standardized evening meal. A lower limit on the median T_{max} in any of the foregoing ranges can alternatively be set at 0.5 or 1.0 hours.

Additional embodiments can be defined by comparing a dose of the modified release formulation of gamma-hydroxybutyrate, administered once nightly, to the same dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a median T_{max} within one hundred fifty, one hundred twenty, ninety, sixty or thirty minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

In still another sub-embodiment a 4.5 g, 6.0 g, 7.5 g or 9.0 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

Additional embodiments can be defined by comparing the pharmacokinetic profile of a dose of the modified release formulation of gamma-hydroxybutyrate administered once nightly to the same dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{3h} to the mean C_{max} of the first half dose of the immediate release liquid solution of sodium oxybate from 0.6 to 1.2, preferably from 0.7 to 1.1 and most preferably from 0.8 to 1. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{4h} to the mean C_{max} of the first half dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1.1, preferably from 0.6 to 1 and most preferably from 0.7 to 0.9. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean $C_{4.5h}$ to the mean C_{max} of the first half dose of the immediate release liquid solution of gamma-hydroxybutyrate from 0.5 to 1, preferably from 0.5 to 0.9 and most preferably from 0.6 to 0.8.

Additional sub-embodiments can be defined by the range of mean blood concentrations of gamma-hydroxybutyrate achieved 3, 4, 4.5 or 5 hours after administration once nightly by a modified release formulation of gamma-hydroxybutyrate according to the invention at the dose of 7.5 g. Thus, in another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{3h} of 43 to 81 microgram/mL, preferably 49 to 75 microgram/mL and more preferably 55 to 69 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean

C_{4h} of 40 to 75 microgram/mL, preferably 45 to 69 microgram/mL and more preferably 51 to 64 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean $C_{4.5h}$ of 35 to 67 microgram/mL, preferably 40 to 62 microgram/mL and more preferably 45 to 56 microgram/mL. In another sub-embodiment, a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a mean C_{5h} of 31 to 59 microgram/mL, preferably 36 to 55 microgram/mL and more preferably 40 to 50 microgram/mL.

In another subembodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 300 hr·microgram/mL and a mean C_{max} of greater than 70 microgram/mL when administered once approximately two hours after a standardized evening meal.

In still another subembodiment, a 7.5 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 350 hr·microgram/mL and a mean C_{max} of greater than 80 microgram/mL when administered once approximately two hours after a standardized evening meal.

In another subembodiment, a 4.5, 6.0, 7.5 and 9.0 g dose of the formulation has been shown to achieve a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95%, 90 or 85% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

Additional embodiments can be defined by comparing the pharmacokinetic profile of a dose of the modified release formulation of gamma-hydroxybutyrate administered once nightly to another dose of an immediate release liquid solution of sodium oxybate divided in half and administered twice nightly, 4 hours apart. Thus, in another sub-embodiment a 7.5 g dose of the modified release formulation of gamma-hydroxybutyrate has been shown to achieve a similar pharmacokinetic profile to the pharmacokinetic profile provided by a 2×4.5 g dose of sodium oxybate as an immediate release liquid solution administered for the first 4.5 g two hours after a standardized evening meal and for the second 4.5 g dose, 4 hours after the first dose. Thus, in another sub-embodiment a modified release formulation of gamma-hydroxybutyrate according to the invention administered at the dose of 7.5 g has been shown to achieve a ratio of its mean C_{3h} to the mean C_{max} of the first 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1.1, preferably from 0.6 to 1 and most preferably from 0.7 to 0.9. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean C_{4h} to the mean C_{max} of the first 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.5 to 1, preferably from 0.6 to 0.9 and most preferably from 0.7 to 0.8. In another sub-embodiment, a modified release formulation of gamma-hydroxybutyrate according to the invention has been shown to achieve a ratio of its mean $C_{4.5h}$ to the mean C_{max} of the 4.5 g dose of the immediate release liquid solution of sodium oxybate from 0.4 to 0.9, preferably from 0.5 to 0.8 and most preferably from 0.6 to 0.7.

In another subembodiment, the modified release formulation of gamma-hydroxybutyrate comprises immediate release and modified release portions, wherein: (a) said immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; (b) said modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and (c) said modified release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

(a) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 40% to 65% at 1 hour,
(ii) from 40% to 65% at 3 hours,
(iii) from 47% to 85% at 8 hours,
(iv) greater or equal to 60% at 10 hours,
(v) greater or equal to 80% at 16 hours, and

(b) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 43% to 94% at 0.25 hour,
(ii) greater or equal to 65% at 0.35 hour, and
(iii) greater or equal to 88% at 1 hour.

In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

(a) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 40% to 65% at 1 hour,
(ii) from 40% to 65% at 3 hours,
(iii) greater or equal to 47% at 8 hours,
(iv) greater or equal to 60% at 10 hours,
(v) greater or equal to 80% at 16 hours, and

(b) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 43% to 94% at 0.25 hour,
(ii) greater or equal to 65% at 0.35 hour, and
(iii) greater or equal to 88% at 1 hour.

In another preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

(a) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 40% to 65% at 1 hour,
(ii) from 40% to 65% at 3 hours,
(iii) from 47% to 85% at 8 hours,

(iv) greater or equal to 60% at 10 hours,

(v) greater or equal to 80% at 16 hours, and

(b) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 45% to 67% at 1 hour, and

(ii) greater or equal to 65% at 3 hours.

In another preferred embodiment, the modified release formulation of gamma-hydroxybutyrate according to the invention achieves an in vitro dissolution profile:

(a) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 40% to 65% at 1 hour,

(ii) from 40% to 65% at 3 hours,

(iii) greater or equal to 47% at 8 hours,

(iv) greater or equal to 60% at 10 hours,

(v) greater or equal to 80% at 16 hours, and

(b) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being:

(i) from 45% to 67% at 1 hour, and

(ii) greater or equal to 65% at 3 hours.

In still another subembodiment, the formulation achieves an in vitro dissolution profile: (a) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) from 40% to 65% at 1 hour, (ii) from 40% to 65% at 3 hours, (iii) greater than 45% at 8 hours, and (b) measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) greater than 40% at 0.5 hour, and (ii) greater than 85% at 1 hour.

Alternatively, the formulation can be described as achieving an in vitro dissolution profile measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) from 40% to 65% at 1 hour, (ii) from 40% to 65% at 3 hours, and (iii) greater than 45% at 8 hours.

In another alternative, the formulation can be described as achieving an in vitro dissolution profile measured in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, characterized by the percentage of gamma-hydroxybutyrate dissolved being: (i) greater than 40% at 0.5 hour, and (ii) greater than 85% at 1 hour.

Structural Sub-Embodiments

The modified release formulations of gamma-hydroxybutyrate of the present invention can be provided in any dosage form that is suitable for oral administration, including tablets, capsules, liquids, orally dissolving tablets, and the like, but they are preferably provided as dry particulate formulations (i.e. granules, powders, coated particles, microparticles, pellets, microspheres, etc.), in a sachet or other suitable discreet packaging units. A preferred particulate formulation will be mixed with tap water shortly before administration, preferably 50 mL.

In one subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; and (b) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

In one subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; and (b) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 40/60 to 60/40.

In another subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; and (c) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40.

In another subembodiment, the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated microparticles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40; and (e) the film coating is from 10 to 50% of the weight of the microparticles.

In another subembodiment the formulation comprises immediate release and modified release portions, wherein: (a) the modified release portion comprises coated particles of gamma-hydroxybutyrate; (b) the coating of said modified release particles of gamma-hydroxybutyrate comprises a polymer carrying free carboxylic groups having a pH trigger of from 5.5 to 6.97 and a hydrophobic compound having a melting point equal or greater than 40° C.; (c) the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4; (d) the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35 or 40/60 to 60/40; and (e) the coating is from 10 to 50% of the weight of the particles.

In a particularly preferred sub-embodiment of the immediately preceding sub-embodiments, the polymer carrying free carboxylic groups comprises from 100% poly (methacrylic acid, ethyl acrylate) 1:1 and 0% poly (methacrylic acid, methylmethacrylate) 1:2 to 2% poly (methacrylic acid, ethyl acrylate) 1:1 and 98% poly (methacrylic acid, methylmethacrylate) 1:2; and the hydrophobic compound comprises hydrogenated vegetable oil.

In a preferred embodiment, the formulation includes excipients to improve the viscosity and the pourability of the mixture of the particulate formulation with tap water. As such, the particulate formulation comprises, besides the

immediate release and modified release particles of gamma-hydroxybutyrate, one or more suspending or viscosifying agents or lubricants.

Preferred suspending or viscosifying agents are chosen from the group consisting of xanthan gum, medium viscosity sodium carboxymethyl cellulose, mixtures of microcrystalline cellulose and sodium carboxymethyl cellulose, mixtures of microcrystalline cellulose and guar gum, medium viscosity hydroxyethyl cellulose, agar, sodium alginate, mixtures of sodium alginate and calcium alginate, gellan gum, carrageenan gum grade iota, kappa or lambda, and medium viscosity hydroxypropylmethyl cellulose.

Medium viscosity sodium carboxymethyl cellulose corresponds to grade of sodium carboxymethyl cellulose whose viscosity, for a 2% solution in water at 25° C., is greater than 200 mPa·s and lower than 3100 mPa·s.

Medium viscosity hydroxyethyl cellulose corresponds to a grade of hydroxyethyl cellulose whose viscosity, for a 2% solution in water at 25° C., is greater than 250 mPa·s and lower than 6500 mPa·s. Medium viscosity hydroxypropylmethyl cellulose corresponds to a grade of hydroxypropylmethyl cellulose whose viscosity, for a 2% solution in water at 20° C., is greater than 80 mPa·s. and lower than 3800 mPa·s.

Preferred suspending or viscosifying agents are xanthan gum, especially Xantural 75™ from Kelco, hydroxyethylcellulose, especially Natrosol 250M™ from Ashland, Kappa carrageenan gum, especially Gelcarin PH812™ from FMC Biopolymer, and lambda carrageenan gum, especially Viscarin PH209™ from FMC Biopolymer.

In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate comprises from 1 to 15% of viscosifying or suspending agents, preferably from 2 to 10%, more preferably from 2 to 5%, and most preferably from 2 to 3% of the formulation.

In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate is in the form of a powder that is intended to be dispersed in water prior to administration and further comprises from 1 to 15% of a suspending or viscosifying agent selected from a mixture of xanthan gum, carrageenan gum and hydroxyethylcellulose or xanthan gum and carrageenan gum.

In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate is in the form of a powder that is intended to be dispersed in water prior to administration and further comprises: from 1.2 to 15% of an acidifying agent selected from malic acid and tartaric acid; and from 1 to 15% of a suspending or viscosifying agent selected from a mixture of xanthan gum, carrageenan gum and hydroxyethylcellulose or xanthan gum and carrageenan gum.

In a most preferred embodiment, the modified release formulation of gamma-hydroxybutyrate comprises about 1% of lambda carrageenan gum or Viscarin PH209™, about 1% of medium viscosity grade of hydroxyethyl cellulose or Natrosol 250M™, and about 0.7% of xanthan gum or Xantural 75™. For a 4.5 g dose unit, these percentages will typically equate to about 50 mg xanthan gum (Xantural 75™), about 75 mg carrageenan gum (Viscarin PH209™) and about 75 mg hydroxyethylcellulose (Natrasol 250M™).

Alternative packages of viscosifying or suspending agents, for a 4.5 g dose, include about 50 mg xanthan gum (Xantural 75™) and about 100 mg carrageenan gum (Gelcarin PH812™), or about 50 mg xanthan gum (Xantural 75™), about 75 mg hydroxyethylcellulose (Natrasol 250M™), and about 75 mg carrageenan gum (Viscarin PH109™).

In a preferred embodiment, the modified release formulation of gamma-hydroxybutyrate further comprises a lubricant or a glidant, besides the immediate release and modified release particles of gamma-hydroxybutyrate. Preferred lubricants and glidants are chosen from the group consisting of salts of stearic acid, in particular magnesium stearate, calcium stearate or zinc stearate, esters of stearic acid, in particular glyceryl monostearate or glyceryl palmitostearate, stearic acid, glycerol behenate, sodium stearyl fumarate, talc, and colloidal silicon dioxide.

The preferred lubricant or glidant is magnesium stearate.

The lubricant or glidant can be used in the particulate formulation in an amount of from 0.1 to 5%. The preferred amount is about 0.5%.

Most preferably, the modified release formulation of gamma-hydroxybutyrate comprises about 0.5% of magnesium stearate.

A preferred modified release formulation of gamma-hydroxybutyrate further comprises an acidifying agent. The acidifying agent helps to ensure that the release profile of the formulation in 0.1N HCl will remain substantially unchanged for at least 15 minutes after mixing, which is approximately the maximum length of time a patient might require before consuming the dose after mixing the formulation with tap water.

In one particular subembodiment the formulation is a powder, and further comprising an acidifying agent and a suspending or viscosifying agent, preferably in the weight percentages recited herein.

The preferred acidifying agents are chosen from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid. In a preferred embodiment, the acidifying agent is present in the formulation from 1.2 to 15%, preferably from 1.2 to 10%, preferably from 1.2 to 5%. Preferred acidifying agents are tartaric acid and malic acid, with malic acid being most preferred.

When tartaric acid is employed, it is preferably employed in an amount of from 1 to 10%, from 2.5 to 7.5%, or about 5%. In a most preferred embodiment, the amount of malic acid in the modified release formulation of gamma-hydroxybutyrate is from 1.2 to 15%, preferably from 1.2 to 10%, preferably from 1.2 to 5%, and most preferably 1.6% or 3.2%.

In a most preferred embodiment, the amount of malic acid in the modified release formulation of gamma hydroxybutyrate is about 1.6%.

The modified release formulation of gamma-hydroxybutyrate preferably includes an immediate release portion and a modified release portion of gamma-hydroxybutyrate, and in a particularly preferred embodiment, the formulation is a particulate formulation that includes a plurality of immediate release gamma-hydroxybutyrate particles and a plurality of modified release gamma-hydroxybutyrate particles. The molar ratio of gamma-hydroxybutyrate in the immediate release and modified release portions preferably ranges from 0.11:1 to 1.86:1, from 0.17:1 to 1.5:1, from 0.25:1 to 1.22:1, from 0.33:1 to 1.22:1, from 0.42:1 to 1.22:1, from 0.53:1 to 1.22:1, from 0.66:1 to 1.22:1, from 0.66:1 to 1.5:1, from 0.8:1 to 1.22:1, and preferably is about 1:1. The molar percentage of gamma-hydroxybutyrate in the immediate release portion relative to the total of gamma-hydroxybutyrate in the formulation preferably ranges from 10% to 65%, from 15 to 60%, from 20 to 55%, from 25 to 55%, from 30 to 55%, from 35 to 55%, from 40 to 55%, from 40 to 60%, or from 45 to 55%, preferably from 40% to 60%. In

a preferred embodiment, the molar percentage of the gamma-hydroxybutyrate in the immediate release portion relative to the total of gamma-hydroxybutyrate in the formulation is about 50%. The molar percentage of gamma-hydroxybutyrate in the modified release portion relative to the total of gamma-hydroxybutyrate in the formulation preferably ranges from 90% to 35%, from 85 to 40%, from 80 to 45%, from 75 to 45%, from 70 to 45%, from 65 to 45%, from 60 to 45%, from 60 to 40%, or from 55 to 45%, preferably from 60% to 40%. In a preferred embodiment, the molar ratio of the gamma-hydroxybutyrate in the modified release portion relative to the total of gamma-hydroxybutyrate in the formulation is about 50%. The weight percentage of the IR microparticles relative to the total weight of IR microparticles and MR microparticles, preferably ranges from 7.2% to 58.2%, from 11.0% to 52.9%, from 14.9% to 47.8%, from 18.9% to 47.8%, from 23.1% to 47.8%, from 27.4% to 47.8%, from 31.8% to 47.8%, from 31.8% to 52.9%, or from 36.4% to 47.8%. In other embodiments, the weight percentage of the IR microparticles relative to the total weight of IR microparticles and MR microparticles preferably ranges from 5.9% to 63.2%, from 9.1% to 58.1%, from 12.4% to 53.1%, from 19.9% to 53.1%, from 19.6% to 53.1%, from 23.4% to 53.1%, from 27.4% to 53.1% from 27.4% to 58.1%, preferably from 31.7% to 53.1%.

In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to 450 microns and 50% of its sodium oxybate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to 170 microns and 50% of its sodium oxybate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its sodium oxybate content in modified release particles consisting of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its sodium oxybate content in immediate-release particles consisting of 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone™ K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its sodium oxybate content in modified release particles consisting of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid,

4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, 16.7% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of calcium salt of gamma-hydroxybutyric acid mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

In a preferred embodiment, the finished formulation comprises 50% of its gamma-hydroxybutyrate content in immediate-release particles consisting of 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns and 50% of its gamma-hydroxybutyrate content in modified release particles consisting of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of calcium salt of gamma-hydroxybutyric acid mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

Other Characteristics of Immediate Release Portion

The immediate release portion of the formulation can take any form capable of achieving an immediate release of the gamma-hydroxybutyrate when ingested. For example, when the formulation is a particulate formulation, the formulation can include unmodified "raw" gamma-hydroxybutyrate, rapidly dissolving gamma-hydroxybutyrate granules, particles or microparticles comprised of a core covered by a gamma-hydroxybutyrate loaded layer containing a binder such as povidone.

The IR granules or particles of gamma-hydroxybutyrate can be made using any manufacturing process suitable to produce the required particles, including:

- agglomeration of the gamma-hydroxybutyrate sprayed preferably in the molten state, such as the Glatt Pro-Cell™ technique,
- extrusion and spheronization of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,
- wet granulation of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,
- compacting of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients,
- granulation and spheronization of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, the spheronization being carried out for example in a fluidized bed apparatus equipped with a rotor, in particular using the Glatt CPS™ technique,
- spraying of the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, for example in a fluidized bed type apparatus equipped with zig-zag filter, in particular using the Glatt MicroPx™ technique, or
- spraying, for example in a fluidized bed apparatus optionally equipped with a partition tube or Wurster tube, the gamma-hydroxybutyrate, optionally with one or more physiologically acceptable excipients, in dispersion or in solution in an aqueous or organic solvent on a core.

Preferably, the immediate release portion of the formulation is in the form of microparticles comprising the immediate release gamma-hydroxybutyrate and optional pharmaceutically acceptable excipients. In a preferred embodiment, the immediate release microparticles of gamma-hydroxybutyrate have a volume mean diameter D(4,3) of from 10 to 1000 microns, preferably from 95 to 600 microns, more preferably from 150 to 400 microns. Most preferably their volume mean diameter is about 270 microns.

The preferred immediate release particles of gamma-hydroxybutyrate of the present invention comprises a core and a layer deposited on the core that contains the gamma-hydroxybutyrate. The core can be any particle chosen from the group consisting of:

crystals or spheres of lactose, sucrose (such as Compressuc™ PS from Tereos), microcrystalline cellulose (such as Avicel™ from FMC Biopolymer, Cellet™ from Pharmatrans or Celphere™ from Asahi Kasei), sodium chloride, calcium carbonate (such as Omyapure™ 35 from Omya), sodium hydrogen carbonate, dicalcium phosphate (such as Dicafos™ AC 92-12 from Budenheim) or tricalcium phosphate (such as Tricafos™ SC93-15 from Budenheim);

composite spheres or granules, for example sugar spheres comprising sucrose and starch (such as Suglets™ from NP Pharm), spheres of calcium carbonate and starch (such as Destab™ 90 S Ultra 250 from Particle Dynamics) or spheres of calcium carbonate and maltodextrin (such as Hubercal™ CCG4100 fromHuber).

The core can also comprise other particles of pharmaceutically acceptable excipients such as particles of hydroxypropyl cellulose (such as Klucel™ from Aqualon Hercules), guar gum particles (such as Grinsted™ Guar from Danisco), xanthan particles (such as Xantural™ 180 from CP Kelco).

According to a particular embodiment of the invention, the cores are sugar spheres or microcrystalline cellulose spheres, such as Cellets™ 90, Cellets™ 100 or Cellets™ 127 marketed by Pharmatrans, or also Celphere™ CP 203, Celphere™ CP305, Celphere™ SCP 100. Preferably the core is a microcrystalline cellulose sphere. Most preferably the core is a Cellets™ 127 from Pharmatrans.

The core preferably has a mean volume diameter of about 95 to about 450 microns, preferably about 95 to about 170 microns, most preferably about 140 microns.

The layer deposited onto the core comprises the immediate release gamma-hydroxybutyrate. Preferably the layer also comprises a binder, which can be chosen from the group consisting of:

low molecular weight hydroxypropyl cellulose (such as Klucel™ EF from Aqualon-Hercules), low molecular weight hydroxypropyl methylcellulose (or hypromellose) (such as Methocel™ E3 or E5 from Dow), or low molecular weight methylcellulose (such as Methocel™ A15 from Dow);

low molecular weight polyvinyl pyrrolidone (or povidone) (such as Plasdone™ K29/32 from ISP or Kollidon™ 30 from BASF), vinyl pyrrolidone and vinyl acetate copolymer (or copovidone) (such as Plasdone™: S630 from ISP or Kollidon™ VA 64 from BASF);

dextrose, pregelatinized starch, maltodextrin; and mixtures thereof.

Low molecular weight hydroxypropyl cellulose corresponds to grades of hydroxypropyl cellulose having a molecular weight of less than 800,000 g/mol, preferably less than or equal to 400,000 g/mol, and in particular less than or equal to 100,000 g/mol. Low molecular weight hydroxypropyl methylcellulose (or hypromellose) corresponds to grades of hydroxypropyl methylcellulose the solution viscosity of which, for a 2% solution in water and at 20° C., is less than or equal to 1,000 mPa·s, preferably less than or equal to 100 mPa·s and in particular less than or equal to 15 mPa·s. Low molecular weight polyvinyl pyrrolidone (or povidone) corresponds to grades of polyvinyl pyrrolidone having a molecular weight of less than or equal to 1,000,000 g/mol, preferably less than or equal to 800,000 g/mol, and in particular less than or equal to 100,000 g/mol.

Preferably, the binding agent is chosen from low molecular weight polyvinylpyrrolidone or povidone (for example, Plasdone™ K29/32 from ISP), low molecular weight hydroxypropyl cellulose (for example, Klucel™ EF from Aqualon-Hercules), low molecular weight hydroxypropyl methylcellulose or hypromellose (for example, Methocel™ E3 or E5 from Dow) and mixtures thereof.

The preferred binder is povidone K30 or K29/32, especially Plasdone™ K29/32 from ISP. The binder can be present in an amount of 0 to 80%, 0 to 70%, 0 to 60%, 0 to 50%, 0 to 40%, 0 to 30%, 0 to 25%, 0 to 20%, 0 to 15%, 0 to 10%, or from 1 to 9%, most preferably 5% of binder based on the total weight of the immediate release coating.

The preferred amount of binder is 5% of binder over the total mass of gamma-hydroxybutyrate and binder.

The layer deposited on the core can represent at least 10% by weight, and even greater than 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85 or 90% by weight of the total weight of the immediate release particle of gamma-hydroxybutyrate. Most preferably, the layer deposited on the core represents about 85% of the weight of the immediate release particle of gamma-hydroxybutyrate.

According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns.

According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of gamma-hydroxybutyrate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns.

According to a preferred embodiment, the immediate-release particles comprise 80.75% w/w of sodium oxybate, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

According to another preferred embodiment, the immediate-release particles comprise 80.75% w/w of potassium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

According to another preferred embodiment, the immediate-release particles comprise 80.75% w/w of calcium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

According to another preferred embodiment, the immediate-release particles comprise 80.75% w/w of magnesium salt of gamma-hydroxybutyric acid, 4.25% w/w of Povidone K30 and 15% of microcrystalline cellulose spheres.

According to another embodiment, the immediate-release particles are manufactured by dissolving the gamma-hydroxybutyrate and the Povidone K30 in a mixture of water/ethanol 40/60 w/w and spraying the resulting solution onto the surface of the microcrystalline cellulose spheres.

Other Characteristics of Modified Release Portion

The modified release portion can be any formulation that provides the desired in vitro dissolution profile of gamma-hydroxybutyrate. The modified release portion is preferably comprised of modified release particles, obtained by coating immediate release particles of gamma-hydroxybutyrate with a coating (or coating film) that inhibits the immediate release of the gamma-hydroxybutyrate. In one sub-embodiment the modified release portion comprises particles comprising: (a) an inert core; (b) a coating; and (c) a layer comprising the gamma hydroxybutyrate interposed between the core and the coating.

In a preferred embodiment, the modified release portion comprises a time-dependent release mechanism and a pH-dependent release mechanism.

In a preferred embodiment, the coating film comprises at least one polymer carrying free carboxylic groups, and at least one hydrophobic compound preferably characterized by a melting point equal or greater than 40° C.

The polymer carrying free carboxylic groups is preferably selected from: (meth)acrylic acid/alkyl (meth)acrylate copolymers or methacrylic acid and methylmethacrylate copolymers or methacrylic acid and ethyl acrylate copolymers or methacrylic acid copolymers type A, B or C, cellulose derivatives carrying free carboxylic groups, preferably cellulose acetate phthalate, cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, carboxymethylethyl cellulose, cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate succinate, polyvinyl acetate phthalate, zein, shellac, alginate and mixtures thereof.

In a preferred embodiment, the methacrylic acid copolymers are chosen from the group consisting of poly (methacrylic acid, methyl methacrylate) 1:1 or Eudragit™ L100 or equivalent, poly (methacrylic acid, ethyl acrylate) 1:1 or Eudragit™ L100-55 or equivalent and poly (methacrylic acid, methyl methacrylate) 1:2 or Eudragit™ S100 or equivalent.

In another subembodiment the coating comprises a polymer carrying free carboxylic groups wherein the free carboxylic groups are substantially ionized at pH 7.5.

The hydrophobic compound with a melting point equal or greater than 40° C. can be selected from the group consisting of hydrogenated vegetable oils, vegetable waxes, wax yellow, wax white, wax microcrystalline, lanolin, anhydrous milk fat, hard fat suppository base, lauroyl macrogol glycerides, polyglyceryl diisostearate, diesters or triesters of glycerol with a fatty acid, and mixtures thereof.

Even more preferably, the hydrophobic compound with a melting point equal or greater than 40° C. is chosen from the group of following products: hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candellila wax, tristearin, tripalmitin, trimyristin, yellow wax, hard fat or fat that is useful as suppository bases, anhydrous dairy fats, lanolin, glyceryl palmitostearate, glyceryl stearate, lauryl macrogol glycerides, polyglyceryl diisostearate, diethylene glycol monostearate, ethylene glycol monostearate, omega 3 fatty acids, and mixtures thereof. A particularly preferred subgroup of products comprises hydrogenated cottonseed oil, hydrogenated soybean oil, hydrogenated palm oil, glyceryl behenate, hydrogenated castor oil, candelilla wax, tristearin, tripalmitin, trimyristin, beeswax, hydrogenated poly-1 decene, carnauba wax, and mixtures thereof.

In practice, and without this being limiting, it is preferable the hydrophobic compound with a melting point equal or greater than 40° C. to be chosen from the group of products sold under the following trademarks: Dynasan™, Cutina™, Hydrobase™, Dub™, Castorwax™, Croduret™, Compritol™, Sterotex™, Lubritab™, Apifil™, Akofine™, Softisan™, Hydrocote™, Livopol™, Super Hartolan™, MGLA™, Corona™, Protalan™ Akosoft™, Akosol™, Cremao™, Massupol™, Novata™, Suppocire™, Wecobee™ Witepsol™, Lanolin™, Incromega™, Estaram™, Suppoweiss™, Gelucire™, Precirol™, Emulcire™, Plurol Diisostéarique™, Geleol™, Hydrine™, Monthyle™, Kahlwax™ and mixtures thereof; and, preferably, from the group of products sold under the following trademarks: Dynasan™ P60, Dynasan™114, Dynasan™116, Dynasan™118, Cutina™ HR, Hydrobase™ 66-68, Dub™ HPH, Compritol™ 888, Sterotex™ NF, Sterotex™ K, Lubritab™, and mixtures thereof.

A particularly suitable coating is composed of a mixture of hydrogenated vegetable oil and a methacrylic acid copolymer. The exact structure and amount of each component, and the amount of coating applied to the particle, controls the release rate and release triggers. Eudragit® methacrylic acid copolymers, namely the methacrylic acid-methyl methacrylate copolymers and the methacrylic acid-ethyl acrylate copolymers, have a pH-dependent solubility: typically, the pH triggering the release of the active ingredient from the microparticles is set by the choice and mixture of appropriate Eudragit® polymers. In the case of gamma hydroxybutyrate modified release microparticles, the theoretical pH triggering the release is preferably from 5.5 to 6.97 or 6.9, more preferably 6.5 up to 6.9. By "pH trigger" is meant the minimum pH above which dissolution of the polymer occurs.

In a particular embodiment, the coating comprises a hydrophobic compound with a melting point equal or greater than 40° C. and a polymer carrying free carboxylic groups are present in a weight ratio from 0.4 or 0.5 to 4, preferably from 0.6 or 0.67 to 2.5, most preferably from 0.6 or 0.67 to 2.33; most preferably about 1.5.

A particularly suitable coating is composed of a mixture of hydrogenated vegetable oil and a methacrylic acid copolymer with a theoretical pH triggering the release from 6.5 up to 6.97 in a weight ratio from 0.4 or 0.5 to 4, preferably from 0.6 or 0.67 to 2.5, most preferably from 0.6 or 0.67 to 2.33; most preferably of about 1.5.

The modified release particles of gamma-hydroxybutyrate preferably have a volume mean diameter of from 100 to 1200 microns, from 100 to 500 microns, from 200 to 800 microns, and preferably of about 320 microns.

The coating can preferably represent 10 to 50%, 15 to 45%, 20 to 40%, or 25 to 35% by weight of the total weight of the coated modified release particles. Preferably, the coating represents 25-30% by weight of the total weight of the modified release particles of gamma-hydroxybutyrate.

In a preferred embodiment, the coating layer of the modified release particles of gamma-hydroxybutyrate is obtained by spraying, in particular in a fluidized bed apparatus, a solution, suspension or dispersion comprising the coating composition as defined previously onto the immediate release particles of gamma-hydroxybutyrate, in particular the immediate release particles of gamma-hydroxybutyrate as previously described. Preferably, the coating is formed by spraying in a fluidized bed equipped with a Wurster or partition tube and according to an upward spray orientation or bottom spray a solution of the coating excipients in hot isopropyl alcohol.

According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of gamma-hydroxybutyrate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of gamma-hydroxybutyrate.

According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of

10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of gamma-hydroxybutyrate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of gamma-hydroxybutyrate.

According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of sodium oxybate.

According to a preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 10.5% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 56.5% w/w of sodium oxybate mixed with 3% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 18% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 4% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 8% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent), all percentages expressed based on the total weight of the final modified release particles of sodium oxybate.

According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of gamma-hydroxybutyrate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of gamma-hydroxybutyrate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 450 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

According to another preferred embodiment, the modified release particles of gamma-hydroxybutyrate consist of 11.3% w/w of microcrystalline cellulose spheres with a volume mean diameter of about 95 microns to about 170 microns, layered with 60.5% w/w of sodium oxybate mixed with 3.2% w/w of Povidone™ K30 and finally coated with a coating composition consisting of 15% w/w of hydrogenated vegetable oil (Lubritab™ or equivalent), 0.75% of methacrylic acid copolymer type C (Eudragit™ L100-55 or equivalent) and 9.25% of methacrylic acid copolymer type B (Eudragit™ S100 or equivalent).

Packaging

The modified release formulation of gamma-hydroxybutyrate is preferably supplied in sachets or stick-packs comprising a particulate formulation. The sachets are preferably available in several different doses, comprising gamma-hydroxybutyrate in amounts equivalents to 0.5 g, 1.0 g, 1.5 g, 3.0 g, 4.5 g, 6.0 g, 7.5 g, 9.0 g, 10.5 g and/or 12 g of sodium oxybate. Depending on the dose required, one or more of these sachets can be opened, and its contents mixed with tap water to provide the nightly dose of gamma-hydroxybutyrate.

Methods of Treatment

The invention further provides a method of treating a disorder treatable with gamma-hydroxybutyrate in a human subject in need thereof comprising orally administering a single bedtime daily dose to said human amounts of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 g of sodium oxybate in the formulation of the present invention. The invention further provides methods of treating narcolepsy, types 1 and/or 2, by orally administering at bedtime a therapeutically effective amount of a gamma-hydroxybutyrate formulation characterized by the novel gamma-hydroxybutyrate pharmacokinetics or dissolution properties of the present invention. The modified release formulation of the present invention is effective to treat narcolepsy Type 1 or Type 2, wherein said treatment of narcolepsy is defined as reducing excessive daytime sleepiness or reducing the frequency of cataplectic attacks. The therapeutically effective amount preferably comprises equivalents from 3.0 to 12.0 g of sodium oxybate, more preferably from to 9.0 g of sodium oxybate, and most preferably 4.5, 6.0, 7.5 or 9.0 g of sodium oxybate. The effectiveness of the treatment can be measured by one or any combination of the following criteria:

- Increase the mean sleep latency, preferably as determined on the Maintenance of Wakefulness Test (MWT)
- Improve the Clinical Global Impression (CGI) rating of sleepiness
- Decrease the number of cataplexy attacks (NCA) preferably determined from the cataplexy frequency item in the Sleep and Symptoms Daily Diary
- Decrease the disturbed nocturnal sleep (DNS), the disturbed nocturnal events or the adverse respiratory events preferably as determined by polysomnographic (PSG) measures of sleep fragmentation
- Decrease the excessive daytime sleepiness (EDS) preferably as measured by patient report via the Epworth Sleepiness Scale (ESS)
- Decrease the daytime sleepiness as measured by the Maintenance of Wakefulness Test based on EEG measures of wakefulness
- Decrease PSG transitions from N/2 to N/3 and REM sleep to wake and N1 sleep (as determined by C Iber, S Ancoli-Israel, A Chesson, S F Quan. *The AASM*

Manual for the Scoring of Sleep and Associated Events. Westchester, Ill.: American Academy of Sleep Medicine; 2007).

Decrease the number of arousals or wakenings, preferably obtained from a PSG as defined by the American Academy of Sleep Medicine

Improve the sleep quality, preferably obtained from one or more of (i) the Sleep and Symptom Daily Diary, (ii) Visual Analog Scale (VAS) for sleep quality and sleep diary, and (iii) VAS for the refreshing nature of sleep

Decrease the Hypnagogic Hallucinations (HH) or sleep paralysis (SP) symptoms in NT1 narcolepsy patients, preferably as measured by the Sleep and Symptom Daily Diary

In a preferred embodiment, the treatment of the present invention is superior, as measured by any one or combination of the foregoing criteria, to an equal dose administered twice nightly of an immediate release liquid solution of sodium oxybate, with the second dose administered 4 hours after the first dose.

The invention further provides a method of treatment of narcolepsy Type 1 or Type 2 wherein, compared to a dosing regimen consisting of administering half the dose at t_0 and another half of the dose at t_{4h} of an immediate release liquid solution of sodium oxybate, a single bedtime daily dose administration of a therapeutically effective amount of the formulation of the invention has been shown to produce less confusion, less depressive syndrome, less incontinence, less nausea or less sleepwalking.

Additional Embodiments

In one additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In a second additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 10% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a third additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 10% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a fourth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 40% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In a fifth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hour 3 when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 40% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a sixth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 3 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 40% to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus **2** according to USP 38

<711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a seventh additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, preferably comprising immediate release and modified release portions, wherein the formulation releases (a) at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, and (b) from 40% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

In an eighth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases from 40% to 65% of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (c) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

In a ninth additional embodiment, the invention provides a modified release formulation of gamma-hydroxybutyrate, comprising immediate release and modified release portions, wherein (a) the formulation releases at least 80% of its gamma-hydroxybutyrate at 1 hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm, (b) the formulation releases 40 to 65%, of its gamma-hydroxybutyrate at one hour and at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, (c) the formulation releases greater than 60% of its gamma-hydroxybutyrate at 10 hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm, and (d) the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at 3 hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

EXAMPLES

Example 1. Formulations

Tables 1a-1d provide the qualitative and quantitative compositions of sodium oxybate IR microparticles, MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **1**.

Briefly, sodium oxybate immediate release (IR) microparticles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of polyvinylpyrrolidone (Povidone K30-Plasdone™ K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 270 microns were obtained.

Sodium oxybate modified release (MR) microparticles were prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), were dissolved in 1542.9 g of isopropanol at 78° C. The solution was sprayed entirely onto 400.0 g of the sodium oxybate IR microparticles described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR microparticles with mean volume diameter of about 320 microns were obtained.

The finished composition, which contains a 50:50 mixture of MR and IR microparticles calculated on their sodium oxybate content, was prepared as follows: 353.36 g of the above IR microparticles, 504.80 g of the above MR microparticles, 14.27 g of malic acid (D/L malic acid), 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.51 g of magnesium stearate were mixed. Individual samples of 7.11 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 1a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		2.786

TABLE 1b

Composition of MR Microparticles

Component	Function	Quantity per 4.5 g dose (g)
IR Microparticles	Core of MR microparticles	2.786
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318

TABLE 1b-continued

Composition of MR Microparticles

Component	Function	Quantity per 4.5 g dose (g)
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.981

TABLE 1c

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

TABLE 1d

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.036
Total		7.116

Example 1bis: Alternative Formulation

An alternative formulation to the formulation described in example 1 is described in Example 1bis.

Sodium oxybate immediate release (IR) microparticles were prepared by coating the IR microparticles described in example 1 with a top coat layer. Microparticles were prepared as follows: 170.0 of hydroxypropyl cellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the IR microparticles of Example 1 in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 298 microns were obtained (see Table 1bis-a).

Sodium oxybate modified release (MR) microparticles were prepared as described in example 1 (see Table 1b).

The finished composition, which contains a 50:50 mixture of MR and IR microparticles based on their sodium oxybate content, was prepared as follows: 412.22 g of the above IR microparticles, 530.00 g of the above MR microparticles, 29.96 g of malic acid (D/L malic acid), 4.96 g of xanthan gum (Xantural™ 75 from Kelco), 4.96 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 9.92 g of magnesium stearate were mixed. Individual samples of 7.45 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose in an immediate-release fraction and half of the dose in a modified release fraction) were weighed (see Table 1bis-b and 1bis-c).

TABLE 1bis-a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Hydroxypropyl cellulose	Top coat	0.310
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Total		3.096

TABLE 1bis-b

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of sodium oxybate	3.096
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.037
Colloidal silicon dioxide	Gliding agent	0.037
Magnesium stearate	Lubricant	0.075
Total		7.451

TABLE 1bis-c

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydroxypropyl cellulose	Top coat	0.310
Hydrogenated Vegetable Oil	Coating excipient	0.716
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.037
Colloidal silicon dioxide	Gliding agent	0.037
Magnesium stearate	Lubricant	0.075
Total		7.451

Compared to the finished composition described in example 1, this alternative composition has the following characteristics: same MR microparticles, same IR micropar-

ticles but with a top coat, increased amount of malic acid, only one suspending agent (xanthan gum) and presence of a glidant.

Finished compositions from Example 1 and 1bis exhibit substantially the same in-vitro dissolution profiles (see FIGS. **7** and **8**).

Example 2: In Vitro Release Profiles of IR, MR and Finished Compositions of Formulations of Examples 1 and 1bis

Dissolution Testing of IR Microparticles

The dissolution profile of 2786 mg of IR microparticles of Example 1, corresponding to 2250 mg of sodium oxybate per vessel, was determined in 0.1N HCl dissolution medium using a USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile of the IR microparticles is shown in FIG. **2** and Table 2a. All the sodium oxybate was released at 1 hour.

TABLE 2a

Percent Sodium Oxybate Released in 0.1N HCl for IR microparticles of sodium oxybate prepared according to Example 1

Time (min)	% released
0	0
5	94
10	97
15	97
30	98
60	98

Dissolution Testing of IR Microparticles from Example 1bis

The dissolution profile of 3096 mg of IR microparticles of Example 1bis, corresponding to 2250 mg of sodium oxybate per vessel, was determined in 0.1N HCl dissolution medium using a USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile of the IR microparticles is shown in FIG. **2** and Table 2b. All the sodium oxybate was released at 1 hour.

TABLE 2b

Percent Sodium Oxybate Released in 0.1N HCl for IR microparticles of sodium oxybate prepared according Example 1bis

Time (min)	% Released
0	0
5	91
10	99
15	100
30	101
60	100

Dissolution Testing of MR Microparticles from Example 1—Protocol (2 h 0.1N HCl/Phosphate Buffer pH 6.8)

49.1 g of MR microparticles from Example 1 were mixed with 0.5 g of magnesium stearate (from Peter Graven) and 0.25 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4040 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

After 2 hours in 750 mL of 0.1N HCl medium, 6.5 g of monobasic potassium phosphate was added to the dissolution vessel. pH and volume were then respectively adjusted to 6.8 and 950 mL, as needed by the addition of NaOH and water. The potassium phosphate concentration was equal to 0.05 M in the dissolution medium after pH and volume adjustment.

The release profile of the MR microparticles is shown in FIG. **3** and Table 2c. The sodium oxybate was not released in the 0.1N HCl dissolution medium during two hours. After the switch to pH 6.8 dissolution medium, all the sodium oxybate was released within 30 minutes.

TABLE 2c

Percent Sodium Oxybate Released in two sequential dissolution media (0.1HCl for 2 hours, then phosphate buffer pH 6.8) for MR microparticles of sodium oxybate prepared according to Example 1

Time (h)	% released
0	0
1	1
2	2
2.25	33
2.5	97
3	103
4	104
6	103

FIG. **4** overlays the dissolution profile of the MR microparticles of Example 1 with the dissolution profile for MR microparticles reported in Supernus U.S. Pat. No. 8,193,211, FIG. 3. It shows that the dissolution profiles are different and that the MR microparticles according to the present invention release greater than 80% of their sodium oxybate at 3 hours, whereas the MR microparticles described in Supernus U.S. Pat. No. 8,193,211, FIG. 3 do not and exhibit a much slower release profile.

Dissolution Testing of Finished Composition According to Example 1 in Deionized Water

The dissolution profile of the quantity equivalent to 4.5 g sodium oxybate of the finished composition according Example 1 was determined in 900 mL of deionized water using the USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 50 rpm. The release profile is shown in FIG. **5** and Table 2d. The IR fraction of sodium oxybate was solubilized in 15 minutes. The release of sodium oxybate from the modified-release fraction started after approximately 4 hours with 90% of the total dose released at 6 hours.

TABLE 2d

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 1

Time (h)	% released
0	0
0.25	53
1	52
2	54
3	55
4	58
5	69
6	92
7	96
8	97

An overlay of the release profile of the finished formulation of Example 1 versus that reported in USP 2012/0076865 FIG. 2 is shown in FIG. **6**. It shows that the

dissolution profiles are different. The formulation described in USP 2012/0076865 FIG. 2 does not exhibit a lag phase after the dissolution of the immediate release part.

Release Testing of Different Batches of MR Microparticles and Finished Dosage Forms

In vitro release profiles obtained in 900 mL of 0.1N HCl dissolution medium for different batches of modified release (MR) microparticles prepared according to Example 1 are described below in Table 2e. The dissolution profile of 4040 mg of microparticles corresponding to 2250 mg of sodium oxybate per vessel is determined using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 2e

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium from different manufacturing lots of MR Particles of Example 1

Time	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5	Lot 6	Lot 7	Lot 8
0.25	2.22	0.62	0.42	0.86	0.56	1.03	0.69	0.26
1.0	2.59	1.14	1.23	1.48	0.96	2.15	1.43	0.97
2.00	3.07	1.71	2.09	1.94	1.36	3.16	2.17	1.39
3	3.55	2.31	2.75	2.29	1.76	4.08	2.82	1.80
4.0	4.23	3.03	3.53	2.75	2.18	4.92	3.50	2.31
6	7.99	7.68	8.69	5.33	3.78	7.52	5.70	8.10
8.0	37.44	33.84	33.84	26.20	17.00	21.59	21.02	37.27
10	77.09	69.85	65.51	61.77	49.89	50.98	53.48	67.64
12	91.26	85.72	84.25	83.55	77.65	75.68	78.00	82.66
16	96.15	90.48	95.35	97.34	96.94	95.19	96.17	90.35

In vitro release profiles obtained in 0.1N HCl for three batches of finished composition comprising IR (50% w/w sodium oxybate dose) and MR microparticles (50% w/w sodium oxybate dose), prepared as described in Example 1, are provided in Table 2f. The sodium oxybate dose per vessel was 4.5 g, 6 g and 7.5 g respectively and dissolution was determined in 900 mL of 0.1N HCl dissolution medium using the USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 2f

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for three batches of finished composition prepared according to Example 1

Time (hour)	Batch 1	Batch 2	Batch 3
0.5	50	49	50
1	50	50	50
3	50	50	50
6	52	52	53
8	61	64	63
12	90	93	97
16	96	94	95

FIG. **7** and Table 2g depict dissolution profiles determined using a USP apparatus **2** in a 900 mL in 0.1N HCl dissolution medium of four finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases from 10 to 65% of its sodium oxybate at 1 and 3 hours and releases greater than 60% at 10 hours.

TABLE 2g

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for four batches of finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis

Time (hour)	Example 1bis	Example 1bis	Example 1	Example 1
0	0	0	0	0
0.25	Nd	Nd	52	50
0.5	51	50	Nd	Nd
1	51	50	54	51
3	51	50	54	52
6	55	52	55	53
8	72	61	60	57
10	Nd	Nd	73	70
12	86	90	85	83
16	88	96	96	94
20	Nd	Nd	99	98

Nd: not determined

FIG. **8** and Table 2h depict dissolution profiles determined using a USP apparatus **2** in a 900 mL phosphate buffer pH 6.8 dissolution medium for four finished compositions prepared according to Example 1 or 1bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases more than 80% of its sodium oxybate at 3 hours.

TABLE 2h

Percent Sodium Oxybate Released in phosphate buffer pH 6.8 Dissolution Medium for four batches of finished compositions, two prepared according to Example 1 and two prepared according to Example 1bis

Time (hour)	Example 1bis	Example 1bis	Example 1	Example 1
0	0	0	0	0
0.25	Nd	Nd	75	84
0.5	99	98	Nd	Nd
1	101	101	100	102
1.5	101	101	106	108
2	100	100	Nd	Nd
3	103	100	Nd	Nd
4	103	100	Nd	Nd
6	102	99	101	102
8	103	99	101	105
10	103	99	101	Nd
12	101	99	101	102
16	Nd	Nd	100	101
20	Nd	Nd	99	98

Nd: not determined

Release Testing of MR Microparticles and Finished Compositions—Effect of Paddle Speed:

FIG. **9** and Table 2i depict dissolution profiles in 0.1N HCl of a batch of MR microparticles prepared according to Example 1. The dissolution profile of 4040 mg of microparticles corresponding to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2**. The dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 or 100 rpm.

TABLE 2i

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for MR microparticles prepared according to Example 1

Time (hour)	75 rpm	100 rpm
0	0	0
0.25	1	1
1	2	1
2	2	2
3	3	2
4	3	3
6	6	5
8	28	26
10	65	62
12	86	84
16	97	97

FIG. **10** and Table 2j depict dissolution profiles in 0.1N HCl of a finished composition prepared according to Example 1. The dose per vessel was 4.5 g and dissolution was determined in 900 mL of dissolution medium using the USP apparatus **2**. The dissolution medium temperature was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 75 or 100 rpm.

Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 2j

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for finished composition prepared according to Example 1

Time (hour)	75 rpm	100 rpm
0	0	0
0.25	48	47
1	53	52
3	54	53
6	56	56

TABLE 2j-continued

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for finished composition prepared according to Example 1

Time (hour)	75 rpm	100 rpm
8	65	65
10	82	79
12	92	89
16	97	96
20	98	98

Example 3. In Vivo Pharmacokinetic Study of Finished Composition According to Example 1bis

Pharmacokinetic testing was undertaken in vivo in healthy human volunteers according to the principles described in FDA's March 2003 Guidance for Industry on BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY ADMINISTERED DRUG PRODUCTS—GENERAL CONSIDERATIONS. All testing was performed in subjects two hours after eating a standardized dinner. Xyrem® doses were administered in two equipotent doses four hours apart. All other tested doses were manufactured as described in Example 1bis. The standardized dinner consisted of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

The finished composition of Example 1bis given as a 4.5 g once-nightly dose rather than a standard Xyrem® dosing twice (2×2.25 g) nightly 4 hours apart, produced a dramatically different pharmacokinetic profile than Xyrem® as shown in FIG. **11**. As summarized below (Tables 3a and 3b), 4.5 g nighttime doses of finished composition of the invention equivalent to twice-nightly doses of Xyrem® (2×2.25 g) provided somewhat less total exposure to sodium oxybate with a later median T_{max} than the initial Xyrem® dose. The relative bioavailability was about 88%. Composition according to the invention avoids the high second-dose peak concentration of Xyrem® and therefore does not exhibit the substantial between-dose fluctuations in concentration, while achieving a comparable mean C_{8h}.

TABLE 3a

Pharmacokinetic Parameters of finished composition of Example 1bis vs. Xyrem ®

	Mean Cmax (μg/mL) (% CV)	Mean AUCinf (h * μg/mL)	Median Tmax (hour) (min-max)
Finished composition of Example 1bis 4.5 g	44.35 (38)	188.88 (44)	1.5 (0.5-4)
Xyrem ® 2 × 2.25 g	1st dose: 33.41 (41) 2nd dose: 65.91 (40)	214.32 (48)	1st dose: 1.00 (0.5-2) 2nd dose: 4.50 (4.33-6.5)

TABLE 3b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 1bis and Xyrem ®

Time (hour)	Finished composition Example 1bis 4.5 g (2 h after meal) pooled mean (N = 26)	Finished composition Example 1bis 6.0 g (2 h after meal) pooled mean (N = 19)	Finished composition Example 1bis 7.5 g (2 h after meal) (N = 11)	Xyrem ® (2 × 2.25 g) part I (N = 15)
0	0.00	0.00	0.00	0.00
0.5	29.31	36.44	43.19	27.44
1	34.93	49.97	63.32	28.97
1.5	36.63	54.66	73.40	26.12

TABLE 3b-continued

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 1bis and Xyrem ®

Time (hour)	Finished composition Example 1bis 4.5 g (2 h after meal) pooled mean (N = 26)	Finished composition Example 1bis 6.0 g (2 h after meal) pooled mean (N = 19)	Finished composition Example 1bis 7.5 g (2 h after meal) (N = 11)	Xyrem ® (2 × 2.25 g) part I (N = 15)
2	36.78	54.82	67.96	21.11
2.5	33.35	53.05	66.59	NA
3	30.28	50.25	62.13	13.93
3.5	27.30	47.22	59.45	10.25
4	23.66	43.06	57.40	6.92
4.5	19.89	39.13	50.85	57.33
5	16.55	34.28	45.09	52.27
5.5	13.62	32.11	44.94	43.55
6	12.40	25.84	42.36	35.20
6.5	11.25	22.36	41.02	27.44
7	11.27	18.07	40.76	19.36
7.5	9.65	15.41	35.83	13.88
8	6.86	12.80	30.94	9.24
10	1.08	2.38	7.99	2.64
12	NC	0.52	1.47	NC

NC: Not Calculated

The pharmacokinetic profile of a single 6 g dose of finished composition produced according to Example 1bis was also tested and found to have a similar pharmacokinetic profile as the 4.5 g dose. FIG. **12** provides a pharmacokinetic profile comparison of a single 4.5 g or 6 g dose of finished composition according to Example 1bis in the same 7 subjects. The pharmacokinetic profile for a 7.5 g dose of finished formulation produced according to Example 1bis was also obtained. FIG. **13** and Table 3c provide data on a single 4.5 g, 6 g and 7.5 g dose, showing effects on T_{max}, C_{max}, C_{8h}, AUC_{8h} and AUC_{inf} related to dose strength. The 7.5 g dose achieved a mean C_{8h} equal to about 31 microgram/mL which represents approximately 128.5% of the C_{8h} obtained for Xyrem® dosed 2×3.75 g which was extrapolated to be approximately 24.07 microgram/mL from published data. The 7.5 g dose achieved a ratio of AUC_{8h} to AUC_{inf} of about 0.89, whereas the ratio was 0.83 and 0.93 for the 4.5 g and 6 g doses respectively.

TABLE 3c

Pharmacokinetic Parameters of 4.5 g, 6 g, and 7.5 g of finished composition produced according to Example 1bis

Finished composition according to Example 1bis	Mean C_{max} (µg/mL) (% CV)	Mean AUC_{inf} (h * µg/mL) (% CV)	Mean $AUC_{8\ h}$ (h * µg/mL) (% CV)	Median T_{max} (h) (min-max)	Mean $C_{8\ h}$ (µg/mL) (% CV)
4.5 g	44.35 (38)	188.88 (47)	174.68 (48)	1.5 (0.5-4)	6.86 (84)
6 g	65.46 (35)	307.34 (48)	290.97 (47)	3 (0.5-5.5)	12.8 (82)
7.5 g	88.21 (30)	454.99 (34)	404.88 (31)	2 (0.5-6)	30.94 (34)

FIG. **14** and table 3d compare the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g of a finished composition according to Example 1bis to the same parameters calculated for 2×4.5 g, i.e. 9 g total dose of Xyrem®. The data show that a 7.5 g dose of a formulation according to the invention given once nightly exhibits a similar PK profile to 9 g of Xyrem® given in two separate equal doses.

TABLE 3d

Pharmacokinetic Parameters of 7.5 g of finished composition produced according to Example 1bis compared to 2 × 4.5 g of Xyrem ®

	Mean $C_{8\ h}$ (µg/mL)	Mean AUC_{inf} (µg/mL * h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®	Ratio (%) $C_{8\ h}$ composition to $C_{8\ h}$ Xyrem ®
Xyrem ® 2 × 4.5 g	28.9	518	NA	NA
Finished composition according to Example 1bis 7.5 g	30.9	455	88%	107%

Example 4. Alternative Formulation

Tables 4a-4d provide the qualitative and quantitative compositions of IR microparticles, MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **15**.

Briefly, sodium oxybate immediate release (IR) microparticle were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of polyvinylpyrrolidone (Povidone K30-Plasdone™ K29/32 from ISP) were solubilized in 1894.3 g of

absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus. IR microparticles with volume mean diameter of about 270 microns were obtained.

Sodium oxybate modified release (MR) microparticles were prepared as follows: 4.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55), 49.3 g of Methacrylic acid copolymer Type B (Eudragit™ S100), 80 g of Hydrogenated cottonseed oil (Lubritab™), were dissolved in 1200.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR microparticles prepared above in a fluid bed spray coater apparatus with an inlet temperature 48° C., spraying rate around 11 g per min and atomization pressure 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR microparticles with volume mean diameter of about 330 microns were obtained.

The finished composition, which contained a 50:50 mixture of MR and IR microparticles calculated on their sodium oxybate content, was prepared as follows: 27.86 g of IR microparticles, 37.15 g of MR microparticles, 1.13 g of malic acid (D/L malic acid), 0.50 g of xanthan gum (Xantural™ 75 from Kelco), 0.75 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 0.75 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.34 g of magnesium stearate were mixed. Individual samples of 6.85 g (corresponding to a 4.5 g sodium oxybate dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 4a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		2.786

TABLE 4b

Composition of MR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
IR Microparticles	Core of MR Microparticles	2.786
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.715

TABLE 4c

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.715
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.848

TABLE 4d

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.848

Example 4bis

An alternative formulation to example 4 is described in example 4bis. Sodium oxybate immediate release (IR) microparticles were prepared by coating the IR microparticles described in example 4 with a top coat layer. IR Microparticles were prepared as follows: 170.0 of hydroxypropyl cellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the IR microparticles of Example 4 in a fluid bed spray coater apparatus. IR Microparticles with volume mean diameter of about 298 microns were obtained (see Table 4bis-a).

Sodium oxybate modified release (MR) microparticles were prepared as described in example 4 (see Table 4b).

The finished composition, which contains a 50:50 mixture of MR and IR microparticles calculated based on sodium oxybate content, was prepared as follows: 424.99 g of the above IR microparticles, 509.98 g of the above MR microparticles, 30.89 g of malic acid (D/L malic acid), 4.93 g of xanthan gum (Xantural™ 75 from Kelco), 4.93 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 9.86 g of magnesium stearate were mixed. Individual samples of 7.18 g (corresponding to a 4.5 g dose of sodium oxybate with half of the dose as an immediate-release fraction and half of the dose as a modified release fraction) were weighed. (see Tables 4bis-b and 4bis-c).

TABLE 4bis-a

Composition of IR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Microcrystalline cellulose spheres	Core	0.418
Povidone K30	Binder and excipient in diffusion coating	0.118
Hydroxypropyl cellulose	Top coat	0.310
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Total		3.096

TABLE 4bis-b

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.715
IR microparticles	Immediate release fraction of sodium oxybate	3.096
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.036
Colloidal silicon dioxide	Gliding agent	0.036
Magnesium stearate	Lubricant	0.072
Total		7.180

TABLE 4bis-c

Quantitative finished composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	Binder	0.237
Hydroxypropyl cellulose	Top coat	0.310
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.028
Methacrylic acid Copolymer Type B	Coating excipient	0.344
Malic acid	Acidifying agent	0.225
Xanthan gum	Suspending agent	0.036
Colloidal silicon dioxide	Gliding agent	0.036
Magnesium stearate	Lubricant	0.072
Total		7.180

Compared to the finished composition described in example 4, this alternative composition has the following characteristics: same MR microparticles, same IR microparticles but with a top coat, increased amount of malic acid, only one suspending agent (xanthan gum) and presence of a glidant.

Example 5 In Vitro Release Profiles of IR, MR and Finished Compositions of Formulation of Example 4 and 4bis

Dissolution Testing of MR Microparticles from Example 4—Protocol (2 h 0.1N HCl/Phosphate Buffer pH 6.8)

49.1 g of MR microparticles from Example 4 were mixed with 0.5 g of magnesium stearate (from Peter Greven) and 0.25 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik).

The dissolution profile of 3770 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

After 2 hours in 750 mL of 0.1N HCl dissolution medium, 6.5 g of monobasic potassium phosphate was added in the dissolution vessel. pH and volume were then respectively adjusted to 6.8 and 950 mL. The potassium phosphate concentration was equal to 0.05 M in the dissolution medium after pH and volume adjustment. The release profile is shown in FIG. **16** and Table 5a.

TABLE 5a

Percent Sodium Oxybate Released in two sequential dissolution media (0.1N HCl for two hours, then phosphate buffer pH 6.8) for MR microparticles of sodium oxybate prepared according to Example 4

Time (h)	% sodium oxybate dissolved
0	0
1	1
2	2
2.25	9
2.5	40
3	89
4	102
6	103

The sodium oxybate was not released in the 0.1N HCl medium during two hours. After the switch at pH 6.8, 40% of the API was released after 30 minutes and 90% of API after 1 hour. FIG. **17** overlays the dissolution profile of the MR microparticles of Example 4 with the dissolution profile for MR microparticles reported in Supernus U.S. Pat. No. 8,193,211, FIG. **3**. It shows that the dissolution profiles are different and especially that the MR microparticles according to the invention release greater than 80% of its sodium oxybate at 3 hours, whereas the MR microparticles described in Supernus U.S. Pat. No. 8,193,211, FIG. 3 do not and exhibit a much slower releasing profile.

Dissolution Testing of Finished Composition According to Example 4 in Deionized Water:

The dissolution profile of the quantity equivalent to 4.5 g of sodium oxybate of the finished composition of the Example 4 was determined in 900 mL of deionized water using the USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 50 rpm. The release profile of is shown in FIG. **18** and Table 5b.

TABLE 5b

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 4

Time (hour)	Example 4
0	0
0.25	52
1	55
2	53
3	54
4	52
5	54

TABLE 5b-continued

Percent Sodium Oxybate Released in deionized water for finished composition of sodium oxybate prepared according to Example 4

Time (hour)	Example 4
6	60
7	78
8	90

The IR fraction of sodium oxybate was solubilized in 15 minutes. The release of sodium oxybate from the modified release fraction started after 5 hours with 90% of the total dose released at 8 hours.

An overlay of the release profile of the finished composition of the Example 4 versus that reported in USP 2012/0076865 FIG. 2 is shown in FIG. **19**. It shows that the dissolution profiles are different. The formulation described in USP 2012/0076865 FIG. 2 does not exhibit a lag phase after the dissolution of the immediate release part.

FIG. **20** and Table 5c depict dissolution profiles determined using a USP apparatus **2** in a 900 mL in 0.1N HCl dissolution medium of three finished compositions prepared according to Example 4bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. It shows that the composition according to the invention releases from 10 to 65% of its sodium oxybate at 1 and 3 hours and releases greater than 60% at 10 hours.

TABLE 5c

Percent Sodium Oxybate Released in 0.1N HCl Dissolution Medium for three batches of finished composition prepared according to Example 4bis

Time (Hour)	Batch 1	Batch 2	Batch 3
0	0	0	0
0.25	50	Nd	Nd
0.5	51	50	49
0.75	51	Nd	Nd
1	51	51	51
1.5	51	Nd	Nd
2	51	Nd	Nd
3	51	52	53
4	51	Nd	Nd
6	55	57	57
8	74	70	71
10	89	Nd	Nd
12	93	90	92
16	94	95	97

Nd = not determined

FIG. **21** and Table 5d depict dissolution profile determined using a USP apparatus **2** in a 900 mL phosphate buffer pH 6.8 dissolution medium for a finished composition prepared according to Example 4bis. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was set at 100 rpm. It shows that the composition according to the invention releases more than 80% of its sodium oxybate at 3 hours.

TABLE 5d

Percent Sodium Oxybate Released in phosphate buffer pH 6.8 Dissolution Medium for finished composition prepared according to Example 4bis

Time (Hour)	Example 4bis
0	0
0.25	54
0.5	54
0.75	55
1.0	56
1.5	63
2	77
3	103
4	105
6	105
8	102
10	101
12	104
16	100

Example 6. In Vivo Pharmacokinetic Study of Finished Composition According to Example 4bis

Pharmacokinetic testing was undertaken in vivo in healthy human volunteers according to the principles described in FDA's March 2003 Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations. All testing was performed in subjects two hours after eating a standardized dinner. Xyrem® doses were administered in two equipotent doses four hours apart. All other tested doses were manufactured as described in Example 4bis. The standardized dinner consisted of 25.5% fat, 19.6% protein, and 54.9% carbohydrates.

The finished composition of Example 4bis given as a 4.5 g once-nightly dose rather than a standard Xyrem® dosing twice (2×2.25 g) nightly 4 hours apart, produced a dramatically different pharmacokinetic profile than Xyrem® as shown in FIG. **22**. As summarized below (Tables 6a and 6b), 4.5 g nighttime doses of finished composition of the invention equivalent to twice-nightly doses of Xyrem® (2×2.25 g) provided somewhat less total exposure to sodium oxybate with a later median T_{max} than the initial Xyrem® dose. The relative bioavailability was about 88%. Composition according to the invention avoids the high second-dose peak concentration of Xyrem® and therefore does not exhibit the substantial between-dose fluctuations in concentration, while achieving a comparable mean C_{8h}.

TABLE 6a

Pharmacokinetic Parameters of finished composition of Example 4bis vs. Xyrem ®

	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h * μg/mL) (% CV)	Mean $AUC_{8\ h}$ (h * μg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (μg/mL) (% CV)
Finished composition of Example 4bis 4.5 g	43.47 (49)	188.96 (57)	179.69 (57)	2 (0.5-7)	6.85 (118)

TABLE 6a-continued

Pharmacokinetic Parameters of finished composition of Example 4bis vs. Xyrem ®

	Mean C_{max} (µg/mL) (% CV)	Mean AUC_{inf} (h * µg/mL) (% CV)	Mean $AUC_{8\ h}$ (h * µg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (µg/mL) (% CV)
Xyrem ® 2 × 2.25 g	1^{st} dose: 33.41 (41) 2^{nd} dose: 65.91 (40)	214.32 (48)	202.78 (46)	1^{st} dose: 1.0 (0.5-2) 2^{nd} dose: 4.5 (4.33-6.5)	9.24 (127)

TABLE 6b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of Example 4bis and Xyrem ®

Time (hour)	Finished composition Example 4bis 4.5 g (2 h after meal) (N = 15)	Xyrem ® (2 × 2.25 g) (N = 15)
0	0.00	0.00
0.5	23.80	27.44
1	33.26	28.97
1.5	35.60	26.12
2	35.57	21.11
2.5	33.81	13.93
3	30.96	10.25
3.5	28.73	6.92
4	26.06	42.32
4.5	23.27	57.33
5	18.68	52.27
5.5	16.67	43.55
6	15.55	35.20
6.5	13.07	27.44
7	11.75	19.36
7.5	9.20	13.88
8	6.85	9.24
10	1.94	2.64
12	NC	NC

NC: Not Calculated

The 4.5 g dose achieved a mean C_{8h} equal to about 6.85 microgram/mL which represents approximately 74.1% of the C_{8h} obtained for Xyrem® dosed 2×2.25 g. The ratio of AUC_{8h} to AUC_{inf} was about 0.89.

Example 7. In Vitro and In Vivo Pharmacokinetic Study of a Comparative Formulation

A formulation having an in vitro dissolution profile comparable to the formulation reported in FIG. 3 of U.S. Pat. No. 8,193,211 was prepared to confirm the in vitro/in vivo correlations reported herein. Tables 7a-7c provide the qualitative and quantitative compositions of the MR microparticles, and mixtures of IR and MR microparticles. The physical structure of the microparticles showing the qualitative and quantitative composition of the IR and MR microparticles is depicted in FIG. **23**.

Briefly, sodium oxybate immediate release (IR) microparticles were prepared according to Example 1bis. Sodium oxybate modified release (MR) microparticles were prepared in two steps:

Step 1: 106.7 g of water insoluble polymer Ethylcellulose (Ethocel™ 20 Premium), 10.7 g of polyvinylpyrrolidone (Plasdone™ K30 from ISP), 10.7 g of castor oil (from Olvea) and 5.3 g of Polyoxyl 40 Hydrogenated Castor Oil (Kolliphor RH40 from BASF), were dissolved in a mixture of 828.0 g of acetone, 552.0 g of isopropanol and 153.3 g of water. The solution was sprayed entirely on 400.0 g of immediate release microparticles of sodium oxybate prepared above in a fluid bed spray coater apparatus Glatt G.P.C.G.1.1 with inlet temperature 57° C., spraying rate around 14.5 g per min and atomization pressure 2.5 bar. Microparticles with volume mean diameter of about 310 microns were obtained.

Step 2: 15.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 30.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 67.5 g of Hydrogenated cottonseed oil (Lubritab™), were dissolved in 1012.5 g of isopropanol at 78° C. The solution was sprayed entirely on 450.0 g of the above prepared microparticles in a fluid bed spray coater apparatus with an inlet temperature 47° C., spraying rate around 10.5 g per min and atomization pressure 1.3 bar. MR microparticles were dried for two hours with inlet temperature set to 56° C. MR Microparticles with volume mean diameter of 335 microns were obtained.

The finished composition, which contains a 60:40 mixture of MR and IR microparticles calculated based on their sodium oxybate content, was prepared as follows: 326.69 g of the above IR microparticles, 735.04 g of the above MR microparticles, 23.74 g of malic acid (D/L malic acid), 5.54 g of xanthan gum (Xantural™ 75 from Kelco), 5.54 g of colloidal silicon dioxide (Aerosil™ 200 from Degussa) and 11.08 g of magnesium stearate were mixed. Individual samples of 8.40 g (corresponding to a 4.5 g dose of sodium oxybate with 40% of the dose as immediate-release fraction and 60% of the dose as modified release fraction) were weighed.

TABLE 7a

Composition of MR Microparticles

Component	Function	Quantity per 2.25 g dose (g)
IR Microparticles	Core of MR Microparticles	2.786
Ethylcellulose 20	Coating excipient	0.743
Povidone K30	Coating excipient	0.074
Polyoxyl 40 Hydrogenated Castor Oil	Coating excipient	0.037
Castor oil	Coating excipient	0.074
Hydrogenated Vegetable Oil	Coating excipient	0.557
Methacrylic acid Copolymer Type C	Coating excipient	0.124
Methacrylic acid Copolymer Type B	Coating excipient	0.248
Ethyl alcohol	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Water	Solvent	Eliminated during processing
Isopropyl alcohol	Solvent	Eliminated during processing
Total		4.644

TABLE 7b

Qualitative Composition of Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	5.573
IR microparticles	Immediate release fraction of sodium oxybate	2.477
Malic acid	Acidifying agent	0.180
Xanthan gum	Suspending agent	0.042
Colloidal silicon dioxide	Gliding agent	0.042
Magnesium stearate	Lubricant	0.084
Total		8.398

TABLE 7c

Quantitative Composition of Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	4.5
Microcrystalline cellulose spheres	Core	0.836
Povidone K30	der and coating excipient	0.326
Hydroxypropyl cellulose	Top coat	0.248
Ethylcellulose 20	Coating excipient	0.892
Polyoxyl 40 Hydrogenated Castor Oil	Coating excipient	0.045
Castor oil	Coating excipient	0.089
Hydrogenated Vegetable Oil	Coating excipient	0.669
Methacrylic acid Copolymer Type C	Coating excipient	0.149
Methacrylic acid Copolymer Type B	Coating excipient	0.297
Malic acid	Acidifying agent	0.180
Xanthan gum	Suspending agent	0.042
Colloidal silicon dioxide	Gliding agent	0.042
Magnesium stearate	Lubricant	0.084
Total		8.398

The dissolution profile obtained for the MR microparticles in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8) is shown in FIG. **24** and Table 7d. These data show that the dissolution profile of the MR microparticles produced according the comparative Example 7 was quite similar to the dissolution profile of FIG. 3 from U.S. Pat. No. 8,193,211. In particular, the MR microparticles according to the comparative Example 7 do not release more than 80% of its sodium oxybate at 3 hours.

TABLE 7d

Dissolution profile obtained for the MR microparticles of Example 7 in two sequential dissolution media (0.1N HCl for 2 hours then phosphate buffer pH 6.8)

Time (hour)	Example 7
0	0
1	0
2	1
2.25	5
2.5	44
3	74
64	89
6	96

The finished composition of Comparative Example 7 was tested in the same pharmacokinetic study than the finished composition of Example 1 and 4. As summarized below (Tables 7e), 4.5 g nighttime dose of finished composition of the comparative Example 7 compared to twice-nightly doses of Xyrem® (2×2.25 g) provided much less total exposure to sodium oxybate with a relative bioavailability of 67%.

TABLE 7e

Pharmacokinetic Parameters of finished composition of Comparative Example 7 vs. Xyrem ®

	Mean C_{max} (µg/mL) (% CV)	Mean AUC_{inf} (h * µg/mL) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (µg/mL) (% CV)
Finished composition of Comparative Example 7 4.5 g	28.99 (45)	143.90 (53)	1.5 (0.5-8)	7.79 (82)
Xyrem ® 2 × 2.25 g	1st dose: 33.41 (41) 2nd dose: 65.91 (40)	214.32 (48)	1st dose: 1.0 (0.5-2) 2nd dose: 4.5 (4.33-6.5)	9.24 (127)

TABLE 7f

Mean plasma concentration (microgram/mL) of gamma-hydroxybutyrate versus time of finished composition of Comparative Example 7 and Xyrem ®

Time (hour)	Comparative Example 7 @ 4.5 g (2 h after meal) pooled mean (N = 27)	Comparative Example 7 @ 6.0 g (2 h after meal) pooled mean (N = 18)	Comparative Example 7 @ 7.5 g (2 h after meal) (N = 12)	Xyrem ® (2 × 2.25 g) part I (N = 15)
0	0.00	0.00	0.00	0.00
0.5	18.84	25.54	31.40	27.44
1	23.93	35.80	46.78	28.97
1.5	24.31	38.59	58.29	26.12
2	24.32	40.78	57.47	21.11
2.5	23.10	38.03	52.25	13.93
3	20.05	35.76	49.00	10.25
3.5	17.47	33.99	45.66	6.92
4	16.48	30.47	40.52	0.00
4.5	15.44	26.87	37.70	57.33
5	14.10	25.59	36.82	52.27
5.5	12.60	24.63	35.93	43.55
6	11.68	23.90	34.47	35.20
6.5	11.45	23.98	31.60	27.44
7	10.64	20.94	31.89	19.36
7.5	9.35	17.93	29.69	13.88
8	7.79	14.36	25.80	9.24
10	1.98	3.71	11.00	2.64
12	0.59	0.78	3.63	NC

NC: not calculated

The pharmacokinetic profiles of single 6 g and 7.5 g doses of the finished composition produced according to comparative Example 7 were also generated. Table 7g provides data on a single 4.5 g, 6 g and 7.5 g dose, showing effects on C_{max}, C_{8h}, AUC_{8h} and AUC_{inf} related to dose strength.

TABLE 7g

Pharmacokinetic Parameters of 4.5 g, 6 g, and 7.5 g of finished composition produced according Comparative Example 7

Finished composition Comparative of Example 7	Mean C_{max} (μg/mL) (% CV)	Mean AUC_{inf} (h * μg/mL) (% CV)	Mean $AUC_{8\ h}$ (h * μg/mL) (% CV)	Median T_{max} (min-max) (h) (% CV)	Mean $C_{8\ h}$ (μg/mL) (% CV)
4.5 g	28.98 (45)	143.90 (53)	128.83 (55)	1.5 (0.5-8)	7.79 (82)
6 g	45.64 (35)	248.24 (47)	225.00 (47)	2 (0.5-6.5)	14.36 (77)
7.5 g	63.31 (33)	379.83 (54)	316.18 (48)	1.75 (1-4.5)	25.80 (74)

Example 8. Alternative Formulations

Example 8.1: Modified Release Formulation of Gamma-Hydroxybutyrate Comprising Immediate Release Microparticles of Potassium Salt of Gamma-Hydroxybutyric Acid and Modified Release Microparticles of Sodium Salt of Gamma-Hydroxybutyric Acid (Sodium Oxybate)

Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid can be prepared as follows: 1615.0 g of potassium salt of gamma-hydroxybutyric acid and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone™ K29/32 from ISP) are solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution is entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127) in a fluid bed spray coater apparatus.

Immediate release (IR) microparticles of sodium salt of gamma-hydroxybutyric acid were prepared as follows: 1615.0 g of sodium salt of gamma-hydroxybutyric acid and 85.0 g of polyvinylpyrrolidone (Povidone K30—Plasdone K29/32 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans Sanaq) in a fluid bed spray coater apparatus.

Sodium oxybate modified release (MR) microparticles are prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), are dissolved in 1542.9 g of isopropanol at 78° C. The solution is sprayed entirely onto 400.0 g of the sodium oxybate IR microparticles described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles are dried for two hours with inlet temperature set to 56° C. MR microparticles with mean volume diameter of about 320 microns were obtained.

The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 398.51 g of the above IR microparticles, 504.80 g of the above MR microparticles, 16.09 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.75 g of magnesium stearate were mixed. Individual samples of 7.49 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8a

Composition of IR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Potassium salt of hydroxybutyric acid	Drug substance	2.537
Microcrystalline cellulose spheres	Core	0.471
Povidone K30	Binder and excipient in diffusion coating	0.134
Ethyl alcohol	Solvent	Eliminated during processing
Purified water	Solvent	Eliminated during processing
Total		3.142

TABLE 8b

Composition of MR Microparticles of gamma-hydroxybutyrate of example 8.1

Component	Function	Quantity per 2.25 g dose (g)
Sodium oxybate	Drug substance	2.25
Povidone K30	Binder	0.118
Microcrystalline cellulose spheres	Core	0.419
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Ethyl alcohol	Solvent	Eliminated during processing
Acetone	Solvent	Eliminated during processing
Water	Solvent	Eliminated during processing
Isopropyl alcohol	Solvent	Eliminated during processing
Total		3.981

TABLE 8c

Qualitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981

TABLE 8c-continued

Qualitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid	3.142
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.487

TABLE 8d

Quantitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	2.25
Potassium salt of gamma-hydroxybutyric acid	Drug substance	2.537
Microcrystalline cellulose spheres	Core	0.890
Povidone K30	Binder	0.252
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.487

Example 8.2: Modified Release Formulation of Gamma-Hydroxybutyrate Comprising Immediate Release Microparticles of Potassium Salt of Gamma-Hydroxybutyric Acid, Immediate Release Microparticles of Magnesium Salt of Gamma-Hydroxybutyric Acid, Immediate Release Microparticles of Calcium Salt of Gamma-Hydroxybutyric Acid and Modified Release Microparticles of Sodium Salt of Gamma-Hydroxybutyric Acid (Sodium Oxybate)

Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid are prepared according to example 8.1.

Immediate release (IR) microparticles of magnesium salt of gamma-hydroxybutyric acid or calcium salt of gamma-hydroxybutyric acid can be prepared using the same manufacturing process by replacing the potassium salt of gamma-hydroxybutyric acid by the same weight of respectively magnesium salt of gamma-hydroxybutyric acid or calcium salt of gamma-hydroxybutyric acid.

Sodium oxybate modified release (MR) microparticles are prepared according to example 8.1.

The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 132.84 g of the IR microparticles of potassium salt of gamma-hydroxybutyric acid, 215.32 g of the IR microparticles of magnesium salt of gamma-hydroxybutyric acid, 230.05 g of the IR microparticles of calcium salt of gamma-hydroxybutyric acid, 504.80 g of the MR microparticles of sodium oxybate, 23.35 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 5.69 g of magnesium stearate were mixed. Individual samples of 8.96 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8e

Qualitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.981
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid + immediate release fraction of magnesium salt of gamma-hydroxybutyric acid + immediate release fraction of calcium salt of gamma-hydroxybutyric acid	4.559
Malic acid	Acidifying agent	0.184
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.97

TABLE 8f

Quantitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
Sodium oxybate	Drug substance	2.25
Potassium salt of gamma-hydroxybutyric acid	Drug substance	0.84
Magnesium salt of gamma-hydroxybutyric acid	Drug substance	1.37
Calcium salt of gamma-hydroxybutyric acid	Drug substance	1.46
Microcrystalline cellulose spheres	Core	1.102
Povidone K30	Binder	0.312
Hydrogenated Vegetable Oil	Coating excipient	0.717
Methacrylic acid Copolymer Type C	Coating excipient	0.159
Methacrylic acid Copolymer Type B	Coating excipient	0.318
Malic acid	Acidifying agent	0.184
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.96

Example 8.3: Modified Release Formulation of Gamma-Hydroxybutyrate Comprising Immediate Release Microparticles of Potassium Salt of Gamma-Hydroxybutyric Acid and Modified Release Microparticles of Calcium Salt of Gamma-Hydroxybutyric Acid

Immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid are prepared according to example 8.1.

Immediate release (IR) microparticles of calcium salt of gamma-hydroxybutyric acid can be prepared using the manufacturing process described in example 8.1 for immediate release (IR) microparticles of potassium salt of gamma-hydroxybutyric acid by replacing the potassium salt of gamma-hydroxybutyric acid by the same weight of calcium salt of gamma-hydroxybutyric acid. These Immediate release (IR) microparticles of calcium salt of gamma-hydroxybutyric acid are used to manufacture modified release (MR) microparticles of calcium salt of gamma-hydroxybutyric acid as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55), 45.8 g of methacrylic acid copolymer Type B (Eudragit™ S100), 102.9 g of hydrogenated cottonseed oil (Lubritab™), are dissolved in 1542.9 g of isopropanol at 78° C. The solution is sprayed entirely onto 400.0 g of the immediate release microparticles of calcium salt of gamma-hydroxybutyric acid described above in a fluid bed spray coater apparatus with an inlet temperature of 48° C., spraying rate around 11 g per min and atomization pressure of 1.3 bar. MR microparticles are dried for two hours with inlet temperature set to 56° C.

The finished formulation, which contains a 50:50 mixture of MR and IR microparticles calculated on their gamma-hydroxybutyrate content, can be prepared as follows: 398.53 g of the IR microparticles of potassium salt of gamma-hydroxybutyric acid, 492.87 g of the MR microparticles of sodium oxybate, 16.10 g of D/L malic acid, 6.34 g of xanthan gum (Xantural™ 75 from Kelco), 9.51 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.51 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.69 g of magnesium stearate were mixed. Individual samples of 7.39 g of the mixture (amount equivalent to a 4.5 g dose of sodium oxybate with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

TABLE 8g

Qualitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of calcium salt of gamma-hydroxybutyric acid	3.887
IR microparticles	Immediate release fraction of potassium salt of gamma-hydroxybutyric acid	3.143
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

TABLE 8h

Quantitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
7Potassium salt of gamma-hydroxybutyric acid	Drug substance	2.54
Calcium salt of gamma-hydroxybutyric acid	Drug substance	2.19
Microcrystalline cellulose spheres	Core	0.880
Povidone K30	Binder	0.249
Hydrogenated Vegetable Oil	Coating excipient	0.700
Methacrylic acid Copolymer Type C	Coating excipient	0.155
Methacrylic acid Copolymer Type B	Coating excipient	0.311
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

TABLE 8h-continued

Quantitative Composition of Finished Formulation of Example 8.3

Component	Function	Quantity per 4.5 g dose (g)
Methacrylic acid Copolymer Type C	Coating excipient	0.155
Methacrylic acid Copolymer Type B	Coating excipient	0.311
Malic acid	Acidifying agent	0.127
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.39

Example 9: Alternative Formulations with Differing Concentrations of Acidic Agents

Different prototypes were developed to evaluate the effect of acidic agent on the dissolution stability of the formulation dispersed in water. Experimental data with 0.8%, 1.6% and 15% malic acid are detailed below.

Example 9.1: 1.6% Malic Acid

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

MR coated particles were prepared as follows: 39.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 180.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 49° C., spraying rate around 11.6 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 324 microns were obtained.

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 655.1 g of the above IR particles, 936.4 g of the above MR particles, 26.5 g of Malic acid (D/L malic acid regular from Bartek), 11.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 17.6 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 17.6 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 8.2 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.11 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **29** and Table 9a below depict dissolution profiles determined in 0.1N HCl using a USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolu-

tion medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9a

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	47	48
1	53	52
3	53	53
6	55	54
8	59	60
10	74	77
12	87	88
16	96	97
20	97	98

Example 9.2: 0.8% Malic Acid

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 273 microns were obtained.

MR coated particles were prepared as follows: 39.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 180.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 47° C., spraying rate around 10.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 60° C. Sodium oxybate MR coated particles with mean diameter of 309 microns were obtained.

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 100.0 g of the above IR particles, 142.9 g of the above MR particles, 2.0 g of Malic acid (D/L malic acid regular from Bartek), 1.2 g of xanthan gum (Xantural™ 75 from CP Kelco), 1.2 g of hydrophilic fumed silica (Aerosil™ 200 from Degussa) and 2.5 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.93 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **30** and Table 9b below depict dissolution profiles determined in 0.1N HCl using a USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9b

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	51	51
1	51	52
3	51	53
6	52	62
8	60	86
10	77	96
12	90	98
16	98	98

Example 9.3: 15% Malic Acid

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 255 microns were obtained.

MR coated particles were prepared as follows: 22.8 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1544.8 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 49° C., spraying rate around 12.0 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 298 microns were obtained.

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 36.2 g of the above IR particles, 51.8 g of the above MR particles, 16.1 g of Malic acid (D/L malic acid regular from Bartek), 0.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 1.0 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 1.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.6 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 8.25 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **31** and Table 9c below depict dissolution profiles determined in 0.1N HCl using a USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 and 15 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 9c

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
0	0	0
0.25	48	49

TABLE 9c-continued

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
1	51	51
3	51	51
4	51	51
6	52	51
8	56	56
10	71	71
12	86	85
16	97	96
20	99	98

Example 10. Alternative Formulations

Suspending agents are present in the formulation to limit microparticles settling after reconstitution. Without suspending agents, microparticles starts settling as soon as shaking stops. In presence of the suspending agents, full microparticles settling does not occur in less than 1 minute. The following data illustrates the good pourability of the suspension assessed by the high recovery of sodium oxybate content in the dissolution test:

IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 271 microns were obtained.

MR coated particles were prepared as follows: 39.9 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 80.1 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 180.0 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2700.0 g of isopropanol at 78° C. The solution was sprayed entirely on 700.0 g of sodium oxybate IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.5 g per min and atomization pressure 1.6 bar. MR coated particles were dried for 2 hours with inlet temperature set to 56° C. MR particles of sodium oxybate with mean diameter of 321 microns were obtained.

The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 634.0 g of the above IR particles, 907.6 g of the above MR particles, 25.7 g of malic acid (D/L malic acid regular from Bartek), 11.4 g of xanthan gum (Xantural™ 75 from CP Kelco), 17.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 17.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 8.1 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 14.20 g (corresponding to a 9 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **32** and Table 10a below depict dissolution profiles of 9 g doses determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel. Dissolution profile was determined with and without rinsing step.

TABLE 10a

Time (h)	with rinsing	without rinsing
0	0	0
0.25	47	46
1	51	51
3	53	52
6.0	54	53
8	61	60
10	77	74
12	91	88
16	98	95
20	98	96

Example 11. Alternative Formulations with a Different Ratio of IR and MR Fractions

Different prototypes were prepared and evaluated to determine the effect of IR/MR ratio.

Example 11a: 15% IR/85% IR with MR pH*6.5 Microparticles

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1896.2 g of absolute ethyl alcohol and 1264.4 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 275 microns were obtained.

MR coated particles were prepared as follows: 22.8 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.1 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 47° C., spraying rate around 10.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 330 microns were obtained.

17.1 g of MR microparticles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown in FIG. **33**, Table 11a, and Table 11b.

TABLE 11a

Dissolution data - 0.1N HCl	
Time (hour)	% dissolved
0	0.0
0.25	1
1	1
3	2

TABLE 11a-continued

Dissolution data - 0.1N HCl	
Time (hour)	% dissolved
4	3
6	6
8	24
10	59
12	83
16	95
20	97

TABLE 11b

Dissolution data - 50 mM phosphate buffer pH 6.8	
Time (hour)	% dissolved
0	0
0.25	18
0.5	80
0.75	97
1	97
2	97

The qualitative composition of 4.5 g dose units comprising 15% of the dose as IR fraction and 85% of the dose as MR fraction is described in Table 11c.

TABLE 11c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	6.767
IR microparticles	Immediate release fraction of sodium oxybate	0.836
Malic acid	Acidifying agent	0.034
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.039
Total		7.876

The finished composition, which contains a 85:15 mixture of MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 100.0 g of the above IR particles, 809.5 g of the above MR particles, 4.0 g of malic acid (D/L malic acid regular from Bartek), 6.0 g of xanthan gum (Xantural™ 75 from CP Kelco), 9.0 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 9.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 4.7 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.88 g (corresponding to a 4.5 g dose with 15% of the dose as immediate-release fraction and 85% of the dose as modified release fraction) were weighed.

After reconstitution with 50 ml of tap water and a rinsing volume of 10 ml of tap water, the finished composition will display the dissolution profiles in FIGS. **34** and **35** and Tables 11d and 11e in 840 ml of 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 11d

Time (hour)	% dissolved
0	0.0
0.25	16
1	16
3	17
4	17
6	20
8	35
10	65
12	85
16	96

TABLE 11e

Time (hour)	% dissolved
0	0
0.25	30
0.5	83
0.75	97
1	98
2	98

Example 11B 30% IR/70% MR with MR pH*6.2 Microparticles

IR particles were prepared as follows: 1615.1 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

MR coated particles were prepared as follows: 36.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 32.1 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 103.0 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.5 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 12.0 g per min and atomization pressure 1.3 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 323 microns were obtained.

17.0 g of sodium oxybate MR particles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile of 4050 mg of the mixture which correspond to 2280 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl dissolution medium using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile in 0.1N HCl is shown in FIG. **36** and Table 11f.

TABLE 11f

Time (hour)	% dissolved
0.0	0
0.3	1
1.0	3
3.0	4
4.0	4

TABLE 11f-continued

Time (hour)	% dissolved
6.0	8
8.0	40
10.0	81
12.0	95
16.0	100
20.0	99

The finished composition, which contains a 70:30 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 92.1 g of the above IR particles, 306.5 g of the above MR particles, 7.5 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.0 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.62 g (corresponding to a 4.5 g dose with 30% of the dose as immediate-release fraction and 70% of the dose as modified release fraction) were weighed.

FIGS. **37** and **38** and Tables 11g and 11h below depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 11g

Time (hour)	% dissolved in 0.1N HCl
0.0	0.0
0.3	29
1.0	31
3.0	32
4.0	32
6.0	35
8.0	70
10.0	94
12.0	99
16.0	99

TABLE 11h

Time (h)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	64
0.5	87
1	100
2	100
3	102

Example 11c: 65% IR/35% MR with MR pH*6.5 Microparticles

IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 270 microns were obtained.

MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 45.8 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.1 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 47° C., spraying rate around 10.8 g per min and atomization pressure 1.3 bar. MR coated particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 330 microns were obtained.

Refer to the Example 11a for the dissolution profile of the MR microparticles. The qualitative composition of 4.5 g dose units comprising 65% of the dose as IR fraction and 35% of the dose as MR fraction is described in Table 11i.

TABLE 11i

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	2.786
IR microparticles	Immediate release fraction of sodium oxybate	3.622
Malic acid	Acidifying agent	0.110
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.752

The finished composition, which contains a 85:15 mixture of sodium oxybate MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 100.0 g of the above IR particles, 76.9 g of the above MR coated particles, 3.0 g of Malic acid (D/L malic acid regular from Bartek), 1.4 g of xanthan gum (Xantural™ 75 from CP Kelco), 2.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 2.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 0.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.75 g (corresponding to a 4.5 g dose with 65% of the dose as immediate-release fraction and 35% of the dose as modified release fraction) were weighed.

Dissolution profile: After reconstitution with 50 ml tap water and rinsing with 10 ml of tap water, the finished composition will display the dissolution profiles in FIGS. **39** and **40** and Tables 11j and 11k in 840 ml of 0.1N HCl and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 11j

Time (hour)	% dissolved in 0.1N HCl
0	0.0
0.25	65
1	65
3	66
4	66

TABLE 11j-continued

Time (hour)	% dissolved in 0.1N HCl
6	67
8	73
10	86
12	94
16	98
20	99

TABLE 11k

Time (hour)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	71
0.5	93
0.75	99
1	99
2	99

Example 12: Alternative Formulations with IR Fraction Obtained Using Different Manufacturing Processes

Prototype formulations were developed to test the impact of different manufacturing processes on the dissolution of the formulations.

Example 12A: IR Portion=Raw Sodium Oxybate

IR particles to serve as cores of the MR coated microparticles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 256 microns were obtained.

MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 45.8 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1542.9 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10 g per min and atomization pressure 1.3 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 308 microns were obtained.

25.2 g of MR microparticles were mixed with 0.26 g of magnesium stearate (from Peter Greven) and 0.13 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl dissolution medium using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile in 0.1N HCl is shown in FIG. **41** and Table 12a.

TABLE 12a

Time (hour)	% dissolved
0	0
0.25	1
1	1
3	2
4	3
6	14
8	40
10	65
12	78
16	89

The finished composition, which contains a 50:50 mixture of sodium oxybate MR coated particles and raw sodium oxybate as IR fraction calculated on their sodium oxybate content, was prepared as follows: 36 g of raw sodium oxybate, 63.7 g of the above MR coated particles, 1.8 g of malic acid (D/L malic acid regular from Bartek), 1.6 g of xanthan gum (Xantural™ 75 from CP Kelco), 2.4 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 0.047 g of an apple aroma and 0.3 g of hydrophilic fumed silica (Aerosil 200 from Degussa) were mixed in a Roue-Roehn mixer. Individual doses of 6.66 g (corresponding to a 4.5 g dose with half of the dose as raw sodium oxybate as IR fraction and half of the dose as modified release fraction) were weighed.

FIG. **42** and Table 12b below depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 12b

Time (hour)	% dissolved
0	0
0.25	50
1	52
4	55
6	57
8	70
10	82
12	87
16	93

Considering that the 0.1N HCl dissolution profile of the MR coated particles is similar to the MR microparticles from examples 1 and 1bis, the dissolution profile in pH 6.8 phosphate buffer of the finished composition is expected to be similar to the profile depicted in FIG. **8**, insofar as the MR particles are similar and only the nature of the immediate-release fraction was changed.

Example 12B: IR=Microparticles Obtained by Extrusion-Spheronization

IR particles were prepared as follows: 97 g of sodium oxybate and 3 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were mixed with 7.5 g of water. The mixture was extruded through a 400 micron mesh and spheronized at 1500 rpm for 1.5 min in an extruder-spheronizer Fuji-Paudal MG-55. After drying for 4

hours at 45° C. in a ventilated oven, microparticles were sieved between 150 microns and 500 microns.

MR coated particles were prepared as described in Example 14.

The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 67.4 g of the above IR particles obtained by extrusion-spheronization, 115.6 g of the above MR coated particles, 3.3 g of malic acid (D/L malic acid regular from Bartek), 0.9 g of xanthan gum (Xantural™ 75 from CP Kelco), 0.9 g of hydrophilic fumed silica (Aerosil 200 from Degussa) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.54 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **43** and Table 12c below depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 12c

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	51
1	53
4	54
6	54
8	56
10	65
12	79
16	92

Based on the dissolution profile of the MR coated particles in pH 6.8 phosphate buffer, finished compositions are expected to have the dissolution profile in pH 6.8 phosphate buffer given in Table 12d and FIG. **44**.

TABLE 12d

Time (h)	% dissolved in pH 6.8 phosphate buffer
0	0
0.25	55
0.50	97
1	101
1.5	102
2	101
3	101

Example 13. Alternative Formulation without Binder

IR particles were prepared as follows: 1700.0 g of Sodium Oxybate are solubilized in 1899.4 g of absolute ethyl alcohol and 1261.3 g of water. The solution is entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 244 microns are obtained.

MR coated particles were prepared as follows: 17.1 g of methacrylic acid copolymer type C (Eudragit L100-55 from Evonik), 34.3 g of methacrylic acid copolymer type B (Eudragit S100 from Evonik), 77.1 g of hydrogenated cottonseed oil (Lubritab from JRS), are dissolved in 1157.9 g of isopropanol at 78° C. The solution is sprayed entirely on 300.0 g of IR particles prepared above in a fluid bed spray coater apparatus Glatt G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.7 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 289 microns are obtained.

25.3 g of MR coated microparticles were mixed with 0.12 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which correspond to 2368 mg of sodium oxybate per vessel was determined in 900 ml of 0.1N HCl and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using the USP apparatus **2**. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown below in FIG. **45** and Tables 13a and 13b.

TABLE 13a

Dissolution data - 0.1N HCl

Time (h)	% dissolved
0	0
0.25	0
1	0
3	1
4	3
6	29
8	50
10	69
12	82
16	97
20	102

TABLE 13b

Dissolution data - 50 mM pH 6.8 phosphate buffer

Time (h)	% dissolved
0	0
0.25	5
1	102
3	106

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 13c.

TABLE 13c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.841
IR microparticles	Immediate release fraction of sodium oxybate	2.647
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075

TABLE 13c-continued

Component	Function	Quantity per 4.5 g dose (g)
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.034
Total		6.835

After reconstitution with 50 ml of tap water and rinsing with 10 ml of tap water, the finished composition is expected to provide the following dissolution profiles in FIGS. **46** and **47** and Tables 13d and 13e in 840 ml of 0.1N HCl and pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 13d

Time (h)	% dissolved in 0.1N HCl
0.0	0
0.3	50
1.0	50
3.0	50
4.0	52
6.0	64
8.0	75
10.0	84
12.0	91
16.0	98
20.0	101

TABLE 13e

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	53
1.0	101
3	103

Example 14. MR Particles with Larger Core Size (160 Microns)

Different prototypes were also developed to evaluate the impact of the core size on the dissolution of the formulation.

IR particles were prepared as follows: 1615.0 g of sodium oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 100 from Pharmatrans) (D[4,3]=160 microns) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 310 microns were obtained.

MR coated particles were prepared as follows: 25.7 g of methacrylic acid copolymer type C (Eudragit™ L100-55 from Evonik), 51.5 g of methacrylic acid copolymer type B (Eudragit™ S100 from Evonik), 115.7 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1735.7 g of isopropanol at 78° C. The solution was sprayed entirely on 450.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 47° C., spraying rate around 9.6 g per min and atomization pressure 1.6 bar. MR particles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 370 microns were obtained.

49.3 g of sodium oxybate MR particles were mixed with 0.52 g of magnesium stearate (from Peter Greven) and 0.26 g of colloidal silicon dioxide (Aerosil™ 200 from Evonik). The dissolution profile of 4000 mg of the mixture which correspond to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm. The release profile in 0.1N HCl and pH 6.8 phosphate buffer is shown below in FIG. **48** and Tables 14a and 14b.

TABLE 14a

Dissolution data - 0.1N HCl

Time (h)	% dissolved
0	0
0.25	0
1	1
3	2
6	3
8	7
10	18
12	37
16	75

TABLE 14b

Dissolution data - 50 mM pH 6.8 phosphate buffer

Time (h)	% dissolved
0	0
0.25	9
0.5	95
1	101
3	101

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 14c.

TABLE 14c

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	2.786
IR microparticles	Immediate release fraction of sodium oxybate	3.981
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.037
Total		7.115

After reconstitution with 50 ml of tap water and rinsing with 10 ml of tap water, the finished composition is expected to provide the dissolution profiles in FIGS. **49** and **50** and Table 14d and 14e in 840 ml of 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 14d

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	51
4	51
6	52
8	53
10	59
12	69
16	87

TABLE 14e

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	55
1	101
3	101

Example 15. MR Microparticles with Different Ratios of Lubritab™ and Eudragit™

Different prototypes were developed to evaluate the effect of the ratio between Lubritab™ and Eudragit™ on the formulation.

Example 15A: 30% Lubritab™; Cellets™ 127; Coating Level=35%

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 100 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

MR coated particles were prepared as follows: 50.2 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 100.6 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 64.6 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1943.5 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.0 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 403 microns were obtained.

17.9 g of sodium oxybate MR microparticles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4308 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **51** and Table 15a.

TABLE 15a

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	3
1	5
3	69
4	96
6	101
8	102
10	102

Alternative MR coated particles of sodium oxybate were prepared according to the above manufacturing protocol with the coating level adjusted to 50% instead of 35%. The dissolution profile of the alternative sodium oxybate MR particles was determined using the same protocol as above. The 0.1N HCl dissolution profile is shown in FIG. **52** and Table 15b.

TABLE 15b

Time (h)	% dissolved
0	0
0.25	1
1	1
3	36
4	67
6	95
8	98
10	98

The finished composition, which contains a 50:50 mixture of MR and IR sodium oxybate particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR microparticles, 235.8 g of the above sodium oxybate MR microparticles with a coating level of 30%, 6.2 g of malic acid (D/L malic acid regular from Bartek), 2.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH109 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.0 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.42 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **53** and Table 15c below depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15c

Time (hour)	% dissolved
0	0
0.25	45
1	52
2	92
3	94
4	97
6	97
8	97
10	96

Example 15B: Celphere™ CP203 as Neutral Cores and Coating Level=35%

IR particles were prepared as follows: 665.0 g of Sodium Oxybate and 35.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 781.2 g of absolute ethyl alcohol and 521.6 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Celphere™ CP203 from Asahi Kasei—mean diameter D[4,3]=250 microns) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 398 microns were obtained.

MR coated particles were prepared as follows: 37.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 75.4 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 48.5 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1458.0 g of isopropanol at 78° C. The solution was sprayed entirely on 300.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 491 microns were obtained.

17.0 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 5210 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **54** and Tables 15d and 15e.

TABLE 15d

Dissolution data - 0.1N HCl	
Time (hour)	% dissolved
0	0
0.25	3
1	3
3	45
4	77
6	96
8	98
10	98

TABLE 15e

Dissolution data - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	1
0.5	22
0.75	87
1	98
2	97

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 15f.

TABLE 15f

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	5.205
IR microparticles	Immediate release fraction of sodium oxybate	3.383
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulo	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.045
Total		8.946

After reconstitution, the finished composition is expected to exhibit the dissolution profiles in FIGS. **55** and **56** and Tables 15g and 15h in 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 15g

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	51
1	51
3	73
4	88
6	98
8	99
10	99

TABLE 15h

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	50
0.5	61
0.75	93
1	99
2	99

Example 15C: 40% Lubritab™ (Coating Level=40%)

IR pellets were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

MR coated particles were prepared as follows: 40.6 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 80.1 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 80.5 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1799.4 g of isopropanol at 78° C. The solution was sprayed entirely on 300.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.5 g per min and atomization pres-

sure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 348 microns were obtained.

20.0 g of MR coated particles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4700 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **57** and Table 15i.

TABLE 15i

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	0
1	0
3	1
4	8
6	52
8	84
10	95
12	97
16	98

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 156.0 g of the above IR particles, 260.0 g of the above MR coated particles, 6.3 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.2 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.2 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.2 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.78 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIGS. **58** and **59** and Tables 15j and 15k below depict dissolution profiles determined in 0.1N HCl and pH 6.8 buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15j

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	48
1	52
3	52
4	62
6	89
8	96
10	97
12	98
16	98
20	97

TABLE 15k

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	49
0.5	85
1	91
2	96
3	104

Example 15D: 70% Lubritab™ (Coating Level 25%)

IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

MR coated particles were prepared as follows: 13.3 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 26.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 93.3 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1200.3 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.6 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 313 microns were obtained.

17.0 g of MR coated particles were mixed with 0.06 g of magnesium stearate (from Peter Greven). The dissolution profile of 3750 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **60** and Tables 15l and 15m.

TABLE 15l

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0.0
0.25	5
1	4
3	5
4	5
6	8
8	33
10	78
12	98
16	103

TABLE 15M

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0.0
0.25	1
0.5	45
1	97
2	108
3	114

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR particles, 204.3 g of the above MR coated particles, 6.2 g of Malic acid (D/L malic acid regular from Bartek), 2.7 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.85 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **61** and Table 15n depict the dissolution profiles determined in 0.1N HCl using a USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 15n

Time (h)	% dissolved
0	0
0.25	48
1	52
3	52
4	52
6	55
8	76
10	95
12	100
16	100
20	100

Based on the dissolution profile of the MR coated particles in pH 6.8 phosphate buffer, single dose units are expected to have the dissolution profile in pH6.8 buffer shown in FIG. **62** and in Table 15o.

TABLE 15o

Time (h)	% dissolved in pH 6.8 buffer
0	0.0
0.25	51
0.5	72
1	99
2	104
3	107

Example 16. Evaluation of Different Hydrophobic Compounds in the Coating

Prototypes with different hydrophobic coatings were prepared and evaluated to determine the effect of coating type on the dissolution of the formulations.

Example 16A: Glyceryl Dibehenate (Compritol™ ATO888)

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

MR coated particles were prepared as follows: 22.9 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of glyceryl dibehenate (Compritol™ ATO 888 from Gattefossé), were dissolved in 1371.8 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.7 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 322 microns were obtained.

17.0 g of MR coated particles were mixed with 0.1 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profile is shown in FIG. **63** and Tables 16a and 16b.

TABLE 16a

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	1
3	3
4	6
6	31
8	67
10	90
12	98
16	100

TABLE 16b

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	1

TABLE 16b-continued

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
1	102
3	105

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 181.1 g of the above IR particles, 258.7 g of the above MR coated particles, 7.3 g of Malic acid (D/L malic acid regular from Bartek), 3.3 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.9 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.9 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.3 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.12 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **64** and Table 16c depict dissolution profiles determined in 0.1N HCl using a USP apparatus **2**. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 16c

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	46
1	50
3	51
4	56
6	78
8	92
10	96
12	97
16	96

Based on the dissolution profile of the MR microparticles alone in pH 6.8 phosphate buffer, single dose units are expected to have the dissolution profile at pH6.8 shown in FIG. **65** and in Table 16d.

TABLE 16d

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	50
1	101
3	102

Example 16B: 60% Candelilla Wax with Coating Level of 20%

IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 255 microns were obtained.

MR coated particles were prepared as follows: 13.3 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 26.7 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 60.0 g of candelilla wax (Kahlwax™ 2039L from Brenntag), were dissolved in 902.2 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 12.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 289 microns were obtained.

21.2 g of MR microparticles were mixed with 0.11 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2570 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm. The release profiles are shown below in FIG. **66** and Tables 16e and 16f.

TABLE 16e

Dissolution profile - 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	0
3	0
4	1
6	2
8	2
10	2
12	2
16	3
20	4

TABLE 16f

Dissolution profile - 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	0
0.5	10
0.75	62
1	89
2	101

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 16 g.

TABLE 16g

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.483
IR microparticles	Immediate release fraction of sodium oxybate	2.786

TABLE 16g-continued

Component	Function	Quantity per 4.5 g dose (g)
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.033
Total		6.615

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, can be prepared as follows: 200.0 g of the above IR particles, 250.0 g of the above MR coated particles, 8.1 g of Malic acid (D/L malic acid regular from Bartek), 3.6 g of xanthan gum (Xantural™ 75 from CP Kelco), 5.4 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 5.4 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.4 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.61 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

After reconstitution, the finished composition is expected to provide the dissolution profiles in FIGS. **67** and **68** and Tables 16h and 16i in 0.1N HCl and in pH6.8 phosphate buffer (0.05M monobasic potassium phosphate solution with pH adjusted to 6.8 with 5N NaOH) using a USP apparatus **2**, at 37.0±0.5° C. and the rotating paddle speed at 75 rpm.

TABLE 16h

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	50
3	50
4	50
6	51
8	51
10	51
12	51
16	52
20	52

TABLE 16i

Time (hour)	% dissolved in pH 6.8 buffer
0	0
0.25	50
0.5	55
0.75	81
1	94
2	100

Example 16C: 40% Candelilla Wax (Coating Level=20%)

IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.4 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 270 microns were obtained.

MR coated particles were prepared as follows: 20.0 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 40.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 40.0 g of candelilla wax (Kahlwax™ 2039 L from Brenntag), were dissolved in 904.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 10.9 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 302 microns were obtained.

17.0 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 3500 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **69** and Tables 16j and 16k. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

TABLE 16j

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	3
3	6
4	8
6	9
8	15
10	37
12	70
16	97
20	100

TABLE 16k

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	24
0.5	86
0.75	99
1	100
2	100

The qualitative composition of 4.5 g dose units comprising 50% of the dose as IR fraction and 50% of the dose as MR fraction is described in Table 16l.

TABLE 16l

Component	Function	Quantity per 4.5 g dose (g)
MR microparticles	Modified release fraction of sodium oxybate	3.483
IR microparticles	Immediate release fraction of sodium oxybate	2.786
Malic acid	Acidifying agent	0.113
Xanthan gum	Suspending agent	0.050
Hydroxyethylcellulose	Suspending agent	0.075

TABLE 16l-continued

Component	Function	Quantity per 4.5 g dose (g)
Carrageenan gum	Suspending agent	0.075
Magnesium stearate	Lubricant	0.033
Total		6.615

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 122.7 g of the above IR particles, 153.2 g of the above MR coated particles, 5.0 g of malic acid (D/L malic acid regular from Bartek), 2.2 g of xanthan gum (Xantural™ 75 from CP Kelco), 3.3 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 3.3 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.5 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 6.62 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **70** and Table 16m depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 16m

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	47
1	51
3	51
4	52
6	52
8	55
10	72
12	89
16	97

Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished compositions are expected to provide the dissolution profile in pH 6.8 phosphate buffer shown in FIG. **71** and in Table 16n.

TABLE 16n

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	62
0.5	93
0.75	99
1	100
2	100

Example 16D—60% Cetyl Alcohol (Kolliwax™ CA)

IR particles were prepared as follows: 1615.1 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1898.7 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 272 microns were obtained.

MR coated particles were prepared as follows: 22.8 g of methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 45.8 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of cetyl alcohol (Kolliwax™ CA from BASF), were dissolved in 1472.5 g of isopropanol and 77.7 g of water at room temperature. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 14.5 g per min and atomization pressure 2.5 bar. Sodium oxybate MR coated particles with mean diameter of 315 microns were obtained.

16.4 g of MR microparticles were mixed with 0.08 g of magnesium stearate (from Peter Greven). The dissolution profile of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium is given in FIG. **72** and Table 16o. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 75 rpm.

TABLE 16o

Time (h)	% dissolved in 0.1N HCl
0	0
0.25	13
1	84
3	103
4	103
6	103
8	103
10	104
12	104
16	103
20	102

Example 17. Effect of Eudragit™ Selection in the Coating of the MR Microparticles

Further prototypes were developed and evaluate to determine the effect of the Eudragit™ selected on the dissolution of the MR microparticles.

Example 17A 100% Eudragit™ 5100

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1894.3 g of absolute ethyl alcohol and 1262.9 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 285 microns were obtained.

Sodium oxybate IR seal-coated particles were prepared by coating the IR particles described above with a seal-coat layer: 170.0 g of hydroxypropylcellulose (Klucel™ EF Pharm from Hercules) were solubilized in 4080.0 g of acetone. The solution was entirely sprayed onto 1530.0 g of the above IR particles in a fluid bed spray coater apparatus.

Sodium oxybate IR particles with volume mean diameter of about 298 microns were obtained.

MR coated particles were prepared as follows: 100.0 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 150.0 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 2250.0 g of isopropanol at 78° C. The solution was sprayed entirely on 750.0 g of the above IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 12.0 g per min and atomization pressure 1.6 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 307 microns were obtained.

The dissolution profile of 2100 mg of the mixture which corresponds to 1253 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 500 ml of 0.1N HCl medium is reported in FIG. **73** and Table 17a. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17a

Time (h)	% dissolved
0	0
0.25	0
1	1
3	3
4	4
6	9
8	30
10	60
12	81
16	92

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 425.0 g of the above IR seal-coated particles, 510.0 g of the above MR coated particles, 30.9 g of malic acid (D/L malic acid regular from Bartek), 4.9 g of xanthan gum (Xantural™ 180 from CP Kelco), 4.9 g of Aerosil™ 200 (amorphous anhydrous colloidal silicon dioxide from Evonik) and 9.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.18 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **74** and Table 17b below depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17b

Time (hour)	% dissolved in 0.1N HCl
0	0
0.25	50
1	50
3	50
4	51
6	55
8	67
10	84

TABLE 17b-continued

Time (hour)	% dissolved in 0.1N HCl
12	91
16	94

FIG. **75** and Table 17c depict the dissolution profile determined using a USP apparatus **2** in phosphate buffer pH 6.8 (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH). The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 100 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of pH 6.8 dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17c

Time (hour)	% dissolved
0	0
0.25	50
1	51
3	54
4	56
6	93
8	99
10	100
12	100
16	97

Example 17B 100% Eudragit™ L100-55

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.1 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1896.2 g of absolute ethyl alcohol and 1264.4 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 275 microns were obtained.

MR coated particles were prepared as follows: 68.7 g of Methacrylic acid copolymer Type C (Eudragit™ L100-55 from Evonik), 102.9 g of hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.2 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 46° C., spraying rate around 12.7 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 328 microns were obtained.

17.0 g of MR microparticles were mixed with 0.09 g of magnesium stearate (from Peter Greven). The dissolution profile in of 4000 mg of the mixture which corresponds to 2250 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **76** and Tables 17d and 17e. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17d

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	2
3	3
4	6
6	53
8	95
10	99
12	99
16	99
20	99

TABLE 17e

Dissolution profile in 50 mM pH 6.8 phosphate buffer	
Time (h)	% dissolved
0	0
0.25	21
0.5	99
0.75	103
1	103
2	103

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 153.3 g of the above IR particles, 219.0 g of the above MR coated particles, 6.2 g of malic acid (D/L malic acid regular from Bartek), 2.8 g of xanthan gum (Xantural™ 75 from CP Kelco), 4.1 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 4.1 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 1.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.12 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **77** and Table 17f depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17f

Time (hour)	% dissolved
0	0
0.25	46
1	51
3	52
4	59
6	94
8	98
10	98
12	98
16	98

Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished compositions are expected to provide the dissolution profile in pH 6.8 phosphate buffer in FIG. **78** and Table 17g.

TABLE 17g

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	61
0.5	99
0.75	101
1	101
2	101

Example 17C Mixture Eudragit™ L100-S100 (50-50)

IR particles were prepared as follows: 1615.0 g of Sodium Oxybate and 85.0 g of water soluble polymer polyvinylpyrrolidone (Povidone—Plasdone™ K30 from ISP) were solubilized in 1903.2 g of absolute ethyl alcohol and 1267.1 g of water. The solution was entirely sprayed onto 300 g of microcrystalline cellulose spheres (Cellets™ 127 from Pharmatrans) in a fluid bed spray coater apparatus GPCG1.1. Sodium oxybate IR particles with mean diameter of 268 microns were obtained.

MR coated particles were prepared as follows: 34.3 g of Methacrylic acid copolymer Type A (Eudragit™ L100 from Evonik), 34.3 g of Methacrylic acid copolymer Type B (Eudragit™ S100 from Evonik), 102.9 g of Hydrogenated cottonseed oil (Lubritab™ from JRS), were dissolved in 1543.0 g of isopropanol at 78° C. The solution was sprayed entirely on 400.0 g of IR particles in a fluid bed spray coater apparatus Glatt™ G.P.C.G.1.1 with inlet temperature 48° C., spraying rate around 11.8 g per min and atomization pressure 1.3 bar. MR microparticles were dried for 2 hours with inlet temperature set to 56° C. Sodium oxybate MR coated particles with mean diameter of 316 microns were obtained.

24.0 g of MR microparticles were mixed with 0.12 g of magnesium stearate (from Peter Greven). The dissolution profile of 4050 mg of the mixture which corresponds to 2280 mg of sodium oxybate per vessel was determined using the USP apparatus **2** in 900 ml of 0.1N HCl medium and in pH 6.8 phosphate buffer (0.05M monobasic potassium phosphate solution—pH adjusted to 6.8 with 5N NaOH) is given in FIG. **79** and Tables 17h and 17i. Dissolution medium temperature was maintained at 37.0±0.5° C., and the rotating paddle speed was set at 100 rpm.

TABLE 17h

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
0	0
0.25	0
1	2
3	2
4	3
6	7
8	31
10	62
12	83
16	98
20	100

TABLE 17i

Dissolution profile in 50 mM pH 6.8 phosphate buffer

Time (h)	% dissolved
0	0
0.25	2
0.5	5
0.75	13
1	47
2	101

The finished composition, which contains a 50:50 mixture of MR and IR particles calculated on their sodium oxybate content, was prepared as follows: 223.0 g of the above IR particles, 318.4 g of the above MR coated particles, 11.2 g of malic acid (D/L malic acid regular from Bartek), 4.0 g of xanthan gum (Xantural™ 75 from CP Kelco), 6.0 g of carrageenan gum (Viscarin™ PH209 from FMC Biopolymer), 6.0 g of hydroxyethylcellulose (Natrosol™ 250M from Ashland) and 2.9 g of magnesium stearate (from Peter Greven) were mixed in a Roue-Roehn mixer. Individual doses of 7.14 g (corresponding to a 4.5 g dose with half of the dose as immediate-release fraction and half of the dose as modified release fraction) were weighed.

FIG. **80** and Table 17j depict dissolution profiles determined using a USP apparatus **2** in 0.1N HCl. The dissolution medium was maintained at 37.0±0.5° C. and the rotating paddle speed was fixed at 75 rpm. Single dose units were poured in a container containing 50 mL of tap water. After 5 minutes, the suspension was poured in the dissolution vessel containing 840 mL of 0.1N HCl dissolution medium. 10 mL of water were used to rinse the container and were added to the dissolution vessel.

TABLE 17j

Time (hour)	% dissolved
0	0
0.25	47
1	51
3	51
6	59
8	80
10	92
12	96
16	97

Based on the dissolution profile of the MR coated particles in pH6.8 phosphate buffer, 4.5 g single dose units of the finished composition are expected to have the dissolution profile in pH 6.8 phosphate buffer given in FIG. **81** and Table 17k.

TABLE 17k

Time (h)	% dissolved in pH 6.8 buffer
0	0
0.25	51
0.5	53
0.75	56
1	73
2	100

Example 18: In Vivo Pharmacokinetic Study of Finished Composition According to Example 1 (Dose Escalating Study)

Pharmacokinetic testing was undertaken in vivo in healthy human volunteers. Pharmacokinetic parameters were normalized by the dose. To assess the dose-proportionality, log-transformed dose-normalized PK parameters were pairwise compared according to the statistical methodology described in FDA's 2013 Draft Guidance entitled BIOEQUIVALENCE STUDIES WITH PHARMACOKINETIC ENDPOINTS FOR DRUGS SUBMITTED UNDER AN ANDA (2013). All testing was performed in subjects two hours after eating a standardized dinner. A test product with finished composition of Example 1 and manufactured at larger scale was administered in sequential ascending doses, 4.5 g, 7.5 g and 9 g, one week apart. The tested samples were manufactured as described in Table 1c for 4.5 g and quantities were homothetically adjusted for the other strengths. The dissolution profiles of the MR portions of the test product are presented in FIGS. **86** and **87**. The dissolution profiles of the test product are presented in FIGS. **88** and **89**. The individual concentrations of gamma-hydroxybutyrate and derived PK parameters are summarized below (Tables 18a and 18b) and in FIG. **90**.

TABLE 18a

Pharmacokinetic Parameters of 4.5 g, 7.5 g, and 9 g

Finished composition of test product	Mean C_{max} (µg/mL) (% CV)	Mean AUC_{inf} (µg/mL * h) (% CV)	Mean $AUC_{8\ h}$ (µg/mL * h) (% CV)	Median T_{max} (hour) (min-max)	Mean $C_{8\ h}$ (µg/mL) (% CV)
4.5 g	42.9 (37)	191 (50)	174 (55)	1.71 (0.333-4)	4.76 (105)
7.5 g	72.0 (32)	357 (48)	320 (46)	1.5 (0.333-7)	19.7 (101)
9.0 g	84.5 (34)	443 (46)	379 (41)	2 (0.5-4)	25.5 (97)

AUC and C_{max} values increased more than dose-proportionally with increasing doses of gamma-hydroxybutyrate formulated as the test product.

TABLE 18b

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of test product

Time (hr)	Test product 4.5 g (2 h after meal) (N = 20)	Test product 7.5 g (2 h after meal) (N = 20)	Test product 9 g (2 h after meal) (N = 12)
0	0.00	0.00	0.00
0.167	12.5	17.7	9.34
0.333	23.4	39.0	32.7
0.5	28.1	48.4	47.5
1	34.7	59.8	60.9
1.5	36.7	63.8	71.6
2	35.7	61.6	79.3
2.5	34.7	56.0	64.9
3	29.8	50.1	65.3
3.5	26.9	46.0	60.0

TABLE 18b-continued

Mean plasma concentration of gamma-hydroxybutyrate (microgram/mL) versus time of finished composition of test product			
Time (hr)	Test product 4.5 g (2 h after meal) (N = 20)	Test product 7.5 g (2 h after meal) (N = 20)	Test product 9 g (2 h after meal) (N = 12)
4	23.5	40.9	60.8
4.5	20.1	36.6	48.8
5	17.3	32.7	45.3
5.5	15.4	30.8	41.3
6	13.4	28.7	37.6
7	9.66	24.7	30.5
8	4.76	19.7	25.5
10	0.727	6.97	13.0
12	0.211	1.35	5.13
14	NC	0.392	0.820

NC: Not Calculated

Table 18c compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 4.5 g of the test product to the same parameters calculated 2×2.25 g, i.e. 4.5 g total dose of Xyrem®.

TABLE 18c

Comparison to 4.5 g divided dose of Xyrem ®				
	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL * h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 2.25 g*	9.24	NA	214	NA
Test product 4.5 g	4.76	52%	191	89%

*data from the pilot PK study of example 3

Table 18d compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g of the test product to the same parameters calculated 2×3.75 g, i.e. 7.5 g total dose of Xyrem®.

TABLE 18d

Comparison to 7.5 g divided dose of Xyrem ®				
	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL * h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 3.75 g (extrapolation from 2 × 4.5 g*)	24.1	NA	432	NA
Test product 7.5 g	19.7	82%	357	83%

*based on data from NDA #21-196

Table 18e compares the pharmacokinetic parameters AUC_{inf} and C_{8h} obtained for 7.5 g and 9 g of the test product to the same parameters calculated for 2×4.5 g, i.e. 9 g total dose of Xyrem®.

TABLE 18e

Comparison to 9 g divided dose of Xyrem ®				
	Mean $C_{8\,h}$ (μg/mL)	Ratio (%) $C_{8\,h}$ composition to $C_{8\,h}$ Xyrem ®	Mean AUC_{inf} (μg/mL * h)	Ratio (%) AUC_{inf} composition to AUC_{inf} Xyrem ®
Xyrem ® 2 × 4.5 g*	28.9	NA	518	NA
Test product 7.5 g	19.7	68%	357	69%
Test product 9 g	25.5	88%	443	86%

*data from NDA #21-196

For the finished composition administered at 4.5 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max} (Xyrem®) is 1.03. The ratio C_{4h}/C_{max} (Xyrem®) is 0.81. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.69.

For the finished composition administered at 7.5 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max} (Xyrem®) is 0.77. The ratio C_{4h}/C_{max} (Xyrem®) is 0.63. The ratio $C_{4.5h}/C_{max}$ (Xyrem®) is 0.57.

For the finished composition administered at 9 g, mean C_{6h}, mean C_{7h} are greater than, and mean C_{10h} are less than, the mean C_{4h} of the dose of Xyrem®. In addition, the ratio C_{3h}/C_{max} (Xyrem®) is 0.84. The ratio C_{4h}/C_{max} (Xyrem®) is 0.78. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.63.

For the finished composition administered at 7.5 g compared to Xyrem® at 2×4.5 g, i.e. total dose of 9 g, the ratio C_{3h}/C_{max}(Xyrem®) is 0.65. The ratio C_{4h}/C_{max}(Xyrem®) is 0.53. The ratio $C_{4.5h}/C_{max}$(Xyrem®) is 0.47.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains. It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

What is claimed is:

1. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion; and

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

2. The formulation of claim **1**, wherein the suspending or viscosifying agent is present at 1% to 15% by weight of the formulation, and the acidifying agent is present at 1.2% to 15% by weight of the formulation.

3. The formulation of claim **2**, wherein:

the suspending or viscosifying agent is a mixture of xanthan gum, carrageenan gum, and hydroxyethylcellulose, or a mixture of xanthan gum and carrageenan gum, and

the acidifying agent is malic acid or tartaric acid.

4. The formulation of claim **1**, wherein the formulation further comprises a lubricant or glidant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate, glycerol behenate, sodium stearyl fumarate, talc, or colloidal silicon dioxide.

5. The formulation of claim **1**, wherein the formulation is a dry particulate formulation or a powdered formulation.

6. The formulation of claim **1**, wherein the formulation comprises 4.5 g, 6.0 g, 7.5 g, or 9.0 g of gamma-hydroxybutyrate.

7. The formulation of claim **1**, wherein the formulation comprises gamma-hydroxybutyrate in the form of sodium oxybate.

8. The formulation of claim **1**, wherein modified release portion comprises a hydrophobic compound having a melting point equal to or greater than 40° C.

9. The formulation of claim **1**, wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

10. The formulation of claim **1**, wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

11. The formulation of claim **1**, wherein a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

12. The formulation of claim **1**, wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

13. The formulation of claim **1**, wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

14. The formulation of claim **1**, wherein the formulation releases at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

15. The formulation of claim **1**, wherein the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1 N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

16. The formulation of claim **1**, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

17. The formulation of claim **1**, wherein the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1 N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

18. The formulation of claim **1**, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

19. The formulation of claim **1**, wherein the immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1 N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

20. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the suspending or viscosifying agent and the acidifying agent are separate and distinct from the immediate release portion and the modified release portion;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate; and

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy.

21. The formulation of claim **20**, wherein:

the suspending or viscosifying agent is selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

the acidifying agent is selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid.

22. The formulation of claim **20**, wherein:

the suspending or viscosifying agent is a mixture of xanthan gum, carrageenan gum, and hydroxyethylcellulose, or a mixture of xanthan gum and carrageenan gum, and

the acidifying agent is malic acid or tartaric acid.

23. The formulation of claim **20**, wherein the formulation further comprises a lubricant or glidant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, glyceryl monostearate, glyceryl palmitostearate, glycerol behenate, sodium stearyl fumarate, talc, and colloidal silicon dioxide.

24. The formulation of claim **20**, wherein the formulation is a dry particulate formulation or a powdered formulation.

25. The formulation of claim **20**, wherein the formulation comprises 4.5 g, 6.0 g, 7.5 g, or 9.0 g of gamma-hydroxybutyrate.

26. The formulation of claim **20**, wherein the formulation comprises gamma-hydroxybutyrate in the form of sodium oxybate.

27. The formulation of claim **20**, wherein the modified release portion comprises a hydrophobic compound having a melting point equal to or greater than 40° C.

28. The formulation of claim **20**, wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

29. The formulation of claim **20**, wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

30. The formulation of claim **20**, wherein a dose of the formulation achieves a median T_{max} within one hundred fifty minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

31. The formulation of claim **20**, wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean C_{4h} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

32. The formulation of claim **20**, wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

33. The formulation of claim **20**, wherein the formulation releases at least 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

34. The formulation of claim **20**, wherein the formulation releases from 10% to 65%, of its gamma-hydroxybutyrate at one hour and three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1 N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

35. The formulation of claim **20**, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.05M monobasic potassium phosphate buffer pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

36. The formulation of claim **20**, wherein the modified release portion releases less than 20% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1 N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

37. The formulation of claim **20**, wherein the modified release portion releases greater than 80% of its gamma-hydroxybutyrate at three hours in a dissolution test started in 750 mL of 0.1N hydrochloric acid for 2 hours then switched to 950 mL 0.05M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

38. The formulation of claim **20**, wherein the immediate release portion releases greater than 80% of its gamma-hydroxybutyrate at one hour when tested in a dissolution apparatus **2** according to USP 38 <711> in 900 mL of 0.1 N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm.

39. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent for improving the formulation's viscosity and pourabilty after mixing with a liquid, the suspending or viscosifying agent being selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent for ensuring that the formulation's release profile remains unchanged for at least 15 minutes after mixing with a liquid, the acidifying agent being selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

40. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent for improving the formulation's viscosity and pourabilty after mixing with a liquid; and

from 1.2% to 15% of an acidifying agent for ensuring that the formulation's release profile remains unchanged for at least 15 minutes after mixing with a liquid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate; and

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy.

41. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate and a coating comprising a hydrophobic compound having a melting point equal to or greater than 40° C.;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

42. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate and a coating comprising a hydrophobic compound having a melting point equal to or greater than 40° C.;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate; and

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy.

43. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

44. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a relative bioavailability (RBA) of greater than 80% when compared to an equal dose of an immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses, when administered approximately two hours after a standardized evening meal.

45. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

46. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a ratio of mean AUC_{8h} to mean AUC_{inf} of greater than 0.80 when administered once approximately two hours after a standardized evening meal.

47. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

48. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

49. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean Co of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

50. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean C_{10h} less than, the mean Co of half the dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

51. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

a suspending or viscosifying agent selected from the group consisting of xanthan gum, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and mixtures thereof; and

an acidifying agent selected from the group consisting of malic acid, citric acid, tartaric acid, adipic acid, boric acid, maleic acid, phosphoric acid, ascorbic acid, oleic acid, capric acid, caprylic acid, and benzoic acid;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35; and

wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

52. A formulation of gamma-hydroxybutyrate comprising:

an immediate release portion comprising gamma-hydroxybutyrate;

a modified release portion comprising gamma-hydroxybutyrate;

from 1% to 15% of a suspending or viscosifying agent; and

from 1.2% to 15% of an acidifying agent;

wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35;

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 g to 12.0 g of sodium oxybate;

wherein the formulation is designed to be orally administered once-nightly to treat cataplexy in narcolepsy or excessive daytime sleepiness ("EDS") in narcolepsy; and

wherein a dose of the formulation achieves a mean AUC_{inf} of greater than 80% of the mean AUC_{inf} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal, and a mean C_{8h} less than 95% of the mean C_{8h} provided by an equal dose of immediate release liquid solution of sodium oxybate administered at t_0 and t_{4h} in equally divided doses approximately two hours after a standardized evening meal.

* * * * *

EXHIBIT I

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.

A P P E A R A N C E S

ON BEHALF OF PLAINTIFF:
FRANK C. CALVOSA, ESQUIRE
GABRIEL P. BRIER, ESQUIRE
QUINN EMANUEL, LLP
51 Madison Avenue
New York, New York 10010

ON BEHALF OF DEFENDANT AVADEL:
DARALYN DURIE, ESQUIRE
REBECCA WEIRES, ESQUIRE
ANDREW JONES, ESQUIRE
MORRISON FOERSTER
425 Market Street
San Francisco, CA 94105-2482

And

ON BEHALF OF DEFENDANT AVADEL:
AUDRA SAWYER, ESQUIRE
LATHAM & WATKINS, LLP
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

103

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.

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

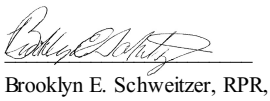
I, STEVEN R. LITTLE, Ph.D., do hereby acknowledge that I have read and examined the foregoing testimony, and the same is a true, correct and complete transcription of the testimony given by me and any corrections appear on the attached errata sheet signed by me.

_____ _____
(DATE) (SIGNATURE)

CERTIFICATE OF SHORTHAND REPORTER-NOTARY PUBLIC

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

No. 488193

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.
Return to: transcripts@planetdepos.com

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)

(Signature)

No. 488193

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.
Return to: transcripts@planetdepos.com

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)

EXHIBIT J

Attorney Docket No. JAZZ-043/02US 306882-2331 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	ALLPHIN, Clark et al.	Confirmation No.:	3698
Application No.:	16/025,487	Group Art Unit:	1619
Filed:	July 2, 2018	Examiner:	Gotfredson, Garen

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

Via EFS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Response to Accompany a Request for Continued Examination

This paper is filed in response to the Final Office Action mailed May 2, 2019. A Request for Continued Examination is being concurrently filed, and a three month extension of time is hereby requested. Accordingly, in light of the Notice of Appeal filed on November 1, 2019, this paper is timely filed. Reconsideration of this application is respectfully requested in view of the following amendments and remarks.

AMENDMENTS TO THE CLAIMS

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough or underlining. This listing also reflects any cancellation and/or addition of claims.

1-108. (Canceled)

109. (Currently Amended) A ~~solid dosage~~ formulation comprising immediate release and ~~controlled~~ sustained release portions, each portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate~~ or a pharmaceutically acceptable salt thereof~~, wherein:

a. the ~~controlled~~ sustained release portion comprises a functional coating and a [[CR]] core, wherein the functional coating is ~~coated onto~~ deposited over the [[CR]] core, wherein the [[CR]] core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate~~ or a pharmaceutically acceptable salt thereof~~;~~, and~~ 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 ~~an amount of gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof that is between~~ 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. wherein a total gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the solid dosage formulation is about 500 mg to about 12 g, and the amount of gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the immediate release portion is about 10% to 50% by weight of the total gamma-hydroxybutyrate or pharmaceutically acceptable salt thereof in the solid dosage formulation;~~

~~d. the controlled release portion releases greater than about 40% of its gamma-hydroxybutyrate over 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;~~

c[[e]]. the ~~solid dosage~~ 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[[f]]. the ~~solid dosage~~ formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 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.

110. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~solid dosage~~ 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.

111. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~solid dosage~~ 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.

112. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~controlled~~ 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.

113. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the ~~controlled~~ sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

114. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

115. (Currently Amended) The ~~solid dosage~~ formulation of claim 114 comprising a sodium salt of gamma-hydroxybutyrate.

116. (Currently Amended) The ~~solid dosage~~ formulation of claim 109 wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

117. (Canceled)

118. (Currently Amended) The ~~solid dosage~~ formulation of claim 109, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

119. (Currently Amended) An oral ~~solid~~ dosage form comprising the ~~solid dosage~~ formulation of claim 109.

120. (New) The formulation of claim 109 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.

121 (New) 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.

REMARKS

I. Status of the Claims

Upon the entry of the amendments, claims 109-116 and 118-121 are pending. Claims 109-116, 118, and 119 have been amended. Claims 120 and 121 are new. Support for these amendments and new claims can be found throughout the specification and in the claims as originally filed, particularly in Paragraphs [0027], [0037], [0038], [0055], [0069], and Figures 3-5.

Entry and consideration of these amendments are respectfully requested. No new matter is believed to have been added by way of these amendments.

II. Interview

Applicant thanks the Examiner and his Supervisor for the productive interview on January 23, 2019, with the co-inventor, Clark Allphin, and Applicant's representatives, Philip McGarrigle, Michael Tuscan, and the undersigned. Applicant also thanks the Examiner for the withdrawn of the 35 U.S.C. §112 (pre-AIA), second paragraph rejection, as well as the obvious-type double patenting rejection.

III. Rejections

A. 35 U.S.C. §112 (pre-AIA)

The Office rejected claims 109-119 under 35 U.S.C. §112 (pre-AIA), first paragraph as allegedly failing to comply with the written description requirement. The Office asserts that the specification fails to describe 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.

Applicant respectfully disagrees and submits that the instant specification provides ample guidance for one skilled in the art to recognize that Applicant was in possession of the claimed dosage formulation at the time of filing. To establish that the claims are adequately described, the specification must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [Applicant] was in possession [of] . . . whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1564 (Fed. Cir. 1991). A genus is adequately described if the

specification permits one of skill in the art to "visualize or recognize members of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

The specification teaches that that the dosage forms of the present invention release gamma-hydroxybutyrate (GHB) over a sustained period of time.[1] Figures 3-5 describe the claimed *in vitro* release rates, and the detailed description provides a discussion of how formulations of the presently claimed invention can be made. The inventors teach that "(i)n 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." [2] The application teaches that a pore-former, such as a methacrylic acid-methyl methacrylate co-polymer can be present at about 20% to about 50% by weight of the functional coating.[3] According to the MPEP, "if the art has established a strong correlation between structure and function, one skilled in the art would be able to predict with a reasonable degree of confidence the structure of the claimed invention from a recitation of its function." [4] The examples, in concert with the general disclosure, provide enough guidance for one of skill in the art to conclude that Applicant was in possession of the claimed dosage formulation.

The Examiner states that the examples do not show an embodiment within the scope of the present claims. Respectfully, it is not necessary to disclose such an example order to meet the written description requirement. As explained in the MPEP by the Federal Circuit "examples are not necessary to support the adequacy of a written description, … the written description standard may be met … even where actual reduction to practice of an invention is absent."[5] Further, the numerous examples in the specification demonstrate a correlation between structure and function. Applicant therefore asserts that the examples show elements of the present invention and that the other support throughout the application is sufficient to prove written description for the present claims.

---

[1] As-filed specification [0037] and [0038].
[2] As-filed specification [0056].
[3] As-filed specification [0051] and [0052].
[4] MPEP 2163 IIA3(a), quoting Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613, quoting the Written Description Guidelines, 66 Fed. Reg. at 1106, n. 49.
[5] MPEP 2163 IIA3(a), quoting Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Therefore, Applicant respectfully requests withdrawal of this rejection.

B. 35 U.S.C. §103(a)

The Office rejected claims 109-119 under 35 U.S.C. §103(a) as unpatentable over Liang *et al*. (U.S. Pat. Pub. No. 2006/0210630, hereinafter "Liang.") Applicant respectfully disagrees. As discussed in more detail below, as well as in the accompanying declaration, the release profile of the claimed invention is distinct from that taught in Liang.

The presently claimed invention is directed to an oxybate formulation with a ***sustained release*** component. Liang however, teaches a ***delayed release*** formulation. These formulations are quite different structurally and functionally, and it would not be obvious to modify a delayed release formulation to make a sustained release formulation. Liang not only fails to teach or suggest the claimed sustained release profile, it fails to provide any motivation for a skilled artisan to modify its teachings of a delayed release formulation and arrive at a sustained release formulation as presently claimed.

1. Liang cannot support a case of *prima facie* obviousness

As an initial matter, the office has failed to establish a *prima facie* case of obviousness. To establish a case of *prima facie* obviousness, the combination of references must teach each and every element in the claims. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). As previously discussed, and as the Office states in the Final Action dated May 2, 2019, Liang does not teach the amount of GHB and methacrylic polymer coating, nor the claimed functional limitations regarding the *in vitro* release of GHB. However, the Office alleges that one of skill in the art would be motivated to modify Liang to arrive at the claimed invention.

Specifically, the Office asserts that the delayed release coatings of Liang could be modified to make a sustained release formulation. However, a skilled artisan would not consider modifying a delayed release formulation to make a sustained release formulation as they produce very different pK profiles.[6] Delayed release formulations quickly release the majority of the drug a certain amount of time after dosing. Essentially, a patient is given a delayed bolus dose. Sustained release formulations, in contrast, provide for a more gradual, but extended release of

[6] The Allphin Declaration, paragraph 12.

the drug over a period of time. Such a formulation could start releasing the drug shortly after dosing, or there could be a lag before the drug starts to release. This sustained release of the drug can then take place over a longer period of time than would typically occur in a delayed release formulation.

Since Liang is directed to *delayed* release, not sustained release, formulations of GHB. Liang's delayed-release coatings comprise about 87% by weight pH-sensitive enteric polymers, specifically pH-sensitive methacrylic acid-methyl methacrylate co-polymers.[7] As the coatings comprise a large percentage of pH-sensitive polymer, these dosage forms would release the majority of the drug relatively rapidly upon exposure to intestinal pH (e.g., about 6 and above), i.e., delayed release. As shown in Example 7 and Figures 1 and 2 of Liang, these "delayed release prototypes" release about 70%-100% of the drug within an hour at intestinal pH.[8]

In contrast, the presently claimed invention is directed to dosage forms comprising an immediate release portion and a *sustained* release portion. The claimed sustained release portion releases less than 10% of the drug within an hour in DI water and at least about 40% of the drug by about four to six hours in DI water, and the sustained release coating comprises about 20-50% by weight methacrylic acid-methyl methacrylate co-polymers. As discussed in the accompanying declaration from inventor Clark Allphin, the inventors were aware of Liang's teachings.[9] The light of these teachings, they conducted a regional GHB absorption study in humans in order to create an improved model of GHB delivery and used pharmacokinetic modeling to predict an *in vitro* release profile that would provide improved bioavailability.

The Office alleges that there is motivation for the skilled artisan to modify the Liang composition. However, the Office has failed to point out with any particularity where Liang provides the motivation to drastically alter its delayed release profile to an entirely different type of release profile. Rather, the Office alleges that modifying coatings is "routine optimization." Applicant disagrees, as there is no such motivation in Liang to change from one type of release profile to a very different type by modifying its delayed release coating to achieve a sustained release formulation as presently claimed. As discussed above, and in the attached declaration,

[7] Liang, Example 6.
[8] Liang, Fig 1-3 and [015]-[017].
[9] The Allphin Declaration, paragraph 5.

delayed release and sustained release are distinctly different types of release, and altering a formulation from delayed release to sustained release is not routine. Further, there is no motivation to modify Liang's coatings to achieve the particular *in vitro* release rate that is presently claimed. By saying one of skill, guided by Liang, would settle on the claimed release rate, the Office is relying on impermissible hindsight. Therefore, the Office has failed to establish a *prima facie* case of obviousness. As such, Applicant maintains that the claimed invention is not obvious in light of the cited art and respectfully requests that the rejection be withdrawn.

2. The claimed sustained release formulations provide superior bioavailability over Liang

As discussed in the Allphin Declaration, and as evidenced by the data in Liang, the delayed release formulations disclosed in Liang did not provide the desired bioavailability. [10] The formulation targeting the colon (DR-1) had about a quarter of the bioavailability of the immediate release dosage form, while the duodenum targeting formulation (DR-2) had about half the bioavailability of the immediate release dosage form.[11] Such a formulation would not provide sufficient GHB, and therefore would not be a useful once-nightly formulation.

The inventors, aware of the poor bioavailability of the Liang formulations, designed experiments to study the regional absorption of GHB in humans. The results of this study showed that substantial GHB absorption occurred in the upper intestinal tract, specifically, the ileum and jejunum.[12] The inventors modeled plasma pharmacokinetic (PK) simulations based on the data from these regional absorption studies, which allowed the inventors to predict a PK profile based on an *in vitro* release profile. As discussed in the Allphin Declaration, this modeling indicated that a sustained release formulation, where at least about 40% of the GHB is released by 4 to 6 hours when tested at a neutral pH (i.e., in DI water) would target the ileum and jejunum, and thereby provide improved absorption and better bioavailability. Additionally, the modeling showed that lag time of 1 hour results in a flatter PK profile, which is preferred. Therefore, the inventors focused on sustained release GHB formulations wherein less than 10%

[10] The Allphin Declaration, paragraph 7.
[11] Liang, Example 7, paragraph [0115], ad Table 3.
[12] The Allphin Declaration, paragraph 8.

of the drug is released within the first hour and a substantial portion of the drug (i.e., at least about 40%) is released by about 4 to 6 hours.

As the cited art teaches neither the presently claimed structural limitations, nor the presently claimed release profile, and one of skill in the art would have no motivation, based on the cited art, to develop a GHB formulation with the claimed *in vitro* release profile, the Office has failed to establish a case of *prima facie* obviousness. Further, as shown in the declaration, the inventors had discovered that the claimed *in vitro* release profile provides superior bioavailability as compared to the formulations in the cited art. As such, the Applicant respectfully requests the withdrawal of this rejection.

CONCLUSION

In view of the foregoing, Applicant respectfully submits that no further impediments exist to the allowance of this application and, therefore, requests an indication of allowability. However, the Examiner is requested to call the undersigned if any questions or comments arise.

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: March 6, 2020

Respectfully submitted,
COOLEY LLP

COOLEY LLP
ATTN: Patent Group
1299 Pennsylvania Ave, Suite 700
Washington, DC 20004

Tel: (202) 842-7800
Fax: (202) 842-7899

By: /Sandhya Deo/
Sandhya Deo
Reg. No. 65,841

EXHIBIT K

From: Yue, Herman (NY)
Sent: Wednesday, April 19, 2023 2:22 PM
To: Propst, Sarah (DC); Gabriel Brier
Cc: ajoyce@mccarter.com; dsilver@mccarter.com; MoFo-Avadel-Jazz; #C-M JAZZ PATENT LITIGATION - LW TEAM; Nick Cerrito; Eric Stops; Evangeline Shih; Andrew Chalson; Frank Calvosa; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel; Weires, Rebecca
Subject: RE: Jazz v. Avadel, Nos. 21-691, 21-1138, 21-1594

Counsel,

We have not received a response to our e-mail. As requested, please confirm Jazz will be supplementing its opening infringement report only in connection with Jazz's proposed claim construction positions.

Regards,
Herman

Herman H. Yue
Pronouns: He/Him/His

LATHAM & WATKINS LLP
1271 Avenue of the Americas | New York, NY 10020
D: +1.212.906.2977

From: Propst, Sarah (DC) <Sarah.Propst@lw.com>
Sent: Tuesday, April 11, 2023 1:02 PM
To: Gabriel Brier <gabrielbrier@quinnemanuel.com>
Cc: ajoyce@mccarter.com; dsilver@mccarter.com; MoFo-Avadel-Jazz <MoFo-Avadel-Jazz@mofo.com>; #C-M JAZZ PATENT LITIGATION - LW TEAM <jazzpatentlitigation.lwteam@lw.com>; Nick Cerrito <nickcerrito@quinnemanuel.com>; Eric Stops <ericstops@quinnemanuel.com>; Evangeline Shih <evangelineshih@quinnemanuel.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; Frank Calvosa <frankcalvosa@quinnemanuel.com>; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel <jazzavadel@quinnemanuel.com>; Weires, Rebecca <RWeires@mofo.com>
Subject: Jazz v. Avadel, Nos. 21-691, 21-1138, 21-1594

Counsel,

Please confirm that Jazz intends to supplement its opening infringement report on April 28, 2023 only in regards to Jazz's proposed construction positions, as Jazz asserted in its Opening *Markman* Brief of 3/24/2023 that under Avadel's construction the claims are inoperable. Specifically, Jazz asserted that "unbound anions do not exist as solids" and therefore claims that "require[] that the gamma-hydroxybutyrate/oxybate begin as a solid formulation" are "scientifically impossible to achieve." Jazz Opening Br. at 7-8; Little decl. ¶ 25. Because all of the asserted claims require an oxybate component that "begin[s] as a solid formulation," *see* '488 patent cl. 1 ("a. the sustained release portion comprises a functional coating and a core … [and] releases greater than about 40% of its gamma-hydroxybutyrate"), Jazz's assertion applies to all of the asserted claims of the patents in both families.

Best,

Sarah Propst
Pronouns: She/Her/Hers

LATHAM & WATKINS LLP
555 Eleventh Street, NW
Suite 1000
Washington, D.C. 20004-1304
Direct Dial: +1.202.637.1076
Email: sarah.propst@lw.com
https://www.lw.com

EXHIBIT L

IN THE CLAIMS

Set forth below in ascending order, with status identifiers, is a complete listing of all claims currently under examination. Changes to any amended claims are indicated by strikethrough or underlining. This listing also reflects any cancellation and/or addition of claims.

1-108. (Canceled)

109. (New) A formulation comprising immediate release and controlled release portions, each comprising gamma-hydroxybutyrate or a pharmaceutically acceptable salt thereof, wherein:

a. the controlled release portion comprises a controlled release coating comprising one or more methacrylic acid-methyl methacrylate co-polymers;

b. the immediate release portion comprises one or more film-formers;

c. the controlled release portion releases greater than about 40% of its gamma-hydroxybutyrate over 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;

d. 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

e. the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 8 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.

110. (New) The formulation of claim 109 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.

111. (New) The formulation of claim 109 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.

112. (New) The formulation of claim 109 wherein the controlled 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.

113. (New) The formulation of claim 109 wherein the controlled release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

114. (New) The formulation of claim 109 comprising a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

115. (New) The formulation of claim 114 comprising a sodium salt of gamma-hydroxybutyrate or mixtures thereof.

116. (New) The formulation of claim 109 wherein the immediate release portion comprises 50% by weight of total gamma-hydroxybutyrate.

117. (New) The formulation of claim 109, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 20% to about 50% by weight of the controlled release coating.

118. (New) The formulation of claim 117, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the controlled release coating.

119. (New) An oral dosage form comprising the formulation of claim 109.

EXHIBIT M

or

Dictionary Thesaurus

or 1 of 8 conjunction (1)

ər, ˈȯr *Southern also* ˈär

1 → used as a function word to indicate an alternative

coffee *or* tea

sink *or* swim

, the equivalent or substitutive character of two words or phrases

lessen *or* abate

, or approximation or uncertainty

in five *or* six days

2 **archaic** : EITHER

3 **archaic** : WHETHER

4 → used in logic as a sentential connective that forms a complex sentence which is true when at least one of its constituent sentences is true

→ compare DISJUNCTION

or 2 of 8 preposition

archaic

: BEFORE

Dictionary Thesaurus

or 3 of 8 conjunction (2)

archaic

: BEFORE

or 4 of 8 noun (1)

ˈȯr

: the heraldic color gold or yellow

OR 5 of 8 noun (2)

ˈȯr

: a logical operator that requires at least one of two inputs to be present or conditions to be met for an output to be made or a statement to be executed

OR gate in a computer

OR 6 of 8 abbreviation

1 operating room

2 operational research; operations research

3 Oregon

4 owner's risk

5 own recognizance

Dictionary Thesaurus

-or 8 of 8 noun suffix (2)

: condition : activity

demean*or*

Etymology

Conjunction (1) and Noun (2)
Middle English, alteration of *other*, alteration of Old English *oththe*; akin to Old High German *eddo* or

Preposition

Noun suffix (1)
Middle English, from Anglo-French *-ur, -our, -eour* & Latin *-or*; Anglo-French *-ur, -our*, from Latin *-or*; Anglo-French *-eour*, from Latin *-ator*, from *-a-*, verb stem + *-tor*, agent suffix; akin to Greek *-tōr*, agent suffix, Sanskrit *-tā*

Noun suffix (2)
Middle English, from Anglo-French, from Latin

First Known Use

Conjunction (1)
13th century, in the meaning defined at sense 1

Preposition
13th century, in the meaning defined above

Conjunction (2)
13th century, in the meaning defined above

Noun (1)
15th century, in the meaning defined above

Noun (2)
1947, in the meaning defined above

Time Traveler

The first known use of *or* was in the 13th century

See more words from the same century

Dictionary Thesaurus

all-or-none

bow down to (someone or something)

See More

Oquirrh Mountains
or
OR

See More Nearby Entries >

Style MLA

"Or." *Merriam-Webster.com Dictionary*, Merriam-Webster, https://www.merriam-webster.com/dictionary/or. Accessed 24 Apr. 2023.

Copy Citation

Dictionary Thesaurus

or 1 of 3 conjunction

ər, (ˌ)ȯ(ə)r

→ used to indicate an alternative

coffee *or* tea

sink *or* swim

-or 2 of 3 noun suffix

ər, ˌȯ(ə)r, ˈȯ(ə)r

: one that does a specified thing

elevat*or*

-or 3 of 3 noun suffix

ər

: condition **:** activity

demean*or*

Etymology

Noun suffix
derived from Latin *-or* or *-ator,* both meaning "one that does something"

Noun suffix
derived from Latin *-or* "condition, activity"

Dictionary Thesaurus

OR abbreviation

operating room

OR abbreviation

own recognizance

Nglish: Translation of *or* for Spanish Speakers
Britannica English: Translation of *or* for Arabic Speakers

EXHIBIT N

Comparison Between Claims of Resinate Patents and Avadel's Claims[1]

I. '079 PATENT

Claims from Jazz's '041 application ('079 patent), filed December 10, 2020	Claims from Avadel's US 2019/0274990 A1 published September 12, 2019
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.	1. *A method of treating* a disorder *treatable with* gamma-hydroxybutyrate *in a* human *in need thereof, the method comprising:* *administering a single daily dose to* said human *an amount of* gamma-hydroxybutyrate *equivalent to from* 3.0 *to 12.0 g of sodium oxybate, wherein the administering comprises opening a sachet containing* a gamma-hydroxybutyrate *formulation,* *mixing the formulation with water, and* *orally administering the mixture.*
2. *The method of claim 1, wherein the orally administering occurs at* night.	2. *The method of claim 1, wherein the orally administering occurs at* bedtime.
3. *The method of claim 1, wherein the* oxybate formulation is mixed with water immediately prior to administration.	3. *The method of claim 1, wherein the* mixing occurs shortly before the orally administering.
4. *The method of claim 1, wherein the* oxybate is administered with food.	4. *The method of claim 1, wherein the* orally administering occurs approximately 2 hours after said human has eaten a meal.
5. *The method of claim 1, wherein* the *administering* promotes the patient *to sleep for 6 to 8 hours.*	5. *The method of claim 1, wherein* said *administering* results in inducing said human *to sleep for 6 to 8 hours.*
6. *The method of claim 1, wherein the amount of* oxybate *administered to the* human *is* 35 mEq, 45 mEq, 60 mEq, or 70 mEq *of oxybate.*	6. *The method of claim 1, wherein the amount of* gamma-hydroxybutyrate *administered to the* human *is* equivalent to 4.5 g, 6.0 g, 7.5 g, or 9.0 g *of* sodium *oxybate.*

[1] Italics denote language in the claims of Jazz's patent application that is the same as language in the claims of Avadel's '990 publication.

7. *The method of claim 1, wherein the mixture is a suspension.*	7. *The method of claim 1, wherein the mixture is a suspension.*

II. '782 PATENT

Claims from Jazz's '064 application, filed March 23, 2021	Claims from Avadel's '866 patent, issued August 11, 2020
1. *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.*	1. *A formulation of gamma-hydroxybutyrate comprising:* *an immediate release portion comprising gamma-hydroxybutyrate;* *a modified release portion comprising gamma-hydroxybutyrate;* a suspending or viscosifying *agent* selected from…; *and* *an acid*ifying agent selected…; *wherein the* suspending or viscosifying *agent and the acid*ifying agent *are separate* and distinct *from the immediate release portion and the modified release portion*; and wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.
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.*	*See* claim 1: a suspending or viscosifying *agent selected from the group consisting of xanthan gum*, carrageenan gum, gellan gum, guar gum, sodium alginate, calcium alginate, agar, sodium carboxymethyl cellulose, *microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropylmethyl 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.*	*See* claim 1: an *acid*ifying agent *selected from the group consisting of malic acid, citric acid, tartaric acid,* adipic acid, *boric acid, maleic acid, phosphoric acid,* ascorbic acid, oleic acid, capric acid, caprylic 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.*	4. *The formulation of claim 1, wherein the formulation further comprises a lubricant* or glidant *selected from the group consisting of magnesium stearate*, calcium stearate, *zinc stearate*, glyceryl monostearate, glyceryl palmitostearate, glycerol behenate, *sodium stearyl fumarate*, talc, or colloidal silicon dioxide.

EXHIBIT O

Newman and Wenslow *AAPS Open* (2016) 2:2
DOI 10.1186/s41120-016-0003-4

AAPS Open
a SpringerOpen Journal

REVIEW Open Access

Solid form changes during drug development: good, bad, and ugly case studies

Ann Newman[1,2*] and Robert Wenslow[2]

Abstract

The relevance of solid form in drug development has been well established over time. In order to fully understand drug properties, attention has been paid to solid state structure of drug molecules and their relationship to the drug formulation. While each drug developer has had their own strategies and workflows for screening and choosing solid forms of drug molecules, the industry is aware of instances where "the best laid plans" often go awry. This manuscript has summarized several case studies in development programs that display the "good, bad, and ugly" of solid form changes.

Keywords: Solid forms, Crystalline forms, Amorphous materials, Polymorphs, Salts, Cocrystals, Amorphous solid dispersions, Case studies

Background

It has been reported that the solid form of active pharmaceutical ingredients (APIs) has significantly impacted quality and consistency of the final dosage form for drug development compounds (Newman and Byrn 2003), especially for solid oral dosage formulations. Therefore, monitoring and controlling the API solid form in both drug substance and drug product has been recommended in order to ensure consistent biopharmaceutical properties throughout a drug development program.

Every innovator drug developer has approached API solid form decisions with a unique paradigm; however, identifying and maintaining the optimal API solid form in early pharmacokinetic studies, as well as maintaining this form through product launch, has been recognized as an ideal situation. This utopian scenario, however, has often been noted to be far removed from reality, especially if the API solid form has been ignored or assumed to be trivial for a particular program. This has often led to significant program delays and cost as bioequivalence studies, new crystallization studies, or formulation development may have been needed.

This manuscript presents the "good, bad, and ugly" aspects of API solid form changes in the pharmaceutical industry. It has explored and elaborated upon specific case studies that outline the impact of API solid form changes brought about by choosing a non-ideal salt form for early preclinical development, relaxed due-diligence for a "fast-tracked" compound, a serendipitous late stage form change, lack of attention to solid form for an in-licensed compound, and a less than bullet-proof intellectual property (IP) landscape surrounding an innovator molecule.

The goal of these examples was to show that adequate attention to API solid form during development will aid in managing risk for a program. Whether an innovator company was looking to out-license a gold molecule as a platinum package, an innovator company was looking to bring a drug to market with a strong patent landscape, or a generic company was looking to enter the market with IP for their molecule, the case studies presented in this manuscript clearly show that API solid form is an important aspect of any development program.

The case studies presented, in addition to many other un-published examples, have confirmed to pharmaceutical scientists that no screening strategy can guarantee that all crystal forms have been discovered. However, appropriate attention to API form and a sound screening

* Correspondence: ann.newman@seventhstreetdev.com
[1]Seventh Street Development Group, Kure Beach, NC 28449, USA
[2]Crystal Pharmatech, New Brunswick, NJ, USA

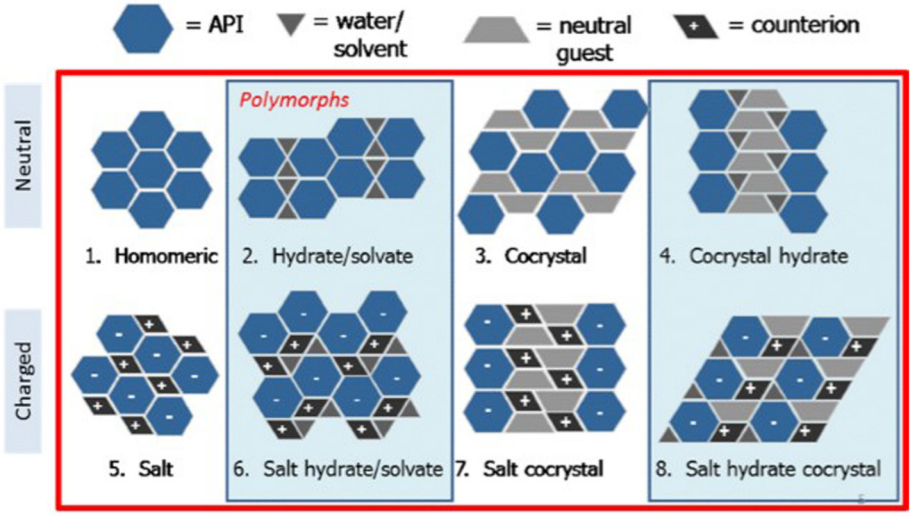


Fig. 1 Classification of crystalline API forms. The red box signifies that polymorphs of all solid form classes are possible; the blue boxes represent classes containing hydrates

strategy has had the potential to mitigate the risk for form changes in the API and drug product.

Solid forms have been defined as both crystalline and amorphous materials in this paper. Crystalline forms have been sub-classified into categories outlined in Fig. 1, and described as neutral (such as free forms and co-crystals) and charged (salts or salts of co-crystals) species. Each category of crystalline materials has the possibility of displaying polymorphism (solvates and hydrates have been included in our polymorph classification based on the regulatory definition). Any material from the crystalline API categories that lacks long range order as characterized by x-ray powder diffraction (XRPD) has been referred to as amorphous API.

Case studies

Indinavir - early salt form change

Indinavir sulfate, marketed as Crixivan® (Fig. 2), was approved in 1996 as a human immunodeficiency virus type 1 (HIV-1) protease inhibitor indicated for treatment of HIV infection and AIDS in adults (Lin 1999; Lin et al. 1998; Crixivan Package Insert. (available at http://www.merck.com/product/usa/pi_circulars/c/crixivan/crixivan_pi.pdf. Accessed 23 Feb 2016). Crixivan® was initially developed as a free base monohydrate, but suffered from significant pH dependent solubility (Fig. 3) and limited adsorption as the free base form (Lin et al. 1998). As a result, a need to identify an acceptable, soluble salt for clinical dosage development arose for researchers. The pH solubility profile and pKa of the molecule suggested a rather acidic salt was necessary to achieve complete dissolution. One issue, however, was that Crixivan® was quite unstable in acidic solutions (Table 1), which presented a stability risk for solid salt forms (Lin et al. 1998). The crystalline sulfate salt ethanolate was chosen as the lead salt form for development. The aqueous solubility for this salt form was in excess of 500 mg/ml with a resulting solution pH of < 3. The main concern for the sulfate salt ethanolate was the excessive hygroscopicity (Fig. 4). Additionally, the ethanolate had the potential to change physical form at elevated humidity, even potentially going amorphous. Because of this, extensive solid-state stability and excipient compatibility studies were performed using controlled humidity conditions. Experiments showed that a shelf life of > 2 years was possible when the humidity was kept < 30 % relative humidity (RH), even for the amorphous sulfate salt. At temperatures and humidity above 40 °C and 30 % RH respectively, the sulfate salt suffered from rapid degradation for both the API and drug product. Because of the need for low RH, a dry granulation formulation process was developed for the drug product (Lui et al. 2003). Human clinical trials were conducted with both the sulfate salt ethanolate

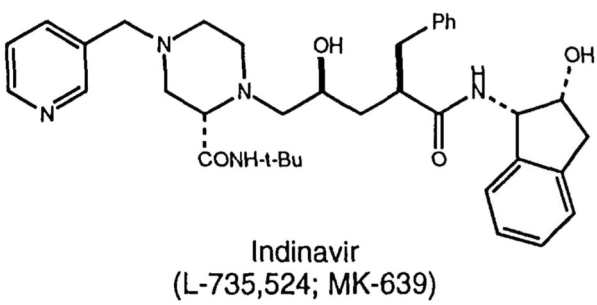


Fig. 2 Structure of indinavir

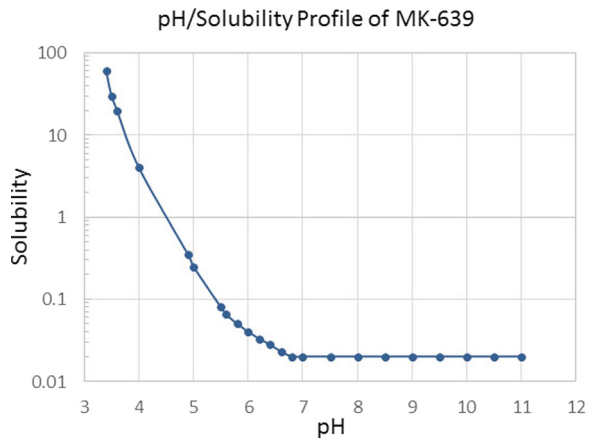


Fig. 3 pH solubility profile of indinavir (adapted from Ref (Lin et al. 1998))

and free base monohydrate (Yeh et al. 1998). The study showed that the sulfate salt in the fasted state or with a low fat meal yielded the highest exposures (Fig. 5).

This example has clearly displayed the utility of identifying the appropriate salt form before clinical trials have been initiated and has also represented a "good" scenario for solid form in development. This case study has presented a classic example of solid state form impacting pharmacokinetic profiles of a drug. The example has also shown that relatively poor physicochemical properties can be mitigated with a thorough understanding of both chemical and physical stability profiles. The sulfate salt ethanolate displayed excessive hygroscopicity and form change potential; however, processing and storage conditions were identified to successfully process and store API and drug product.

DPC 961 – Form change on a fast track compound

DPC 961 (Fig. 6) was a development compound indicated for the treatment of HIV infections and was developed as a neutral molecule (Staszewski et al. 1999). The compound was designated as Biopharmaceutics Classification System (BCS) II, with high permeability, low aqueous solubility and therefore would display dissolution limited behavior (Aungst et al. 2002). As a result, physicochemical characteristics such as particle size, crystal form, and surface area may have had a direct impact on bio-performance. Early in development, this compound had been known to exist in many solvated forms in addition to a single, anhydrous crystal form (Form I) (Desikan et al. 2005). Preliminary screening work had never identified crystallization solvents that directly isolated Form I. All pathways to Form I involved forming a solvate and then de-solvating to obtain Form I. The first 29 development batches of DPC 961 involved isolation of the API through crystallization from toluene/heptane, followed by re-crystallization from methanol (MeOH). Anhydrous Form I was the product in all 29 batches; however, this form was not directly crystallized, but instead, formed through de-solvation of the stoichiometric MeOH solvate by elevated temperature drying. On the 30th batch, a lower melting crystal form, anhydrous Form III, was the product. Form III was determined to be enantiotropically related to Form I, with Form III being the low temperature stable polymorph with transition temperature between 120 and 174 °C, as determined from DSC data using Burger's rules. A van't Hoff investigation had not been performed in this polymorph system, presumably since no solvent had been found that had not formed a solvate with either Form I or III.

After the serendipitous discovery of Form III, Form I was never again manufactured at large scale. When the desolvation employed in the first 29 batches was attempted after Form III was discovered, the product was now Form III, and not Form I. Form I had been prepared on small scale by heating Form III above melting point, but a manufacturing process could not be developed. This circumstance was a clear example of the phenomenon labeled as a "disappearing polymorph" (Dunitz and Bernstein 1995). Due to this change in form, researchers were now left with Form III. Since the compound was BCS II, dissolution may have critically impacted bioperformance. Thus, the first set of experiments necessary when Form III was discovered and realized to be the future chosen phase was to understand bio-relevant dissolution and solubility. Fortunately, Form III had comparable aqueous solubility and intrinsic

Table 1 pH Stability Data for Indinavir (used with permission from Ref (Crixivan Package Insert. (available at http://www.merck.com/product/usa/pi_circulars/c/crixivan/crixivan_pi.pdf. Accessed 2 March 2015))

pH	Buffer	k_1 (hr^{-1}) at 40 °C	$t_{1/2}$ (days) at 40 °C
1	0.1 M HCl	2.16×10^{-3}	13
2	0.1 M maleate	1.14×10^{-3}	25
3	0.1 M citrate	7.12×10^{-4}	41
4	0.1 M citrate	3.36×10^{-4}	86
5	0.1 M citrate	1.10×10^{-4}	262
11	0.1 M carbonate (1/1 MeOH/H_2O)	1.23×10^{-3}	23

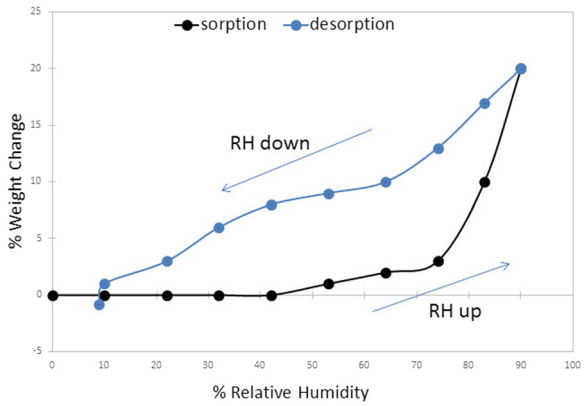


Fig. 4 Water sorption/desorption profile of indinavir (adapted from Ref (Lin et al. 1998))

dissolution rates. An oral absorption study in animals was necessary to confirm that bio-performance would not be impacted by the crystal form change. When Form I and Form III were formulated into tablets and orally administered to dogs at 100mpk, the oral absorption profiles were statistically identical (Fig. 7). If this had not been the case, and formulated Form I resulted in a unique absorption profile compared to Form III, a human bridging study would have been necessary. The cost and program delays would have been substantial. While statistics are not available, the chances of Form III and Form I having identical bio-performance for a BCS II compound was likely to be low. The more probable result would have been distinct solubility and/or dissolution differences between the polymorphs. Even though a clinical bridging study was not necessary after the polymorph change, the research team still had to develop a unique API isolation process and update analytical methods, in addition to providing the necessary data to prove polymorph stability and bio-equivalence, which would have likely taken a minimum of six months to perform.

The lessons learned from this case study would vary based on the company's risk-management strategy. It has been generally accepted that isolating the final crystal form through desolvation would be a non-ideal process; rather, a process where the final form has been directly nucleated and grown (with or without seeds) would be preferred. However, there have been compounds that, when developed initially, have only appeared to form solvates. These solvates may or may not have had the potential to de-solvate to a physically stable anhydrous crystal form. In this case study, Form I

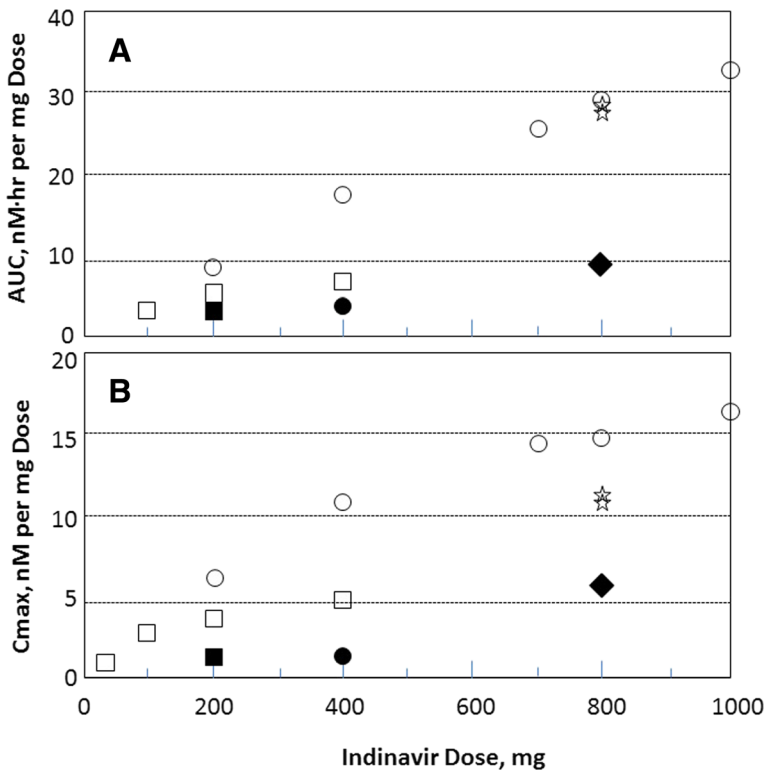


Fig. 5 AUC (**a**) and Cmax (**b**) curves for indinavir as a function of the administered single-dose; AUC and Cmax values were normalized to a 1-mg dose. ○ sulfate salt fasted state; ● sulfate salt following a high-fat meal; ☆ sulfate salt following low fat meal; □ free-base capsules fasted state; ▪ free base capsules following a high-fat meal; ♦ free base oral suspension fasted state (used with permission from Ref (Yeh et al. 1998))

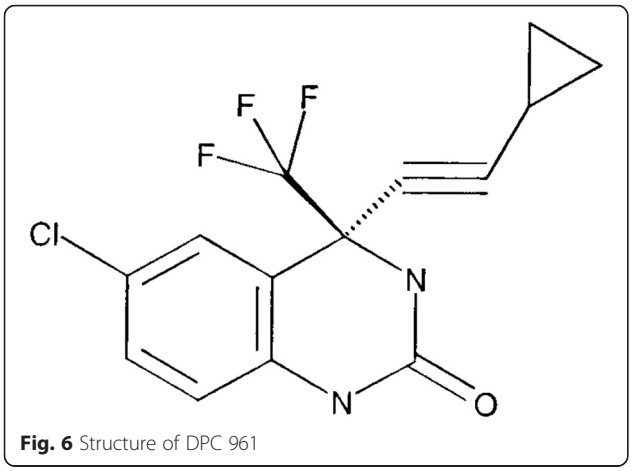


Fig. 6 Structure of DPC 961

appeared to exhibit adequate physical stability, but was not found to be an anhydrous crystal form that could have been directly nucleated and grown in an appropriate solvent system. Due to the speed of the program, it could have easily been argued that the process was robust in isolating Form I, as 29 batches had been completed without incident. The opportune discovery of Form III may have occurred due to a variety of causes including, but not limited to: impurity differences (either level or actual type of impurities) in the process stream, unique levels of supersaturation, or foreign particle providing heteronuclear templates for nucleation. It is not known whether extensive screening early in the program would have uncovered Form III. However, many compounds that have only been isolated as a solvate had often times masked an anhydrous crystal form that had been anticipating the right trigger in order to be discovered. Therefore, an appropriate and diligent level of crystal form screening should be applied to this type of compound, especially since the compound was designated at BCS II. The screening strategy should have involved conditions attempting to avoid solvate formation (Campeta et al. 2010). This "fast-track" compound could be deemed a "bad" scenario when the time delays and increased costs to the project have been added to the development plan.

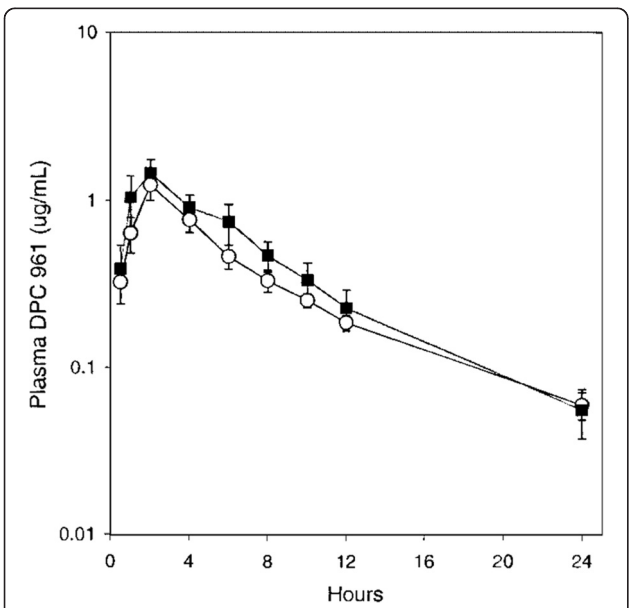


Fig. 7 Comparison of DPC 961 oral absorption in dogs administered 100 mg tablet formulations prepared with polymorph form I (○) or form III (■). (used with permission from Ref (Aungst et al. 2002))

Atorvastatin - crystalline form change in late development

Atorvastatin (CI-981) is an HMG CoA reductase inhibitor marketed as Lipitor® (Fig. 8). As a BCS II drug, it has exhibited poor solubility and high permeability (Wu and Benet 2005). The compound was originally discovered at Warner-Lambert in the 1980's, and the amorphous form of the hemi calcium salt pure enantiomer was used for early clinical trials. Phase 1 studies were conducted by the Parke-Davis Clinical Research Unit (CRU) recruiting twenty-four (24) males from within the company (Lie 2009). Phase 2 clinical trials showed an improvement in performance when compared to data from four marketed drugs (Fig. 9). Priority review status was requested in 1994, but was denied because the drug had not met an unmet medical need. The company proceeded to fund a clinical study for familial hypercholesterolemia, where the compound showed efficacy, and they were granted priority review status which helped to shorten the development time. Atorvastatin calcium was approved by the Food and Drug Administration (FDA) in late 1996.

The only known solid form for atorvastatin calcium in Phase 1 and 2 clinical trials was the amorphous form. It exhibited poor filtration and drying characteristics for large scale batches and required protection from heat, light, oxygen, and moisture (Briggs et al. 1999). During Phase 3 clinical trials, a crystalline form was produced at scale which was determined to be a trihydrate and referred to as Form I (Briggs et al. 1999). This crystalline form possessed a number of advantages over the amorphous form including higher purity, improved

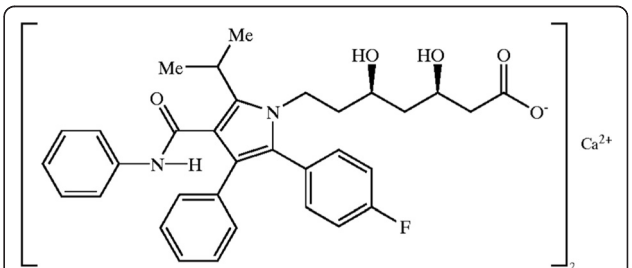


Fig. 8 Structure of atorvastatin

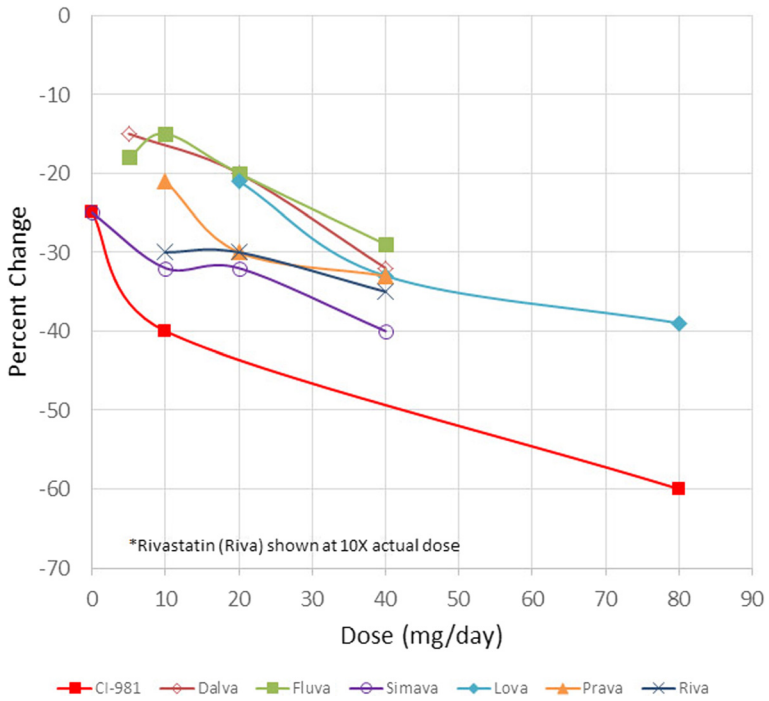


Fig. 9 Atorvastatin (CI-981) Phase II results compared with marketed products (adapted from Ref (Lie 2009))

chemical stability, tighter uniformity in particle size distribution, and better filtration and drying properties. While finding a new form at this stage of development would normally be undesirable, the improvements gained with the new crystalline form were substantial enough for researchers to change the solid form during late development. All aspects of the project needed to be repeated, such as the API manufacturing process development, formulation development, stability studies, analytical methods, and human bioequivalence testing. Tablets produced with amorphous and crystalline trihydrate atorvastatin calcium showed a difference in the rate of absorption, but equivalent extent of absorption in the bioequivalence test (Pfizer Citizen Petition. Docket no 2005P).

Other crystalline forms were patented along with Form I (designated Forms II and IV) (Briggs et al. 1999), and additional forms followed in subsequent patent applications (Byrn et al. 2003; Tesslor et al. 2003; Van Der Schaaf et al. 2009). The next challenge for the team was to develop a crystallization process that produced uniquely Form I with the desired characteristics they needed. One patented process reported that adding methyl-t butyl ether (MTBE) to the reaction mixture after forming the salt, followed by subsequent seeding, had produced the desired Form I (Tully 2003).

The FDA orange book has listed a number of patents for atorvastatin calcium, including the composition of matter patent (expired September 24, 2009), a salt patent including the calcium salt (expired Dec 28, 2010), and the crystalline Form I patent (expires July 8, 2016). By using a form other than Form I, generic products were technically allowed on the market in 2010. After numerous legal battles and an agreement between Pfizer and Ranbaxy, the generic version of Lipitor® was available in late 2011 (Lie 2009).

The atorvastatin story has covered a number of teaching points regarding solid forms. Polymorph screens were not routinely performed when atorvastatin was under development and it was common to find forms during scale-up, especially when conditions were changed. In the case of atorvastatin, a screen was performed after the crystalline form was found and a number of forms were produced, based on the patent literature (Briggs et al. 1999; Byrn et al. 2003; Tesslor et al. 2003; Van Der Schaaf et al. 2009). In present day cases, a solid form screen should be performed in early development to find a suitable form long before Phase 3 clinical trials. An earlier solid form screen would also have prevented the repeat of major studies late in development, as seen when atorvastatin Form I was found. Screening studies do not guarantee that all forms have been found, but they have significantly reduced the risk for most programs. The patents listed in the Orange Book and the strategy of using patents to maintain market share have also been recognized as an important lesson from this example since it has necessitated consideration of a patent strategy whenever new forms (polymorphs,

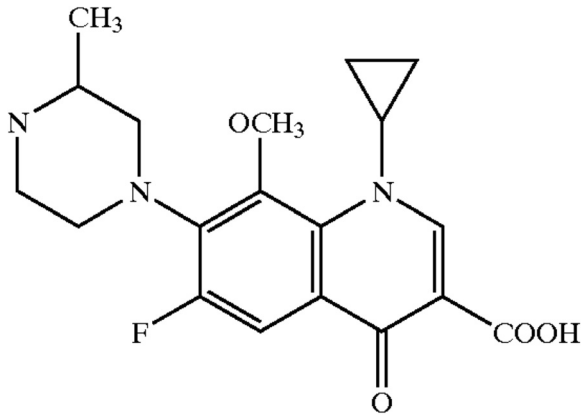


Fig. 10 Structure of gatifloxacin

hydrates, solvates, salts, cocrystals, amorphous solid dispersions, etc.) have been found during development.

While the initial discovery of a crystalline form during Phase 3 clinical trials would have normally been considered a "bad" scenario, the atorvastatin story has proven that after the extra work has been completed, a very "good" scenario and a successful product resulted.

Gatifloxacin - crystalline form changes with a licensed compound

Gatifloxacin (also known as AM-1155, CG5501, and BMS-206584) has been established as a fluoroquinoline broad-spectrum antibiotic (Fukuda et al. 1998) (Fig. 10). It was originally discovered by Kyorin Pharmaceuticals in the late 1980s as a hemihydrate that was recrystallized from methanol (Masuzawa et al. 1991). This crystalline form was found to be hygroscopic and resulted in poor tablet disintegration and dissolution. In the mid-1990s, a sesquihydrate was found by Kyorin with improved properties (Matsumoto et al. 1999). The compound was licensed to Bristol-Myers Squibb (BMS) in 1996 with two hydrated forms disclosed.

Initial clinical formulations at BMS utilized the sesquihydrate in a wet granulation process. The clinical batch failed specifications when a new crystal form was discovered in the batch. The new crystal form was confirmed as a pentahydrate (Raghaven et al. 2002), which was found to be less soluble and more stable in various formulations (wet granulations, dry blends, and aqueous suspensions). Issues with the initial clinical sesquihydrate formulation, as well as difficulty producing pure sesquihydrate material, had prompted crystallization studies to find a better understanding of the solid form landscape.

Crystallization studies using only ethanol, water, and various drying conditions resulted in 12 additional forms for gatifloxacin (Fig. 11) (Raghaven et al. 2002). These studies added considerable elements to the development timeline of the compound, including finding the forms, developing API processes for the desired forms, optimizing clinical formulations, and requalifying analytical

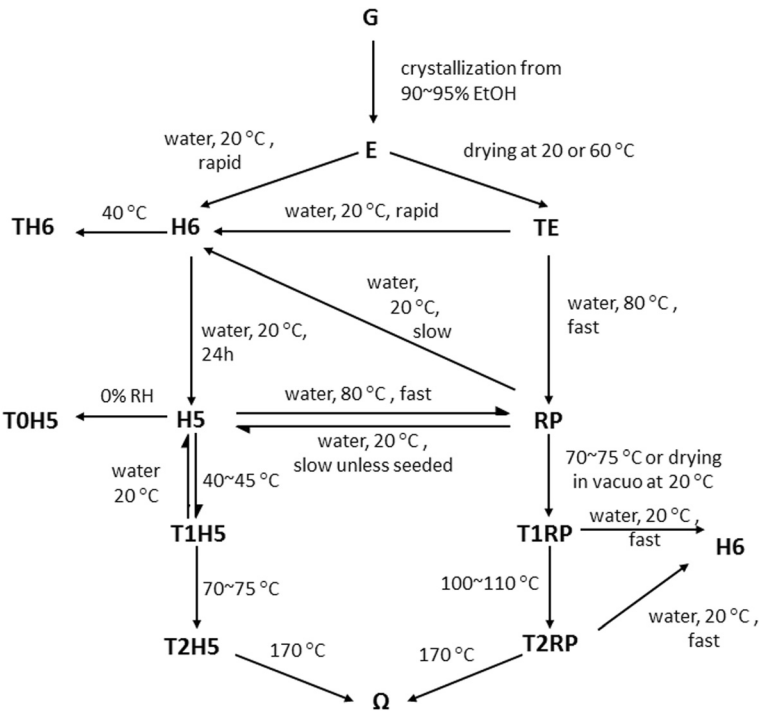


Fig. 11 Gatifloxacin crystalline forms from ethanaol, water, and various drying conditions (adapted from reference (Raghaven et al. 2002))

methods. While the pentahydrate exhibited superb physical properties for the API and formulation, it was also found to be less bioavailable compared to the sesquihydrate. This resulted in a switch back to the sesquihydrate form for the marketed tablet formulation Tequin®, approved in 1999 (Fish and North 2001). Potentially fatal blood sugar problems resulted in a blackbox warning for Tequin®, as well as a subsequent removal of Tequin® from the US and Canadian markets in 2006. The sesquihydrate was subsequently used in the production of ophthalmic solutions, Zymar® and Zymaxid®. After the compound patent had expired in 2010, Apotex started to use the hemihydrate in their generic product.

Gatifloxacin has provided an example of multiple form changes throughout mid to late stage development. These changes created significant additional work around API crystallization development, formulation processing, analytical methods, and biological studies (i.e., bridging and bioequivalence studies). This case study has also demonstrated the criticality of due diligence for in-licensed compounds, including proper screening. Companies that in-license a compound should ask specific questions about the solid form studies that were performed to determine the scope of knowledge and inter-relationships between forms, and how the solid form landscape would impact the desired dosage form and development plan. For companies that out-license a compound, a solid form study targeted toward the most stable form, crystallization conditions, and formulation processes have resulted in a much stronger package.

While the initial package for gatifloxacin seemed straightforward with only two hydrated forms, it should be classified as an "ugly" scenario due to the solid form changes and additional studies.

Lifecycle management

Olanzapine - crystalline change from free acid to salt

Olanzapine (Fig. 12), a Biopharmaceutics Drug Disposition Classification System (BDDCS) 2 drug (Benet et al. 2011) with poor solubility and high permeability, has been marketed towards treating schizophrenia. Olanzapine has been shown to exhibit a number of different crystalline forms including hydrates (Reutzel-Edens et al. 2003) and solvates (Cavallari et al. 2013). Form I has been deemed the most stable unsolvated form (Reutzel-Edens et al. 2003). A variety of dosage forms have been developed to target different patient populations. These products have included Zyprexa® tablets (once a day oral tablets), Zyprexa Zydis® orally disintegrating tablets (that can be taken without water), and Zyprexa Intra Muscular® (rapid acting intramuscular injection). A combination capsule product with fluoxetine hydrochloride (HCl) (Symbyax®) was also launched when indications were expanded

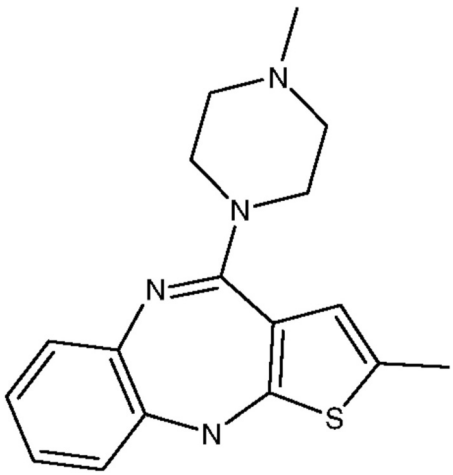


Fig. 12 Structure of olanzapine

to include treatments of bipolar disorder and resistance depression in its marketing.

A major issue with this patient group was compliance; as a result, a dosage form that lasted longer than once daily would have provided a significant benefit for the patients. To address this issue, researchers developed a long acting injection (LAI) using olanzapine pamoate monohydrate and sold as Zyprexa Relprevv® in 2010 (Chue and Chue 2012). The pamoate salt was shown to be poorly soluble in aqueous media, and micron sized crystals were suspended in a diluent containing carboxymethylcellulose sodium, mannitol, polysorbate 80, sodium hydroxide and/or hydrochloric acid for pH adjustment and water for injection (Zyprexa Relprevv Package Insert 2014). As a result, the salt slowly dissolved after injection into the muscle, resulting in an absorption of olanzapine systemically over a period of several weeks (Citrome 2009). The half-life of the pamoate salt became 30 days, in comparison to 33 h for an oral dose (Di Lorenzo and Brogli 2010). One injection has been noted to last three to four weeks, providing better efficacy and compliance for patients (Fig. 13) (Agency et al. 2015). The efficacy and tolerability profiles for the LAI were found to be the same as the oral formulation. The olanzapine Form II patent listed in the Orange Book (US 6960577) is set to expire in 2017. The olanzapine pamoate monohydrate patent listed in the Orange Book (US 6169084) has an expiry date of 2018, which has given the LAI dosage form a year of extra patent coverage.

This case study has illustrated the advantages of using novel solid forms for innovative drug products. The change in solid form to a crystalline pamoate salt resulted in a less soluble salt, which has previously not been desired by researchers. However, in this case, the less soluble salt exhibited all the properties needed for

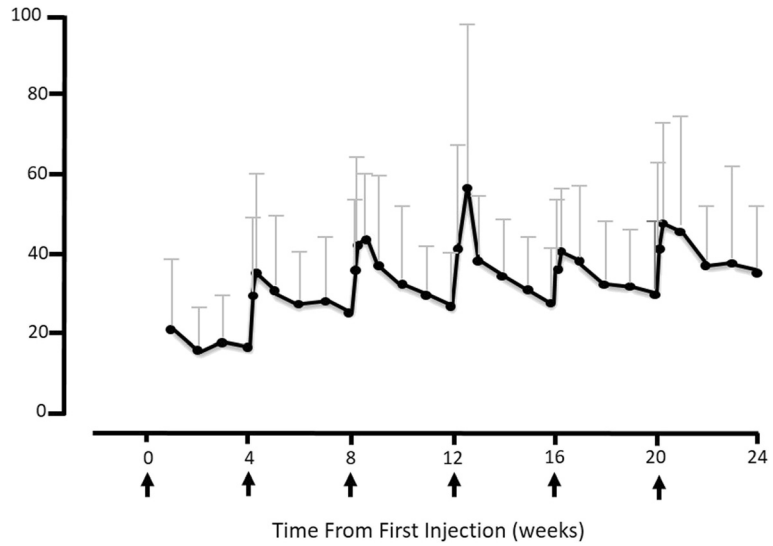


Fig. 13 Mean olanzapine plasma concentrations for the Multiple-Dose Group receiving 405 mg/4 weeks; arrows along x-axis indicate injections (adapted from reference (Agency et al. 2015))

an improved sustained release formulation. Rather than an oral dosage form, an intramuscular injection was produced to capitalize on the lower solubility. The result became a dosage form with good efficacy and superior compliance. Additionally, patent coverage around the new salt has also extended coverage for a year after the olanzapine free base expires.

Oxybutynin- crystalline change from salt to free base

Oxybutynin HCl (Fig. 14) has been recognized as a BDDCS I compound exhibiting high solubility and permeability (Benet et al. 2011). It has been used in a variety of marketed products for the treatment of overactive bladder (Gamble and Sand 2008). The first oral formulation from Hoechst Marion Roussel in 1975 was an immediate release tablet (Ditropan®), which was dosed three times a day. The major side effect was dry mouth, which was the primary reason for patients discontinuing use (Sathyan et al. 2001). The side effect of dry mouth was caused by the metabolite desethyloxybutynin. The metabolite was reduced by developing a controlled release dosage form, which maintained a zero order release. This resulted in lower peak to trough variations in plasma levels and bypassed the pre-systemic metabolism and conversion to the active metabolite. Ditropan XL® was launched in 1999 using Alza's osmotic delivery (OROS) formulation approach, which reduced the severity of dry mouth side effects (Sathyan et al. 2001). This formulation approach also allowed one daily dose, as opposed to the original three daily doses, which was more convenient for the patient and helped improve patient compliance.

Another way to reduce the metabolite and side effects was to bypass the first pass metabolism using a different administration route. Watson launched an Oxytrol® transdermal patch in 2003, which was designed to deliver oxybutynin over a three to four day interval. Reformulation into the patch required researchers to use the oxybutynin free base, instead of the hydrochloride salt, for better skin transport. Bypassing the oral delivery route significantly reduced the metabolite (Fig. 15), which resulted in minimal side effects and better patient compliance (Gamble and Sand 2008). In January 2013, an over-the-counter (OTC) patch was approved by the FDA for commercial use (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm336815.htm. Accessed 2 March 2015).

This case study shows how a change in form and delivery route has not only reduced side effects, but also resulted in a more efficient and convenient drug product for the patient. The development of the patch required a change in form from the hydrochloride salt to free base, which enabled the drug to pass through the skin. Finding a different form to develop an improved

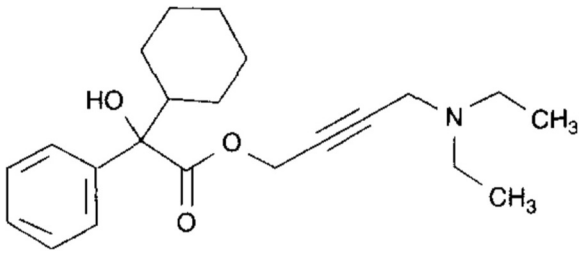


Fig. 14 Structure of oxybutynin HCl

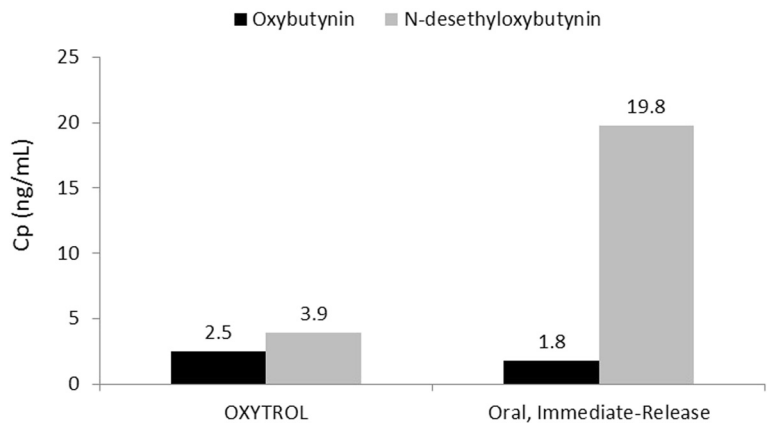


Fig. 15 Comparison of blood levels of oxybutynin and its metabolite, N-desethyloxybutynin, showing that the patch resulted in significantly lower levels of the metabolite, which reduced the dry mouth side effect, compared to the oral immediate release formulation (Oxytrol Package Insert. (available at http://pi.watson.com/data_stream.asp?product_group=1295&p=pi&language=E. Accessed 2 March 2015)

drug product required an understanding of the properties needed for a particular dosage form and thorough characterization of various forms. This change in form could include a polymorph, free acid/base, salt, cocrystal, or amorphous solid dispersion. Specific counterions or guest molecules would need to be considered for certain delivery routes, such as dermal, ophthalmic, intravenous, or intramuscular formulations (Paulekuhn et al. 2007). Determining the issues with current products and finding creative solutions using form and formulation to produce an improved product has been recognized as a true "win-win" in lifecycle management.

Conclusions

The case studies in this manuscript have been presented to show why it has been critical to characterize, understand, and monitor the solid form in all stages of drug discovery and development. While these case studies have been presented in the literature, there have been even "uglier" cases that have not been published. It is important for researchers to realize that form selection is not a unit operation, but an integral part of the entire drug development process, with no clear beginning or end; instead, there should be continuous scrutiny and monitoring as a candidate progresses from discovery to development to market and beyond.

Abbreviations

API: active pharmaceutical ingredient; BCS: Biopharmaceutics Classification System; BDDCS: Biopharmaceutics Drug Disposition Classification System; CRU: Clinical Research Unit; FDA: Food and Drug Administration; HCl: hydrochloride; HIV-1: human immunodeficiency virus type 1; IP: intellectual property; LAI: long acting injection; OTC: over-the-counter; RH: relative humidity.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Both AN and RW contributed to the information gathering and writing of the manuscript. All authors read and approved the final manuscript.

Authors' information

Ann Newman

AN is currently a pharmaceutical consultant at Seventh Street Development Group and the Vice President of Scientific Development at Crystal Pharmatech, with over 25 years of large pharma and contract research experience. For ten years, AN performed characterization studies on a wide range of pharmaceutical systems at Bristol-Meyers Squibb, covering drug substance and product scale-up from late drug discovery to launch and manufacturing. After that, she became Vice President of Materials Science at SSCI, Inc., overseeing characterization of API and drug product samples, crystallization and polymorph screens, salt selections, quantitative assays, amorphous projects and problem solving for the pharmaceutical industry. As Vice President of Research and Development at Aptuit, AN instituted a company-wide R&D initiative over six global sites and covering areas such as API, preclinical (toxicology, safety, pharmacokinetics), formulation, solids, analytical, clinical packaging, and regulatory. She currently holds an adjunct faculty position in Industrial and Physical Pharmacy at Purdue University and is a collaborator on over 50 publications, 90 technical presentations, and 60 webinars.

Robert Wenslow

RW is currently Vice President of Business Development for Crystal Pharmatech. Prior to joining Crystal Pharmatech, RW spent 14 years at Merck & Co. His group supported, on average, 30 drug development projects per year. They contributed to salt and polymorph selection, crystallization development and optimization, preparation of registration documents, and specification setting in the area of solid-state support for both bulk drug substance and drug product. RW received his Ph.D. in Analytical Chemistry from The Pennsylvania State University; has presented as invited lecturer at over 15 conferences; has published over 25 peer reviewed journal articles, and is co-author on over 10 patents.

Received: 9 November 2015 Accepted: 17 February 2016
Published online: 25 February 2016

References

European medicines Agency, Assessment Report for Zypadhera, Doc Ref: 608654/2008. p 31. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000890/WC500054428.pdf. Accessed 23 Feb 2016)

Aungst BJ, Nguyen H, Taylor NJ, Bindra DS (2002) Formulation and food effects on the oral absorption of a poorly water soluble, highly permeable antiretroviral. J Pharm Sci 91:1390–1395

Benet LZ, Brocatelli F, Oprea TI (2011) BDDCS applied to over 900 drugs. AAPS J 13:519–547

Briggs CA, Jennings RA, Wade R, Harasawa K, Ichikawa S, Minohara K, Nakagawa S (1999) Crystalline [R-(R*,R*]-2-(4-difluorophenyl)-β,δ-dihydroxy-5-(1-methylehtyl)-3-phenyl-4-[phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (atorvastatin). US Patent 5,969,156, 19 Oct 1999

Byrn SR, Coates DA, Gushurst KS, Krzyzaniak JF, Li ZJ, Morrison HG, Park A, Vlahova PI (2003) Crystalline Forms of [R-(R*,R*]-2-(4-difluorophenyl)-β,δ-dihydroxy-5-(1-methylehtyl)-3-phenyl-4-[phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (2:1). US Patent 6,605,729, 12 Aug 2003

Campeta AM, Chekal BP, Abramov YA, Meenan PL, Henson MJ, Shi B, Singer RA, Horspool KR (2010) Development of a targeted polymorph screening approach for a complex polymorphic and highly solvating API. J Pharm Sci 99:3874–3886

Cavallari C, Santos BP, Fini A (2013) Olanzapine solvates. J Pharm Sci 102:4046–4056

Chue P, Chue J (2012) A review of olanzapine pamoate. Expert Opin Pharmacother 13:1661–1670

Citrome L (2009) Olanzapine pamoate: a stick in time? Int J Clin Pract 63:140–150

Crixivan Package Insert. (available at http://www.merck.com/product/usa/pi_circulars/c/crixivan/crixivan_pi.pdf. Accessed 23 Feb 2016)

Desikan S, Parsons RL, Davis WP, Ward JE, Marshall WJ, Toma PH (2005) Process development challenges to accommodate a late-appearing stable polymorph: a case study on the polymorphism and crystallization of a fast-track drug development compound. Org Proc Res Dev 9:933–942

Di Lorenzo R, Brogli A (2010) Profile of olanzapine long-acting injection for the maintenance treatment of adult patients with schizophrenia. Neuropsychiatr Dis Treat 6:573–581

Dunitz JD, Bernstein J (1995) Disappearing polymorphs. Acc Chem Res 28:193–200

Fish DN, North DS (2001) Gatifloxacin, an advanced 8-methoxy fluoroquinolone. Pharmacotherapy 21:35–39

Fukuda H, Hori S, Hiramatsu K (1998) Antibacterial activity of gatifloxacin (AM-1155, CG5501, BMS-206584), a newly developed fluoroquinolone, against sequentially acquired quinolone-resistant mutants and the *norA* transformant of *Staphylococcus aureus*. Antimicrob Agents Chemother 42:1917–1922

Gamble T, Sand P (2008) Patient perspectives in the management of overactive bladder, focus on transdermal oxybutynin. Patient Prefer Adherence 2:349–356

FDA approves over-the-counter Oxytrol for Women to treat overactive bladder. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm336815.htm. Accessed 23 Feb 2016

Lie JJ (2009) Triumph of the Heart. The Story of Statins. Oxford University Press, New York

Lin JH (1999) Role of pharmacokinetics in the discovery and development of indinavir. Adv Drug Deliv Rev 39:33–49

Lin JH, Ostovic D, Vacca JP (1998) Chapter 11. The integration of medicinal chemistry, drug metabolism, and pharmaceutical research and development in drug discovery and development. The story of Crxivan®, an HIV protease inhibitor. In: Borchardt RT, Freidinger RM, Sawyer TK, Smith PL (eds) Integration of Pharmaceutical Discovery and Development: Case Studies. Plenum Press, New York

Lui CY, Ostovic D, Katdare AV,Stemach C (2003) Dry granulation formulation for an HIV protease inhibitor. US Patent 6,645,961, 11 Nov 2003

Masuzawa K, Suzue S, Hirai K, Ishizaki T (1991) 8-Alkoxyquinolonecarboxylic acid and salts thereof. US patent 5,043,450, 27 Aug 1991

Matsumoto T, Hara M, Miyashita K, Kato Y (1999) 8-Alkoxyquinolonecarboxylic acid hydrate with excellet stability and process for producing the same. US patent 5,880, 283, 9 Mar 1999

Newman AW, Byrn SR (2003) Solid-state analysis of the active pharmaceutical ingredient in drug products. Drug Deliv Today 8:898–905

Oxytrol Package Insert. (available at http://pi.watson.com/data_stream.asp?product_group=1295&p=pi&language=E. Accessed 23 Feb 2016)

Paulekuhn GS, Dressman JB, Saal C (2007) Trends in active pharmaceutical ingredient salt selection based on analysis of the orange book database. J Med Chem 50:6665–6672

Pfizer Citizen Petition. Docket no 2005P-0452. 2005. (available at http://www.fda.gov/ohrms/dockets/dockets/05p0452/05p-0452-cp00001-01-vol1.pdf. Accessed 23 Feb 2016)

Raghaven KS, Ranadive SA, Gougoutas JZ, DiMarco JD, Parker WL, Davidovich M, Newman A (2002) Gatifloxacin pentahydrate. US patent 6,413, 969, 2 Jul 2002

Reutzel-Edens SM, Bush JK, Magee PA, Stephenson GA, Byrn SR (2003) Anhydrates and hydrates of olanzapine: crystallization, solid-state characterization, and structural relationships. Cryst Growth Des 3:897–907

Sathyan G, Chancellor MB, Gupta SK (2001) Effect of OROS® controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. Br J Clin Phrmacol 52:409–417

Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, Stryker R, Johnson P, Labriola DF, Farina D, Manion DJ, Ruiz NM (1999) Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 in adults. New Engl J Med 341:1865–1873

Tesslor L, Aronhime J, Lifshitz-Liron R, Maidan-Hanoch D, Hasson N (2003) Crystal forms of atorvastatin hemi-calcium and processes for their preparation as well as novel processes for preparing other forms. US Patent 7,256,212, 14 Aug 2007

Tully W (2003) Factory scale process for producing crystalline atorvastatin trihydrate hemi calcium salt. US patent 6,600,051 B2, 29 Jul 2003

Van Der Schaaf PA, Blatter F, Szelagiewicz M, Schoning K-U (2009) Crystalline Forms of Atorvastatin. US Patent 7,538,136, 26 May 2009

Wu C-Y, Benet LZ (2005) Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res 22:11–23

Yeh KC, Deutsch PJ, Haddix H, Hesney M, Hoagland V, Ju WD, Justice SJ, Osborne B, Sterrett AT, Stone JA, Woolf E, Waldman S (1998) Single-dose pharmacokinetics of indinavir and the effect of food. Antimicrob Agents Chemother 42:332–338

Zyprexa Relprevv Package Insert December 2014. (available at http://pi.lilly.com/us/zyprexa_relprevv.pdf. Accessed 23 Feb 2016)