IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. _____
	)	
AVADEL PHARMACEUTICALS PLC, AVADEL US HOLDINGS, INC., AVADEL SPECIALTY PHARMACEUTICALS, LLC, AVADEL LEGACY PHARMACEUTICALS, LLC, AVADEL MANAGEMENT CORPORATION and AVADEL CNS PHARMACUEITCALS LLC,	)	
	)	
Defendants.	)	

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Jazz Pharmaceuticals, Inc. ("Jazz Pharmaceuticals" or "Plaintiff"), by its undersigned attorneys, for its Complaint against Defendants Avadel Pharmaceuticals plc, Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC (collectively "Avadel" or "Defendants"), alleges as follows:

Nature of the Action

1. This is an action for patent infringement and for a declaratory judgement of patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.* and 28 U.S.C. §§ 2201 and 2202, arising from Avadel's filing of a New Drug Application ("NDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a sodium oxybate drug product prior to the expiration of United States Patent Nos. 8,731,963 (the "'963 patent"), 10,758,488 (the "'488 patent"), 10,813,885 (the "'885 patent"), 10,959,956

(the "'956 patent"), and 10,966,931 (the "'931 patent") owned by Jazz Pharmaceuticals (collectively, "the patents-in-suit").

The Parties

2. Plaintiff Jazz Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 3170 Porter Drive, Palo Alto, California 94304.

3. On information and belief, Defendant Avadel Pharmaceuticals plc is a corporation organized and existing under the laws of Ireland, having a principal place of business at 10 Earlsfort Terrace, Dublin 2, Ireland, D02 T380. On information and belief, Avadel Pharmaceuticals plc is in the business of, *inter alia*, developing, manufacturing, marketing, offering for sale, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC.

4. On information and belief, Defendant Avadel US Holdings, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 16640 Chesterfield Grove Road, Suite 200, Chesterfield, Missouri 63005. On information and belief, Avadel US Holdings, Inc. is in the business of, *inter alia*, developing, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC.

5. On information and belief, Avadel US Holdings, Inc. is a wholly-owned subsidiary of Avadel Pharmaceuticals plc.

6. On information and belief, Defendant Avadel Specialty Pharmaceuticals, LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 16640 Chesterfield Grove Road, Suite 200, Chesterfield, Missouri 63005. On information and belief, Avadel Specialty Pharmaceuticals, LLC is in the business of, *inter alia*, developing, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Avadel US Holdings, Inc., Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC.

7. On information and belief, Defendant Avadel Legacy Pharmaceuticals, LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 16640 Chesterfield Grove Road, Suite 200, Chesterfield, Missouri 63005. On information and belief, Avadel Legacy Pharmaceuticals, LLC is in the business of, *inter alia*, developing, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC.

8. On information and belief, Defendant Avadel Management Corporation is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 16640 Chesterfield Grove Road, Suite 200, Chesterfield, Missouri 63005. On information and belief, Avadel Management Corporation is in the business of, *inter alia*, developing, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical

products throughout the United States, including within this District, either on its own or through its affiliates, including Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, and Avadel CNS Pharmaceuticals LLC.

9. On information and belief, Defendant Avadel CNS Pharmaceuticals LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 16640 Chesterfield Grove Road, Suite 200, Chesterfield, Missouri 63005. On information and belief, Avadel CNS Pharmaceuticals LLC is in the business of, *inter alia*, developing, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products throughout the United States, including within this District, either on its own or through its affiliates, including Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, and Avadel Management Corporation.

10. On information and belief, Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC are wholly-owned subsidiaries of Avadel US Holdings, Inc.

11. On information and belief, following any FDA approval of their NDA for a sodium oxybate product, Defendants Avadel Pharmaceuticals plc, Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC will work in concert with one another to make, use, offer to sell, and/or sell the product that is the subject of their NDA for a sodium oxybate product throughout the United States, and/or import such a product into the United States.

Jurisdiction and Venue

12. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

13. On information and belief, Avadel Pharmaceuticals plc is subject to personal jurisdiction in Delaware because Avadel Pharmaceuticals plc has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court in Delaware. On information and belief, Avadel Pharmaceuticals plc manufactures, markets, offers for sale, and/or sells drug products throughout the United States and within the State of Delaware and, therefore, transacts business within the State of Delaware related to Plaintiff's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware.

14. On information and belief, Avadel US Holdings, Inc. is subject to personal jurisdiction in Delaware because Avadel US Holdings, Inc. has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court in Delaware. Avadel US Holdings, Inc. is a corporation organized and existing under the laws of the State of Delaware. On information and belief, Avadel US Holdings, Inc. manufactures, markets, imports, offers for sale, and/or sells drug products throughout the United States and within the State of Delaware and, therefore, transacts business within the State of Delaware related to Plaintiff's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware. On information and belief, Avadel US Holdings, Inc. is registered to do business in Delaware (business identification number 5123065) and has appointed Corporate Creations Network Inc., located at 3411 Silverside Road Tatnall, Building, Suite 104, Wilmington, Delaware 19810, as its registered agent for the receipt of service of process.

15. On information and belief, Avadel Specialty Pharmaceuticals, LLC is subject to personal jurisdiction in Delaware because Avadel Specialty Pharmaceuticals, LLC has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court in Delaware. Avadel Specialty Pharmaceuticals, LLC is a limited liability company organized and existing under the laws of the State of Delaware. On information and belief, Avadel Specialty Pharmaceuticals, LLC manufactures, markets, imports, offers for sale, and/or sells drug products throughout the United States and within the State of Delaware and, therefore, transacts business within the State of Delaware related to Plaintiff's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware. On information and belief, Avadel Specialty Pharmaceuticals, LLC is registered to do business in Delaware (business identification number 6507288) and has appointed Corporate Creations Network Inc., located at 3411 Silverside Road Tatnall, Building, Suite 104, Wilmington, Delaware 19810, as its registered agent for the receipt of service of process.

16. On information and belief, Avadel Legacy Pharmaceuticals, LLC is subject to personal jurisdiction in Delaware because Avadel Legacy Pharmaceuticals, LLC has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court in Delaware. Avadel Legacy Pharmaceuticals, LLC is a limited liability company organized and existing under the laws of the State of Delaware. On information and belief, Avadel Legacy Pharmaceuticals, LLC manufactures, markets, imports, offers for sale, and/or sells drug products throughout the United States and within the State of Delaware and, therefore, transacts business within the State of Delaware related to Plaintiff's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware. On information and belief, Avadel Legacy Pharmaceuticals, LLC is registered to do

business in Delaware (business identification number 4886228) and has appointed Corporate Creations Network Inc., located at 3411 Silverside Road Tatnall, Building, Suite 104, Wilmington, Delaware 19810, as its registered agent for the receipt of service of process.

17. On information and belief, Avadel Management Corporation is subject to personal jurisdiction in Delaware because Avadel Management Corporation has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court in Delaware. Avadel Management Corporation is a corporation organized and existing under the laws of the State of Delaware. On information and belief, Avadel Management Corporation manufactures, markets, imports, offers for sale, and/or sells drug products throughout the United States and within the State of Delaware and, therefore, transacts business within the State of Delaware related to Plaintiff's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware. On information and belief, Avadel Management Corporation is registered to do business in Delaware (business identification number 6201113) and has appointed Corporate Creations Network Inc., located at 3411 Silverside Road Tatnall, Building, Suite 104, Wilmington, Delaware 19810, as its registered agent for the receipt of service of process.

18. On information and belief, Avadel CNS Pharmaceuticals LLC is subject to personal jurisdiction in Delaware because Avadel CNS Pharmaceuticals LLC has purposely availed itself of the benefits and protections of Delaware's laws such that it should reasonably anticipate being haled into court in Delaware. Avadel CNS Pharmaceuticals LLC is a limited liability company organized and existing under the laws of the State of Delaware. On information and belief, Avadel CNS Pharmaceuticals LLC manufactures, markets, imports, offers for sale, and/or sells drug products throughout the United States and within the State of

Delaware and, therefore, transacts business within the State of Delaware related to Plaintiff's claims, and/or has engaged in systematic and continuous business contacts within the State of Delaware. On information and belief, Avadel CNS Pharmaceuticals LLC is registered to do business in Delaware (business identification number 7734658) and has appointed Corporate Creations Network Inc., located at 3411 Silverside Road Tatnall, Building, Suite 104, Wilmington, Delaware 19810, as its registered agent for the receipt of service of process.

19. On information and belief, Avadel Pharmaceuticals plc, Avadel US Holdings, Inc., Avadel Specialty Pharmaceuticals, LLC, Avadel Legacy Pharmaceuticals, LLC, Avadel Management Corporation, and Avadel CNS Pharmaceuticals LLC are agents and/or alter egos of one another and work in concert with respect to the regulatory approval, manufacturing, marketing, sale, and distribution of pharmaceutical products throughout the United States, including in this Judicial District.

20. On information and belief, by virtue of, *inter alia*, Defendants' continuous and systematic contacts with Delaware, including, but not limited to, the above-described contacts, and the actions on behalf of Defendants in connection with their NDA seeking FDA approval to commercially market a sodium oxybate drug product, this Court has personal jurisdiction over Defendants. These activities satisfy due process and confer personal jurisdiction over Defendants consistent with Delaware law.

21. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patents-In-Suit

22. On May 20, 2014, the USPTO duly and lawfully issued the '963 patent entitled, "Sensitive Drug Distribution System and Method." A copy of the '963 patent is attached hereto as Exhibit A.

23. On September 1, 2020, the USPTO duly and lawfully issued the '488 patent entitled, "Controlled Release Dosage Forms for High Dose, Water Soluble and Hygroscopic Drug Substances." A copy of the '488 patent is attached hereto as Exhibit B.

24. On October 27, 2020, the USPTO duly and lawfully issued the '885 patent entitled, "Controlled Release Dosage Forms for High Dose, Water Soluble and Hygroscopic Drug Substances." A copy of the '885 patent is attached hereto as Exhibit C.

25. On March 30, 2021, the USPTO duly and lawfully issued the '956 patent entitled, "Controlled Release Dosage Forms for High Dose, Water Soluble and Hygroscopic Drug Substances." A copy of the '956 patent is attached hereto as Exhibit D.

26. On April 6, 2021, the USPTO duly and lawfully issued the '931 patent entitled, "Controlled Release Dosage Forms for High Dose, Water Soluble and Hygroscopic Drug Substances." A copy of the '931 patent is attached hereto as Exhibit E.

27. The claims of the patents-in-suit cover, *inter alia*, methods of use and administration of sodium oxybate or pharmaceutical compositions containing sodium oxybate. Jazz Pharmaceuticals owns the patents-in-suit.

Background

28. Jazz Pharmaceuticals holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for sodium oxybate oral solution (NDA No. 21-196), which it sells under the trade name XYREM®. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the '963 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to XYREM®.

29. Pursuant to its FDA-approved labeling, XYREM® is available only through a restricted distribution program called the XYWAV™ and XYREM® Risk Evaluation and

Mitigation Strategy ("REMS") because of the risks of central nervous system depression and abuse, misuse, and diversion.[1]

30. The XYWAV™ and XYREM® REMS is covered by the '963 patent.

Acts Giving Rise to This Suit

31. Pursuant to Section 505(b)(2) of the FFDCA, Avadel filed an NDA ("Avadel's NDA") seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of a sodium oxybate product ("Avadel's Proposed Product"), before the patents-in-suit expire.

32. On December 16, 2020, Avadel announced the submission of its NDA to the FDA. On information and belief, on February 26, 2021, the FDA notified Avadel of formal acceptance of Avadel's NDA with an assigned Prescription Drug User Fee Act ("PDUFA") target action date of October 15, 2021.[2]

33. Avadel has identified its Proposed Product using the code name FT218.[3]

34. Avadel has acknowledged that a REMS will be required for Avadel's Proposed Product.[4]

35. Under applicable laws and regulations, the FDA will not approve Avadel's Proposed Product without a REMS.

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[1] XYWAV™ (calcium, magnesium, potassium, and sodium oxybates) oral solution is a product that contains 92% less sodium than XYREM®.

[2] *See* Avadel's 2020 Annual Report at p. 7 (available at https://www.sec.gov/ix?doc=/Archives/edgar/data/1012477/000101247721000004/avdl-20201231.htm)

[3] *See id.*

[4] *See id.* at p. 29; *see also* Avadel's May 10, 2021 Q1 2021 Earnings Call Transcript, attached hereto as Exhibit F.

36. Under applicable laws and regulations, the FDA will not approve professional labeling (also called a package insert) for Avadel's Proposed Product without reference to a REMS in that professional labeling.

37. The FDA-approved REMS for sodium oxybate are covered by the '963 patent.

38. On information and belief, to be approvable by the FDA, the REMS for Avadel's Proposed Product must include protections required in the currently-approved REMS for sodium oxybate products that are covered by the '963 patent.

39. On information and belief, the REMS for Avadel's Proposed Product is covered by the '963 patent.

40. Avadel has published data comparing the pharmacokinetic properties of Avadel's Proposed Product with twice-nightly sodium oxybate (*i.e.*, XYREM®).[5]

41. Avadel owns U.S. Patent No. 10,272,062 ("Avadel's '062 patent") entitled "Modified Release Gamma-Hydroxybutyrate Formulations Having Improved Pharmacokinetics," attached hereto as Exhibit H.

42. On information and belief, Avadel's published data concerning the pharmacokinetic properties of Avadel's Proposed Product correspond to the Examples of Avadel's '062 patent.

43. At least Example 1 and Example 1bis of Avadel's '062 patent are covered by Jazz Pharmaceuticals' '488, '885, '956, and '931 patents.

44. On information and belief, Avadel has made, and continues to make, substantial preparation in the United States to manufacture, offer to sell, sell, and/or import Avadel's

[5] Seiden, et al., *Pharmacokinetics of FT218, a Once-Nightly Sodium Oxybate Formulation in Healthy Adults*, Clin. Ther. 2021 Feb 22; S0149-2918(21)00044-8; doi: 10.1016/j.clinthera.2021.01.017, attached hereto as Exhibit G.

Proposed Product prior to expiration of the patents-in-suit.[6] Avadel recently confirmed that is has "accelerated" its launch planning for its Proposed Product.[7]

45. On information and belief, Avadel continues to seek approval of its NDA from the FDA and, if approved, intends to commercially have Avadel's Proposed Product manufactured for marketing and sale in the United States.

Count I: Infringement of the '963 Patent

46. Plaintiff repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

47. Avadel, by the submission of its NDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '963 patent.

48. Avadel's NDA has been pending before the FDA since at least December 16, 2020, the date that Avadel announced the submission of its NDA to the FDA.

49. Avadel's submission of its NDA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '963 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

50. There is a justiciable controversy between the parties hereto as to the infringement of the '963 patent.

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[6] *See* Avadel's 2020 Annual Report at pp. 18, 29, 48 (available at https://www.sec.gov/ix?doc=/Archives/edgar/data/1012477/000101247721000004/avdl-20201231.htm); *see also* Avadel's March 9, 2021 Q4 2020 Earnings Call Transcript, attached hereto as Exhibit I.

[7] *See* Avadel's May 10, 2021 Q1 2021 Earnings Call Transcript, attached hereto as Exhibit F.

51. Avadel has made, and will continue to make, substantial preparation in the United States to manufacture, offer to sell, sell and/or import Avadel's Proposed Product prior to the expiration of the '963 patent.

52. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will infringe one or more claims of the '963 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States.

53. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will induce infringement of one or more claims of the '963 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, upon FDA approval of Avadel's NDA, Avadel will encourage acts of direct infringement with knowledge of the '963 patent and knowledge that its acts are encouraging infringement, with specific intent to induce infringement of the '963 patent.

54. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will contributorily infringe one or more claims of the '963 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, Avadel has had and continues to have knowledge that Avadel's Proposed Product is especially adapted for a use that infringes one or more claims of the '963 patent and that there is no substantial non-infringing use for Avadel's Proposed Product.

55. Plaintiff will be substantially and irreparably damaged and harmed if Avadel's infringement of the '963 patent is not enjoined.

56. Plaintiff is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Avadel's Proposed Product prior to expiration of the '963 patent by Avadel will constitute direct infringement, induced infringement, and/or contributory infringement of the '963 patent.

57. Plaintiff does not have an adequate remedy at law.

58. This case is an exceptional one, and Plaintiff is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '488 Patent

59. Plaintiff repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

60. Avadel, by the submission of its NDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '488 patent.

61. Avadel's NDA has been pending before the FDA since at least December 16, 2020, the date that Avadel announced the submission of its NDA to the FDA.

62. Avadel's submission of its NDA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '488 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

63. There is a justiciable controversy between the parties hereto as to the infringement of the '488 patent.

64. Avadel has made, and will continue to make, substantial preparation in the United States to manufacture, offer to sell, sell and/or import Avadel's Proposed Product prior to the expiration of the '488 patent.

65. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will infringe one or more claims of the '488 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States.

66. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will induce infringement of one or more claims of the '488 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, upon FDA approval of Avadel's NDA, Avadel will encourage acts of direct infringement with knowledge of the '488 patent and knowledge that its acts are encouraging infringement, with specific intent to induce infringement of the '488 patent.

67. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will contributorily infringe one or more claims of the '488 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, Avadel has had and continues to have knowledge that Avadel's Proposed Product is especially adapted for a use that infringes one or more claims of the '488 patent and that there is no substantial non-infringing use for Avadel's Proposed Product.

68. Plaintiff will be substantially and irreparably damaged and harmed if Avadel's infringement of the '488 patent is not enjoined.

69. Plaintiff is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Avadel's Proposed Product prior to expiration of

the ’488 patent by Avadel will constitute direct infringement, induced infringement, and/or contributory infringement of the ’488 patent.

70. Plaintiff does not have an adequate remedy at law.

71. This case is an exceptional one, and Plaintiff is entitled to an award of its reasonable attorneys’ fees under 35 U.S.C. § 285.

Count III: Infringement of the ’885 Patent

72. Plaintiff repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

73. Avadel, by the submission of its NDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel’s Proposed Product, prior to the expiration of the ’885 patent.

74. Avadel’s NDA has been pending before the FDA since at least December 16, 2020, the date that Avadel announced the submission of its NDA to the FDA.

75. Avadel’s submission of its NDA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel’s Proposed Product, prior to the expiration of the ’885 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

76. There is a justiciable controversy between the parties hereto as to the infringement of the ’885 patent.

77. Avadel has made, and will continue to make, substantial preparation in the United States to manufacture, offer to sell, sell and/or import Avadel’s Proposed Product prior to the expiration of the ’885 patent.

78. Unless enjoined by this Court, upon FDA approval of Avadel’s NDA, Avadel will infringe one or more claims of the ’885 patent under 35 U.S.C. § 271(a), including at least claim

1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States.

79. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will induce infringement of one or more claims of the '885 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, upon FDA approval of Avadel's NDA, Avadel will encourage acts of direct infringement with knowledge of the '885 patent and knowledge that its acts are encouraging infringement, with specific intent to induce infringement of the '885 patent.

80. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will contributorily infringe one or more claims of the '885 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, Avadel has had and continues to have knowledge that Avadel's Proposed Product is especially adapted for a use that infringes one or more claims of the '885 patent and that there is no substantial non-infringing use for Avadel's Proposed Product.

81. Plaintiff will be substantially and irreparably damaged and harmed if Avadel's infringement of the '885 patent is not enjoined.

82. Plaintiff is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Avadel's Proposed Product prior to expiration of the '885 patent by Avadel will constitute direct infringement, induced infringement, and/or contributory infringement of the '885 patent.

83. Plaintiff does not have an adequate remedy at law.

84. This case is an exceptional one, and Plaintiff is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '956 Patent

85. Plaintiff repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

86. Avadel, by the submission of its NDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '956 patent.

87. Avadel's NDA has been pending before the FDA since at least December 16, 2020, the date that Avadel announced the submission of its NDA to the FDA.

88. Avadel's submission of its NDA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '956 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

89. There is a justiciable controversy between the parties hereto as to the infringement of the '956 patent.

90. Avadel has made, and will continue to make, substantial preparation in the United States to manufacture, offer to sell, sell and/or import Avadel's Proposed Product prior to the expiration of the '956 patent.

91. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will infringe one or more claims of the '956 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States.

92. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will induce infringement of one or more claims of the '956 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, upon FDA approval of Avadel's NDA, Avadel will encourage acts of direct infringement with knowledge of the '956 patent and knowledge that its acts are encouraging infringement, with specific intent to induce infringement of the '956 patent.

93. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will contributorily infringe one or more claims of the '956 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, Avadel has had and continues to have knowledge that Avadel's Proposed Product is especially adapted for a use that infringes one or more claims of the '956 patent and that there is no substantial non-infringing use for Avadel's Proposed Product.

94. Plaintiff will be substantially and irreparably damaged and harmed if Avadel's infringement of the '956 patent is not enjoined.

95. Plaintiff is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Avadel's Proposed Product prior to expiration of the '956 patent by Avadel will constitute direct infringement, induced infringement, and/or contributory infringement of the '956 patent.

96. Plaintiff does not have an adequate remedy at law.

97. This case is an exceptional one, and Plaintiff is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '931 Patent

98. Plaintiff repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

99. Avadel, by the submission of its NDA to the FDA, has indicated that it seeks approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '931 patent.

100. Avadel's NDA has been pending before the FDA since at least December 16, 2020, the date that Avadel announced the submission of its NDA to the FDA.

101. Avadel's submission of its NDA to engage in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Avadel's Proposed Product, prior to the expiration of the '931 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

102. There is a justiciable controversy between the parties hereto as to the infringement of the '931 patent.

103. Avadel has made, and will continue to make, substantial preparation in the United States to manufacture, offer to sell, sell and/or import Avadel's Proposed Product prior to the expiration of the '931 patent.

104. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will infringe one or more claims of the '931 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States.

105. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will induce infringement of one or more claims of the '931 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's

Proposed Product in the United States. On information and belief, upon FDA approval of Avadel's NDA, Avadel will encourage acts of direct infringement with knowledge of the '931 patent and knowledge that its acts are encouraging infringement, with specific intent to induce infringement of the '931 patent.

106. Unless enjoined by this Court, upon FDA approval of Avadel's NDA, Avadel will contributorily infringe one or more claims of the '931 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Avadel's Proposed Product in the United States. On information and belief, Avadel has had and continues to have knowledge that Avadel's Proposed Product is especially adapted for a use that infringes one or more claims of the '931 patent and that there is no substantial non-infringing use for Avadel's Proposed Product.

107. Plaintiff will be substantially and irreparably damaged and harmed if Avadel's infringement of the '931 patent is not enjoined.

108. Plaintiff is entitled to a declaratory judgment that future commercial manufacture, use, offer for sale, sale, and/or importation of Avadel's Proposed Product prior to expiration of the '931 patent by Avadel will constitute direct infringement, induced infringement, and/or contributory infringement of the '931 patent.

109. Plaintiff does not have an adequate remedy at law.

110. This case is an exceptional one, and Plaintiff is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

(A) A Judgment be entered that Avadel has infringed the patents-in-suit by submitting its NDA for its sodium oxybate drug product;

(B) A Judgment be entered that Avadel has infringed, and that Avadel's making, using, selling, offering to sell, and/or importing Avadel's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of Avadel's NDA for its sodium oxybate drug product be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Avadel and its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from making, using, selling, offering to sell, and/or importing Avadel's Proposed Product until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(E) A permanent injunction be issued, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Avadel, its officers, agents, attorneys and employees, and those acting in privity and/or concert with them, from practicing any methods as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Plaintiff is or becomes entitled;

(F) A Declaration that the commercial manufacture, use, sale, or offer for sale, and/or importation into the United States of Avadel's Proposed Product will directly infringe, induce, and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Avadel has committed any acts with respect to the compositions or methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), that Plaintiff be awarded damages for such acts;

(H) If Avadel engages in the commercial manufacture, use, sale, or offer for sale, or importation into the United States of Avadel's Proposed Product prior to the expiration of the patents-in-suit, a Judgment awarding damages to Plaintiff resulting from such infringement, together with interest;

(I) Attorneys' fees in this action as an exceptional case pursuant to 35 U.S.C. § 285;

(J) Costs and expenses in this action; and

(K) Such further and other relief as this Court may deem just and proper.

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May 12, 2021

EXHIBIT A

US008731963B1

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

(10) **Patent No.: US 8,731,963 B1**
(45) **Date of Patent: *May 20, 2014**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Shorewood, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/592,202**

(22) Filed: **Aug. 22, 2012**

Related U.S. Application Data

(63) Continuation of application No. 13/013,680, filed on Jan. 25, 2011, now abandoned, which is a continuation of application No. 12/704,097, filed on Feb. 11, 2010, now Pat. No. 7,895,059, which is a continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2012.01)

(52) **U.S. Cl.**
USPC **705/2**; 705/3; 707/803

(58) **Field of Classification Search**
USPC 707/803; 705/2, 3
See application file for complete search history.

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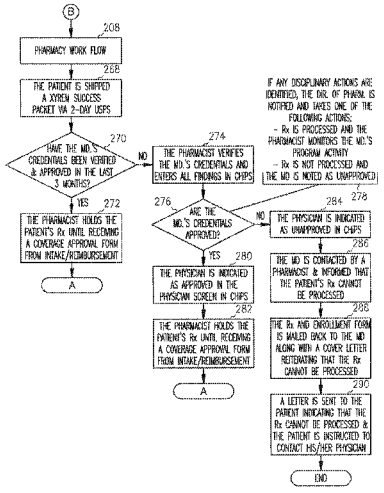
Primary Examiner — Lena Najarian
(74) *Attorney, Agent, or Firm* — Schwegman Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

28 Claims, 16 Drawing Sheets



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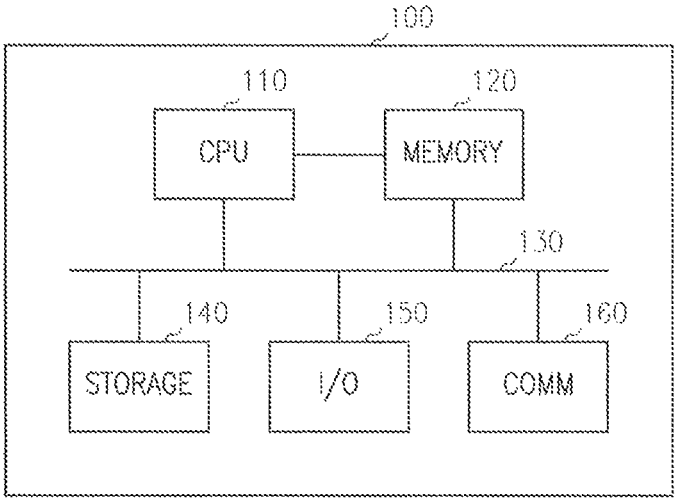

FIG. 1

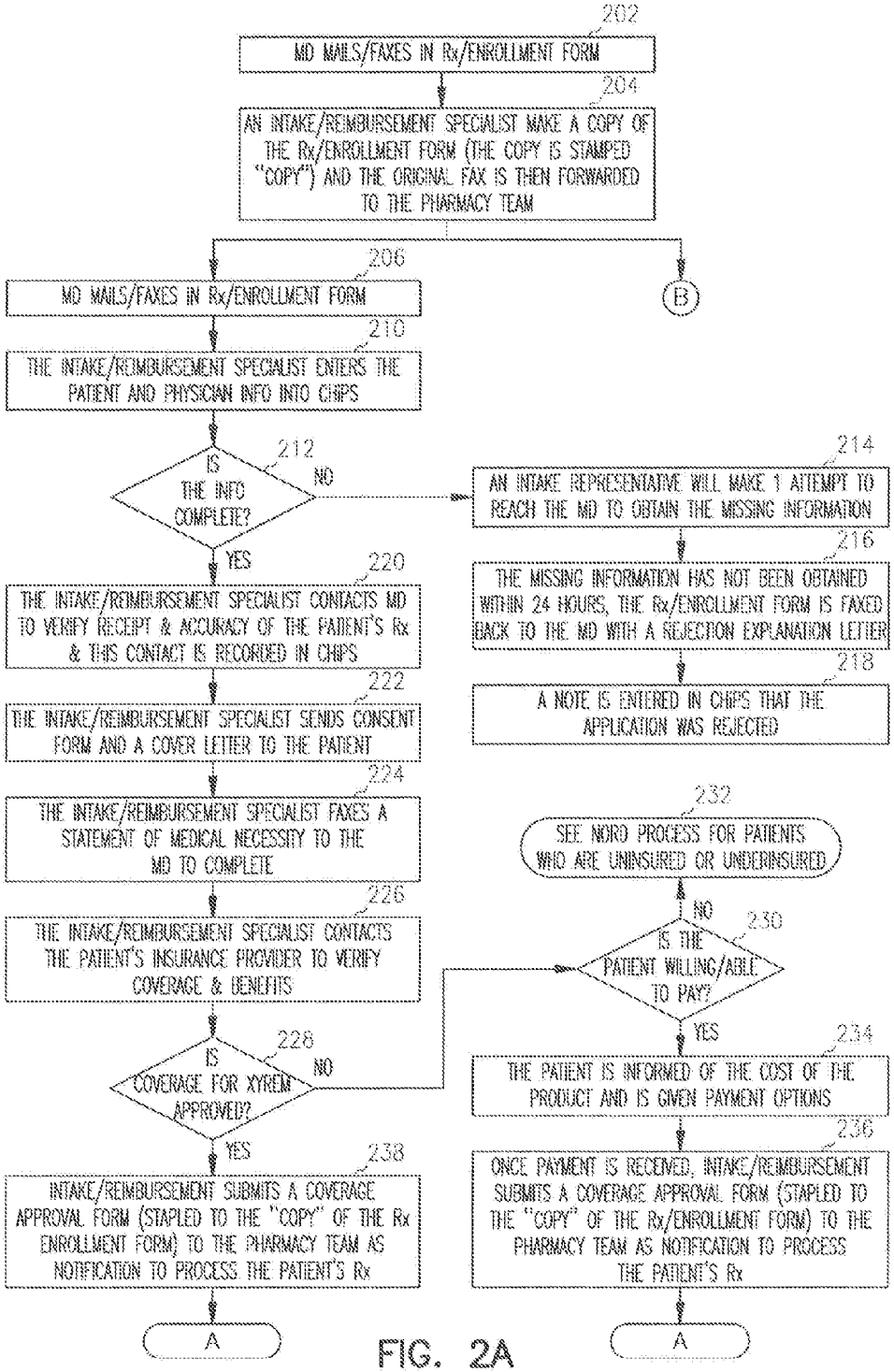
202
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
YES
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
230
IS THE PATIENT WILLING/ABLE TO PAY?
NO
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

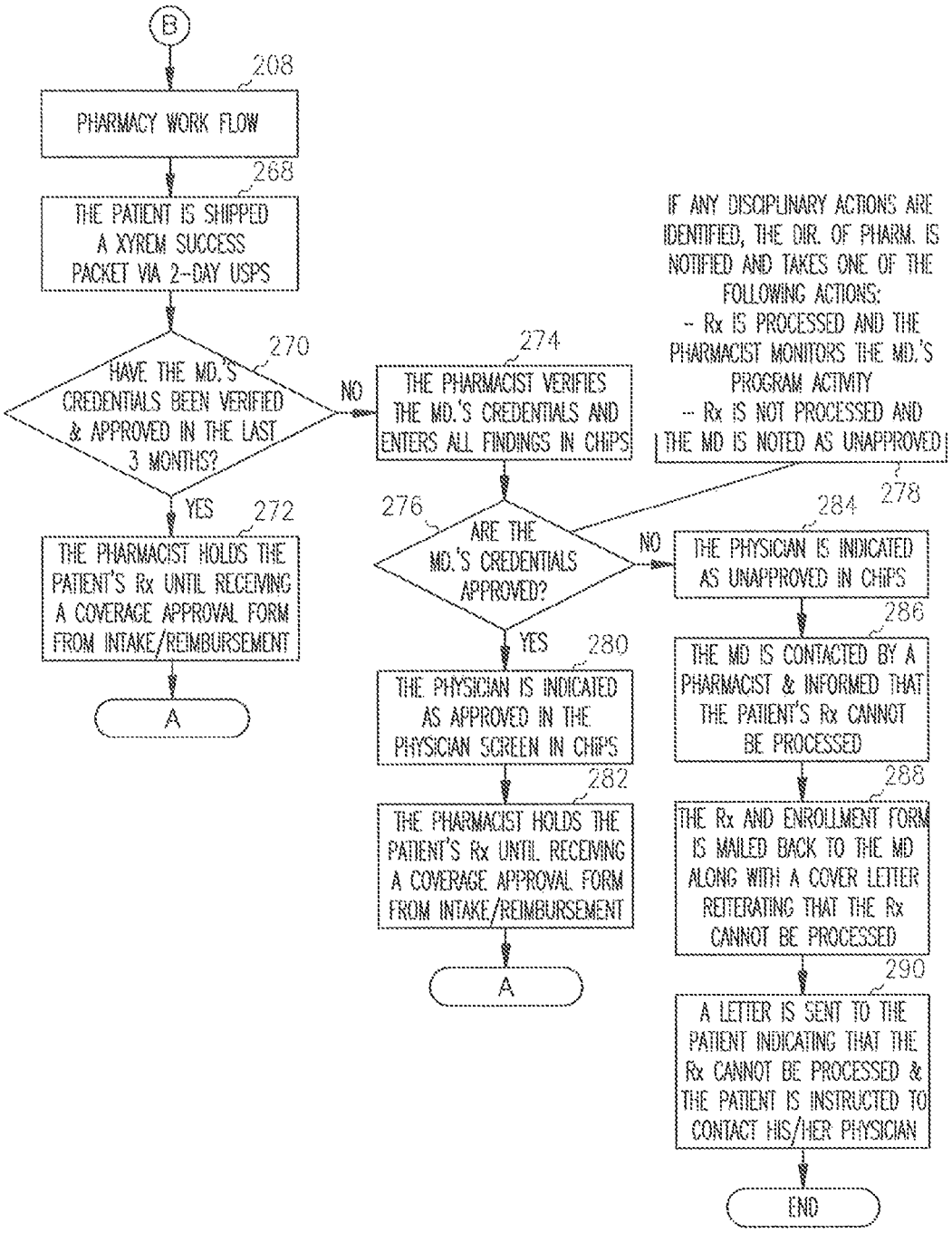
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
278
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
-- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHIPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

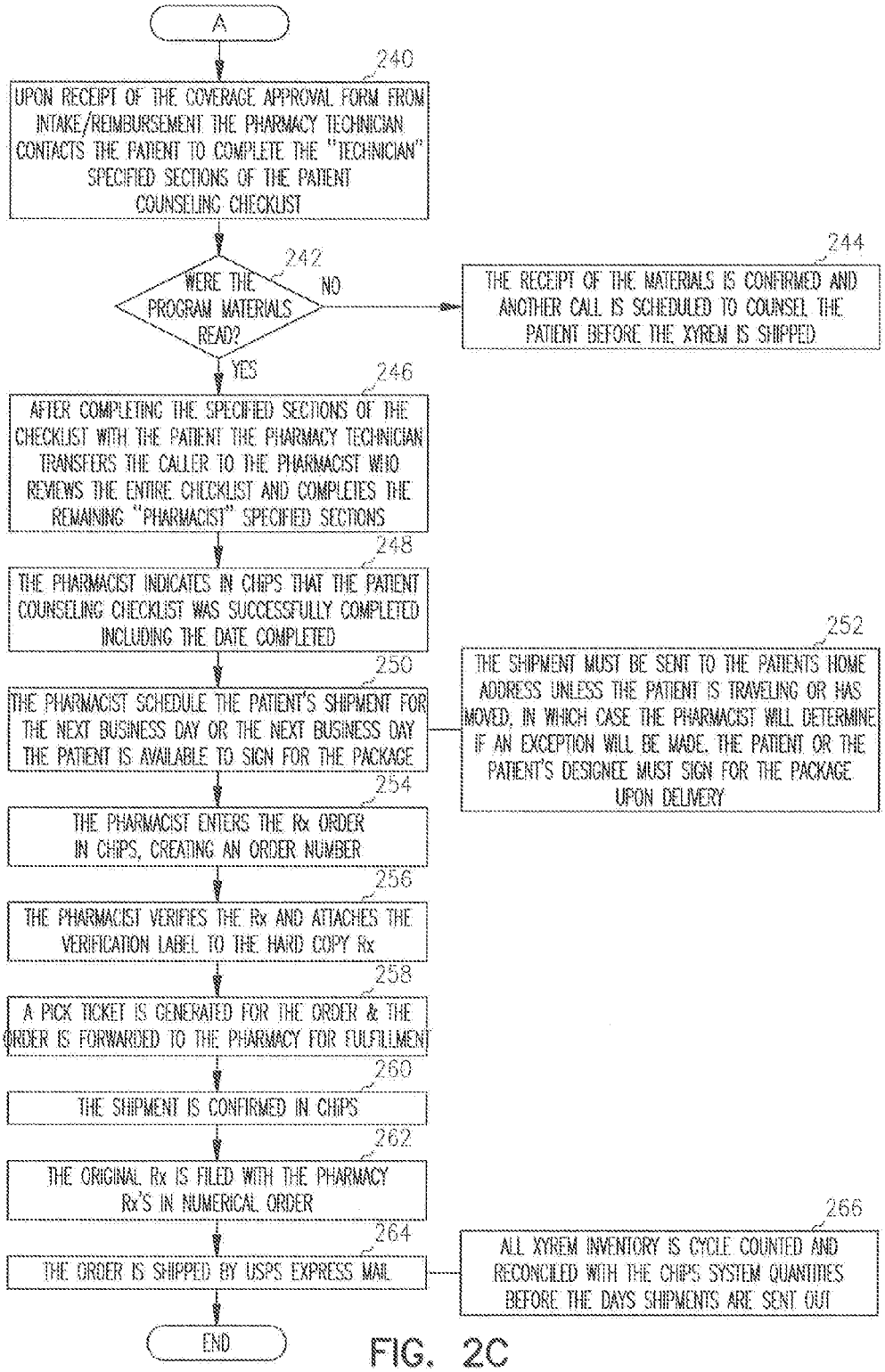
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

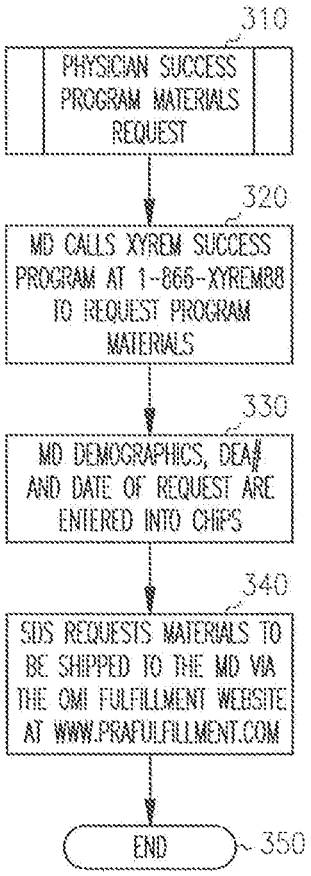
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

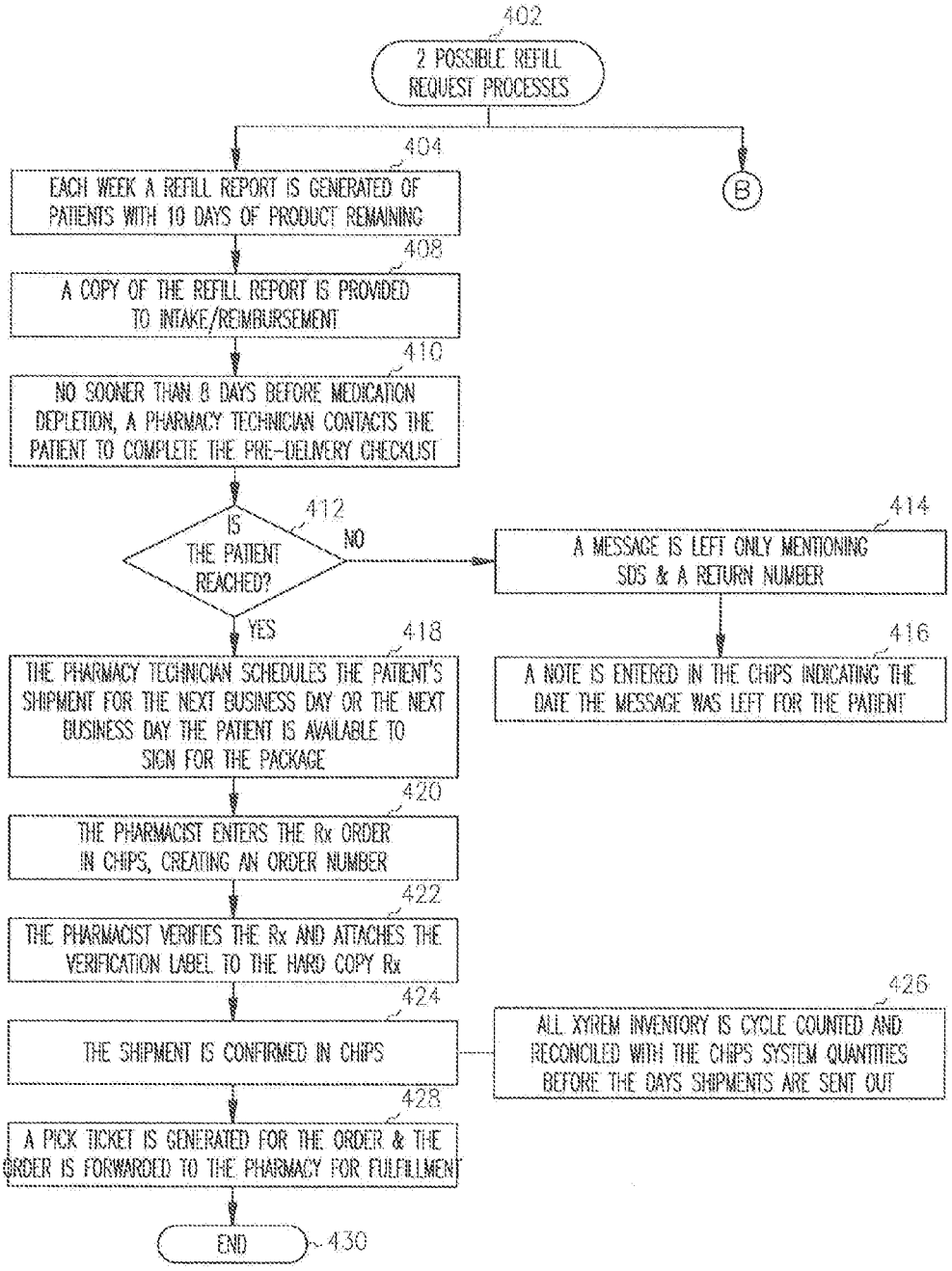
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SDS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

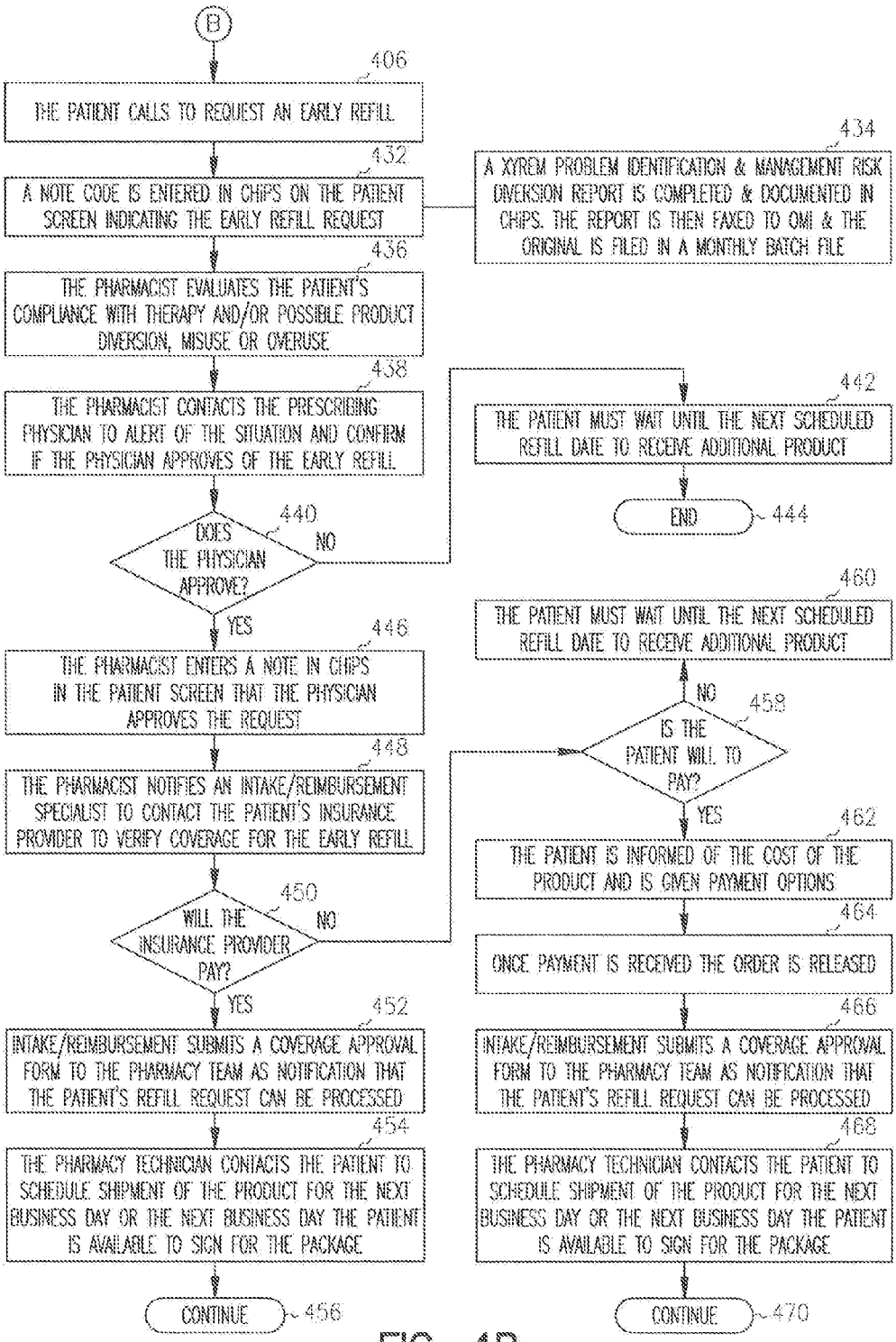
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYROM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
YES
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
NO
458
IS THE PATIENT WILL TO PAY?
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
470

FIG. 4B

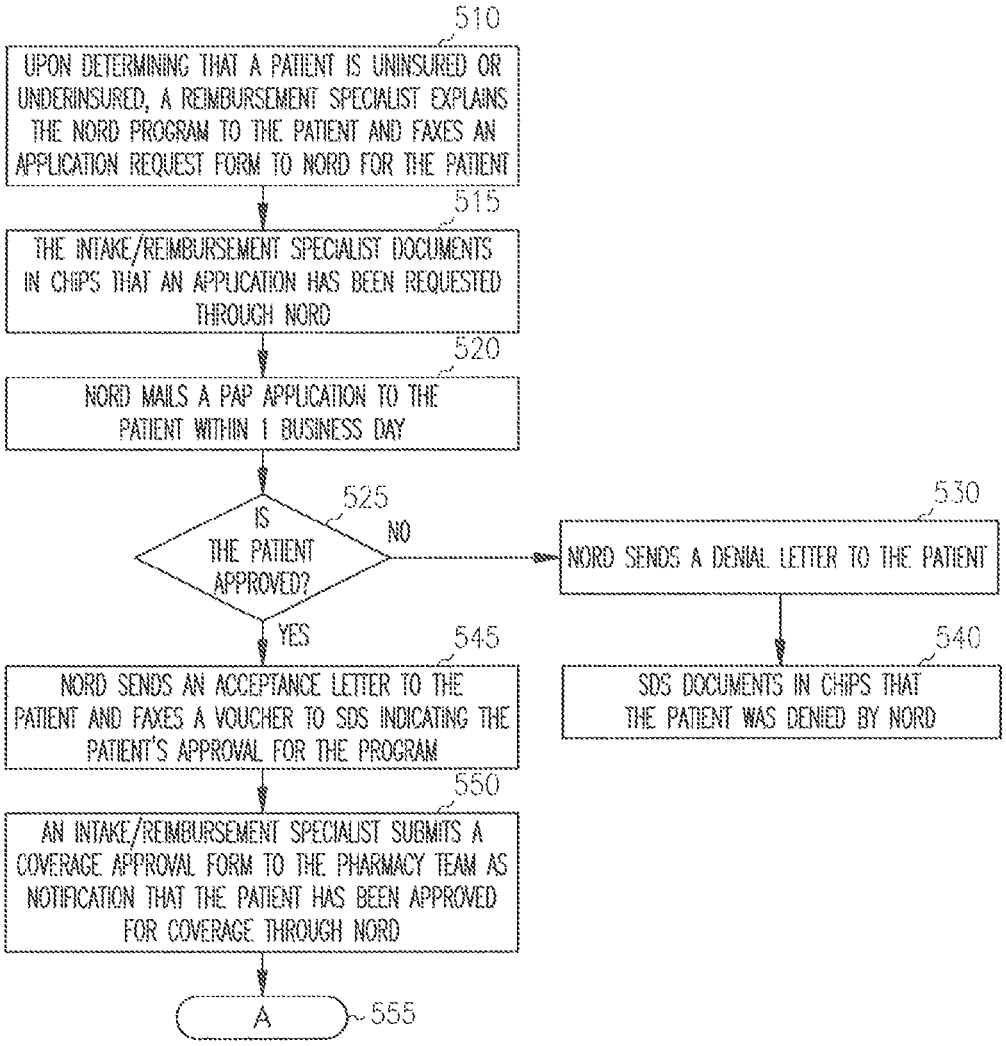
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

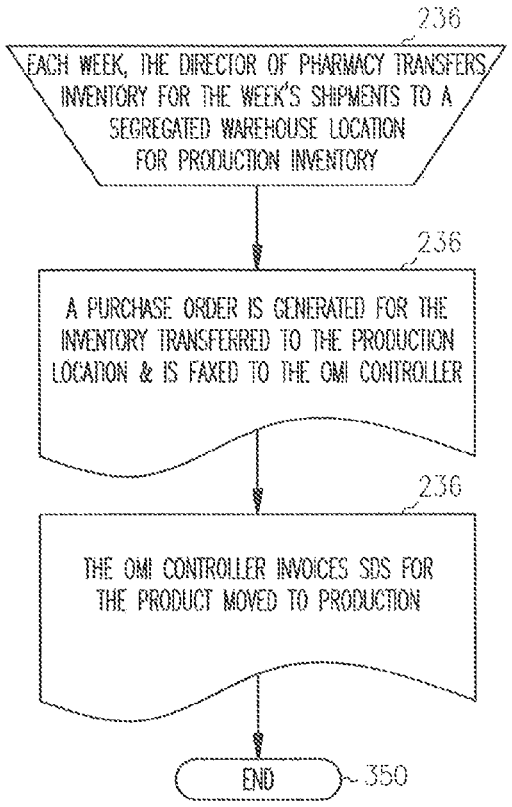

FIG. 6

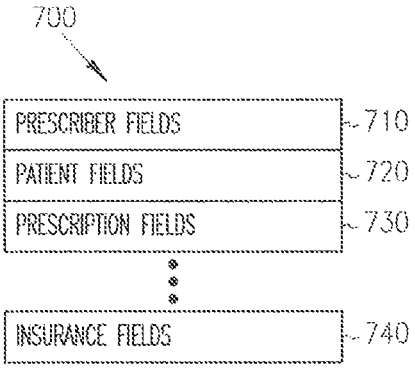

FIG. 7

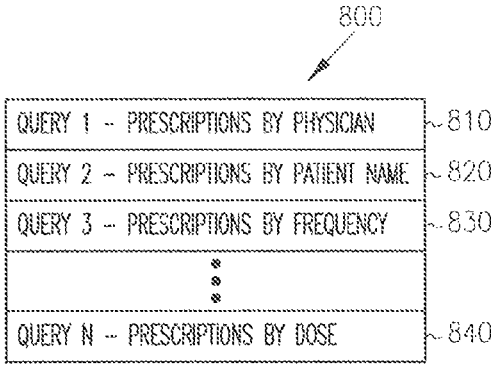

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION			
PRESCRIBER'S NAME:		OFFICE CONTACT:	
STREET ADDRESS:			
CITY:	STATE:		ZIP:
PHONE:	FAX:		
LICENSE NUMBER:	DEA NUMBER:		
MD SPECIALTY:			

PRESCRIPTION FORM			
PATIENT NAME:	SS#:	DOB:	SEX M / F
ADDRESS:			
CITY:	STATE:	ZIP:	

Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: ..... MONTHS SUPPLY

SIG: TAKE ..... CMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER

REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)

..... DATE: ...../...../.....

PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX	TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM

☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.

☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.

☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION			
BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT			
DAY #:		EVENING #:	
INSURANCE COMPANY NAME:		PHONE #:	
INSURED'S NAME:		RELATIONSHIP TO PATIENT:	
IDENTIFICATION NUMBER:		POLICY/GROUP NUMBER:	
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER:		POLICY #:	GROUP:

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744

FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9

1000

PATIENT ASSISTANCE APPLICATION REQUEST FORM

DATE:

TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS

FAX #: 203-798-2291

PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:

PATIENT NAME .....

ADDRESS .....

.....

.....

TELEPHONE: ( ) .....

PATIENT DOSAGE: _____ (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF ..... (GRAMS)

_____ BOTTLES (THREE MONTHS SUPPLY)

BACKGROUND INFORMATION:

.....

.....

.....

.....

.....

.....

FIG. 10

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM 1100

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

CASE CODE: ********

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml btl	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

1200

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....

ICD-9: .....

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): .....

PHYSICIAN'S SIGNATURE: ..... DATE: .....

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF RxS SHIPPED WITH 1, 2, 3, 4 ETC. DAYS FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY			
# OF PHYSICIAN SUCCESS PACKETS SHIPPED			X
# OF COMPLETED SHIPMENTS			X
# OF INCOMPLETE SHIPMENTS AND REASON			X
# OF SHIPPING ERRORS			X
# OF PAP SHIPMENTS			X
# OF PAP APPLICATIONS			X
# OF PAP APPROVALS			X
# OF CANCELED ORDERS			X
# OF USPS ERRORS			X
INVENTORY			X
# OF RETURNED PRODUCTS AND REASON			X
# OF OUTDATED BOTTLES OF PRODUCT			X
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY			X
# OF UNITS RECEIVED			X
LOTS RECEIVED			X
REIMBURSEMENT			X
# OF PENDED AND WHY			X
# OF APPROVALS			X
# OF DENIALS			X
# OF REJECTIONS			X
PAYOR TYPES			X

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE			
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application a Continuation of U.S. application Ser. No. 13/013,680, filed on Jan. 25, 2011, which is a Continuation of U.S. application Ser. No. 12/704,097, filed on Feb. 11, 2010 and issued on Feb. 22, 2011 as U.S. Pat. No. 7,895,059, which is a Continuation of U.S. application Ser. No. 10/322,348, filed on Dec. 17, 2002 and issued on Feb. 23, 2010 as U.S. Pat. No. 7,668,730, which applications are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized

to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in

which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved

at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery **30** checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment

options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor configured to:

process a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug; and

reconcile inventory of the prescription drug before the shipments for a day or other time period are sent by using

said database query to identify information in the prescription fields and patient fields;

wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

2. The system of claim **1**, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

3. The system of claim **1**, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

4. The system of claim **1**, wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that is associated with the company.

5. The system of claim **1**, wherein an exclusive central pharmacy controls the single computer database.

6. The system of claim **1** wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

7. The system of claim **1**, wherein the single computer database comprises a relational database.

8. The system of claim **1**, wherein the single computer database is distributed among multiple computers and the database query operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

9. The system of claim **1**, wherein the data processor is configured to initiate an inquiry to a prescriber when one or more prescription fields, patient fields, or prescriber fields are incomplete in the computer database.

10. The system of claim **1**, wherein the data processor is configured to process a third database query that identifies an expected date for a refill of the prescription drug.

11. The system of claim **10**, wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription.

12. The system of claim **11**, wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug.

13. The system of claim **1**, wherein the database schema further contains and interrelates insurance fields, wherein the insurance fields, contained within the database schema, store information sufficient to identify an insurer to be contacted for payment for prescription drugs of an associated patient.

14. The system of claim **1**, wherein the single computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug; wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

15. The system of claim **14**, wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

16. The system of claim **15**, wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug.

17. The system of claim **1**, wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

18. The system of claim **17**, wherein the data processor is used to add further controls until approval is obtained.

19. The system of claim **18**, wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

20. The system of claim **1**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

21. The system of claim **1**, wherein the single computer database comprises an exclusive computer database of the company that obtained approval for distribution of the prescription drug, wherein all prescriptions for the company's prescription drug are stored only in the exclusive computer database of the company, and wherein the company's prescription drug is sold or distributed by the company using only the exclusive computer database of the company.

22. The system of claim **1**, wherein the single computer database comprises a single computer database of the company that obtained approval for distribution of the prescription drug, wherein the prescription fields store all prescription requests, for all patients being prescribed the company's prescription drug, only in the single computer database of the company, from all physicians or other prescribers allowed to prescribe the company's prescription drug, such that all prescriptions for the company's prescription drug are processed using only the single computer database of the company.

23. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor for processing a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said database query identifying information in the prescription fields and patient fields for reconciling inventory of the prescription drug before the shipments for a day or other time period are sent, wherein an inventory reconciliation is performed where current inventory is counted and reconciled with database quantities before shipments for a day or other time period are sent, and wherein the data processor is configured to selectively block shipment of the prescription drug based on the inventory reconciliation;

wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

24. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

one or more computer memories for storing a central computer database of the company that obtained approval for distribution of the prescription drug, for receiving prescriptions from any and all patients being prescribed the company's prescription drug, said central computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said central computer database being distributed over multiple computers;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are authorized to prescribe the company's prescription drug;

one or more data processors for processing one or more database queries that operate over data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said one or more database queries checking for abuse within the central computer database, wherein the filling of the prescriptions is authorized for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and prescriber and if there is a record of such incidents, the central computer database indicates that such incidents have been investigated, and the central computer database indicates that such incidents do not involve abuse, misuse or diversion.

25. The system of claim **24**, wherein the one or more database queries are processed by the one or more data processors for identifying: that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

26. The system of claim **24**, where the central computer database is distributed among multiple computers, and where the one or more database queries operate over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

27. The system of claim **24**, wherein the central computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug;

wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

28. The system of claim **24**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,731,963 B1
APPLICATION NO. : 13/592202
DATED : May 20, 2014
INVENTOR(S) : Reardan et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

ON THE TITLE PAGE:

On page 2, in column 2, under "Other Publications", line 1, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 24, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 42, delete "mailed" and insert --filed--, therefor

On page 2, in column 2, under "Other Publications", line 54, delete "mailed" and insert --filed--, therefor

On page 3, in column 2, under "Other Publications", line 54, delete "Sodiium" and insert --Sodium--, therefor

On page 3, in column 2, under "Other Publications", line 57, delete "Sodiium" and insert --Sodium--, therefor

IN THE DRAWINGS:

On sheet 9 of 16, Fig. 6, delete "236" and insert --610--, therefor

On sheet 9 of 16, Fig. 6, delete "236" and insert --612--, therefor

On sheet 9 of 16, Fig. 6, delete "236" and insert --630--, therefor

Signed and Sealed this
Eighteenth Day of November, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

On sheet 9 of 16, Fig. 6, delete "350" and insert --640--, therefor

On sheet 12 of 16, Fig. 11, delete "XYREEM" and insert --XYREM--, therefor

IN THE SPECIFICATION:

In column 4, line 21, delete "RX/enrollment" and insert --Rx/enrollment--, therefor

In column 6, line 16, delete "302" and insert --402--, therefor

In column 6, line 25, after "pre-delivery", delete "30", therefor

IN THE CLAIMS:

In column 11, line 14, in Claim 24, after "drug,", insert --and--, therefor

(12) **INTER PARTES REVIEW CERTIFICATE** (1148th)
United States Patent
Reardan et al.

(10) **Number: US 8,731,963 K1**
(45) **Certificate Issued: Apr. 3, 2019**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**; **Patti A. Engel**; **Bob Gagne**

(73) Assignee: **Jazz Pharmaceuticals, Inc.**

Trial Number:

IPR2015-01903 filed Sep. 14, 2015

Inter Partes Review Certificate for:

Patent No.: **8,731,963**
Issued: **May 20, 2014**
Appl. No.: **13/592,202**
Filed: **Aug. 22, 2012**

The results of IPR2015-01903 are reflected in this inter partes review certificate under 35 U.S.C. 318(b).

INTER PARTES REVIEW CERTIFICATE
U.S. Patent 8,731,963 K1
Trial No. IPR2015-01903
Certificate Issued Apr. 3, 2019

AS A RESULT OF THE INTER PARTES REVIEW PROCEEDING, IT HAS BEEN DETERMINED THAT:

Claims **24**, **26** and **27** are cancelled.

* * * * *

EXHIBIT B

US010758488B2

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

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

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

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

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

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

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

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

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

(65) **Prior Publication Data**

US 2018/0318222 A1 Nov. 8, 2018

Related U.S. Application Data

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

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

(51) **Int. Cl.**

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

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

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

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Patricia Duffy

Assistant Examiner — Garen Gotfredson

(74) *Attorney, Agent, or Firm* — Cooley LLP

(57) **ABSTRACT**

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

12 Claims, 9 Drawing Sheets

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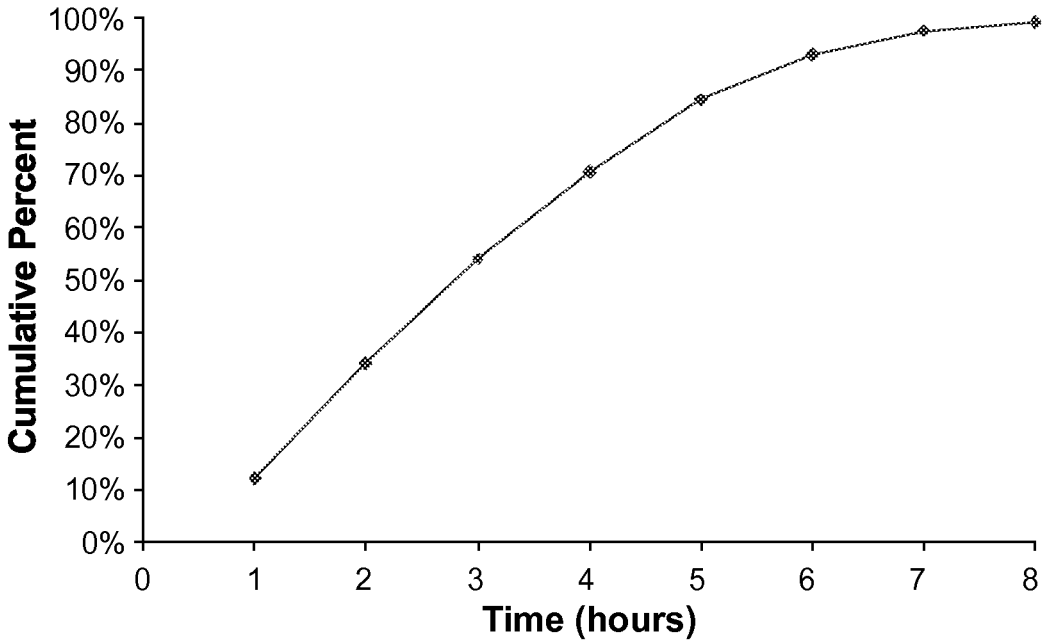
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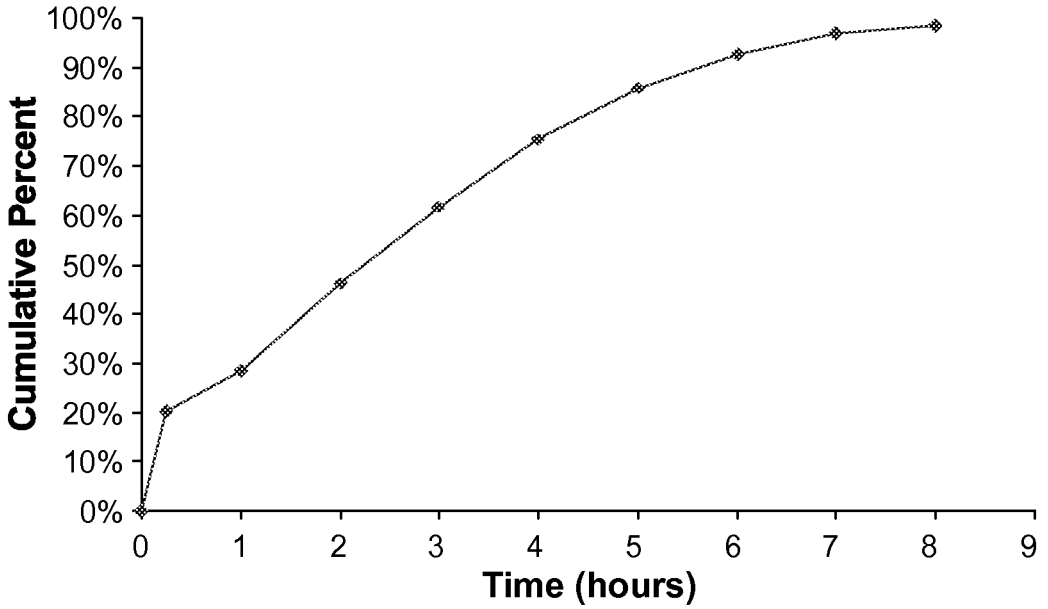
Time (hours)

FIG. 1


Cumulative Percent
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80%
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60%
50%
40%
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9
Time (hours)

FIG. 2

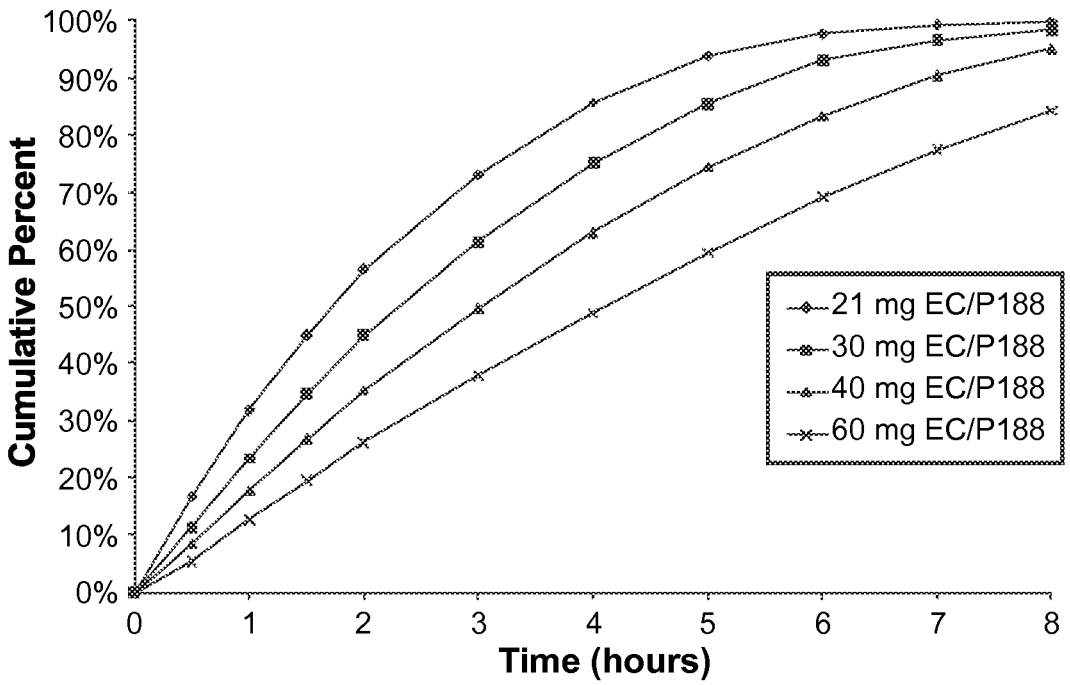

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3

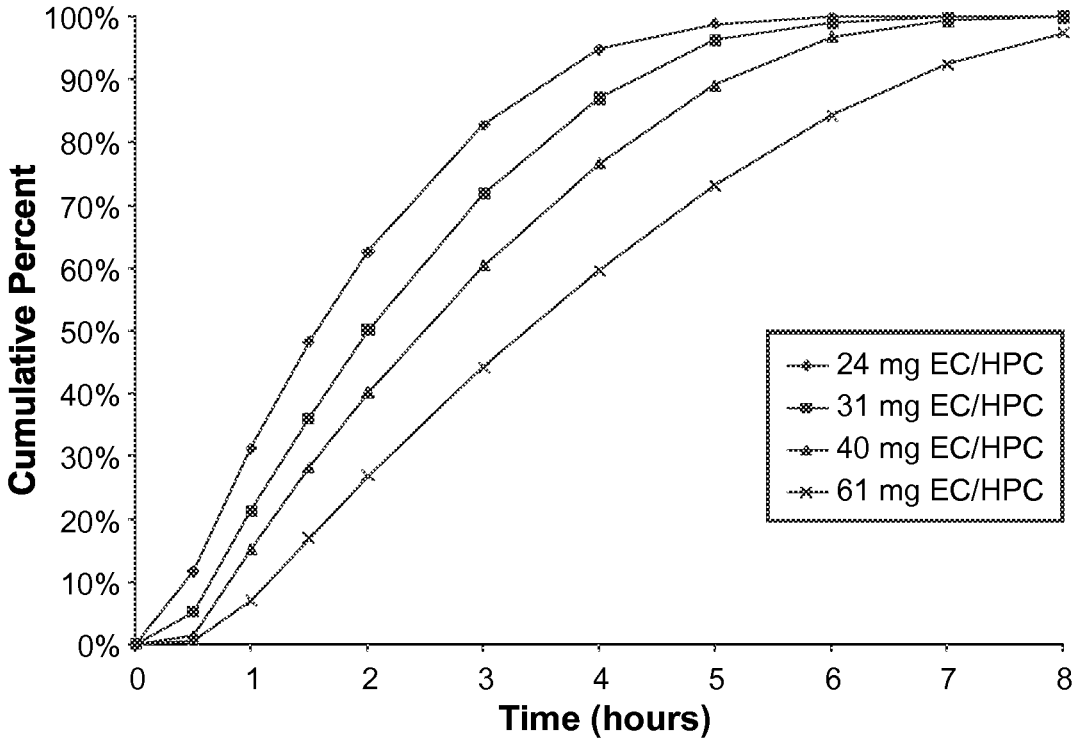

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4

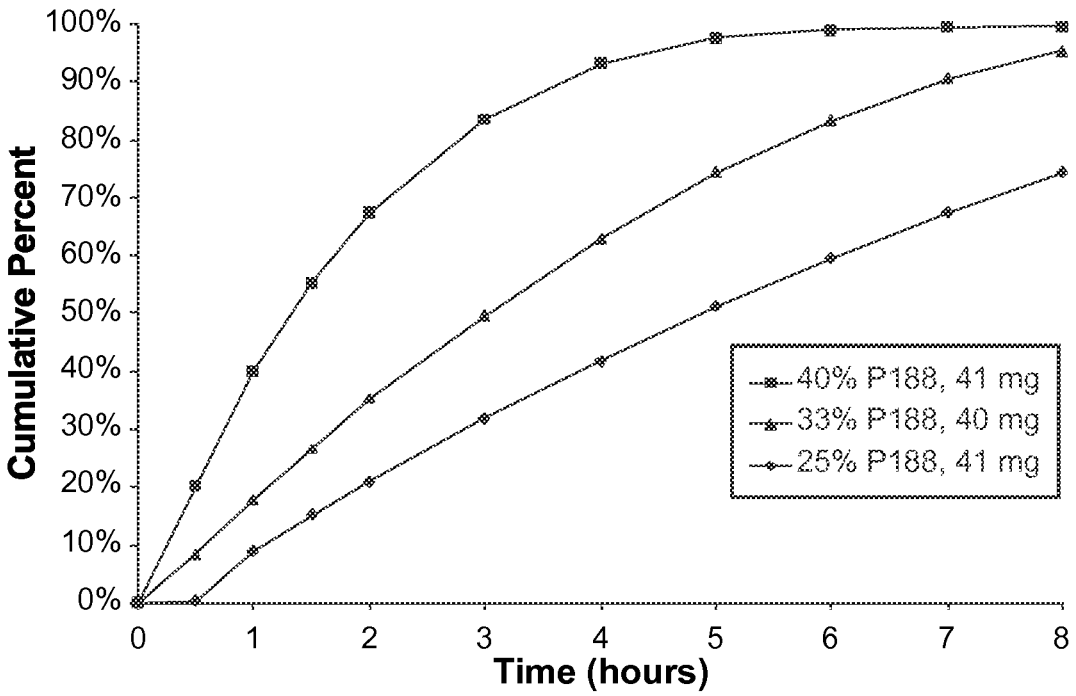

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5

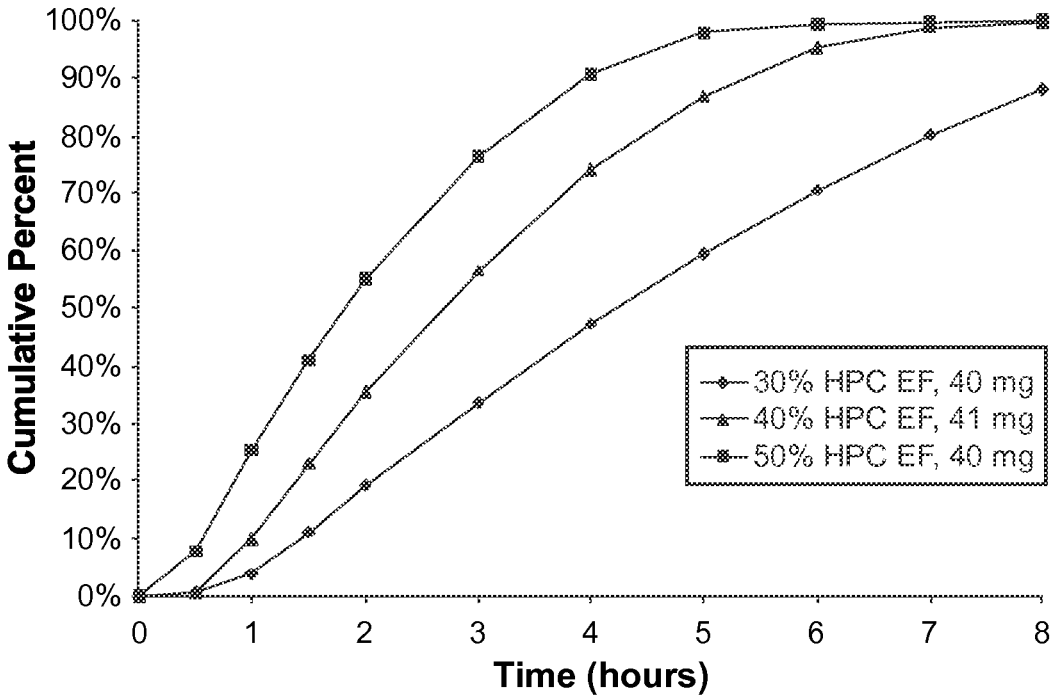
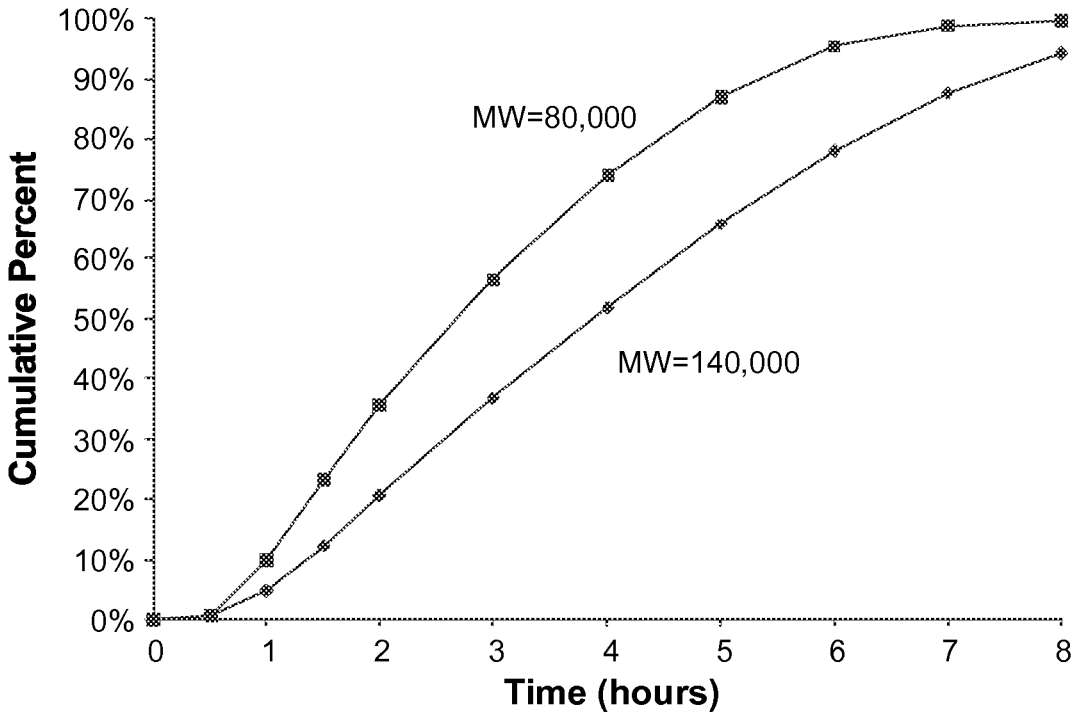

Cumulative Percent
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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MW=140,000
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 7

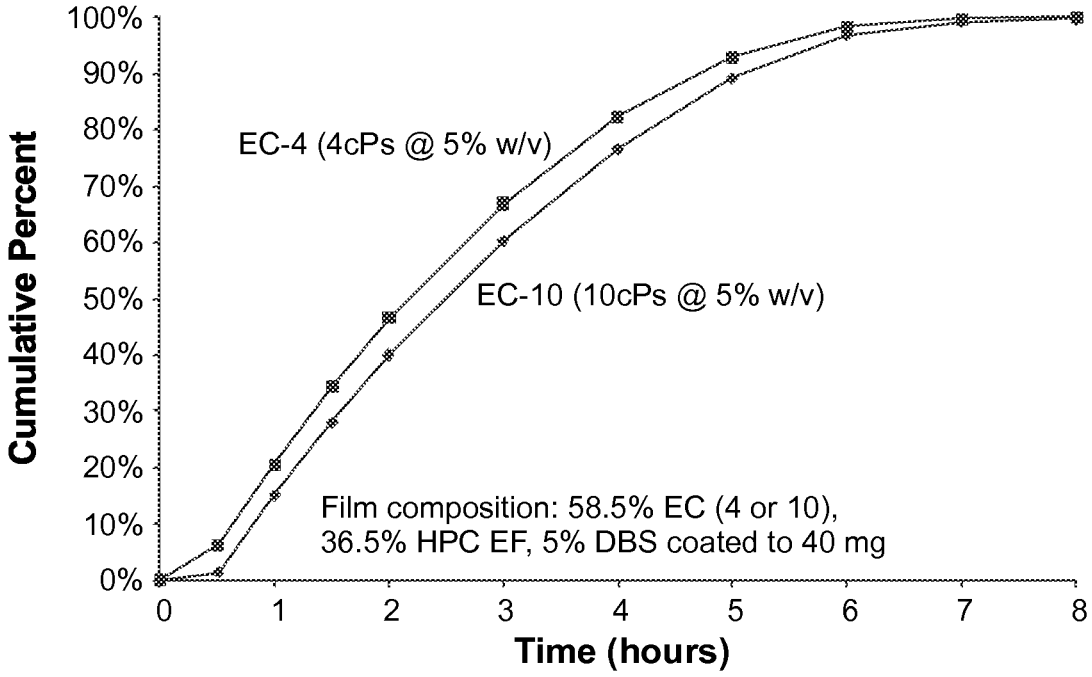

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 8

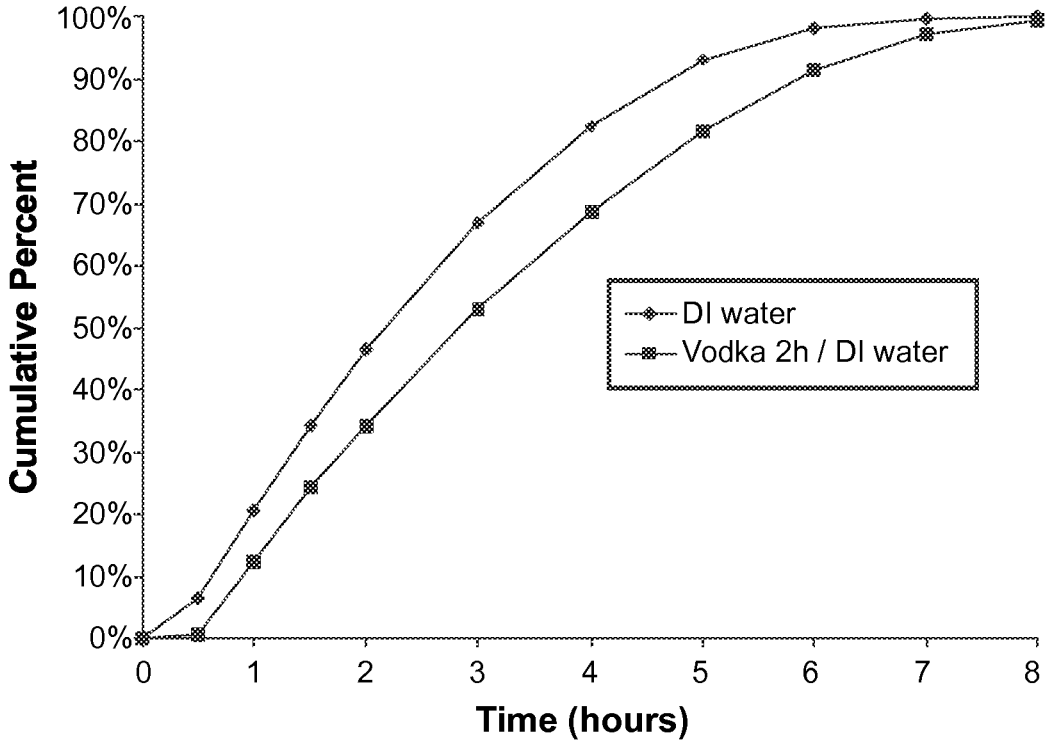

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A

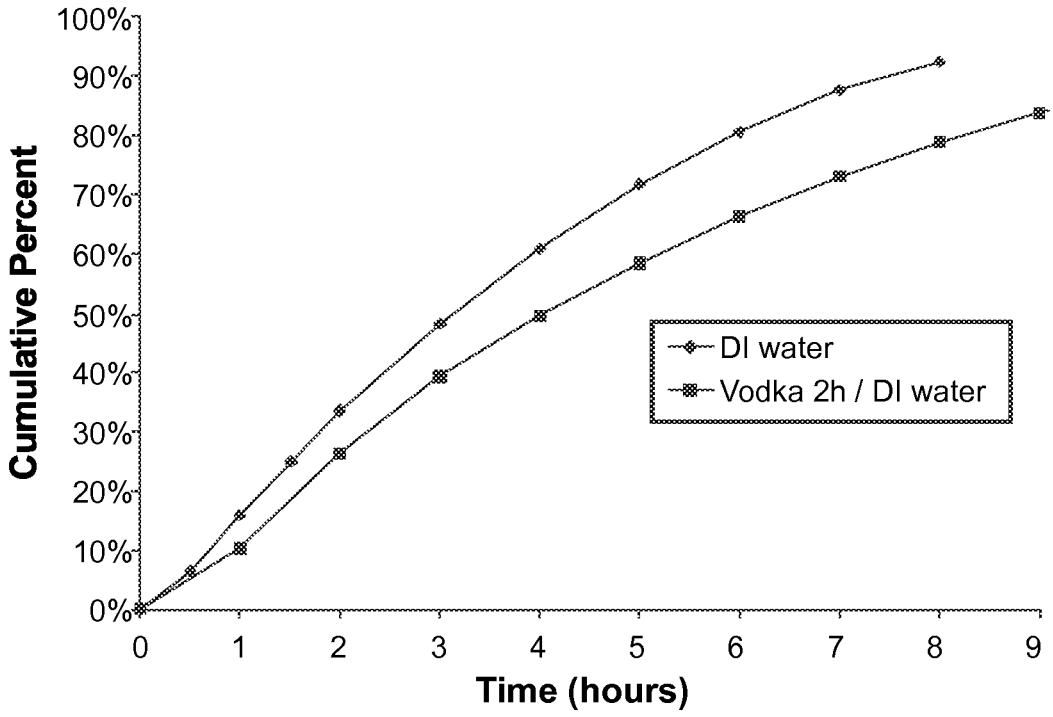

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B

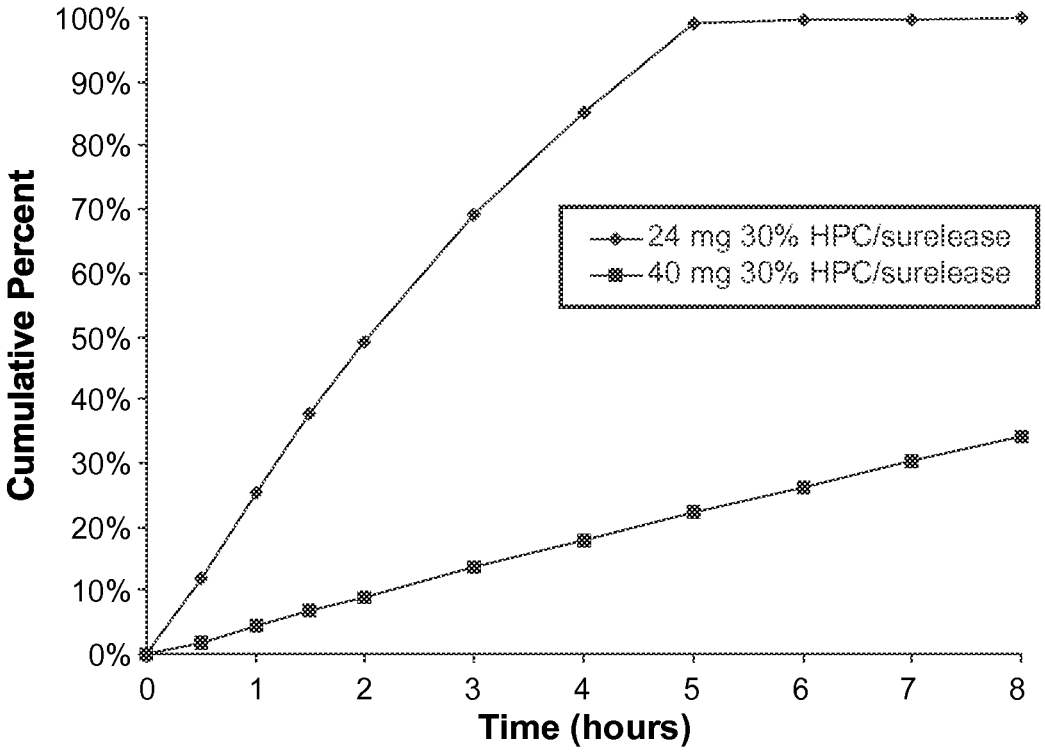

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10

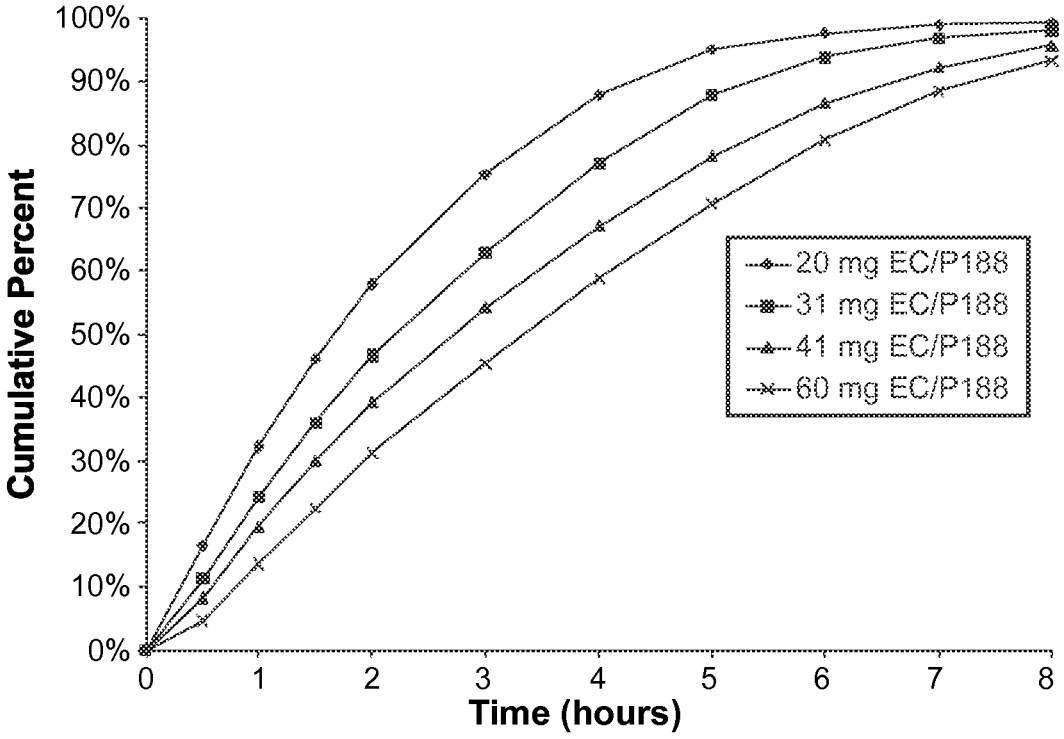

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
20 mg EC/P188
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11

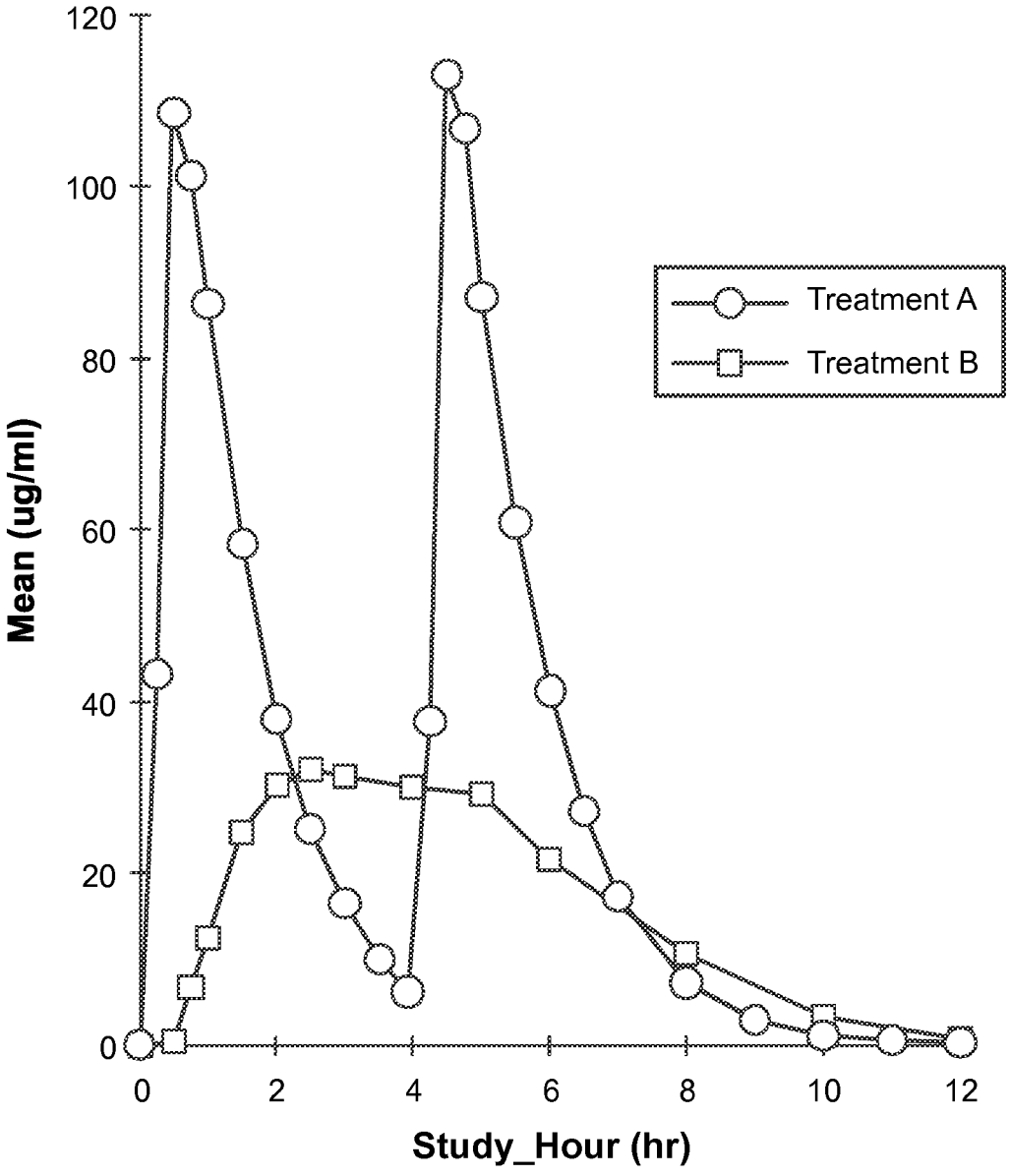

120
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12

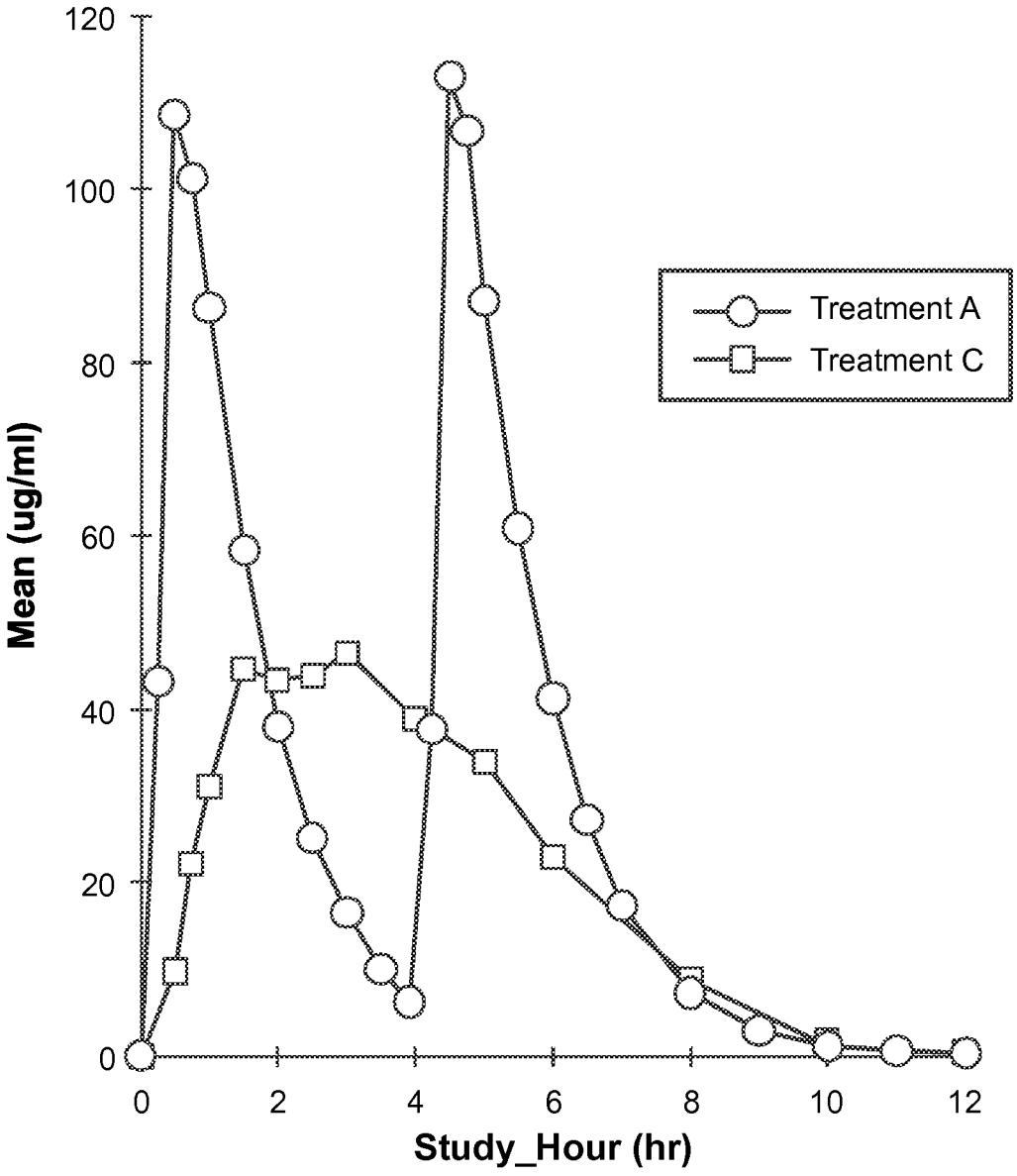

120
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13

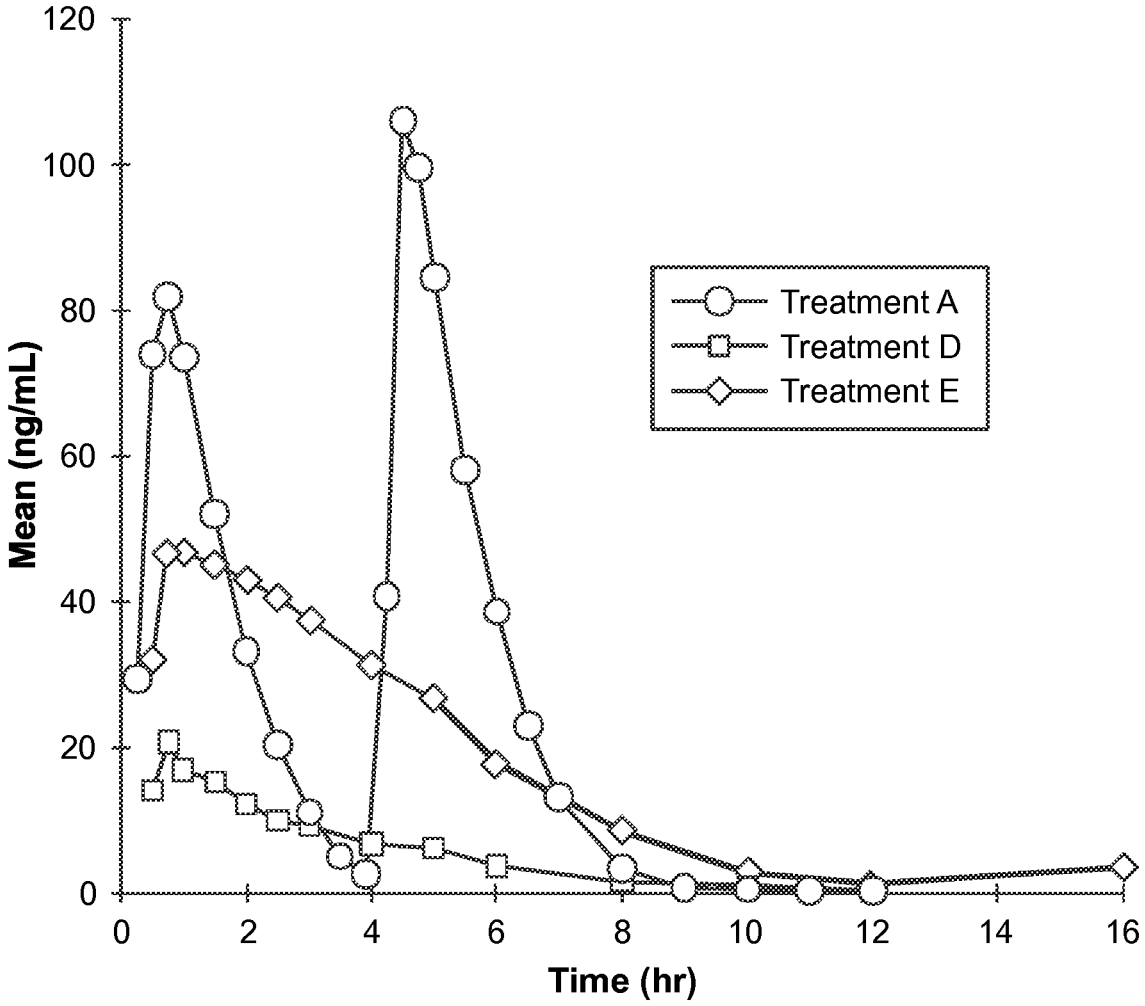

120
100
80
60
40
20
0
Mean (ng/mL)
0
2
4
6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

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

RELATED APPLICATIONS

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

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

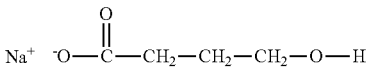
DETAILED DESCRIPTION

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

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

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

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



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

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

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

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

A. Controlled Release Formulations

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

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

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

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

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

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

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

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

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

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

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

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

I. Controlled Release Component

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

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

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

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

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

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

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

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

II. Functional Coating Composition

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

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

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

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

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

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

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

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

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

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

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

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

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

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

III. Moisture Barrier/Cosmetic Coatings

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

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

B. Immediate Release Formulations

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

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

I. Immediate Release Component

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

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

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

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

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

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

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

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

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

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

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

EXAMPLES

Example 1

Controlled Release Core

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

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

TABLE 1A

Controlled Release Core Tablet Formulation

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

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters
WET GRANULATION

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

TABLE 1C

Screen Analysis of Milled Granulation

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

Example 2

Functional Coating

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

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

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets

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

TABLE 2A-continued

Formulation of Sodium Oxybate Sustained-Release Tablets

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

*Coating solvent, removed during processing

TABLE 2A

Coating Parameters for Driam 8" Pan Coater

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

Example 3

Immediate-Release Overcoat

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

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

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater

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

TABLE 3A-continued

Parameters for Immediate-Release Overcoating with 8" Driam Coater

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

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

Example 4

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

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

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

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

TABLE 4A

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

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

Example 5

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

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

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

Example 6

Effect of Poloxamer Level in Functional Coating

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

Example 7

Effect of Hydroxypropyl Cellulose Level in Functional Coating

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

Example 8

Effect of Hydroxypropyl Cellulose Molecular Weight when used in Functional Coating

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

Example 9

Effect of Ethylcellulose Molecular Weight or Viscosity

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

Example 10

Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

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

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

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

Example 11

Aqueous Coating of Controlled Release Film

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

Example 12

Calcium Oxybate Controlled Release

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

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

Example 13

Clinical Evaluation of Controlled Release Dosage Forms

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

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

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

TABLE 5

Summary of PK Parameters for Treatments A, B, C

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

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

TABLE 6

Summary of PK Parameters for Treatments A, D, E

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

TABLE 6-continued

Summary of PK Parameters for Treatments A, D, E

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

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

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

The invention claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,758,488 B2
APPLICATION NO. : 16/025487
DATED : September 1, 2020
INVENTOR(S) : Allphin et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Claim 3, Column 28, Lines 5-6, replace "when tested in a dissolution apparatus 2 when tested in a dissolution apparatus 2 in deionized water" with --when tested in a dissolution apparatus 2 in deionized water--.

Signed and Sealed this
Twenty-seventh Day of October, 2020

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT C

US010813885B1

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

(10) **Patent No.: US 10,813,885 B1**
(45) **Date of Patent: *Oct. 27, 2020**

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

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

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/916,677**

(22) Filed: **Jun. 30, 2020**

Related U.S. Application Data

(63) Continuation of application No. 16/712,260, filed on Dec. 12, 2019, which is a continuation of application No. 16/025,487, filed on Jul. 2, 2018, now Pat. No. 10,758,488, which is a continuation of application No. 13/071,369, filed on Mar. 24, 2011, now abandoned.

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

(51) **Int. Cl.**

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

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

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

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

15 Claims, 9 Drawing Sheets

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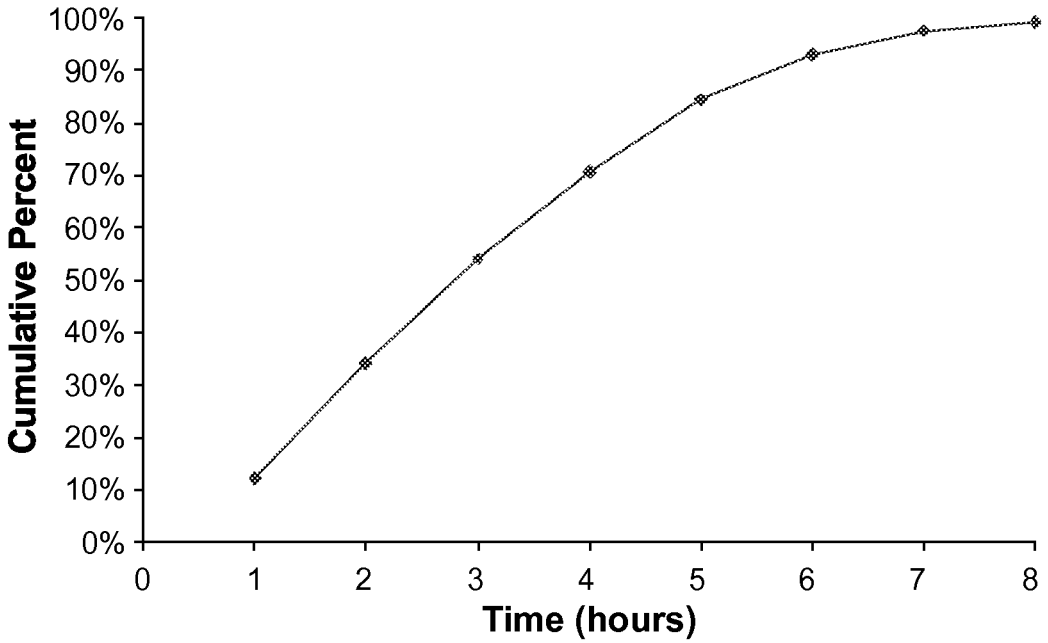
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80%
70%
60%
50%
40%
30%
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0
1
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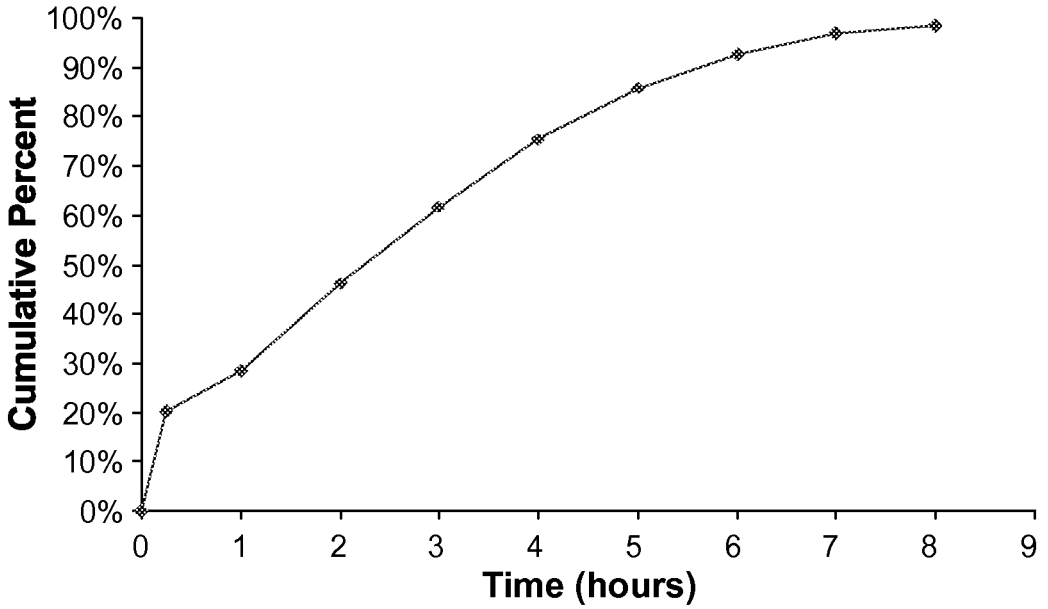
3
4
5
6
7
8
Time (hours)

FIG. 1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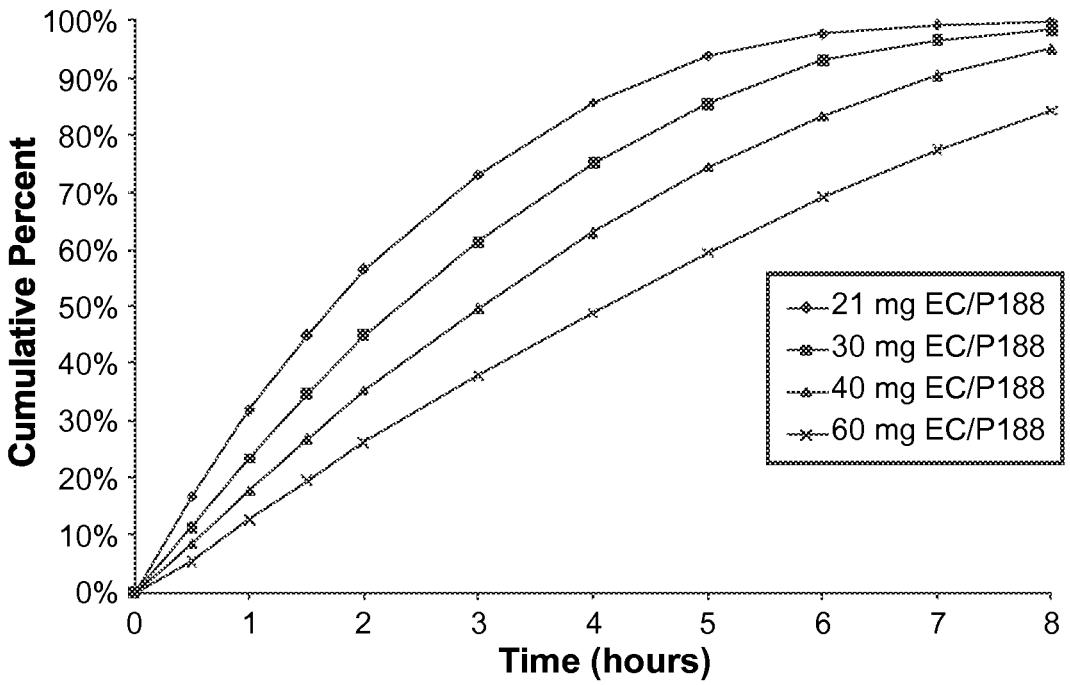
4
5
6
7
8
9
Time (hours)

FIG. 2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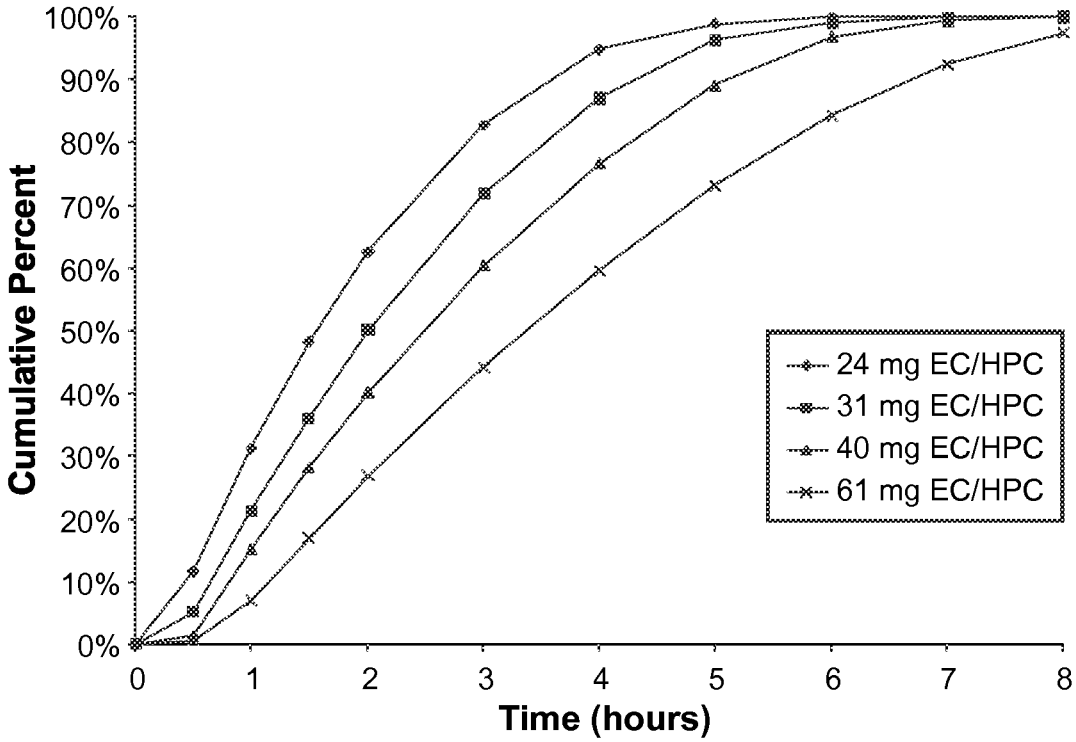
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3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90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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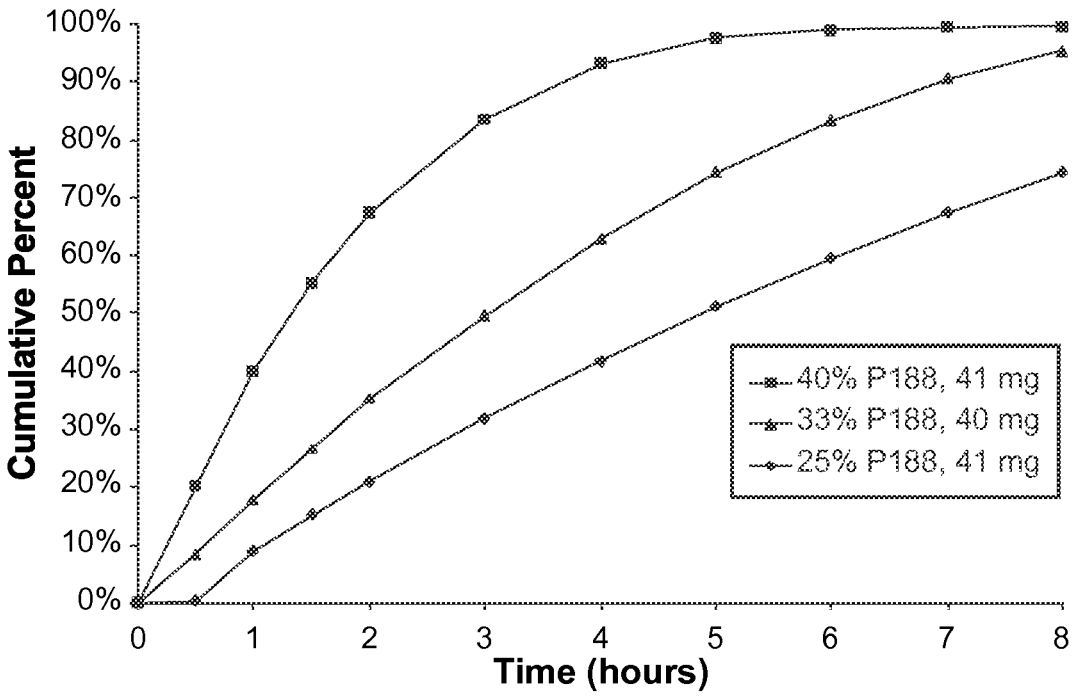
1
2
3
4
5
6
7
8
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4


Cumulative Percent
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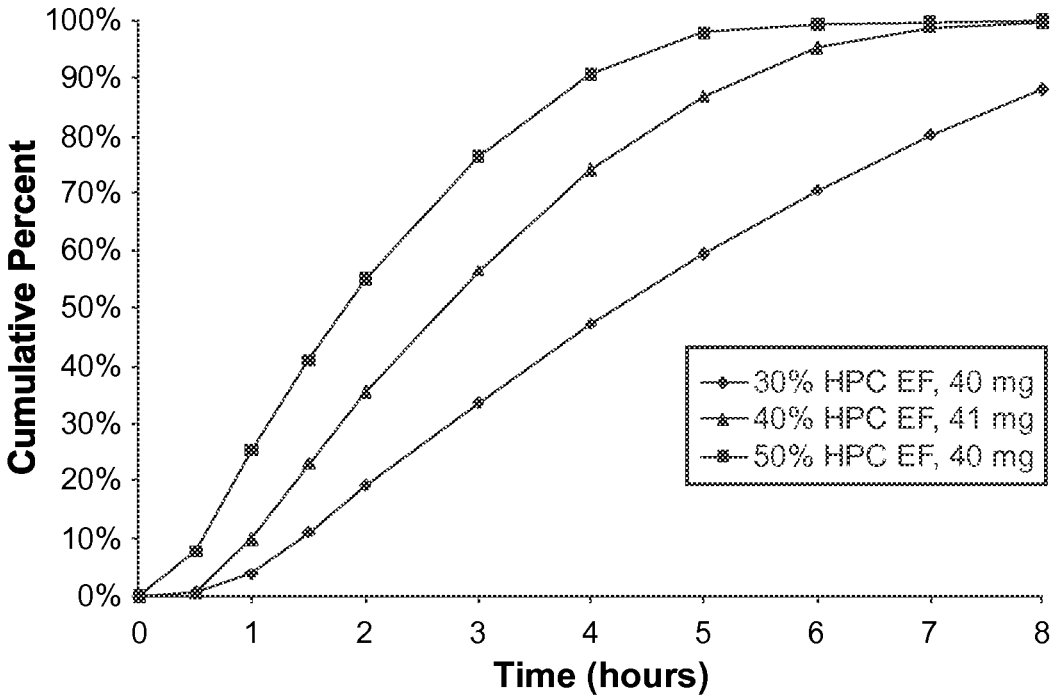
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5


Cumulative Percent
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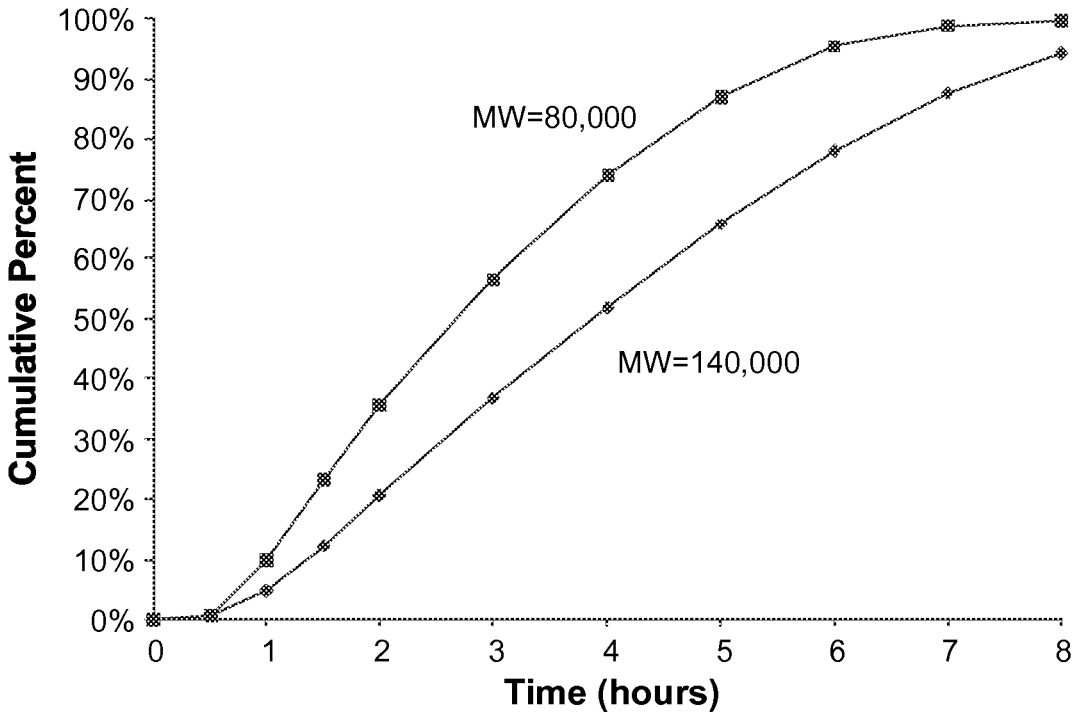
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6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60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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MW=140,000
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1
2
3
4
5
6
7
8
Time (hours)

FIG. 7

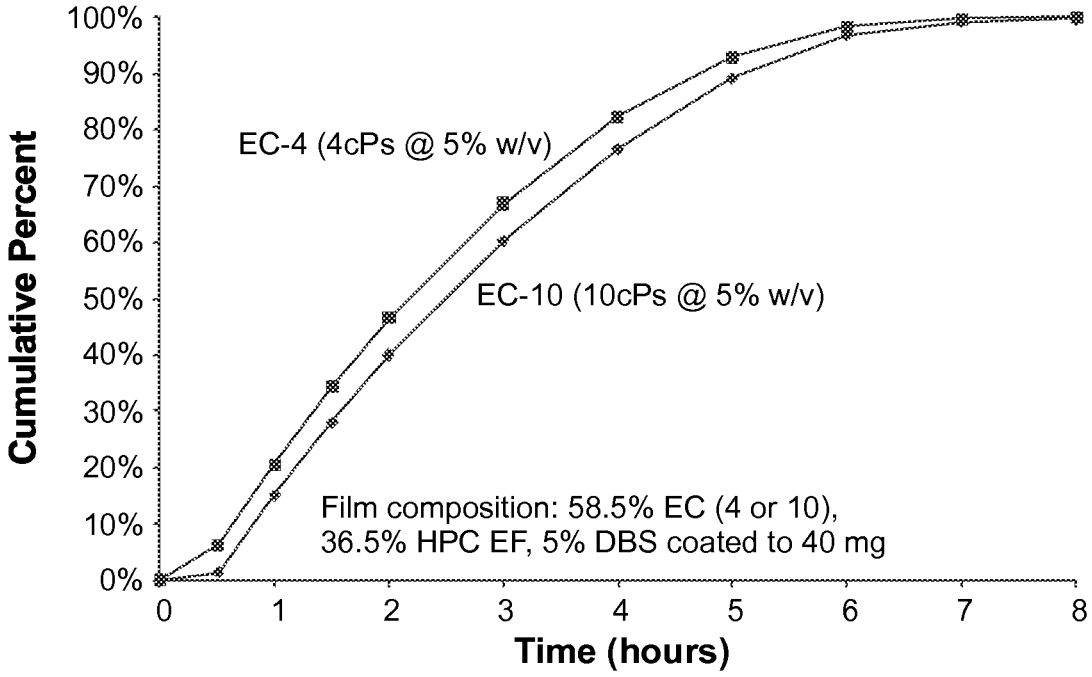
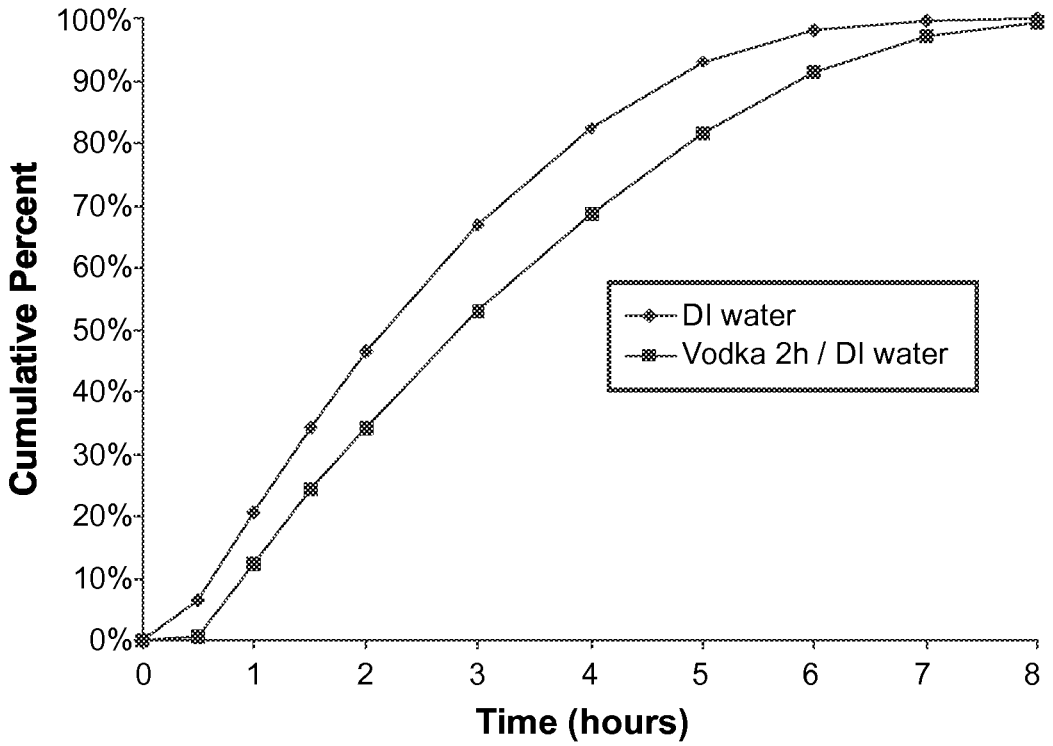

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 8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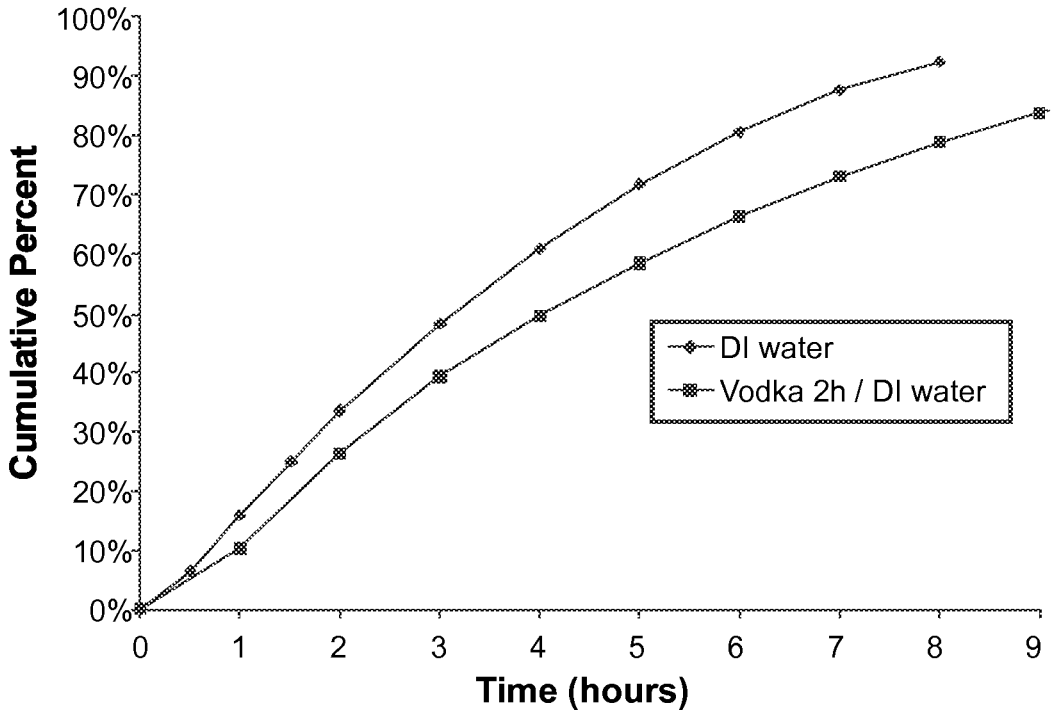
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A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90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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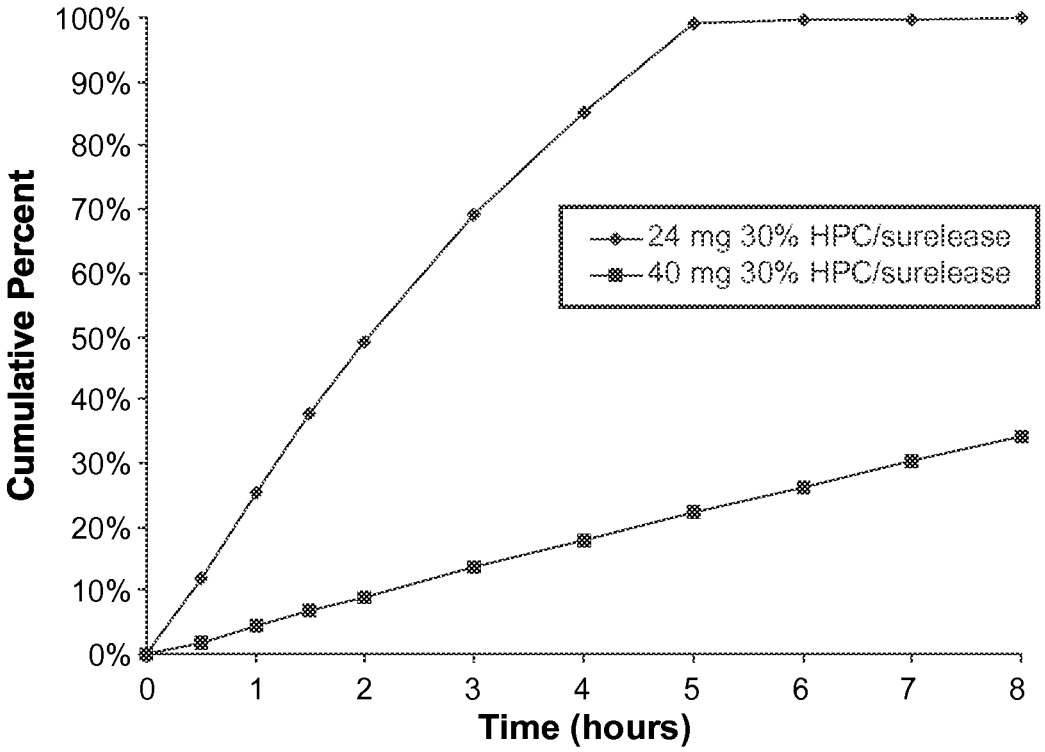
1
2
3
4
5
6
7
8
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B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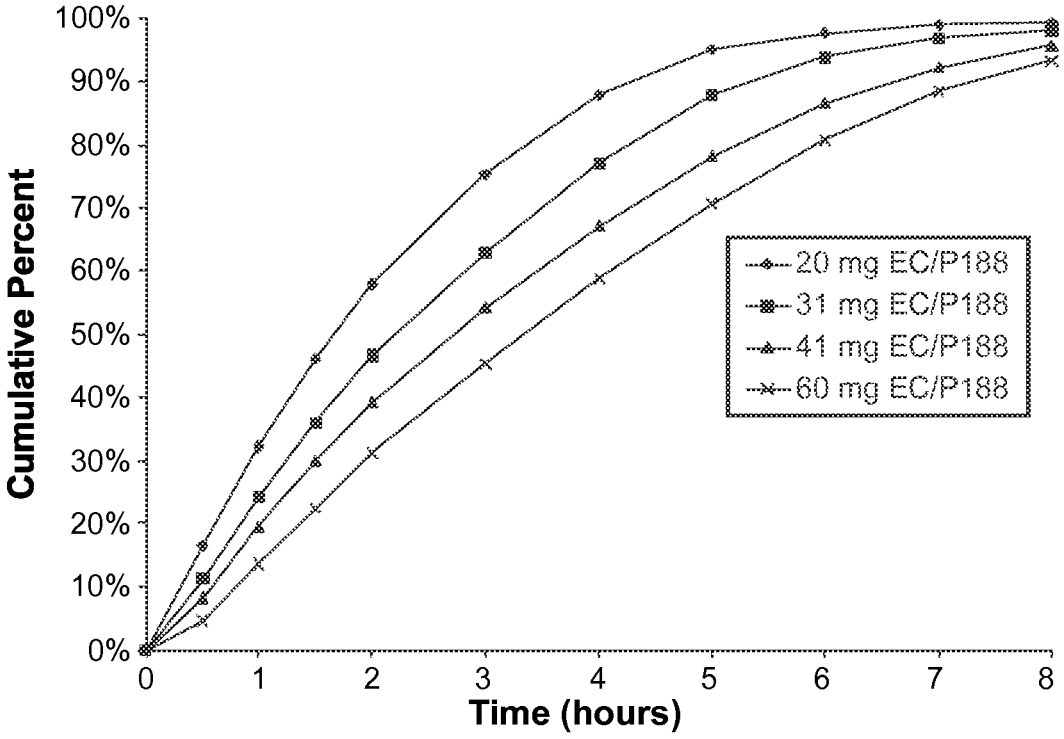
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10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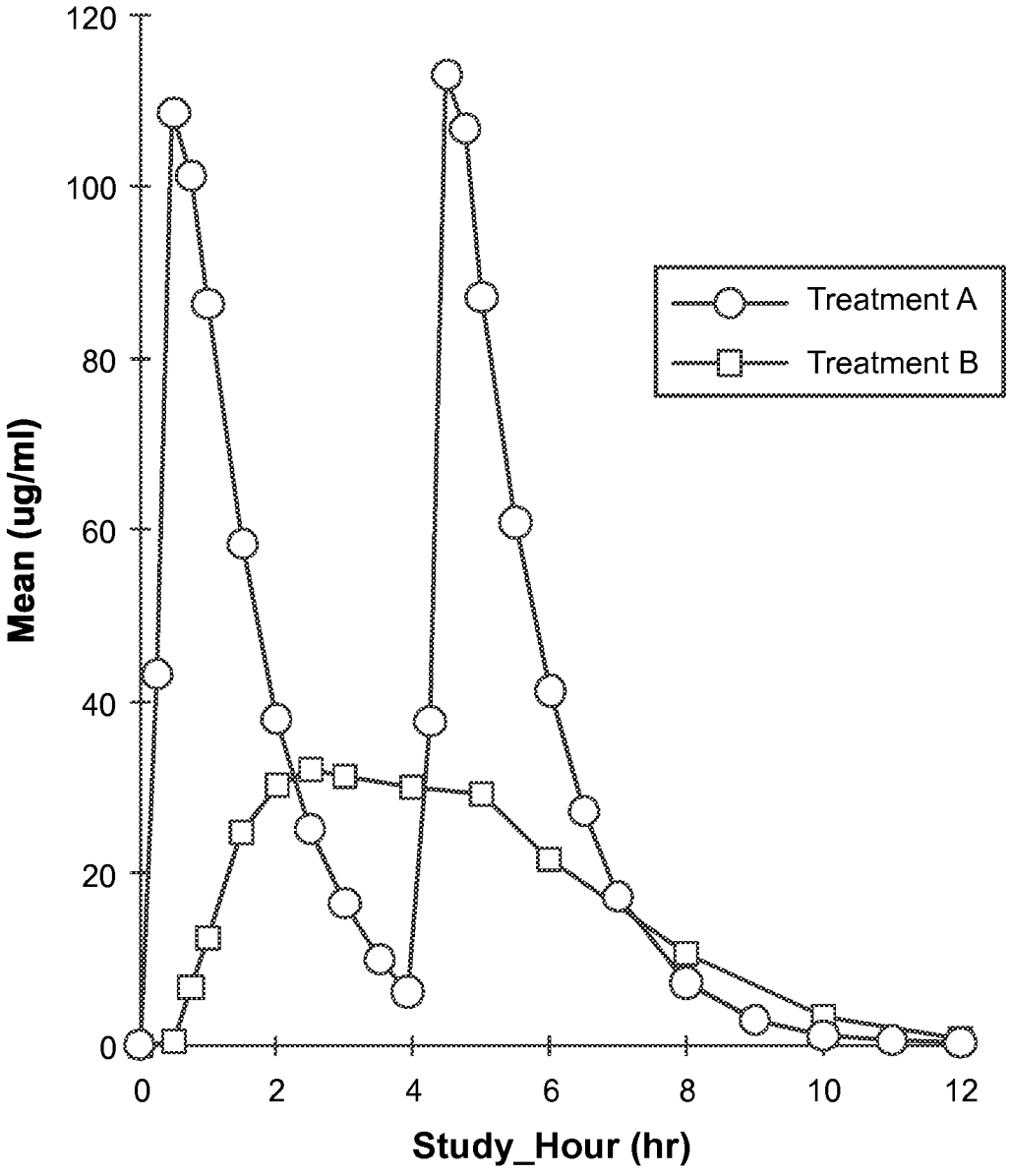
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
20 mg EC/P188
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11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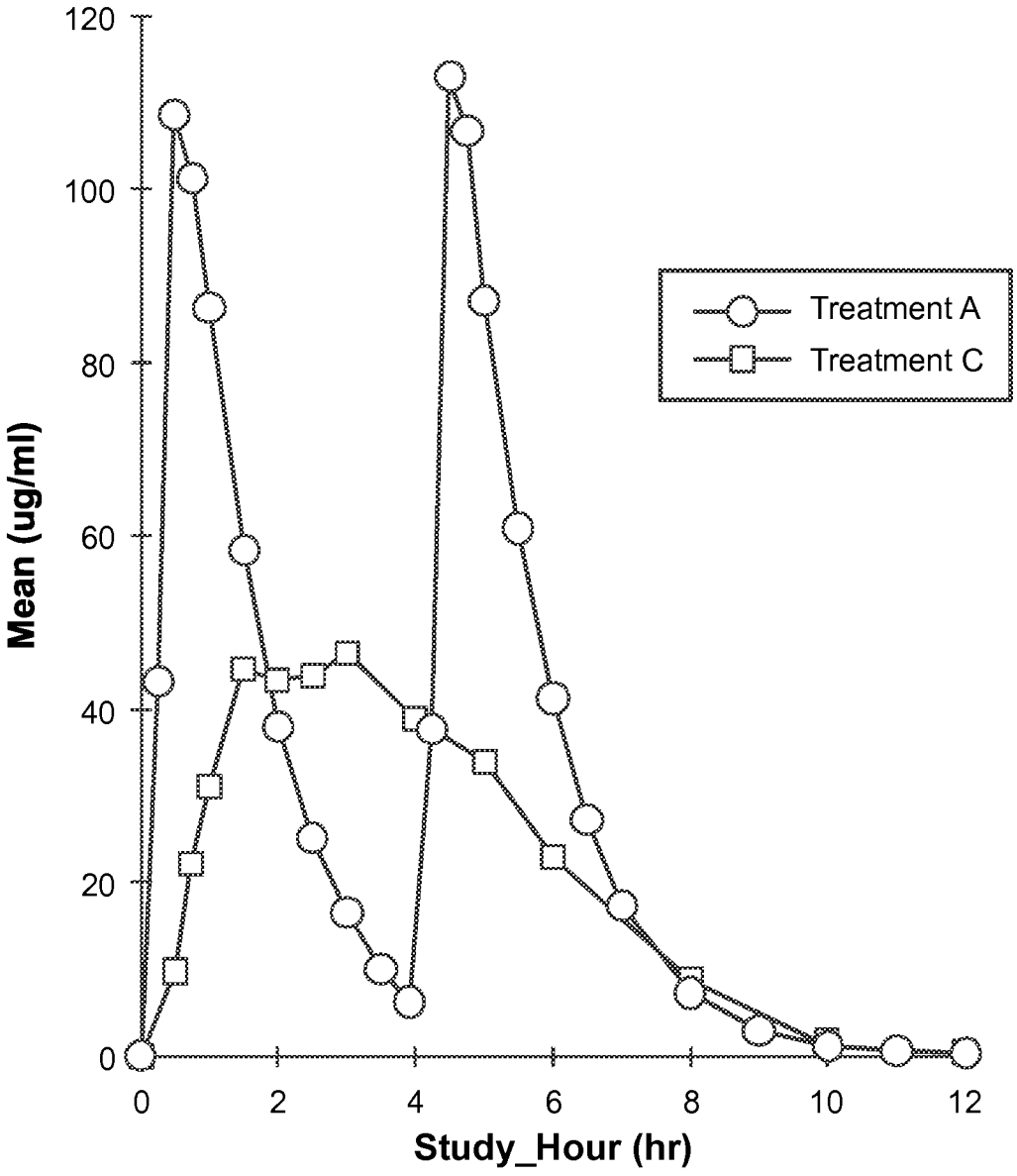
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12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100
80
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Mean (ug/ml)
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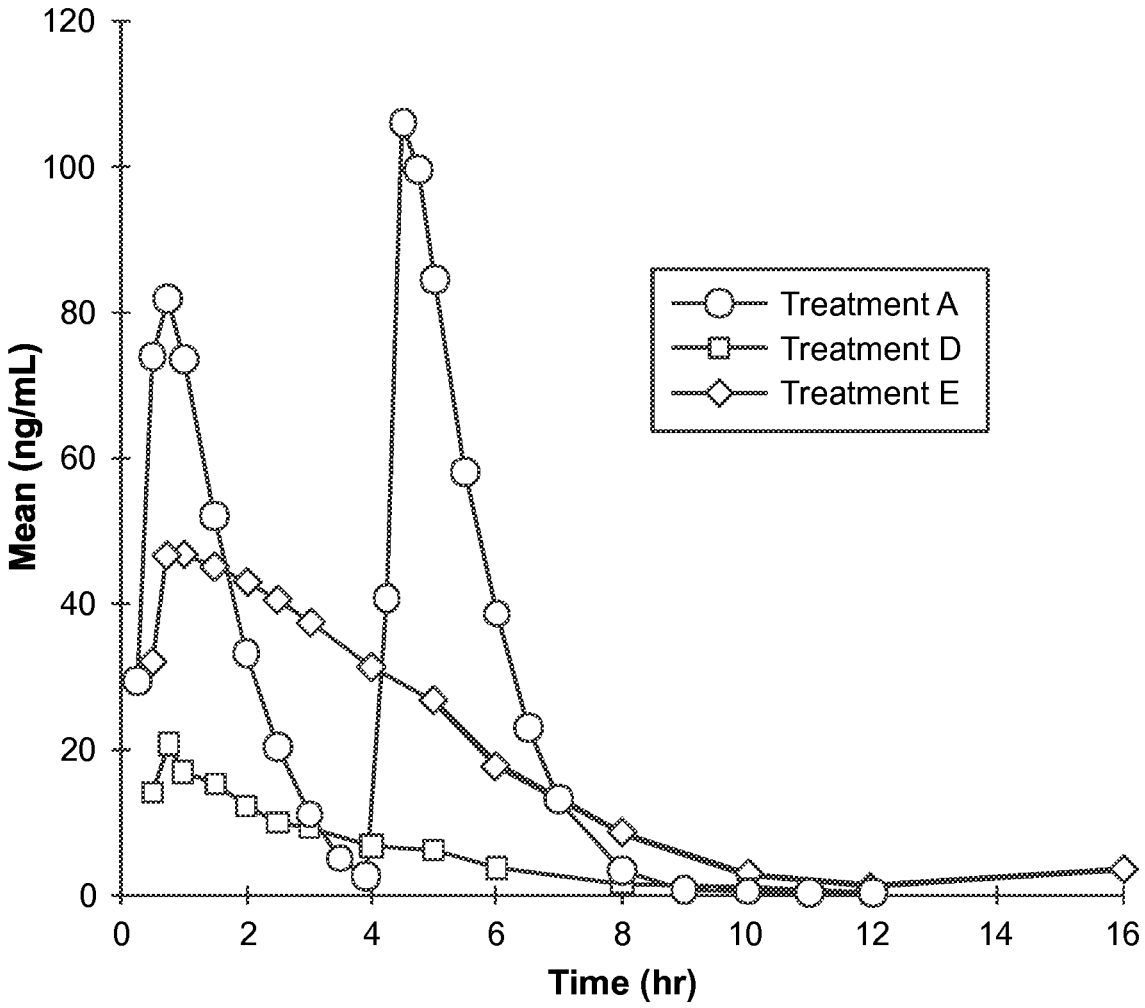
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13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100
80
60
40
20
0
Mean (ng/mL)
0
2
4
6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

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

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/712,260, filed Dec. 12, 2019, which is a continuation of U.S. patent application Ser. No. 16/025,487, filed Jul. 2, 2018, which is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, now abandoned, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

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

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

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative

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

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

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

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

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

solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration during the night.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

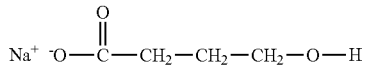
DETAILED DESCRIPTION

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

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

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

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



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

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

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

A. Controlled Release Formulations

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

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

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

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

release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

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

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

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

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present descrip-

tion is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

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

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

I. Controlled Release Component

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

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

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

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic

acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

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

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

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

II. Functional Coating Composition

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

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

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

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore

former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former, such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

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

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

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

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

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

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

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

pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

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

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

B. Immediate Release Formulations

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

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

I. Immediate Release Component

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

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

the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

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

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

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

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

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

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

In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form maybe formulated and configured such that start-up of delivery of drug from the controlled release

composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag time is desired, the delay may be accomplished or adjusted by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

EXAMPLES

Example 1—Controlled Release Core

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

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

TABLE 1A

Controlled Release Core Tablet Formulation

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

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters WET GRANULATION	
GRANULATION SOLUTION ADDITION RATE (G/MIN)	250
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES
IMPELLER SPEED (RPM)	300
CHOPPER SPEED (RPM)	1800

TABLE 1B-continued

DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET TEMPERATURE (° C.)	70	70
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE AT END OF DRYING (° C.)	47	48
LOD (% WT LOSS)	0.84	0.92

TABLE 1C

Screen Analysis of Milled Granulation

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

Example 2—Functional Coating

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

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

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
5	Sodium Oxybate tablet core		95.13	781.25
6	Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80	14.80
7	Dibutyl sebacate	5.0	0.24	2.00
8	Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82	23.20
9	Ethanol, USP (200 proof)*			
10	Purified water*			
	TOTAL	100.0	100.00	821.25

*Coating solvent, removed during processing

TABLE 2A

Coating Parameters for Driam 8" Pan Coater

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

Example 3—Immediate-Release Overcoat

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

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

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	59	55-63
EXHAUST TEMPERATURE (° C.)	51	50-53
PRODUCT TEMPERATURE (° C.)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

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

Example 4—Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

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

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

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

TABLE 4A

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

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

Example 5—Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting of 7% solids in 95/5 alcohol/water. The results shown in FIG. **4** demonstrate that controlled release over a relevant time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6—Effect of Poloxamer Level in Functional Coating

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

poloxamer level can be adjusted at least over the range of 25%-40% by weight, while still providing controlled release of the drug.

Example 7—Effect of Hydroxypropyl Cellulose Level in Functional Coating

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

Example 8—Effect of Hydroxypropyl Cellulose Molecular Weight when Used in Functional Coating

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

Example 9—Effect of Ethylcellulose Molecular Weight or Viscosity

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

Example 10—Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

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

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

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

Example 11—Aqueous Coating of Controlled Release Film

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

Example 12—Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"×0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. **11**. These results using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13—Clinical Evaluation of Controlled Release Dosage Forms

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

Four different sodium oxybate formulations were administered to patients. The first, designated herein as Treatment A, was the sodium oxybate oral solution containing 375 mg/ml sodium oxybate. Treatments B through E, as designated herein, involved administration of three controlled release dosage forms (Treatments B through D), with one of the controlled release dosage forms being used to administer

two different doses of sodium oxybate (Treatments D and E). The controlled release dosage forms administered as Treatment B included 750 mg sodium oxybate per dosage form and were produced with a CR core and functional overcoat as described in Example 1 and Example 2, the controlled release dosage forms administered as Treatment C included 750 mg sodium oxybate per dosage form and were produced as described in Example 1 and Example 4, and the controlled release dosage forms administered as Treatments D and E included 1,000 mg sodium oxybate per dosage form and were produced with a CR core (750 mg sodium oxybate), functional overcoat, and IR overcoat (250 mg sodium oxybate) as described in Examples 1 through 3.

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

TABLE 5

Summary of PK Parameters for Treatments A, B, C

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

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

TABLE 6

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
Treatment A						
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
Treatment D						
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

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

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

The invention claimed is:

1. A formulation comprising 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, wherein:

the sustained release portion comprises a functional coating and a core, the functional coating is deposited over the core;

the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

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 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.

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

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

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

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

6. The formulation of claim **5**, comprising a sodium salt of gamma-hydroxybutyrate.

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

8. The formulation of claim **1**, further comprising an immediate release portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate.

9. The formulation of claim **8**, wherein the immediate release portion comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

10. The formulation of claim **9**, wherein the immediate release portion comprises a sodium salt of gamma-hydroxybutyrate.

11. The formulation of claim **8**, wherein the immediate release portion is a dry powder formulation, an immediate release tablet, an encapsulated formulation, a liquid solution, or liquid suspension.

12. The formulation of claim **8**, 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.

13. The formulation of claim **8**, wherein 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 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.

14. The formulation of claim **13**, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

15. The formulation of claim **13**, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 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.

* * * * *

EXHIBIT D

US010959956B2

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

(10) **Patent No.: US 10,959,956 B2**
(45) **Date of Patent: *Mar. 30, 2021**

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

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/012,823**

(22) Filed: **Sep. 4, 2020**

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(51) **Int. Cl.**

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

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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

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

27 Claims, 9 Drawing Sheets

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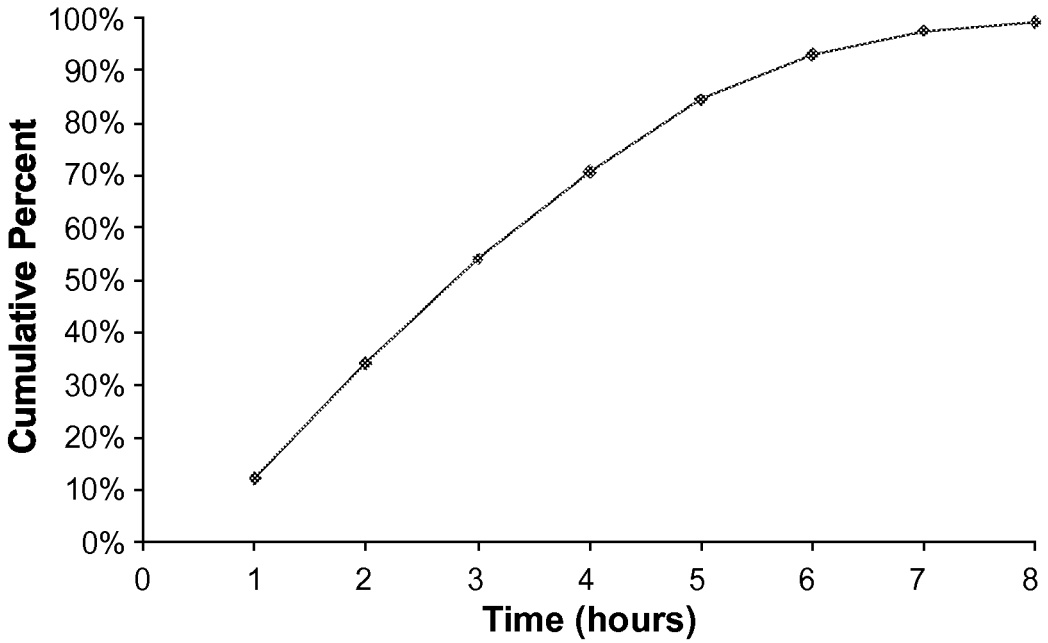
Walden et al., "The Effect of Ethanol on the Release of Opioids 30 from Oral Sustained-Release Preparations," Drug Development and Industrial Pharmacy, 2007, 33:10, 1101-1111.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80%
70%
60%
50%
40%
30%
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1
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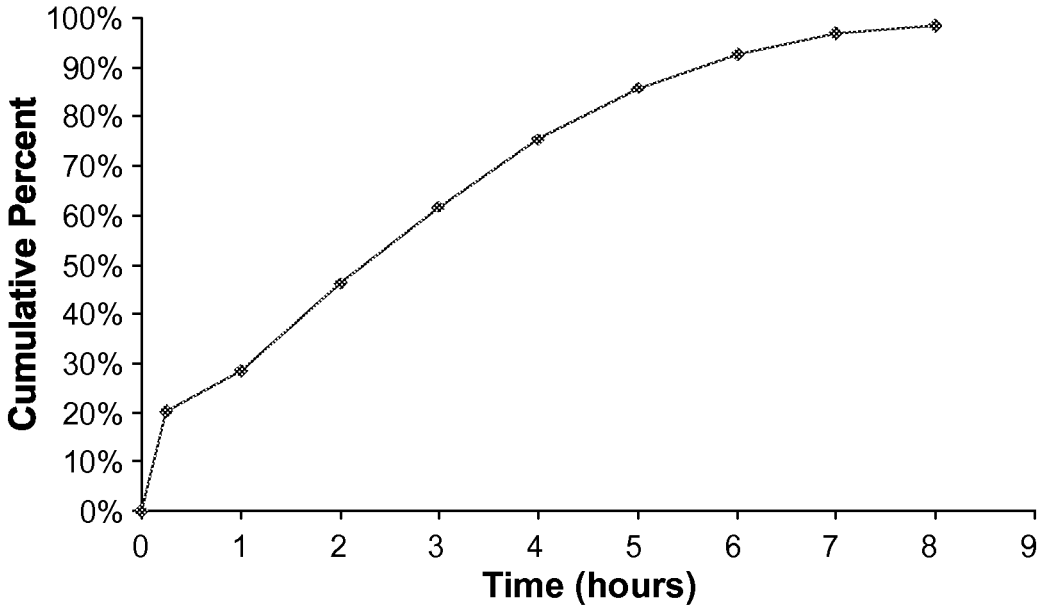
3
4
5
6
7
8
Time (hours)

FIG. 1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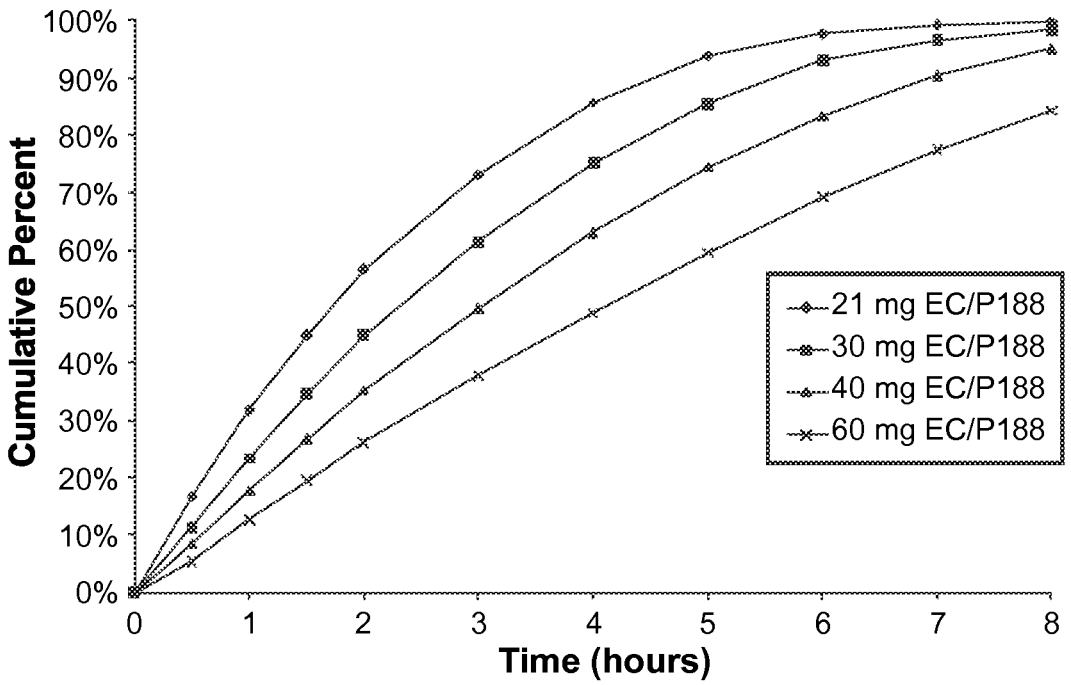
4
5
6
7
8
9
Time (hours)

FIG. 2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70%
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40%
30%
20%
10%
0%
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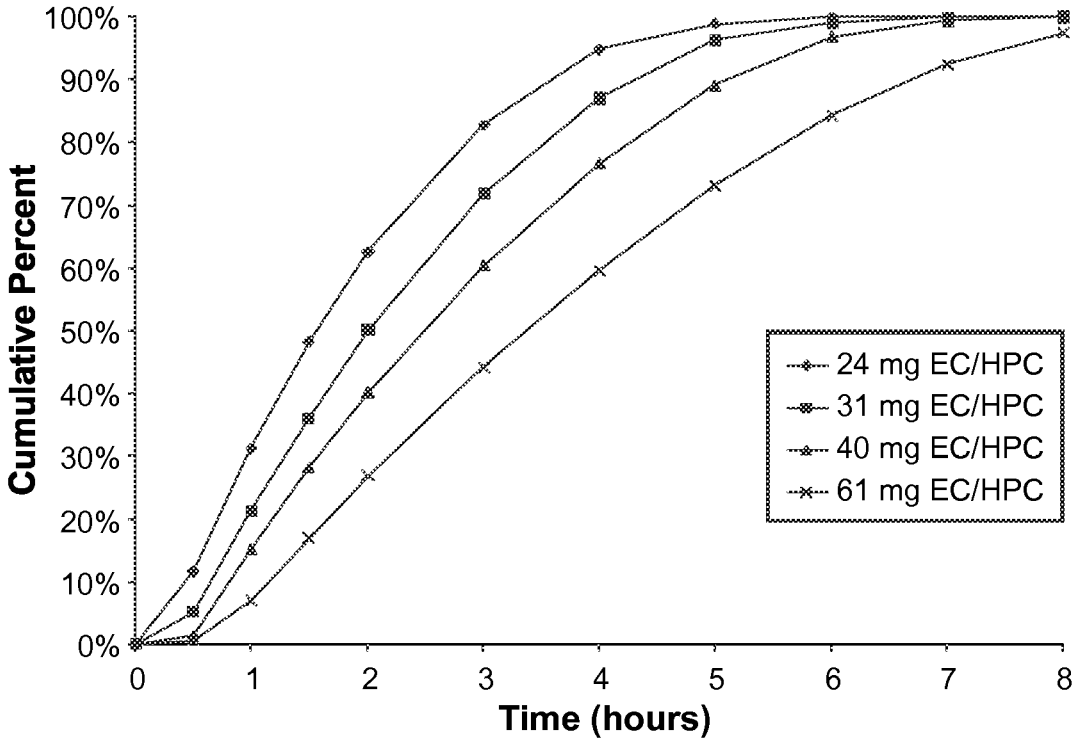
1
2
3
4
5
6
7
8
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3


Cumulative Percent
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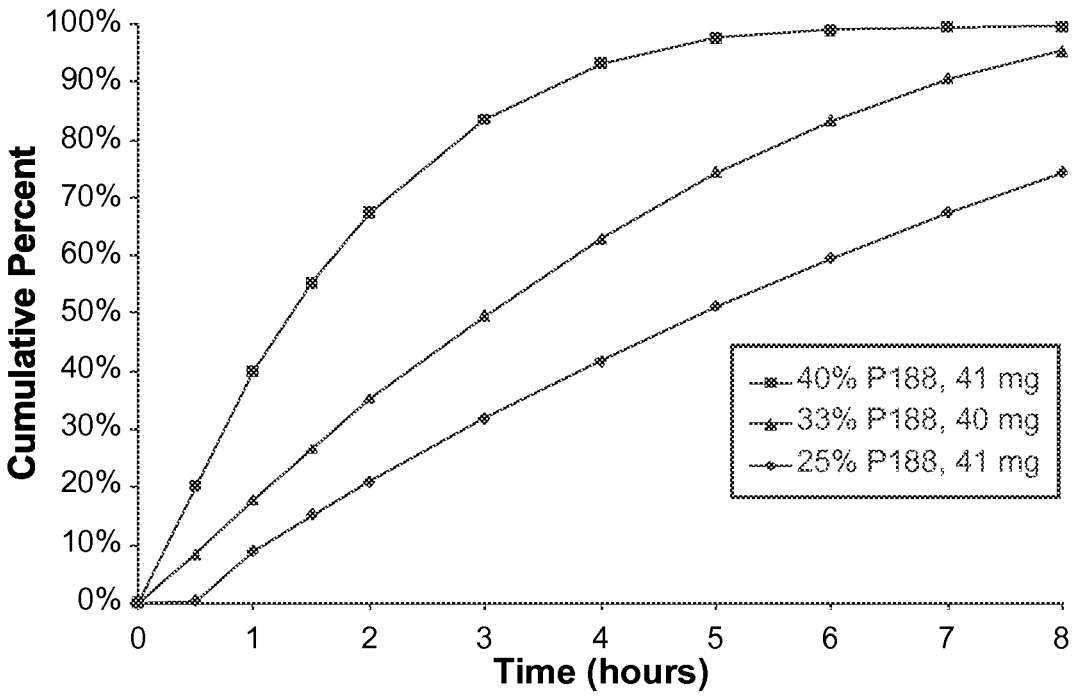
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4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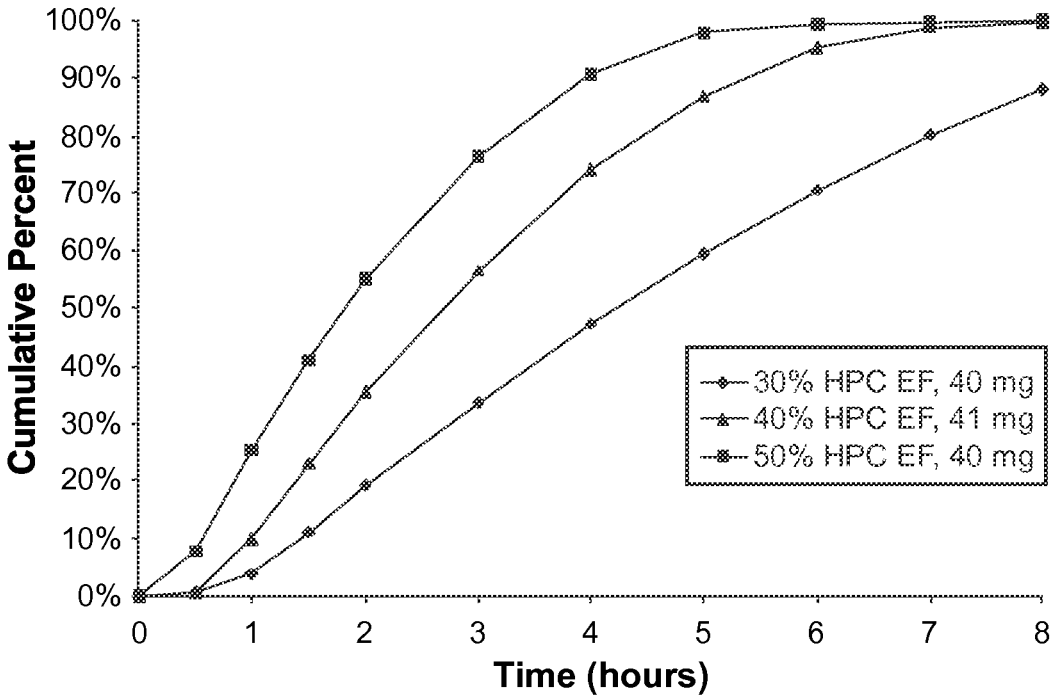
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5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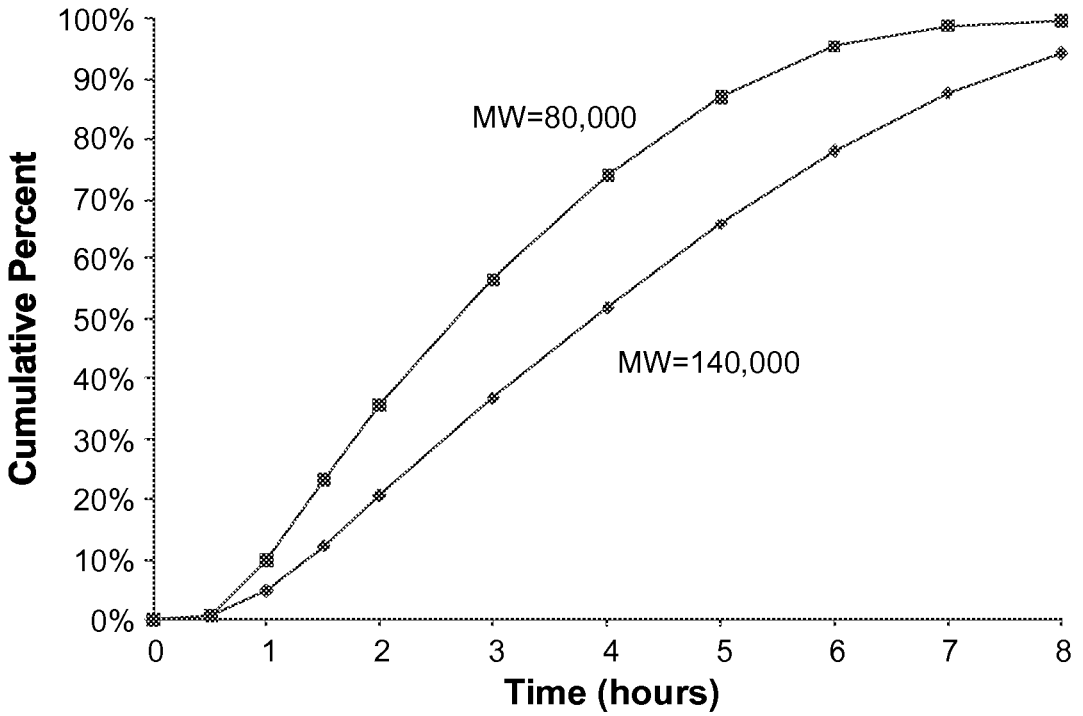
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6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60%
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40%
30%
20%
10%
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Cumulative Percent
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MW=140,000
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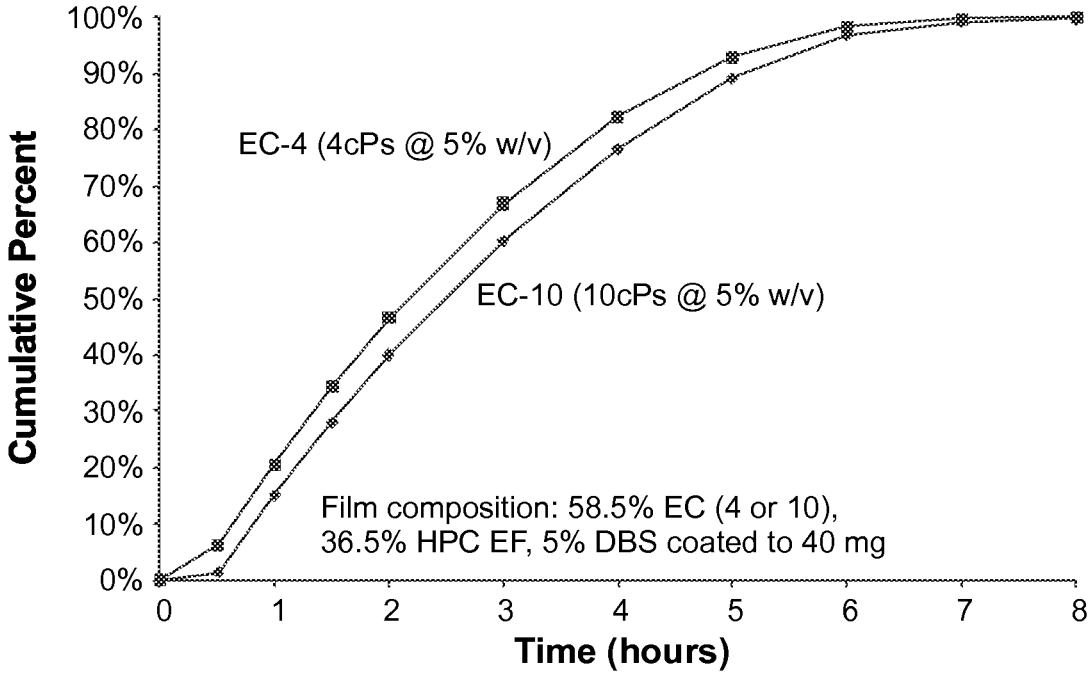
1
2
3
4
5
6
7
8
Time (hours)

FIG. 7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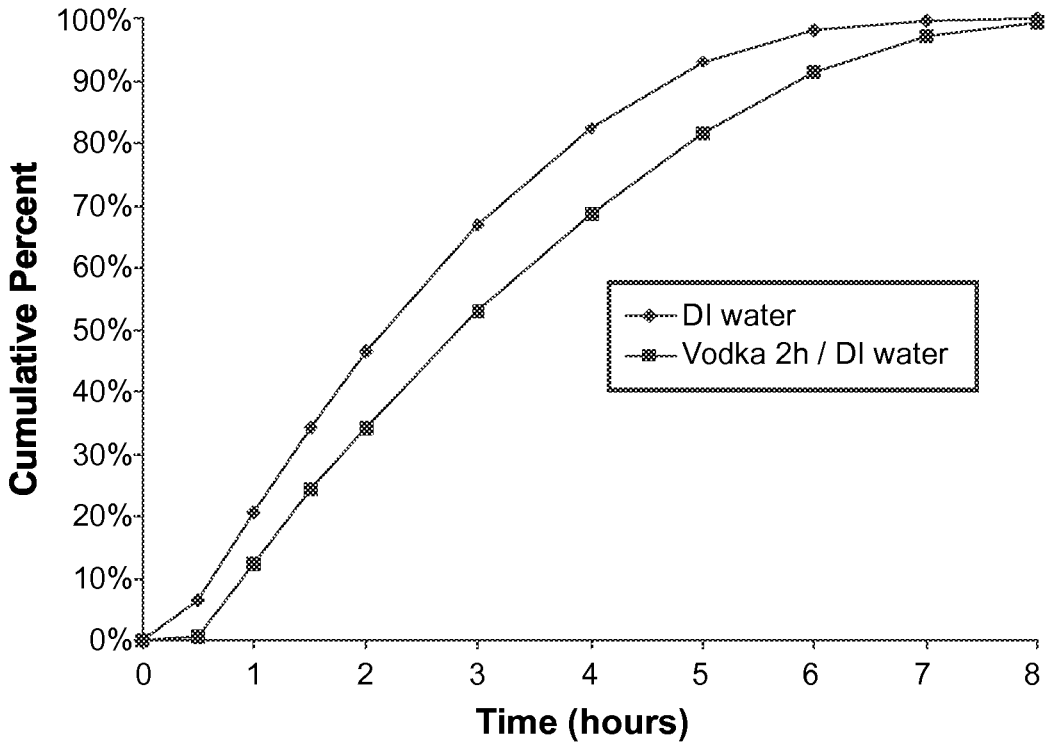
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 8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90%
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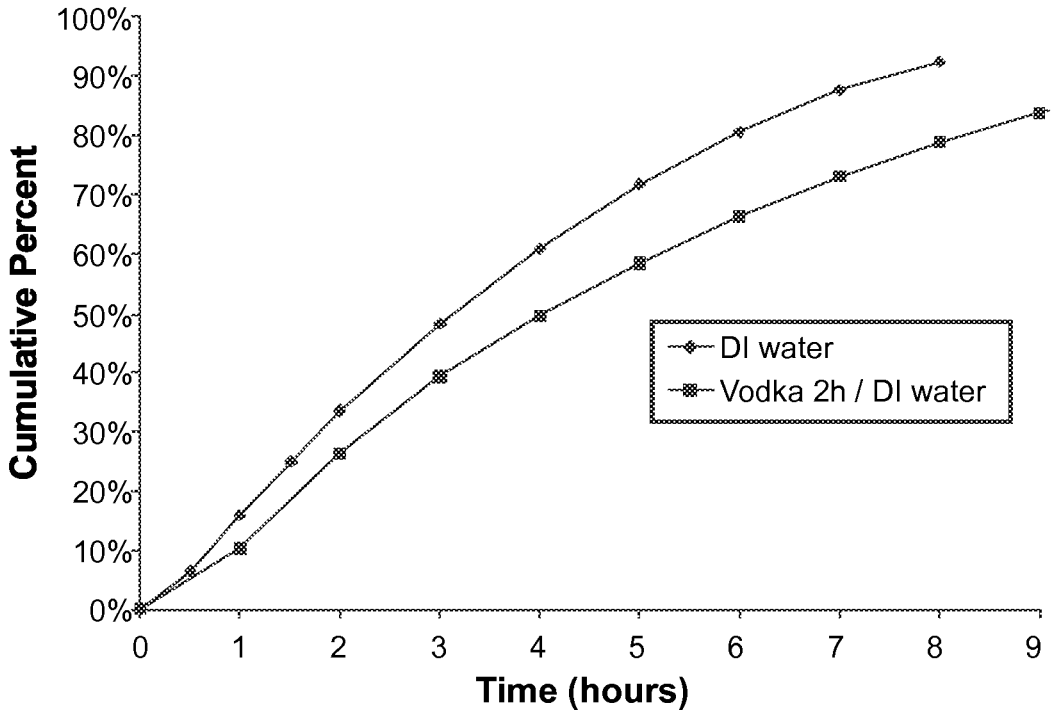
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A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20%
10%
0%
Cumulative Percent
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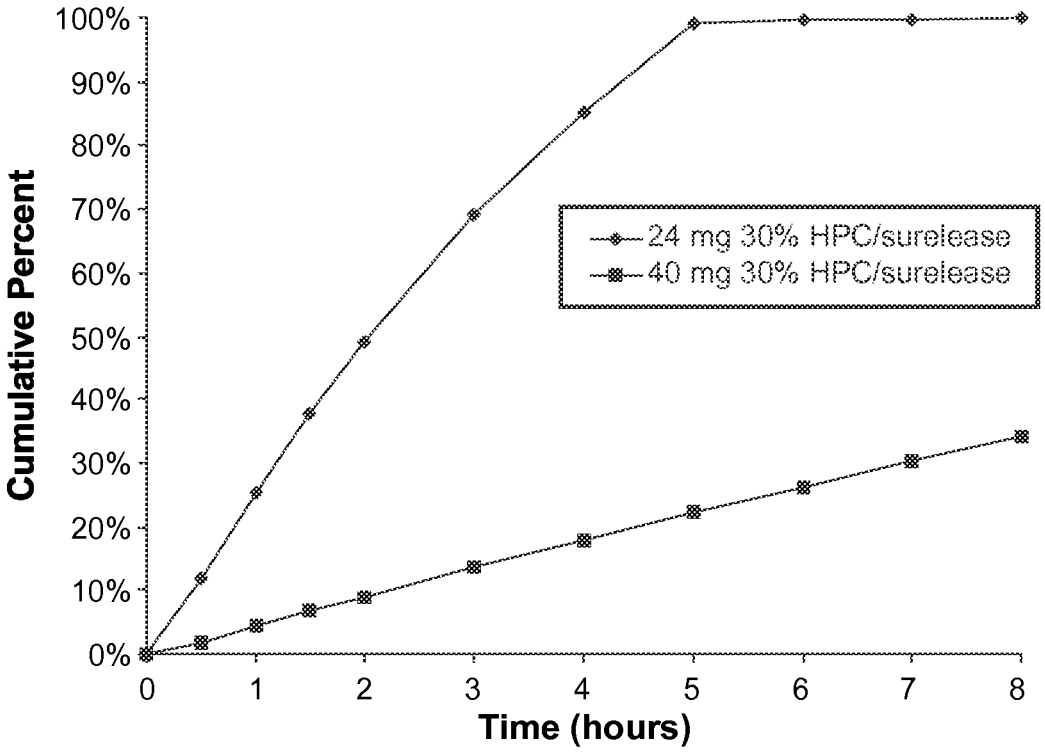
1
2
3
4
5
6
7
8
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B


Cumulative Percent
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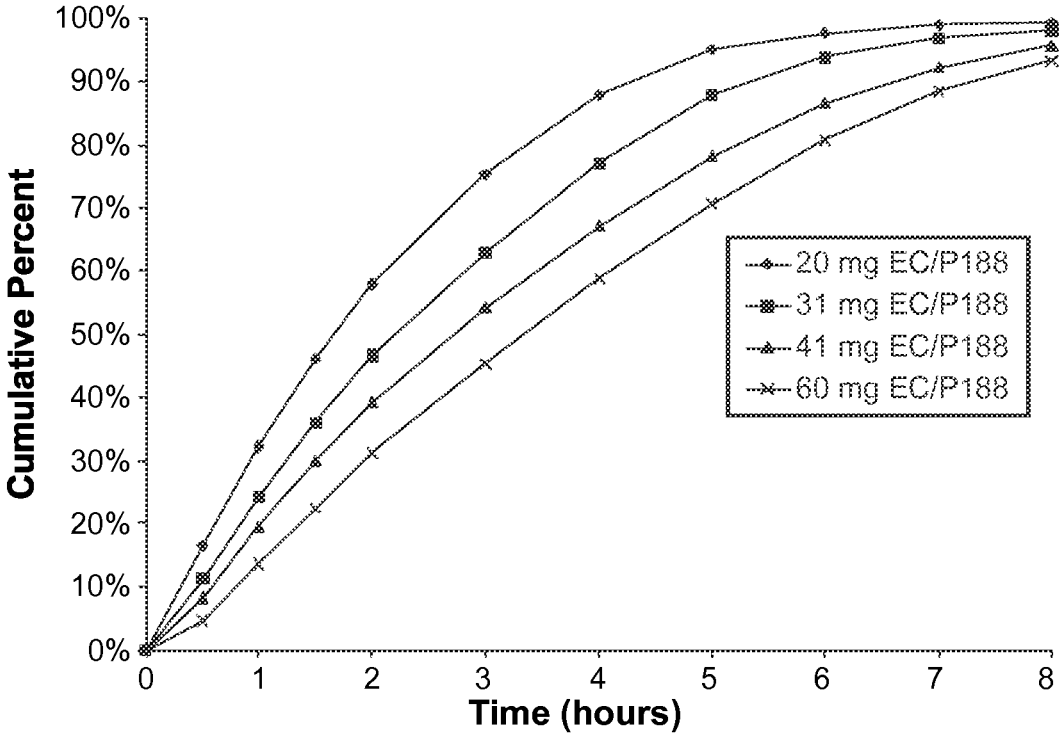
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10


Cumulative Percent
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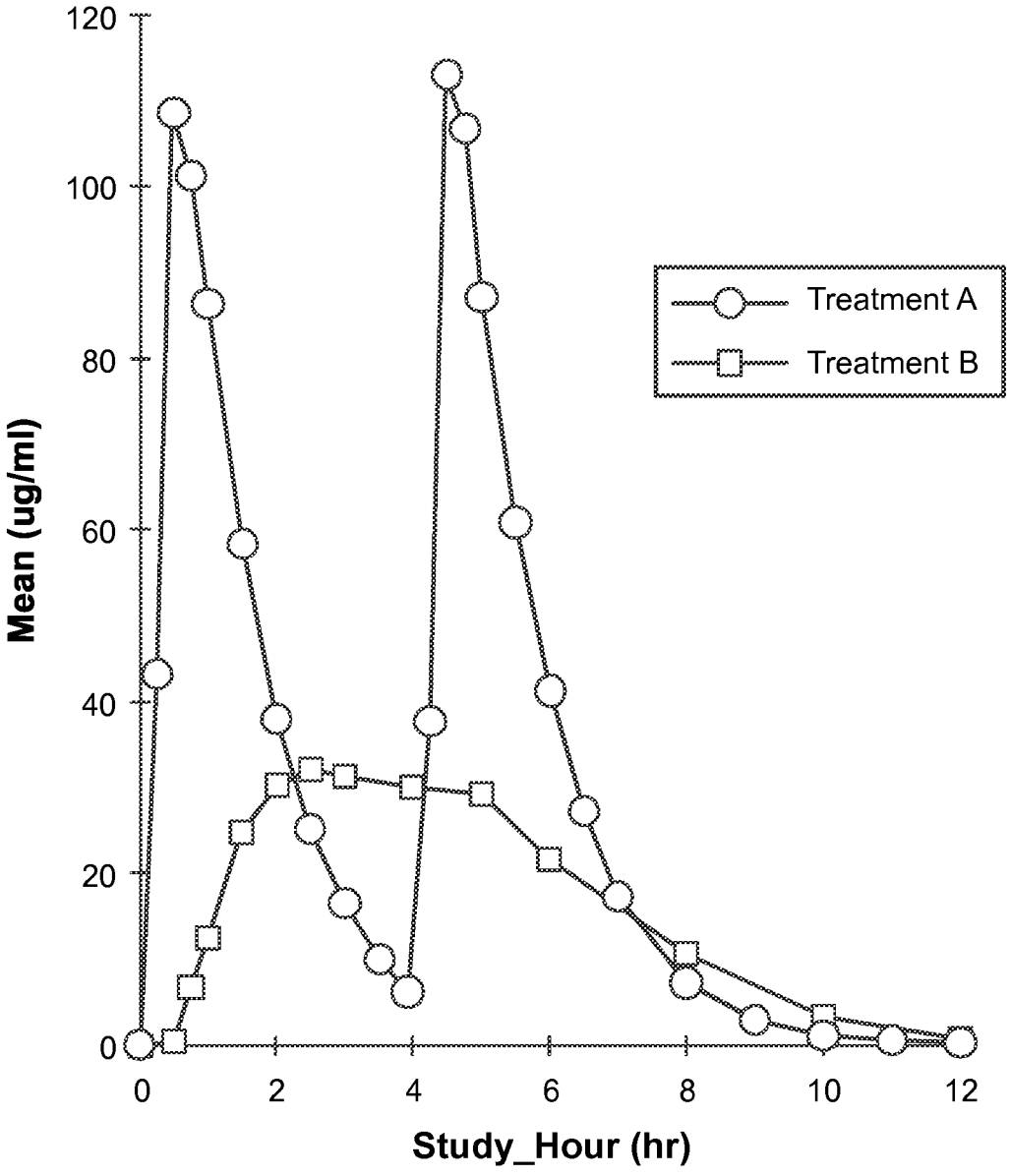
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
20 mg EC/P188
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11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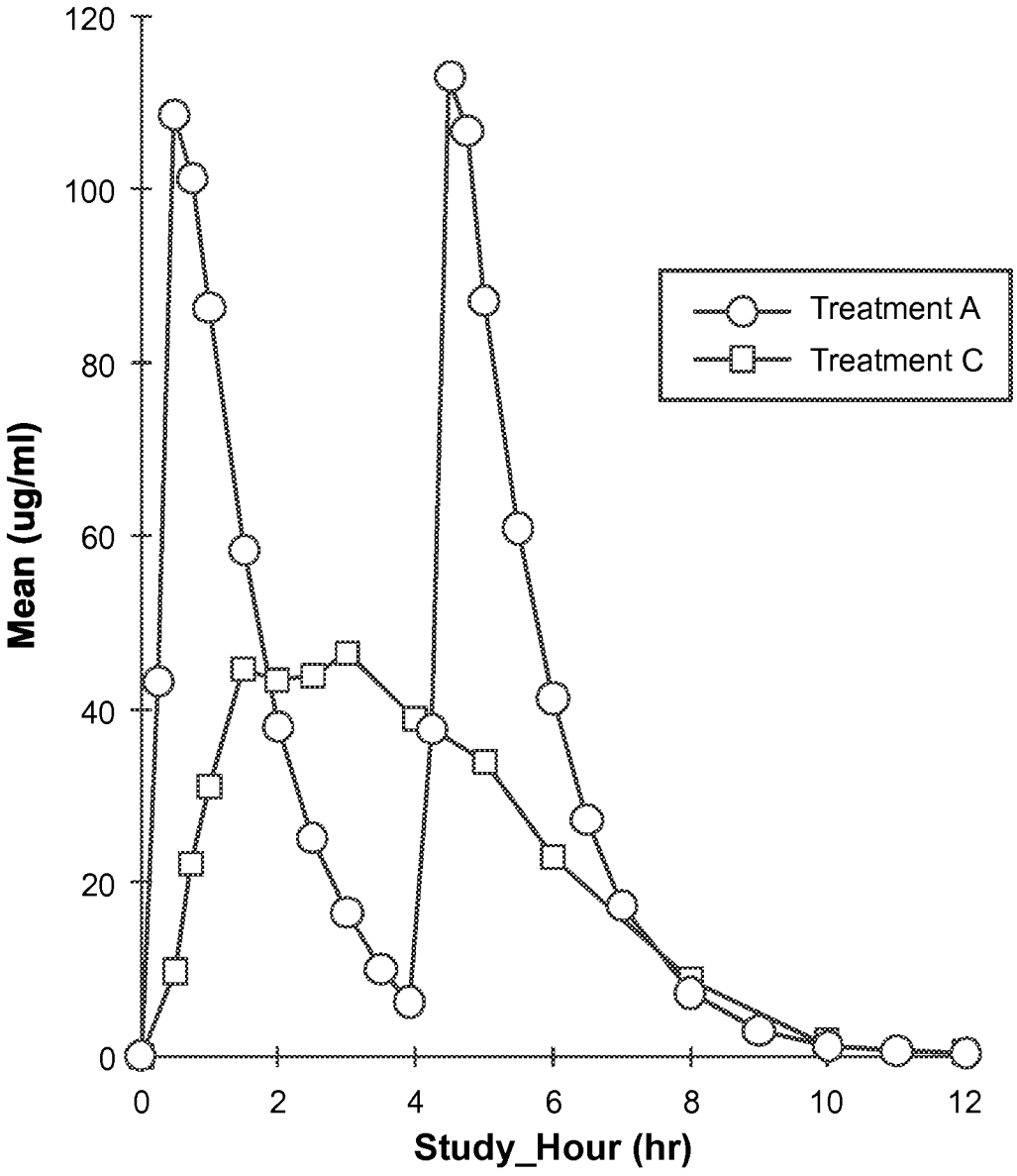
100
80
60
40
20
0
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12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100
80
60
40
20
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Mean (ug/ml)
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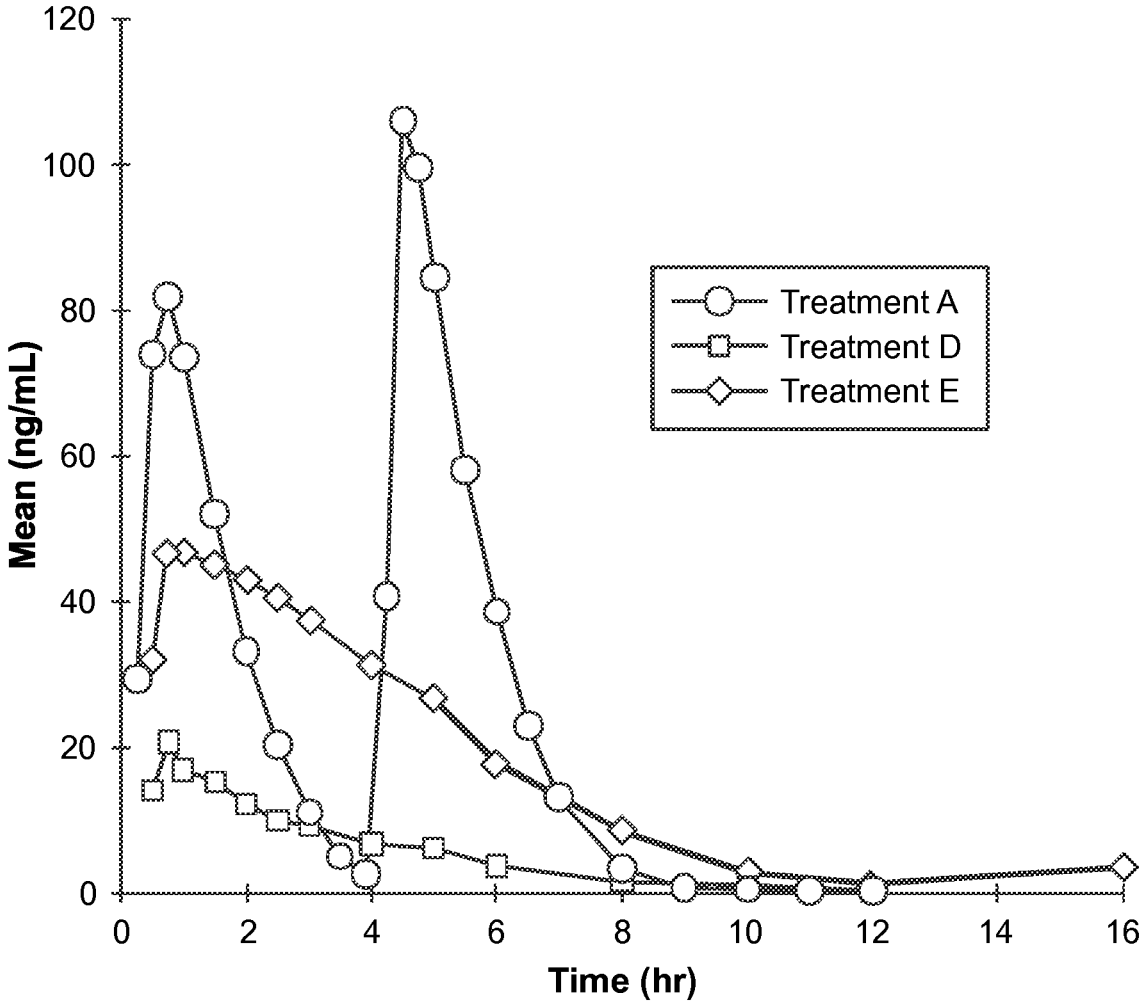
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13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100
80
60
40
20
0
Mean (ng/mL)
0
2
4
6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

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

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/916,677, filed Jun. 30, 2020, which is a continuation of U.S. patent application Ser. No. 16/712,260, filed Dec. 12, 2019, which is a continuation of U.S. patent application Ser. No. 16/025,487, filed Jul. 2, 2018, now U.S. Pat. No. 10,758,488, which is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, now abandoned, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

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

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

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia

syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., J. Muscoloskel. Pain, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., Psychosom. Med., 37, 341 (1975).

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

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

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

XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with

administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration during the night.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

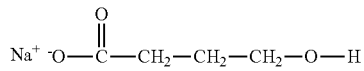
DETAILED DESCRIPTION

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

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

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

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



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

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

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

A. Controlled Release Formulations

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

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

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

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

release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

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

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

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

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present descrip-

tion is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

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

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

I. Controlled Release Component

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

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

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

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic

acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

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

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

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

II. Functional Coating Composition

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

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

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

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore

former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former, such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

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

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

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

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

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

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

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

pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

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

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

B. Immediate Release Formulations

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

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

I. Immediate Release Component

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

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

the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

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

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

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

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

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

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

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

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

EXAMPLES

Example 1—Controlled Release Core

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

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

TABLE 1A

Controlled Release Core Tablet Formulation

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

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters

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

TABLE 1C

Screen Analysis of Milled Granulation

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

Example 2—Functional Coating

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

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

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets

	Ingredient(s)	% of coat solids	% w/w of tablet	mg/tablet
5	Sodium Oxybate tablet core		95.13	781.25
6	Hydroxypropyl cellulose, NF (Klucel EF)	37.0	1.80	14.80
7	Dibutyl sebacate	5.0	0.24	2.00
8	Ethylcellulose, NF (Ethocel Standard Premium 10)	58.0	2.82	23.20
9	Ethanol, USP (200 proof)*			
10	Purified water*			
	TOTAL	100.0	100.00	821.25

*Coating solvent, removed during processing

TABLE 2A

Coating Parameters for Driam 8" Pan Coater

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

Example 3—Immediate-Release Overcoat

A solution of 20% sodium oxybate as active and 2.0% hypromellose E-15 (HPMC E-15) as film-former was pre-

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

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

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater

DRUG OVER-COATING	AVERAGE	RANGE
INLET TEMPERATURE (° C.)	59	55-63
EXHAUST TEMPERATURE (° C.)	51	50-53
PRODUCT TEMPERATURE (° C.)	43	41-49
INLET AIRFLOW (PASCAL)	>300	>300
ATOMIZATION PRESSURE (BAR)	2	2
SPRAY RATE (G/MIN)	16	14-17
PAN SPEED (RPM)	8	7-8
TOTAL RUN TIME (HRS)	4 HRS 47 MIN (COATING) 15 MIN (DRYING)	

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

Example 4—Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

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

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

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

TABLE 4A

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

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

Example 5—Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting of 7% solids in 95/5 alcohol/water. The results shown in FIG. **4** demonstrate that controlled release over a relevant time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6—Effect of Poloxamer Level in Functional Coating

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

Example 7—Effect of Hydroxypropyl Cellulose Level in Functional Coating

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

Example 8—Effect of Hydroxypropyl Cellulose Molecular Weight when used in Functional Coating

Hydroxypropyl cellulose is supplied in several molecular weight grades, many of which may be suitable for use as pore-formers in ethylcellulose films. Two such grades (Klu-

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

Example 9—Effect of Ethylcellulose Molecular Weight or Viscosity

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

Example 10—Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

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

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

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

Example 11—Aqueous Coating of Controlled Release Film

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

Example 12—Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"×0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. **11**. These results using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13—Clinical Evaluation of Controlled Release Dosage Forms

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

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

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

TABLE 5

Summary of PK Parameters for Treatments A, B, C

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

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

TABLE 6

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
			Treatment A			
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
			Treatment D			
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55
			Treatment E			
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

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

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

The invention claimed is:

1. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient 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 total gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate in the formulation;

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

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

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

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

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

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

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

7. The method of claim **6** wherein the formulation comprises a sodium salt of gamma-hydroxybutyrate.

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

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

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

11. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient 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.

12. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient 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 further comprises one or more pharmaceutically acceptable excipients selected from the group consisting of copovidone, plasacryl, hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxymethyl cellulose, 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 totalgamma-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.

13. The method of claim **12**, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

14. The method of claim **12**, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 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.

15. The method of claim **12**, wherein the sustained release portion releases about 60% to about 90% of its gamma-hydroxybutyrate by about 6 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

16. The method of claim **12**, wherein the sustained release portion comprises hydrogenated vegetable oil, hydrogenated castor oil, or mixtures thereof.

17. The method of claim **12**, wherein the formulation comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

18. The method of claim **17**, wherein the formulation comprises a sodium salt of gamma-hydroxybutyrate.

19. The method of claim **12**, wherein the immediate release portion comprises 50% by weight of the total gamma-hydroxybutyrate.

20. The method of claim **12**, wherein the one or more methacrylic acid-methyl methacrylate co-polymers comprise from about 30% to about 45% by weight of the functional coating.

21. The method of claim **12**, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl cellulose.

22. The method of claim **12**, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl methylcellulose.

23. The method of claim **12**, wherein the one or more pharmaceutically acceptable excipients are about 10% by weight of the immediate release portion.

24. The method of claim **12**, 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.

25. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient 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 and about 10% by weight of one or more pharmaceutically acceptable excipients selected from the group consisting of copovidone, plasacryl, hydroxypropyl cellulose, hydroxypropyl methylcellulose and hydroxymethyl cellulose;

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.

26. The method of claim **25**, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl methylcellulose.

27. The method of claim **25**, wherein the one or more pharmaceutically acceptable excipients comprise hydroxypropyl cellulose.

* * * * *

EXHIBIT E

US010966931B2

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

(10) **Patent No.: US 10,966,931 B2**
(45) **Date of Patent: *Apr. 6, 2021**

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

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/012,831**

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(63) Continuation of application No. 16/916,677, filed on Jun. 30, 2020, now Pat. No. 10,813,885, which is a continuation of application No. 16/712,260, filed on Dec. 12, 2019, which is a continuation of application No. 16/025,487, filed on Jul. 2, 2018, now Pat. No. 10,758,488, which is a continuation of application No. 13/071,369, filed on Mar. 24, 2011, now abandoned.

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(51) **Int. Cl.**

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

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

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

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

15 Claims, 9 Drawing Sheets

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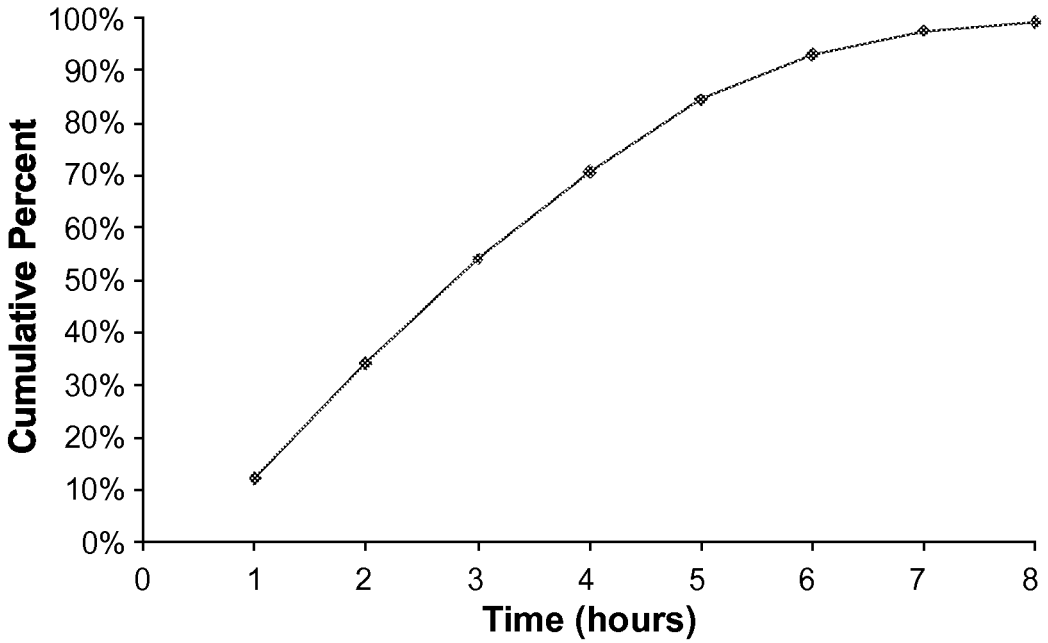
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60%
50%
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30%
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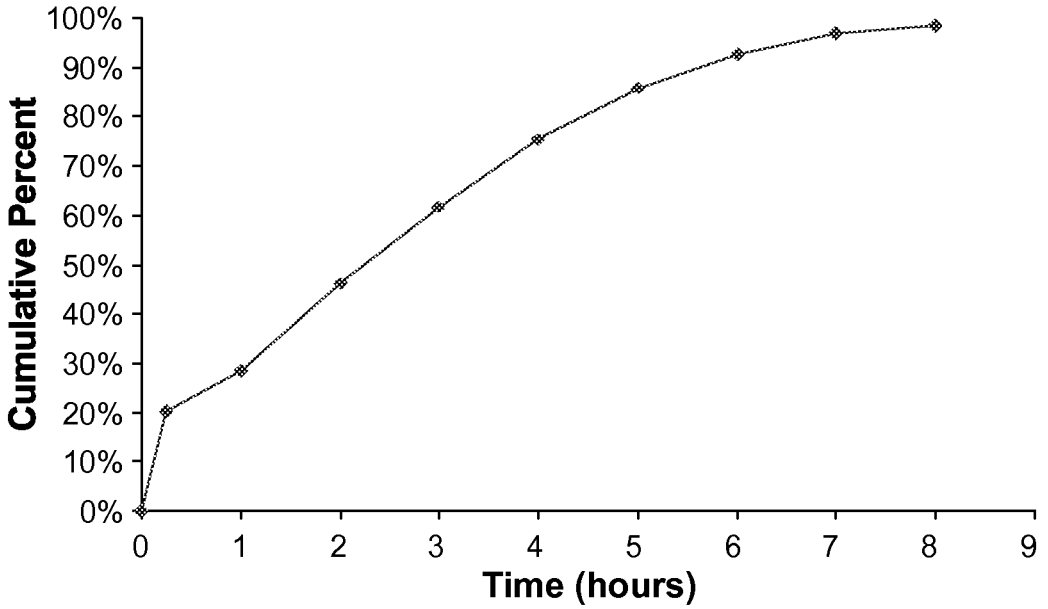
10%
0%
Cumulative Percent
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 1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Cumulative Percent
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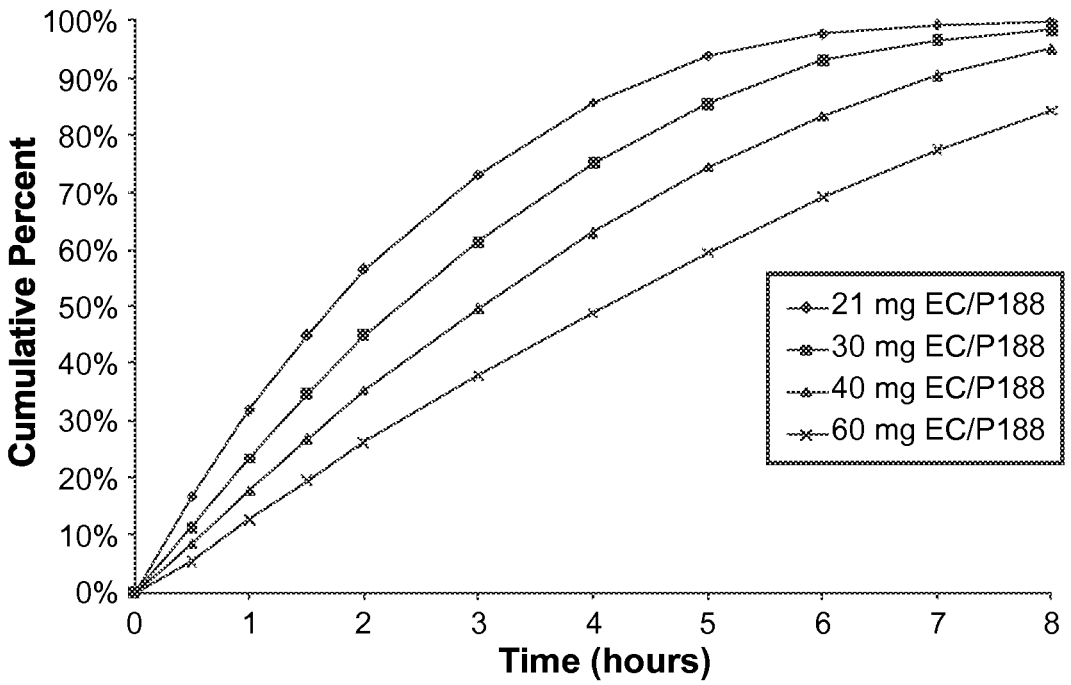
9
Time (hours)

FIG. 2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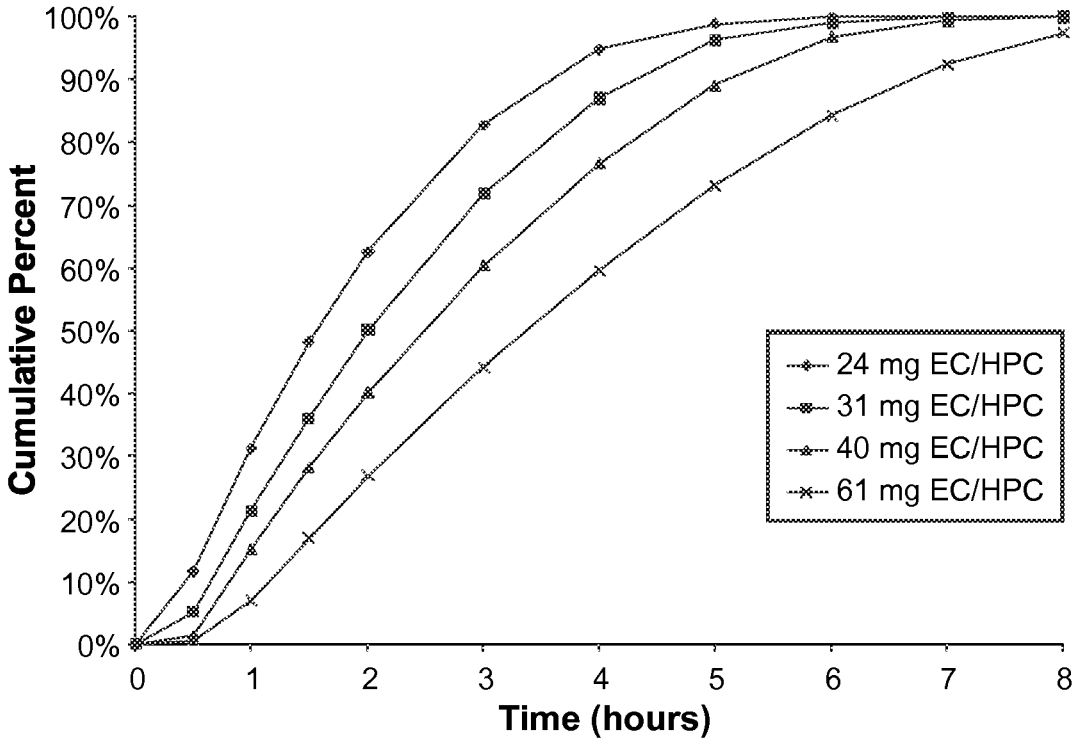
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
21 mg EC/P188
30 mg EC/P188
40 mg EC/P188
60 mg EC/P188

FIG. 3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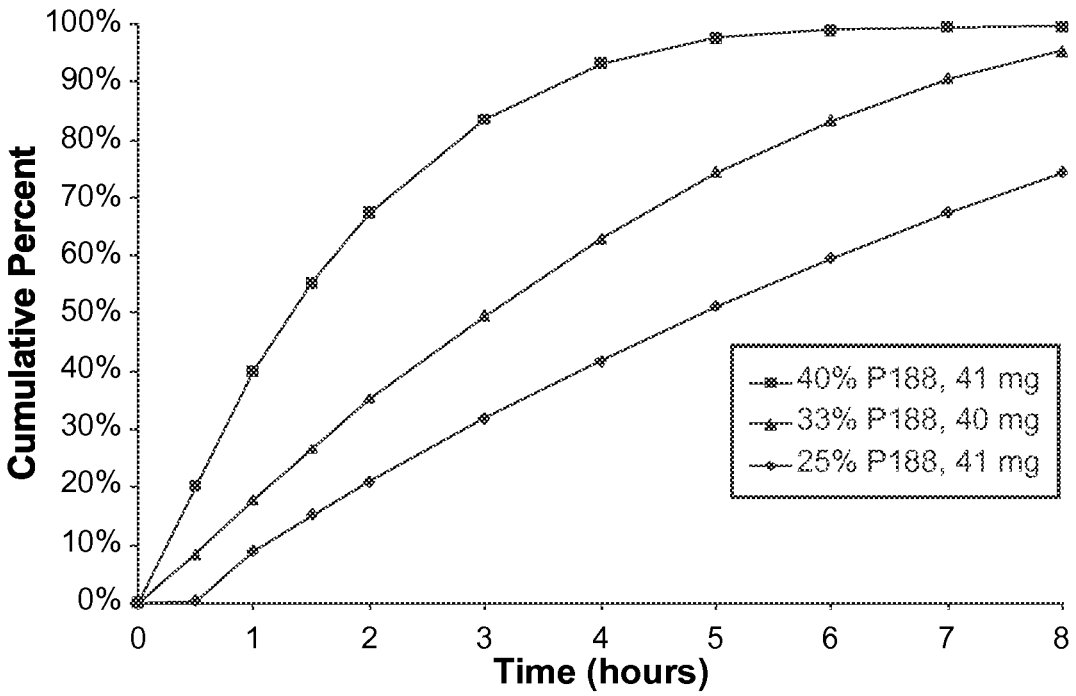
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg EC/HPC
31 mg EC/HPC
40 mg EC/HPC
61 mg EC/HPC

FIG. 4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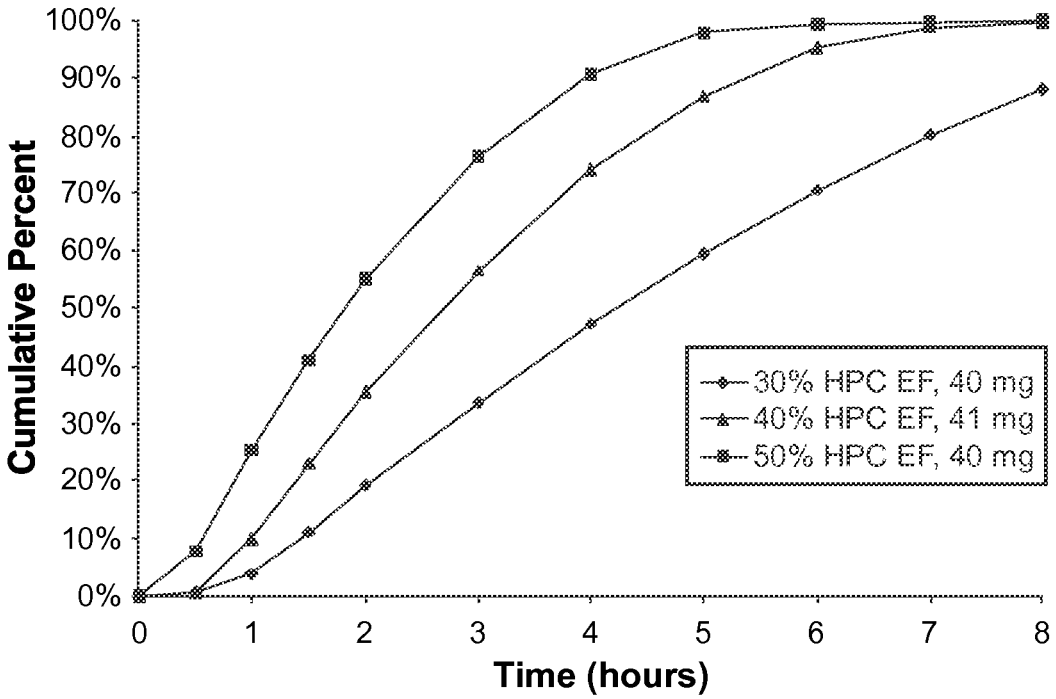
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
40% P188, 41 mg
33% P188, 40 mg
25% P188, 41 mg

FIG. 5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60%
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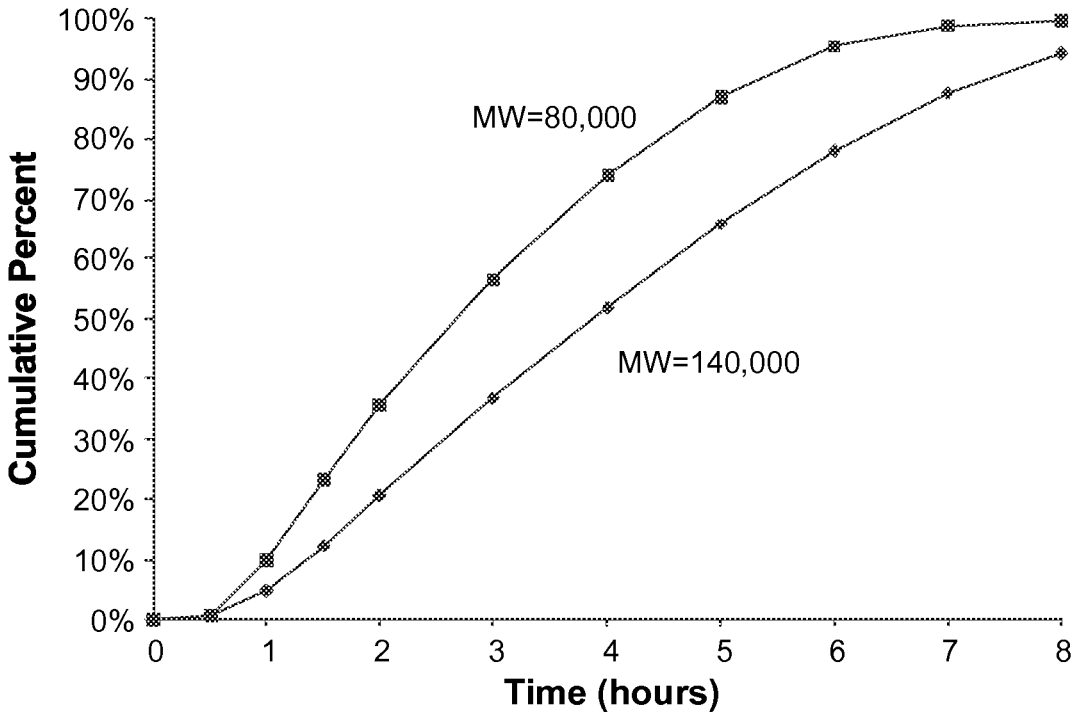
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
30% HPC EF, 40 mg
40% HPC EF, 41 mg
50% HPC EF, 40 mg

FIG. 6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40%
30%
20%
10%
0%
Cumulative Percent
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MW=140,000
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2
3
4
5
6
7
8
Time (hours)

FIG. 7

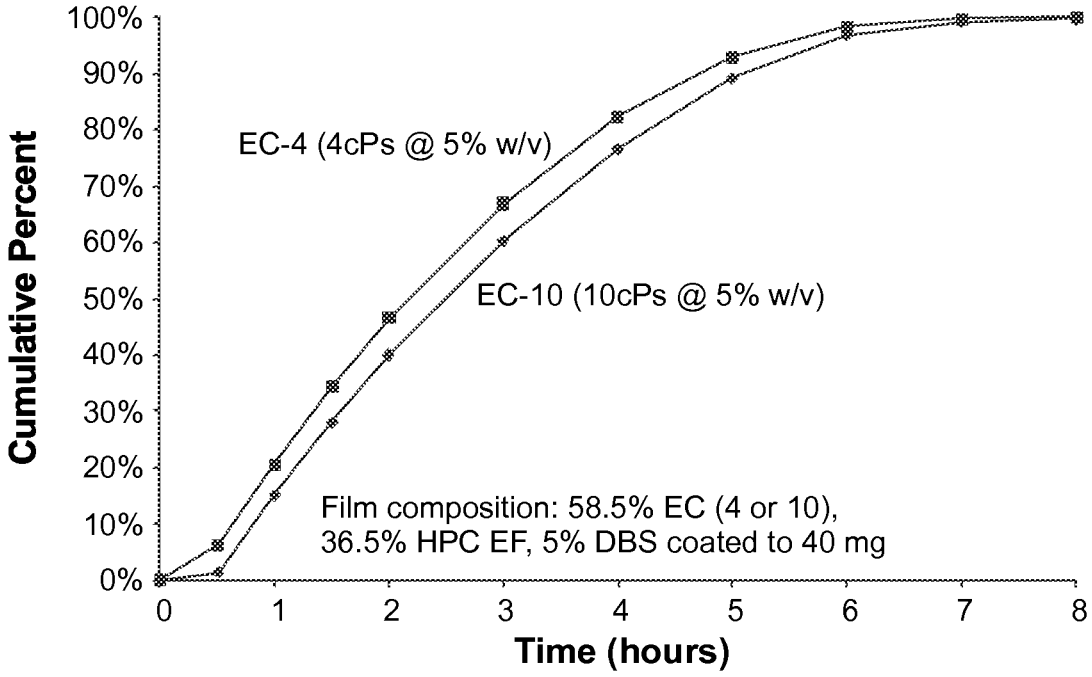
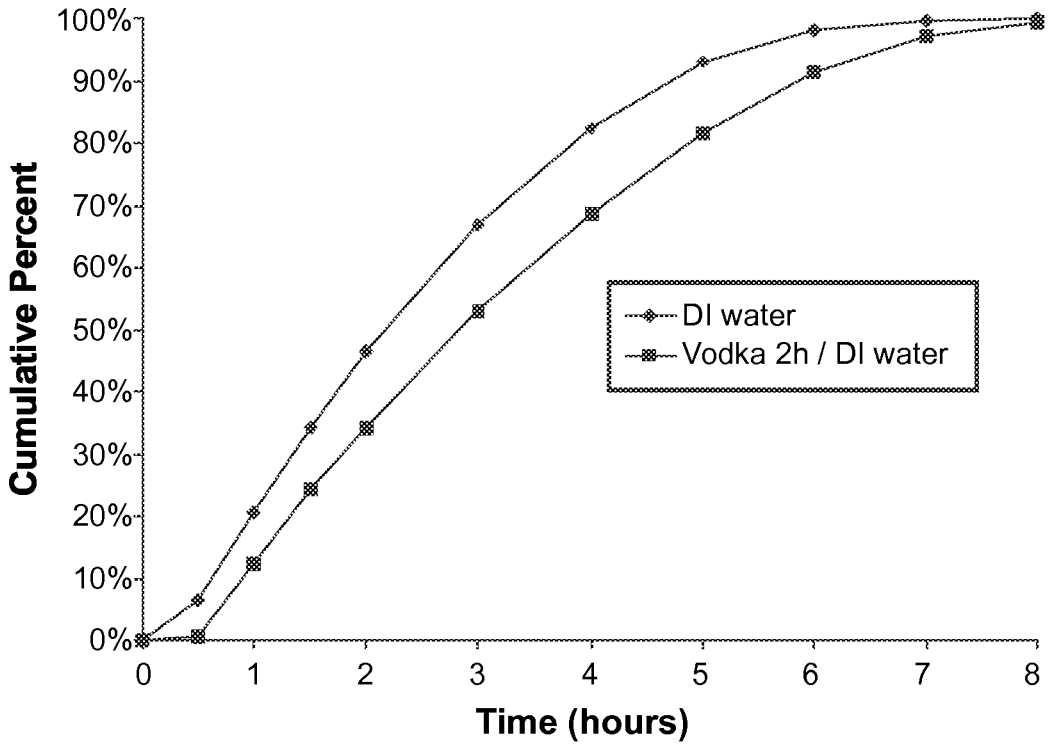

100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
EC-4 (4cPs @ 5% w/v)
EC-10 (10cPs @ 5% w/v)
Film composition: 58.5% EC (4 or 10),
36.5% HPC EF, 5% DBS coated to 40 mg
0
1
2
3
4
5
6
7
8
Time (hours)

FIG. 8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90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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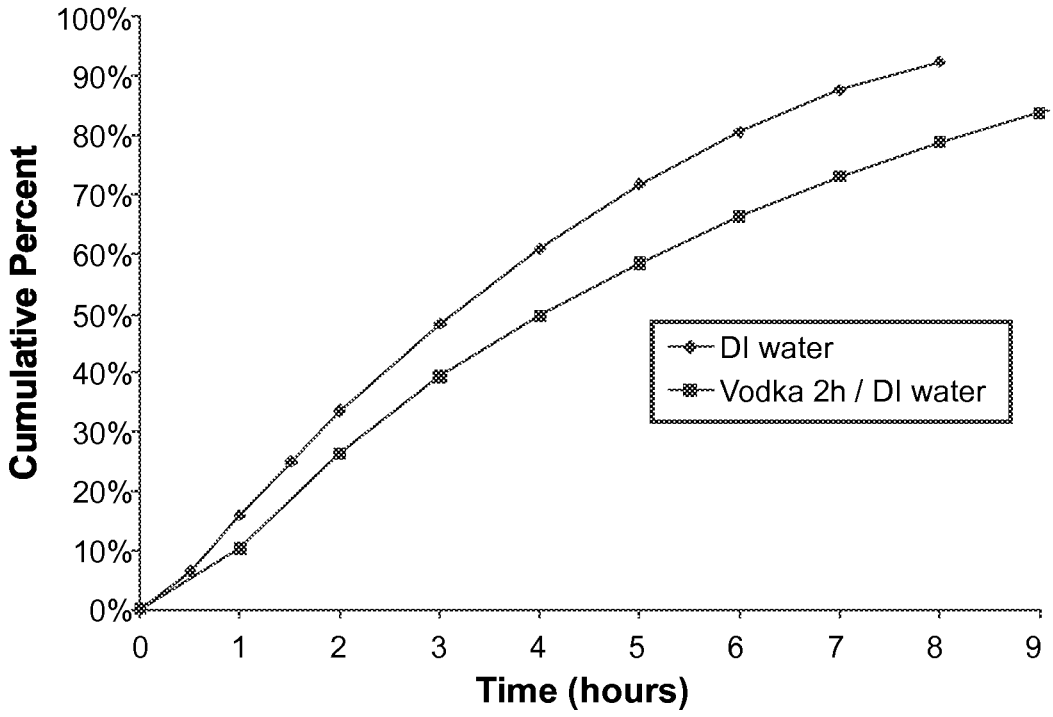
1
2
3
4
5
6
7
8
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9A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80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percent
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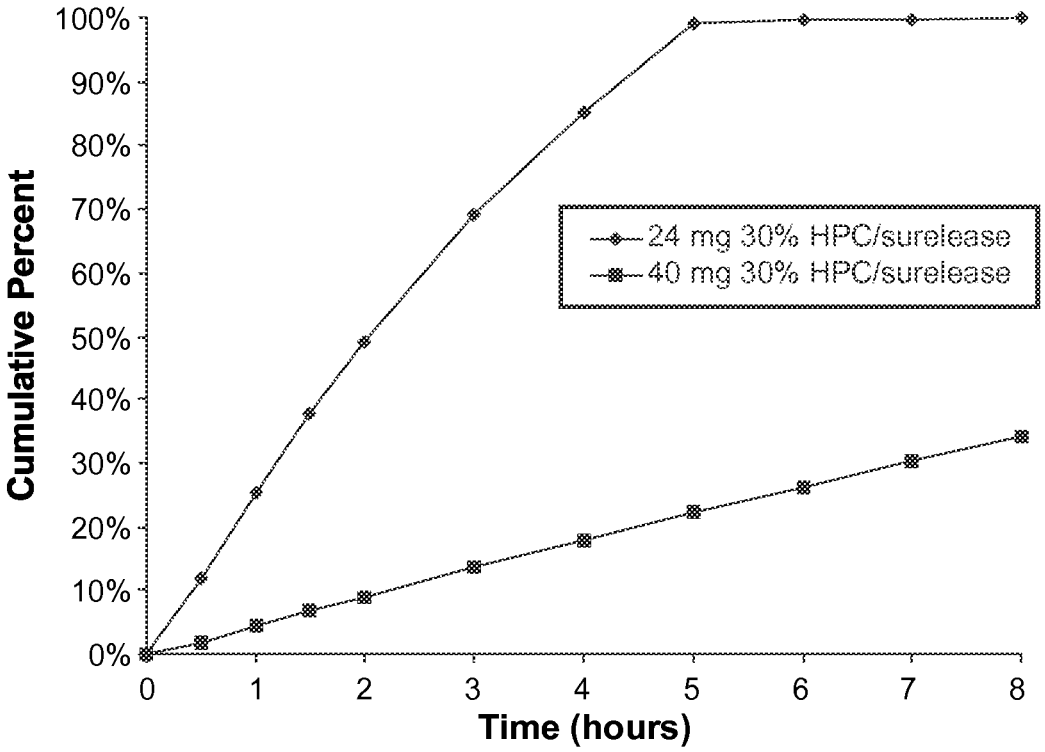
1
2
3
4
5
6
7
8
9
Time (hours)
DI water
Vodka 2h / DI water

FIG. 9B


Cumulative Percent
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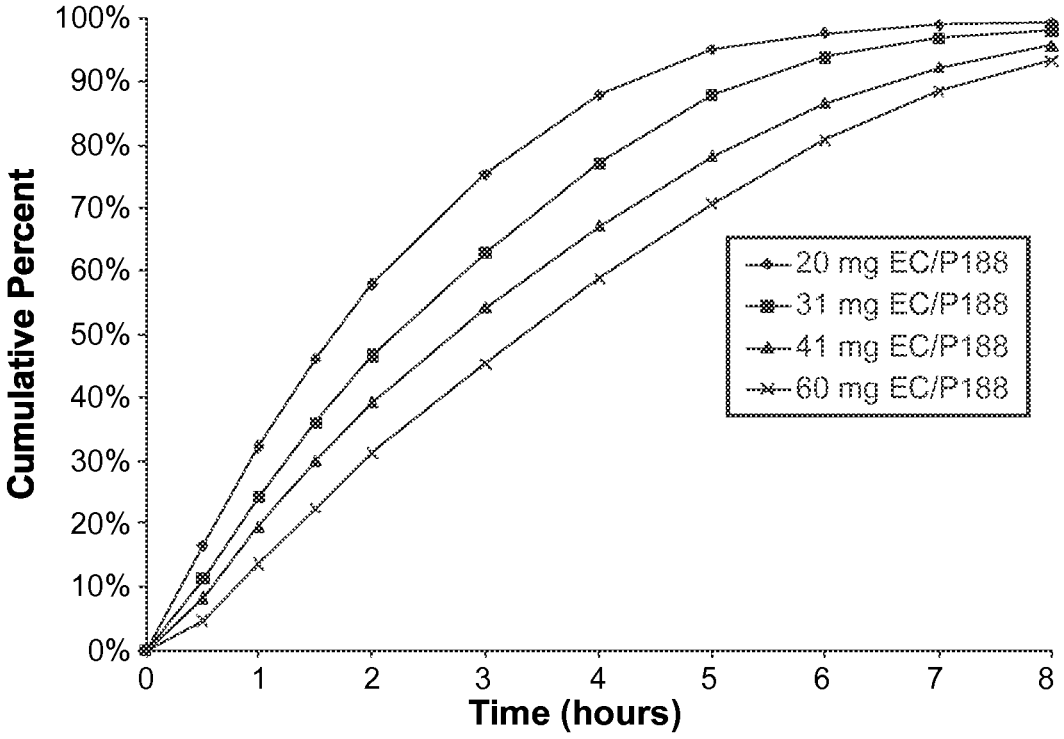
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
24 mg 30% HPC/surelease
40 mg 30% HPC/surelease

FIG. 10


Cumulative Percent
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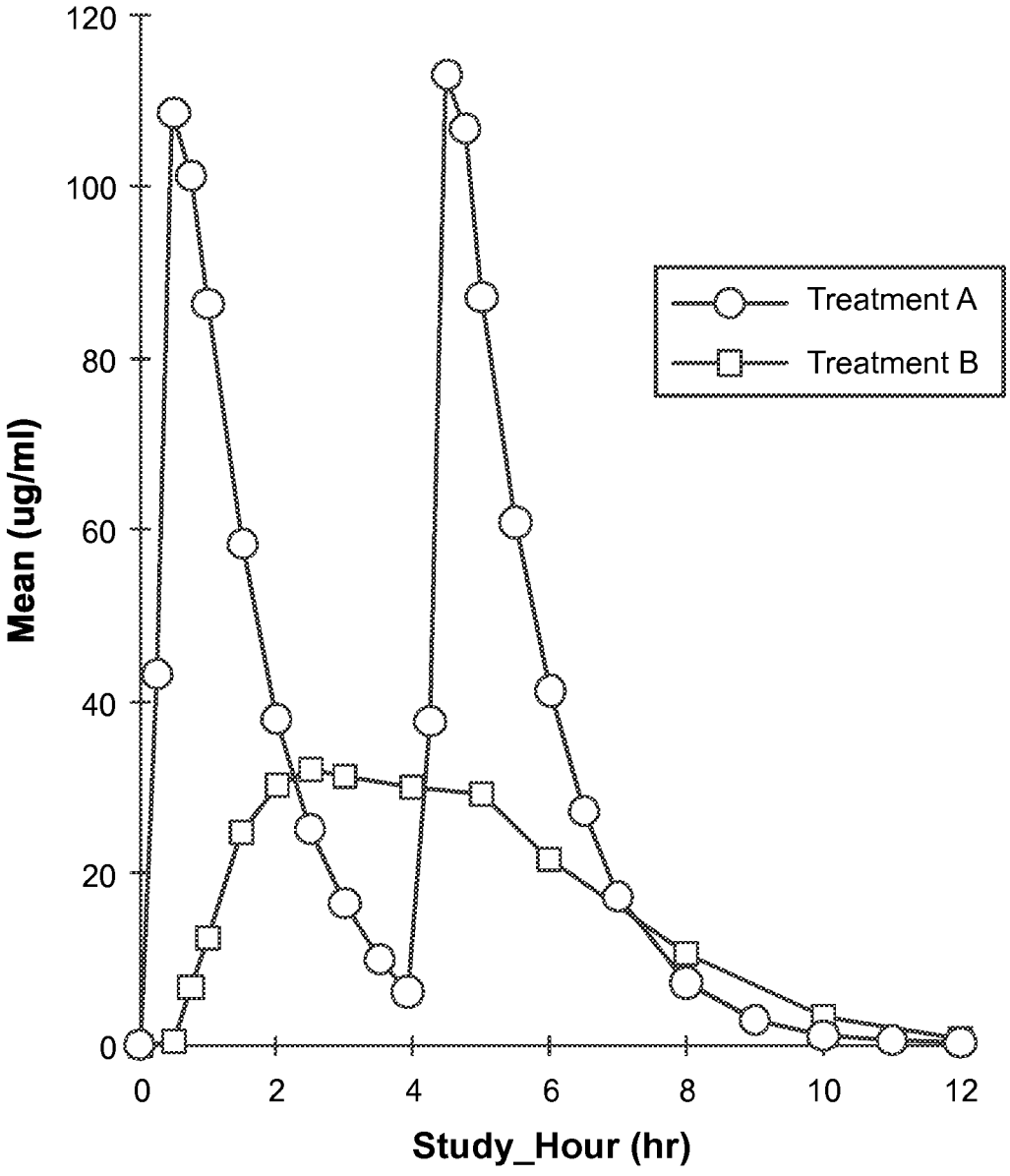
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
1
2
3
4
5
6
7
8
Time (hours)
20 mg EC/P188
31 mg EC/P188
41 mg EC/P188
60 mg EC/P188

FIG. 11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100
80
60
40
20
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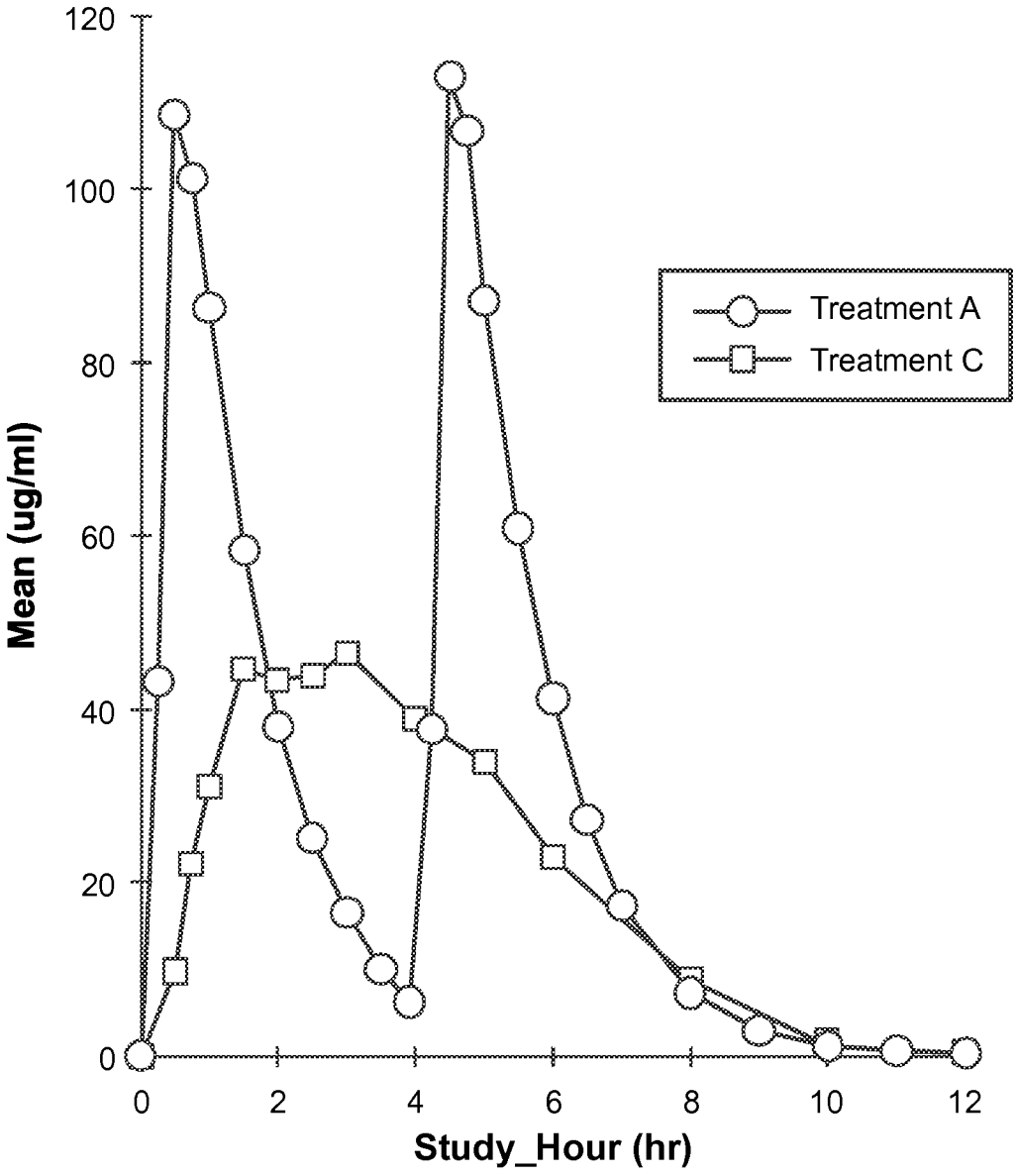
Mean (ug/ml)
0
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment B

FIG. 12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Mean (ug/ml)
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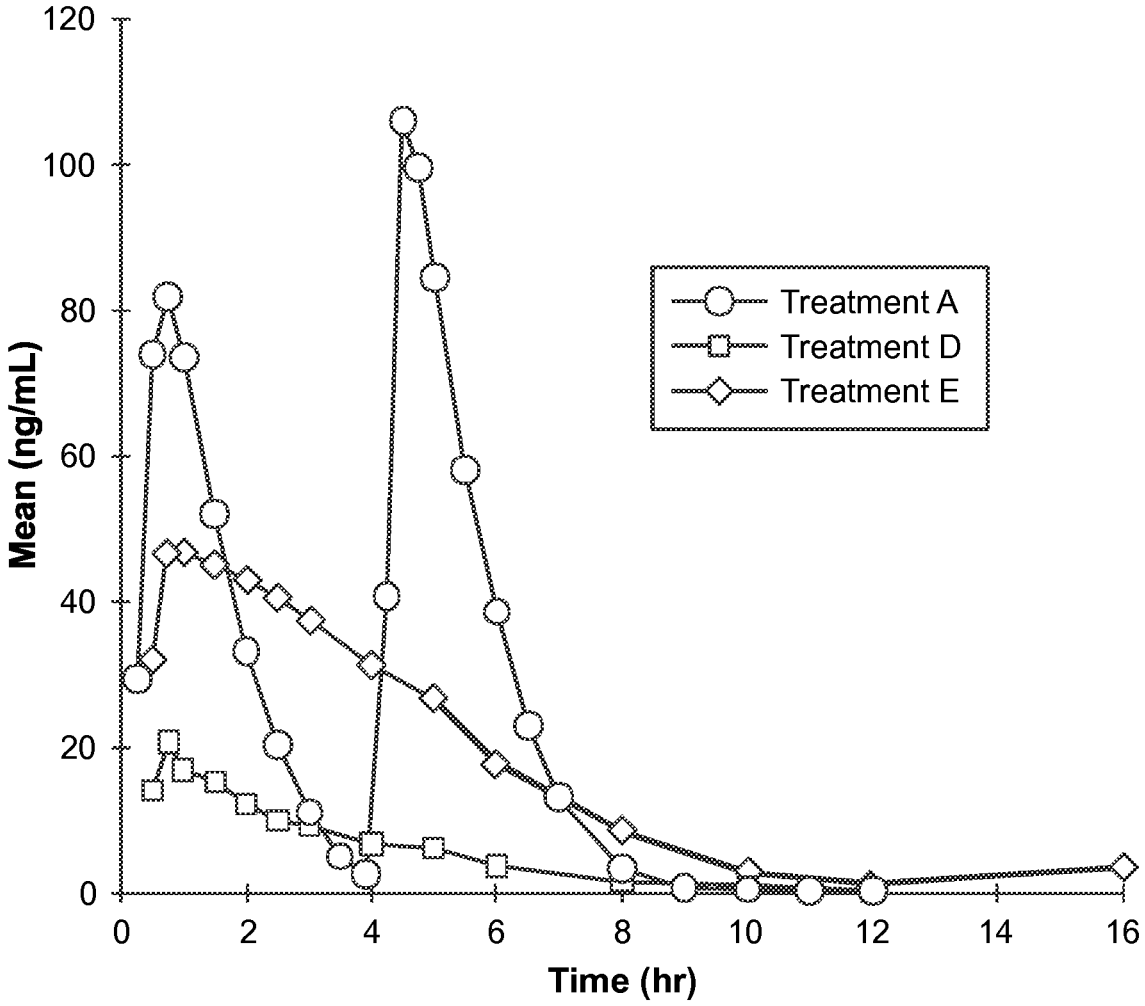
2
4
6
8
10
12
Study_Hour (hr)
Treatment A
Treatment C

FIG. 13


120
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80
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40
20
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Mean (ng/mL)
0
2
4
6
8
10
12
14
16
Time (hr)
Treatment A
Treatment D
Treatment E

FIG. 14

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

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 16/916,677, filed Jun. 30, 2020, which is a continuation of U.S. patent application Ser. No. 16/712,260, filed Dec. 12, 2019, which is a continuation of U.S. patent application Ser. No. 16/025,487, filed Jul. 2, 2018, now U.S. Pat. No. 10,758,488, which is a continuation of U.S. patent application Ser. No. 13/071,369, filed Mar. 24, 2011, now abandoned, which claims the benefit of U.S. Provisional Application No. 61/317,212, filed on Mar. 24, 2010, the contents of each of which are incorporated herein by reference.

TECHNICAL FIELD

This disclosure relates to controlled release drug compositions.

BACKGROUND

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

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

An estimated 6 million Americans suffer the often baffling symptoms of fibromyalgia or chronic fatigue syndrome. Patients with fibromyalgia, also referred to as fibromyalgia

syndrome, FMS or fibrositis syndrome, report widespread musculoskeletal pain, chronic fatigue, and non-restorative sleep. These patients show specific regions of localized tenderness in the absence of demonstrable anatomic or biochemical pathology, and patients suffering from fibromyalgia typically describe light and/or restless sleep, often reporting that they awaken feeling unrefreshed with pain, stiffness, physical exhaustion, and lethargy. See, H. D. Moldofsky et al., J. Muscoloskel. Pain, 1, 49 (1993). In a series of studies, Moldofsky's group has shown that aspects of the patients' sleep pathology are related to their pain and mood symptoms. That is, patients with fibrositis syndrome show an alpha (7.5 to 11 Hz) electroencephalographic (EEG), non-rapid-eye-movement (NREM) sleep anomaly correlated with musculoskeletal pain and altered mood. Moldofsky has interpreted this alpha EEG NREM sleep anomaly to be an indicator of an arousal disorder within sleep associated with the subjective experience of non-restorative sleep. See H. D. Moldofsky et al., Psychosom. Med., 37, 341 (1975).

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

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

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

XYREM® sodium oxybate oral solution, the FDA approved treatment for cataplexy and excessive daytime sleepiness associated with narcolepsy, contains 500 mg sodium oxybate/ml water, adjusted to pH=7.5 with malic acid. In man, the plasma half-life of sodium oxybate given orally is about 45 minutes and doses of 2.25 grams to 4.5 grams induce about 2 to 3 hours of sleep (See, L. Borgen et al., *J. Clin. Pharmacol.*, 40, 1053 (2000)). Due to the high doses required and very short half-life of sodium oxybate, optimal clinical effectiveness in narcolepsy typically requires dosing of the drug twice during the night, with

administration typically recommended at 2.5 to 4 hour intervals. For each dose, a measured amount of the oral solution is removed from the primary container and transferred to a separate container where it is diluted with water before administration. The second dose is prepared at bedtime and stored for administration during the night.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

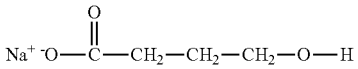
DETAILED DESCRIPTION

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

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

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

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



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

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

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

A. Controlled Release Formulations

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

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

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

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

release component after two hours, between about 30% and about 50% of the initial drug content of the controlled release component after 4 hours, between about 50% and about 70% of the initial drug content of the controlled release component after 6 hours, and not less than about 80% of the initial drug content of the controlled release component after 10 hours post administration. In yet other embodiments, a controlled release dosage form as described herein may be formulated to release to the gastro-intestinal tract not more than about 20% of the initial drug content of the controlled release component after the first hour post-administration, between about 20% and about 50% of the initial drug content of the controlled release component after 2 hours, between about 50% and about 80% of the initial drug content of the controlled release component after 4 hours, and not less than 85% of the initial drug content of the controlled release component after 8 hours post-administration. The rate and extent of the absorption of GHB varies along the length of the GI tract with lower amounts absorbed in the more distal portions (i.e., the ileum and the colon).

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

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

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

Controlled release formulations described herein may be formulated to completely release a drug within a desired time interval. As has been reported, the bioavailability of GHB decreases in the lower GI, with bioavailability decreasing the lower the drug is delivered in the GI (See, e.g., U.S. Patent Publication No. US2006/0210630). Therefore, in certain embodiments, the controlled release dosage forms are provided that deliver substantially all the GHB contained therein over a sustained period of time that is long enough to increase patient convenience, yet short enough to reduce dosing of GHB in the lower GI. In specific embodiments, controlled release GHB dosage forms are provided that deliver approximately 90% or more of the GHB contained within the controlled release formulation within about 4 to about 10 hours of administration. For example, dosage forms for the controlled release of GHB as described herein may be formulated to deliver approximately 90% or more of the drug included within the controlled release formulation within about 4, 5, 6, 7, 8, 9, 10, or 12 hours of administration. In one such embodiment, a dosage form for the sustained delivery of GHB according to the present descrip-

tion is formulated to deliver more than 90% of the GHB included within the controlled release formulation within 12 hours post-administration. Such embodiments serve to not only provide controlled release of GHB, but they also work to deliver GHB where bioavailability is highest, which can also provide increased dose consistency.

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

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

I. Controlled Release Component

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

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

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

The CR core may include one or more lubricants to improve desired processing characteristics. In one embodiment, the CR core may include one or more lubricants selected from at least one of magnesium stearate, stearic

acid, calcium stearate, hydrogenated castor oil, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium stearyl fumarate, and zinc stearate. In another embodiment, one or more lubricants may be added to the CR core in a range of about 0.5% to 5% by weight. In particular embodiments, a CR core as disclosed herein may comprise a lubricant in a range of about 0.5% to 2% by weight, about 1% to 2% by weight, about 1% to 3% by weight, about 2% to 3% by weight, and about 2% to 4% by weight. In one such embodiment, one or more lubricants may be present in the CR core in an amount selected from about 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, and 5% by weight. Still lower lubricant levels may be achieved with use of a "puffer" system during tabletting, which applies lubricant directly to the punch and die surfaces rather than throughout the formulation.

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

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

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

II. Functional Coating Composition

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

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

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

The permeability of the base polymer included in a functional coating as described herein may be modified by including a pore former in the base polymer. In one such embodiment, the functional coating composition including the pore former may be obtained by combining the pore

former with the base polymer material in solution according to conventional techniques. A pore former as disclosed herein may include at least one polymeric pore former, such as hydroxyalkyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycols, polyvinyl alcohol, povidone, copovidone, and poloxamers, such as 188 or 407. In one embodiment, a pore former as disclosed herein may include at least one small-molecule pore former, such as a water soluble sugar or organic acid, including, for example, citric acid or sorbitol. In one such embodiment, a small-molecule pore former may be water soluble active agent, such as a pharmaceutically acceptable salt of GHB. In yet another embodiment, the pore former may comprise a polymer that expands in the presence of the drug included in the CR core, wherein expansion of the pore former may cause an increase in permeability of the functional coating composition. For example, in some embodiments, the functional coating composition may comprise a pore former that that expands or swells in the presence of sodium oxybate. In one such embodiment, the pore former includes a suitable carbomer.

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

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

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

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

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

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

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

pan-coating process may include the use of an alcohol solvent, such as ethanol. For example, an alcohol-solvent based pan-coating process may utilize a 95% ethanol and 5% water (w/w) solvent.

In one embodiment, the functional coating compositions as described herein may be applied using a fluid bed coating process such as a Wurster fluid bed film coating process. In another embodiment, the functional coating composition may be applied using a compression coating process. In yet another embodiment, the functional coating composition may be applied using a phase inversion process. In certain embodiments, the functional coating composition as disclosed herein may be applied over a suitable subcoating.

III. Moisture Barrier/Cosmetic Coatings

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

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

B. Immediate Release Formulations

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

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

I. Immediate Release Component

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

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

the IR component may comprise sodium oxybate in an amount of selected from a range of between about 75% and 98%, between about 80% and 98%, between about 85% and 98%, between about 90% and 98%, and between about 95% and 98% by weight.

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

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

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

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

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

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

In particular embodiments, the integrated dosage form may be formulated such that the controlled release formulation begins release of drug substantially simultaneously with delivery of the drug from the IR component. Alternatively, the integrated dosage form may be formulated such that controlled release formulation exhibits a start-up time lag. In one such embodiment, for example, the integrated dosage form maybe formulated and configured such that start-up of delivery of drug from the controlled release

composition occurs after delivery of drug from the IR component is substantially complete. Where a start-up lag time is desired, an enteric coating may be applied over the controlled release component (e.g., over a functional coating), but such a coating would necessarily limit the start-up lag to gastric residence and its associated variability. Use of enteric pore-formers would also impart a start-up lag, and such an embodiment would be more sensitive to food effects and gastric motility. Where a less pH-sensitive start-up lag time is desired, the delay may be accomplished or adjusted by the use of one or more coatings and films, including the functional coating provided over a CR core and, where utilized, the moisture barrier or cosmetic overcoats. In particular, start-up lag time as disclosed herein may be adjusted by modifying the formulation, thickness, and/or weight of the functional coating provided over the CR core, the moisture barrier layer or one or more non-functional or cosmetic overcoats.

EXAMPLES

Example 1—Controlled Release Core

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

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

TABLE 1A

Controlled Release Core Tablet Formulation

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

*Granulation solvent, removed during drying step

TABLE 1B

Granulation Parameters WET GRANULATION	
GRANULATION SOLUTION ADDITION RATE (G/MIN)	250
TOTAL GRANULATION TIME (INCLUDING SOLUTION ADDITION AND WET MASSING TIME)	7 MINUTES
IMPELLER SPEED (RPM)	300
CHOPPER SPEED (RPM)	1800

DRYING	SUBLOT 1	SUBLOT 2
DRYING INLET TEMPERATURE (° C.)	70	70
TOTAL DRYING TIME (MIN)	17	18
EXHAUST TEMPERATURE AT END OF DRYING (° C.)	47	48
LOD (% WT LOSS)	0.84	0.92

TABLE 1C

Screen Analysis of Milled Granulation

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

Example 2—Functional Coating

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

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

TABLE 2A

Formulation of Sodium Oxybate Sustained-Release Tablets

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

TABLE 2A-continued

Formulation of Sodium Oxybate Sustained-Release Tablets

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

*Coating solvent, removed during processing

TABLE 2B

Coating Parameters for Driam 8" Pan Coater

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

Example 3—Immediate-Release Overcoat

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

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

TABLE 3A

Parameters for Immediate-Release Overcoating with 8" Driam Coater

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

TABLE 3A-continued

Parameters for Immediate-Release Overcoating with 8" Driam Coater

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

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

Example 4—Effect of Membrane Weight with Poloxamer as Pore Former in Functional Coating

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

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

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

TABLE 4A

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

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

Example 5—Effect of Membrane Weight with Hydroxypropyl Cellulose as Pore Former in Functional Coating

Following procedures of Example 4, 12 tablets from Example 1 were coated with a film consisting of 36.5% HPC-EF, 5.0% dibutyl sebacate (DBS), and 58.5% EC-10 (all percentages by weight) coated from a solution consisting of 7% solids in 95/5 alcohol/water. The results shown in FIG. **4** demonstrate that controlled release over a relevant

time period is achieved with membrane weights ranging from at least 21-60 mg/tablet, and that duration of delivery increases as the membrane weight increases.

Example 6—Effect of Poloxamer Level in Functional Coating

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

Example 7—Effect of Hydroxypropyl Cellulose Level in Functional Coating

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

Example 8—Effect of Hydroxypropyl Cellulose Molecular Weight when Used in Functional Coating

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

Example 9—Effect of Ethylcellulose Molecular Weight or Viscosity

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

Example 10—Demonstration of Alcohol Ruggedness of Controlled Release Sodium Oxybate Tablets

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

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

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

Example 11—Aqueous Coating of Controlled Release Film

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

Example 12—Calcium Oxybate Controlled Release

A controlled release dosage form for delivery of calcium oxybate was prepared by generally following procedures of Example 1 found in U.S. Pat. No. 4,393,296 (Klosa, Production of Nonhygroscopic Salts of 4-Hydroxybutyric Acid). The isolated calcium oxybate was milled to pass through a 16-mesh screen. For this study, a small sample comprising 9.3 grams of calcium oxybate was blended with 0.19 grams of sodium stearyl fumarate (Pruv, JRS Pharma, Rosenberg, Germany). 800 mg aliquots of this 98% calcium oxybate and 2% sodium stearyl fumarate were then directly compressed into tablets using 0.325"×0.705" modified oval tooling and a Carver press with 1-ton applied force. Following procedures of Example 4, nine tablets were coated with a film having 33% poloxamer 188 and 67% EC-10 from a solution of 7% w/w solids in 95/5 alcohol/water. Two tablets were removed at each intermediate coating weight corresponding to 20 mg, 32 mg, 41 mg, and finally at 60 mg. The dissolution profiles are shown as FIG. **11**. These results

using calcium oxybate follow the general behavior of sodium oxybate demonstrated in Example 4.

Example 13—Clinical Evaluation of Controlled Release Dosage Forms

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

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

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

TABLE 5

Summary of PK Parameters for Treatments A, B, C

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

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

TABLE 6

Summary of PK Parameters for Treatments A, D, E

	λ_z (1/hr)	$T_{1/2}$ (hr)	Tmax (hr) [a]	Cmax (ug/ml)	AUClast (hr * ug/ml)	AUCinf (hr * ug/ml)
Treatment A						
N	30	30	30	30	30	30
Mean	1.08	0.71	4.50 (0.50, 5.50)	114.59	301.28	301.59
SD	0.31	0.27		27.91	100.85	100.87
CV %	29.00	37.90		24.36	33.47	33.45
Mean	1.03	0.67		111.20	285.47	285.79
Treatment D						
N	30	30	30	30	30	30
Mean	0.46	1.63	0.75 (0.50, 2.50)	25.10	64.44	65.58
SD	0.14	0.47		7.33	20.36	20.26
CV %	30.27	29.00		29.20	31.60	30.90
Mean	0.44	1.56		24.01	61.31	62.55
Treatment E						
N	30	30	30	30	30	30
Mean	0.59	1.36	1.00 (0.50, 5.00)	59.52	242.30	243.80
SD	0.20	0.64		17.72	117.15	116.79
CV %	34.57	46.91		29.77	48.35	47.91
Mean	0.55	1.25		56.89	216.33	218.12

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

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

The invention claimed is:

1. A method for treating cataplexy or excessive daytime sleepiness associated with narcolepsy in a patient in need thereof comprising delivering to the patient a formulation comprising 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, wherein:

the sustained release portion comprises a functional coating and a core, the functional coating is deposited over the core;

the core comprises at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate;

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 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.

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

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

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

5. The method of claim **1**, wherein the sustained release portion comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

6. The method of claim **5**, wherein the sustained release portion comprises a sodium salt of gamma-hydroxybutyrate.

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

8. The method of claim **1**, wherein the formulation further comprises an immediate release portion comprising at least one pharmaceutically active ingredient selected from gamma-hydroxybutyrate and pharmaceutically acceptable salts of gamma-hydroxybutyrate.

9. The method of claim 8, wherein the immediate release portion comprises a calcium, lithium, potassium, sodium or magnesium salt of gamma-hydroxybutyrate or mixtures thereof.

10. The method of claim 9, wherein the immediate release portion comprises a sodium salt of gamma-hydroxybutyrate.

11. The method of claim 8, wherein the immediate release portion is a dry powder formulation, an immediate release tablet, an encapsulated formulation, a liquid solution, or liquid suspension.

12. The method of claim 8, 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.

13. The method of claim 8, wherein 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 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.

14. The method of claim 13, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 7 hours when tested in a dissolution apparatus 2 in deionized water at a temperature of 37° C. and a paddle speed of 50 rpm.

15. The method of claim 13, wherein the formulation releases greater than about 90% of its gamma-hydroxybutyrate by 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.

* * * * *

EXHIBIT F

Seeking Alpha

Transcripts Healthcare

Avadel Pharmaceuticals plc (AVDL) CEO Greg Divis on Q1 2021 Results - Earnings Call Transcript

May 10, 2021 1:22 PM ET | **Avadel Pharmaceuticals plc (AVDL)**

Avadel Pharmaceuticals plc (NASDAQ:AVDL) Q1 2021 Earnings Conference Call May 10, 2021 8:30 AM ET

Company Participants

Tom McHugh - Chief Financial Officer

Greg Divis - Chief Executive Officer

Jennifer Gudeman - Vice President of Medical and Clinical Affairs

Richard Kim - Chief Commercial Officer

Conference Call Participants

Paul Matteis - Stifel

David Amsellem - Piper Sandler

Francois Brisebois - Oppenheimer

Madhu Yennawar - SVB Leerink

David Sherman - Lifesci Capital

Robin Garner - Craig-Hallum

Oren Livnat - HC Wainwright

Operator

Greetings and welcome to the Avadel Pharmaceuticals First Quarter 2021 Earnings Call. At this time, all participants are in a listen-only mode. A question-and-answer session will follow the formal presentation. [Operator Instructions] As a reminder, this conference is being recorded.

It is now my pleasure to introduce Tom McHugh, Chief Financial Officer. Thank you. You may begin.

Tom McHugh

Good morning and thank you for joining us on our conference call. This morning, we issued a press release providing a corporate update and financial results for the quarter-ended March 31, 2021. The release can be accessed on our website www.avadel.com.

As a reminder, before we begin, the following presentation includes several matters that constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those contemplated in such forward-looking statements.

These risks include risks that products in the development stage may not achieve scientific objectives or milestones or meet stringent regulatory requirements, uncertainties regarding market entry and acceptance of products and the impact of competitive products and pricing. These and other risks are described more fully in Avadel's public filings under the Exchange Act, including the Form 10-K for the year ended December 31, 2020, which was filed on March 9, 2021 and subsequent SEC filings. Except as required by law, Avadel undertakes no obligation to update or revise any forward-looking statements contained in this presentation to reflect new information, future events, or otherwise.

On the call with me today are Greg Divis, our Chief Executive Officer; Richard Kim, our Chief Commercial Officer; and Dr. Jennifer Gudeman, our VP of Medical and Clinical Affairs.

At this time, I'll turn the call over to Greg.

Greg Divis

Thank you, Tom. Good morning everyone and thank you for joining us on our first quarter 2021 conference call. I will begin by providing an update on our business highlighting the significant progress we continue to make towards achieving FDA approval of and preparation for the potential commercialization of once-nightly FT218. If approved, FT218 will be the first and only once-nightly oxybate treatment available for people suffering from the debilitating orphan disease of narcolepsy.

I will then turn the call over to Jennifer who will offer an overview of the progress we've made with our medical affairs and scientific communication plans for FT218. Richard will then provide an update on our commercialization and launch planning as we move closer to the PDUFA date and a potential approval. Finally, Tom will provide a review of the financial results to the quarter and we will conclude with a Q&A session. With that as an outline for the call, let's get started.

As we are now nearly halfway into 2021, I can say that it has already been a significant year for Avadel with several key regulatory, clinical and launch readiness milestones achieved as we continue to rapidly advance our investigational once-nightly FT218 program. Most notably being the acceptance of the NDA filing with an assigned PDUFA date of October 15.

Considering this progress, and the momentum we are experiencing across the entire FT218 program from NDA execution to data dissemination and launch readiness, the second half of 2021 is lining up to be both exciting and potentially historic for Avadel and for people suffering from narcolepsy. In this regard, the progress we're making on the regulatory front is arguably the most relevant and important near-term milestone for Avadel.

As we have said in the past, as it relates to our public disclosures on the NDA process and specifically our regulatory filing strategy, we've said no news is good news. And as such, I am pleased to report as it relates to our regulatory filing strategy perspective we have no news to share. As we are now approaching the mid-point of the review timeline for the NDA, and based on the actual review to date, we still have not been asked by the agency to certify Paragraph IV against any Orange Book-listed patents, and we don't believe based on the data and regulatory filing strategy of our FT218 NDA submission, there is any basis to request such a certification.

Our team over the last two years has executed this program and specifically this NDA exceptionally well. And we remain highly confident in our regulatory filing strategy, as we head toward our October 15 PDUFA date. Furthermore, as Jennifer will cover, the data from the REST-ON study for key secondary endpoints, recently presented at the American Academy of Neurology conference, confirms the clinical profile and promise of our investigational once-nightly FT218. We look forward to even more data being presented and disseminated throughout the scientific community in the balance of 2021.

Lastly, this promise of FT218 can only be realized through both the successful execution of our NDA and the subsequent commercialization of FT218 if approved. Over the past few months, we've accelerated our launch planning and execution with the appointment of Richard Kim, as our Chief Commercial Officer, and Richard has quickly immersed himself into our plans, continues to actively engage with key stakeholders, and is building a team of exceptional and proven industry professionals, that is quickly advancing our level of readiness across multiple work streams.

The caliber of the people who are raising their hand wanting to join us in this journey is some of the best I've seen in my over 30 years of industry experience, which we believe is reflective of the opportunity and the value that once-nightly FT218 can deliver. As many of you know, with just a little more than 24 months ago, when we decided to focus our business on the prospects and the potential of our investigational once-nightly FT218.

That is exactly what we have done. And our execution on that decision has brought us to where we are today, with a strong balance sheet, having over $200 million of cash on hand to support our launch readiness, and a regulatory pathway to a potential approval and future launch.

Our team has remained incredibly focused, has executed at the highest level, and is building great momentum across the company and in the narcolepsy community as we seek to establish our investigational once-nightly FT218 as the oxybate of choice and disrupt this multi-billion dollar narcolepsy market.

So to summarize, the overall key takeaway from today's call, is that we remain on track across all aspects of the once-nightly FT218 plan. This includes NDA execution, which continues to advance according to plan, and we remain confident in our regulatory filing strategy as we head toward mid-cycle review.

Furthermore, the opportunity for FT218 only improves as we continue to announce new relevant data and actively engage the medical community, while accelerating our overall launch readiness. We look forward to what would be an exciting second half of 2021 and beyond. And with that as the backdrop let's get into some of the details.

For now, I'll turn the call over to Jennifer.

Jennifer Gudeman

Thanks, Greg. It's great to be here today to discuss the progress we've made with our scientific communications for FT218. Well, the Avadel team has known for some time how robust the broader rest on data set is, we are now fully engaged in externalizing these data so that the medical and payer community can also fully appreciate our positive findings with once-nightly FT218.

Additionally, we have expanded our medical affairs team to further our connectivity in scientific exchange with key opinion leaders. As Greg mentioned, we were excited to present new positive secondary endpoint data at the 2021 American Academy of Neurology annual meeting, which was held last month. There are two key takeaways from these secondary data including.

First FT218 demonstrated significant consolidation of sleep, significant increase in time in deep sleep, and significant decrease in light sleep compared to placebo for all doses evaluated, 6 gram, 7.5 gram and 9 gram beginning by week three. Disturbed nocturnal sleep is a frequent and bothersome complaint of patients living with narcolepsy. While most therapies for narcolepsy address only daytime symptoms, this newly presented sleep data from REST-ON supports that once-nightly FT218, if approved, could address nighttime symptoms of narcolepsy without having to wake up in the middle of the night.

Second, FT218 demonstrated a significant improvement in the Epworth Sleepiness Scale, a patient-reported outcome, as well as significantly improving patient perceptions of both the quality and the refreshing nature of sleep, also for all doses evaluated. The Epworth Sleepiness Scale is commonly used in clinical practice, as it evaluates 8 domains to ask patients about their likelihood of dozing off during various activities, such as watching TV, or when stopped at a traffic light. At all doses, and beginning at week three, which was the first formal evaluation, FT218 significantly improved, that is reduced the Epworth score.

For context, a score of 16 out of 24 is characteristic of narcolepsy, a score of 10 or below is considered normal. At week 13, with the 9 gram dose, the endpoint mean with a score of 10.4, indicating not only market improvement from baseline, but also approaching a normal Epworth score for many of the participants. As a reminder, we have previously shared the top line data from the pivotal phase 3 REST-ON restaurant trial, which reported that FT218 met all three co-primary efficacy endpoints, compared to placebo for all three doses evaluated.

These results were highly statistically significant with all p-values less than 0.001, and clinically meaningful, as assessed by the maintenance of wakefulness test, clinical global impression improvement, and mean weekly cataplexy attacks. With the new secondary endpoint data presented at AAN, clinicians can now begin to more fully appreciate the totality of the positive results demonstrated with FT218.

The upcoming annual SLEEP congress, which commences in exactly one month, is dedicated to clinicians focused on sleep disorders. As such, I am really looking forward to our expansive data dissemination strategy that we have scheduled. We will be presenting a total of six posters with one oral presentation. These educational assets, along with a newly created mechanism of action video will be housed in our virtual medical affairs booth as we look to engage with these narcolepsy specialists.

Additionally, we are supporting a symposium titled, how narcolepsy management is evolving, which will be comprised of an expert panel discussion conveying three primary points. First, it is often necessary to manage both daytime and nighttime symptoms. Second, the importance of shared decision making and criticality of considering the patient's perspective for treatment of this chronic condition. And third, reviewing the nearly 20 year’s worth of immediate release sodium oxybate data showing no signal of increased cardiovascular risk.

Turning now to our publication plans, as you would expect, there are numerous publications planned and already in process. We very recently reached an important milestone with the submission of our primary manuscript from the REST-ON trial with an excellent group of key opinion leaders and investigators as co-authors. I look forward to providing updates on the content and timing of this primary manuscript, as well as additional publications in the future.

As a final remark, what really excites me is the perspective we hear from key opinion leaders for what FT218 could mean for their patients suffering from this chronic condition. Whether it is working on publications, holding advisory boards, or simply one-on-one meetings, the consistent takeaway from our interactions is that FT218, if approved, will provide a significant clinical advancement in the treatment of narcolepsy as the only once-nightly oxybate product.

Let me now hand the call over to Richard for an update on the commercial cleaning activities. Richard, the floor is yours.

Richard Kim

Thanks, Jennifer. And let me say that I am excited to be on the call today, and provide an update on our launch preparations for once-nightly FT218. During the March earnings call, I shared some of my initial insights and enthusiasm for joining the Avadel team, and for the amazing opportunity we have to transform the narcolepsy market. Well, I can say that over the last few months, I've had a chance to validate my initial impressions that if approved, once-nightly FT218 has the potential to gain market leading share in the oxybate class.

Previously, I shared from our market research some key insights about unmet needs in the oxybate market, including that almost half of patients report refusing twice-nightly sodium oxybate when offered by a physician, primarily due to the need to take a second dose in the middle of the night, two-and-a-half to four hours later. And almost 60% of patients reported negative treatment experiences.

What we see is that despite a time [up to] diagnosis of about 8 years to 15 years, patients on average, are usually initiated with pharmacotherapy around 3 months post diagnosis. In addition, patients tend to have their of narcolepsy treatment switched, or supplemented relatively quickly, with the average time to modify treatment from first to second line being about a month and a half., and the average time to modify from second to third line treatment being about only two weeks.

From this research and other work we have done, the data sheds light on the challenges with twice-nightly oxybate treatment, and the propensity for patients to seek new options when available, as they continue to search for new ways to get more control over the daily impact that narcolepsy has on their lives. In the last couple of months, I have also had the opportunity to speak with treating physicians, as well as patients living with narcolepsy.

Here are a few key insights that continue to stick with me from those conversations. It's hard for someone who does not suffer from narcolepsy to really understand the challenges that those with it go through every day. Like the choices some patients make to not participate in happy life events, because of the fear that positive emotions will trigger Major cataleptic event. Like when I heard about a father not attending his daughter's wedding.

Narcolepsy can have a profound impact on what most of us would consider regular day-to-day activities like cooking, driving, or sleeping through the night. One of the amazing patients I spoke with said that since her diagnosis and treatment of stimulants, antidepressants, and twice-nightly oxybate she has not slept through the night in 21 years. At the end of the day, like most of us, people with narcolepsy are seeking more normalcy in their lives, and the opportunity to live more independently.

I have also learned that oxybate therapy can be a game changer for some patients, but also that the challenges of twice nightly therapy go well beyond having a wake up during the middle of the night. I'm so appreciative of the time people spent with me, as the conversations have been both emotional and inspirational.

And overall, I continue to appreciate just how relentless narcolepsy can be. That's why we will continue to base our decisions on what we learned from patients, physicians, and peers. And why we will also be relentless in how we bring once-nightly FT218 to the market if approved.

Now, let me transition to an update on some of our specific launch preparations. Overall, we continue to make significant progress in ensuring we are ready to launch once-nightly FT218 and that we develop and execute programs focused on bringing exceptional clinical value to all of our customers. On the REMS, patient hub and distribution fronts, we've made significant progress choosing our partners to ensure our network is ready and will deliver customer focused support when [ACPs and patients are seeking to get] once-nightly FT218 if approved.

We also continue to focus on gaining more patient insights under the guidance of pre-approval information exchange, which provides opportunity to engage with payers about once-nightly FT218. In addition, our team keeps In addition, our team keeps advancing on other key launch initiatives like targeting field force sizing, data integration, pricing and messaging. And we will roll-out our first corporate narcolepsy campaign to coincide with a SLEEP congress next month as we ramp up our customer engagement activities.

To support these and other commercial planning activities, we are also actively growing our launch team. And we have the momentum in the marketplace to attracting top tier talent to lead our launch. For example, we have recently made key leadership hires in marketing, patient services and distribution, and insight and data analytics, and are making great progress against our overall hiring plan.

It's been really cool to see that our top candidates clearly understand our value proposition and embrace what we are doing to reshape the narcolepsy market for patients. Well, it's been a quick first three months for me, but I am really pleased with our progress in our launch preparations.

I am more convinced today that we have a unique opportunity to transform a market, to build a world-class team, to create exceptional clinical value, deliver strong shareholder returns, and most importantly, potentially bring an essential once-nightly treatment option to patients suffering from narcolepsy. I look forward to providing further updates on our progress on future calls.

I will now turn the call back over to Tom to provide an overview of our financial results for the quarter. Over to you, Tom.

Tom McHugh

Thank you, Richard and I'm pleased to provide an overview of Avadel's financial results. From a balance sheet perspective, we ended the quarter on a strong cash position with 205 million of cash, cash equivalents, and marketable securities. And as a reminder, in addition to the cash on hand at March 31, we expect to collect the remaining 8.3 million from the sale of sterile injectable drug portfolio that we sold last year on June 30 of 2020.

Turning to our income statement, as a result of the sale of the sterile injectable products, we did not record any revenue in the quarter ended March 31, 2021 and we also did not record any expense for cost of products, intangible asset amortization, and changes in fair value of contingent consideration.

The total of our R&D and SG&A expenses in the first quarter of 2021 were 14.8 million, compared to 13.4 in the prior year. As our preparations for the launch of FT218 continue to accelerate, we expect that our operating expenses will increase quarter-over-quarter during the remainder of the year, and be more heavily weighted in the second half of 2021 as we approach the PDUFA date in Q4.

With regards to R&D, expenses decreased 1.6 million year-over-year to 3.9 million in the first quarter of 2021 versus 5.5 million in the prior year. The decrease is due primarily to the completion of phase 3 REST-ON clinical study for FT218, which concluded during the first quarter of 2020.

SG&A expenses increased 3.1 million year-over-year to 11 million in the first quarter 2021 versus 7.9 million in the prior year. The majority of the year-over-year increase is attributable to costs for planning and preparing for the launch of FT218 if approved. Income tax benefit was 2.6 million in the first quarter 2021, compared to 9.5 million in the prior year. The year-over-year decrease is primarily due to benefits recognized in 2020 from the Coronavirus Aid, Relief and Economic Security Act.

Net loss for the first quarter of 2021 was 13.4 million or $0.23 per diluted share, compared to a net loss of 0.9 million or $0.02 per diluted share for the same period of 2020. The increase in net loss and diluted loss per share is primarily the result of the year-over-year decrease in revenue due to the sale of the sterile injectable products.

Diluted shares outstanding increased to [58.4 million] shares this year versus 41.1 million shares last year. The increase in the number of shares is due primarily to the 190 million of gross proceeds raised from equity issuances during the first half of 2025.

Finally, as Greg noted earlier, we are incredibly pleased with our progress to date and the momentum we are carrying into the rest of the year. We believe we're in a strong financial position with 205 million of cash on hand to fund the financial investments needed to complete the NDA review process, compile additional supporting scientific data to position FT218 in the market and continue to ramp up our launch preparations for FT218.

Before turning the call back to Greg for closing remarks, we're going to open up the call for Q&A, and I'll now turn the call over to the operator.

Question-and-Answer Session

Operator

Thank you. [Operator Instructions] Our first questions come from the line of Paul Matteis with Stifel. Please proceed with your questions.

Paul Matteis

Great. Thanks so much. Appreciate the call and the questions. So, you guys said again that no news is good news, I guess, how do you think about certain inflection points in the review? And if there's any kind of like, I guess it's a mid-type of review meeting or some other kind of scheduled interaction where key issues that are related to certification and possible labeling are going to come up? Just kind of curious if there is anything that you would point to or having to think about the timelines as it relates to freedom to operate? And then separately, I wanted to ask are you expected to get orphan drug to exclusivity? How should we think about that? And if you do, what do you think that means for other once-nightly sodium oxybate that are in the pipeline, even though that might be low sodium? Thanks so much.

Greg Divis

Yeah. Thanks, Paul. Appreciate the questions. I think it relates to the review. I think, you know, our commentary, you know, we've tried to provide a little bit of context here that we're very, you know, again, we haven't been asked to certify, we're very pleased with the progress we've made on this front. And really the types of questions or the comments we've received during the review process to date, right. I think the one thing I will say is that, you know, the FDA doesn't typically notify an applicant when, you know, some portion of NDA is kind of complete, and they've checked the box and moved on, they really just move on.

So, you know, as we enter, the second half of the review, we'll certainly move to label negotiations and things of that matter that we would expect. I would say that our position remains the same. We certainly are not aware and don't believe there's any basis for certification on our side whatsoever, given the data we've provided, how that is reflected in our label and our overall regulatory filing strategy.

That being said, even if we've been confirmed already, or we learn at a later date during review process that we've effectively navigated through any sort of certification risk, we certainly aren't going to speak on a publicly in advance of the FDA making the first comment publicly in the form of their decision on or around October 15. That being said, I think we feel really good about where we are, how we progress this aspect of the NDA, and where we sit today currently?

As it relates to orphan drug, you're correct. We have – we were granted orphan drug designation on the plausible hypothesis that once-nightly FT218 could be clinically superior to the reference product, right. We believe that we provided a robust and complete rationale for our exclusivity request that has been in and is part of our NDA review. So, we certainly look forward to the FDA's decision on it. It's not something we're relying on for our exclusivity protection, because I'll remind you that we've had a number of intellectual property patents granted already and many more in the queue, so to speak, that we believe will build the appropriate protections for the company.

It was the first one to innovate and demonstrate a modified or extended release control GHP related product that, you know, can work for patients, and we certainly are going to protect that in every way, shape, or form. So, as its impact on other potential products that can come in the marketplace, if we're granted orphan drug, it would be something that they would have to demonstrate that their clinically superior to our once-nightly product, is how we think about it. Thanks.

Paul Matteis

Thanks, Greg. Appreciate it.

Operator

Thank you. Our next question is come from the line of David Amsellem with Piper Sandler. Please proceed with your questions.

David Amsellem

Hi, thanks. So, just a couple. So, on the review, I don't know if you can talk about this, but has the REMS portion of the discussion come up and when or when in the review does the REMS piece actually come up? [Indiscernible] understand that if you can. And then secondly, on the commercial landscape, I'm sure you're going to get this question an awful lot, but I have to ask it, which is with Jazz converting a significant number of patients over to low sodium what are your thoughts on getting some of those patients capturing some of those patients? And I guess as part of that, with Jazz a success here, does that mean you have to contract more aggressively in order to try to capture some share? So, how philosophically do you think about that? Thank you.

Greg Divis

Yes. Thanks, David. I'll take the first question. And then Richard, maybe I'll turn it over to you to have any perspective on the commercial question. As it relates to the REMS program, I would say, you know, again, I think for context and background it is not a topic that the first time we would be engaging the FDA on, it would be during the review. It's something we would have, obviously, given the criticality of it engaged with the agency in advance of our, even our initial submission. And I just, you know, remind everyone that as a 505(b) (2) application, it's not subject to any sort of single shared system. And we can, in essence, have our own REMS program from that perspective that will be obviously geared and specific to our own label, you know, should we get approved?

In terms of the review process, I would say that, you know, there's little I think we can say specifics around it, other than, overall, I would say we're quite confident that the FDA has been through, you know, all aspects of our NDA, and it wouldn't get accepted if it wasn't in there already and for sure, because it's part of our submission. So, I would say generally speaking, whether it's REMS or anything else, we're quite confident the FDA has been through, at least initially, all aspects of our NDA.

Richard Kim

Yeah, thanks Greg. I'll take over the rest of the question from you, David. So, you know, I guess first from our perspective, David, it's always great to see new treatment options come to the market, no matter how large or small the benefit is that's added. I think the key thing that we think of the early uptake of the mixed salt is that it really shows us – confirms our market research that there – in general there's a high degree of patient willingness to try new treatments, to gain more normalcy in their lives and a fair degree of dissatisfaction in the market.

And we actually think this bodes well for the value proposition that, you know, for once-nightly FT218 as we believe that the majority of patients switching to mixed salt now to – they'll continue to demonstrate a propensity to seek new ways to improve their treatment as they go forward. Especially with [this, we have] an advancement like a once-nightly [indiscernible] coming to the marketplace.

So, and for us, you know, we remind ourselves that sodium was really not much of an issue. It's clearly when there's no other options, it makes sense. But we also know that from the systematic literature review, that's been done, that experts in the field have concluded that the sodium and sodium oxybate really doesn't create any additional cardiovascular risk for patients.

So, at the end of the day, for us, the sodium oxybate has demonstrated a lot of great utility over the last couple of years, and new to nearly two decades safety profile. And that's really why we believe that ultimately, when given options, narcolepsy patients will also focus on getting more consolidated sleep without the need to take a second dose during the middle of the night. And as far as the payers are concerned, it's always been our position that we're going to fight this battle on our clinical value proposition.

We don't want this to turn into convenience or soft play. So, having said that, we're clearly going to be very active with the payers, we don't want to get into pricing wars, anything. But we also know that at some point in time in the United States there usually is some sort of contracting that we will build in. But we are beginning that next level discussions with Paris, and we're looking forward to providing some more updates in the future.

David Amsellem

Great, thanks.

Operator

Thank you. Our next questions come to the line of Francois Brisebois with Oppenheimer. Please proceed with your questions.

Francois Brisebois

Hey, thanks for taking the questions. In terms of the data at AAN, is there anything, you know that some of the data [indiscernible] extremely old, but any comparisons here to twice-nightly for the extra secondary endpoints or is it mostly placebo? Any kind of, I know it's difficult to do, but any cross comparisons that are out there?

Greg Divis

Jennifer, you want to answer that?

Jennifer Gudeman

Yes. Hi, good morning Francois. Thank you for your question. You know, my general philosophy is that I think FT218 status should stand on its own. We know that there are inherent challenges whenever we're having any sort of cross study comparisons, obviously, potentially differences in trial design, as well as in patient demographics or clinical characteristics.

That being said, I talked a little bit about the Epworth score in my opening remarks, and perhaps that's relevant to highlight. We're extremely pleased with the fact that our [end of study] score with the 9 gram dose was 10.4. As I mentioned, the score of 10 or below is considered normal, and with all of the caveats that I described, in terms of limitations with cross-study comparisons, I think it is still relevant to recognize with the twice-nightly sodium oxybate, their of [end of study] score with the 9 gram dose was 12.

So, you know, as Richard had mentioned in his remarks, our belief is that patients who have this chronic condition that once they're diagnosed they're living with for the rest of their life then their aspiration is returning to normal. And with our Epworth scores coupled with the fact that one does not need to wake up in the middle of the night to take that second dose, we believe that that's going to be a very attractive option for patients suffering from this condition.

Greg Divis

Yeah, Francois, and I would just add to Jen, thanks, great comments. As she noted, it's hard to make those comparisons. And I think just to reiterate, the point, I think, everything we present and all the data we've looked at, and the data we're going to share in sleep only continues to just reinforce and support the overall pivotal study results that really like that you can't quite – our data is compelling. And with an adverse reaction profile that looks exceptionally well, you know, strong as well.

So, we're just excited about the prospects of how 218 looks and the data it presents and I think the more we get an opportunity to share this data with the medical community, you can see the more interesting and excited they get about it, as they're learning more about us from that perspective.

Francois Brisebois

That's great. Thank you very much. And just in terms of the education, maybe this is more for Richard, I would assume that, you know, this is a fairly straightforward, kind of new product in terms of, you know, comparing it to twice-nightly, is this something when you speak to physicians that is, you feel like the physician education will be difficult, or, you know, at conferences, from your interviews, there's something that's pretty straightforward, and they get it?

Richard Kim

[Frank], I've learned to realize in my life not to take anything for granted. So, I think the messaging is straightforward and simple. But you know, I think the great news is with the work at Jennifer has done is, now we have this great scientific foundation to go forward with. And if approved, of course, it'll really give us great foundation to really have a very clear, simple message.

So, the good news is, as you know, physicians are very deeply familiar with using oxybate treatment. We just hope this message and deliver something that's simpler for them and their patients to be able to use. So, yeah, I look forward to getting out there and having more of those conversations when we can, but I think they should be, our goal is to make this a simple communication to build off of their experience that physicians already have.

Francois Brisebois

Okay, great. And then just all that data that you guys are working on the extra secondary endpoint, now that it's all filed and accepted, there's nothing here on the NDA or that can affect the label? Or is this still something that the FDA can look at?

Greg Divis

Yeah, I think, when you think about the label, it's predominantly your primary endpoint data that will be most represented in our label. So, I don't – any post hoc analysis that we'll do that you'll see at the SLLEP meeting will not be in our label at this stage, but it's additional analysis, we think is relevant for the clinical community to understand, you know, in different patient populations as an example, that we think is important for as they think about the use of once-nightly FT218 in the future to have more data to look at, and really just to round out the complete clinical profile of FT218.

Francois Brisebois

Okay. Okay, great. And I guess my plan is a little more from the sales reps perspective, if it's not in the label, how much can they discuss it? And on that note, have you shared how many reps or when you would hire them?

Greg Divis

Yeah. Richard you want to take that?

Richard Kim

Absolutely, great. Sorry. And Frank, you know, as far as the label, I mean, first, Jennifer's team is doing a fantastic job in beginning this real push for our clinical data that'll be out there. So, we really believe and trust in the work that they continue to do. And as far as the Salesforce is concerned, we haven't made any final decisions yet. I think we're getting into stages now where we're really starting to get zoned in some of the numbers.

We sort of traditionally guided towards 50 or 60, but I think for us, we're still assessing, sort of the face-to-face, the digital communications that will go on. And the other thing for me, as well is that ultimately we know that this is a relatively concentrated marketplace, as we've spoken about. Around 1,600 physicians make up 80% of the prescription volume and less than 500 make up 50%.

So, the good news for us is that will give us some flexibility and how we go want to go to this marketplace. So, those decisions will be coming up in the upcoming months as we get ready to support the launch at once-nightly FT218.

Francois Brisebois

Great, thank you very much.

Greg Divis

Thanks, Frank.

Operator

Thank you. Our next questions come from the line of Marc Goodman with SVB Leerink. Please proceed with your questions.

Madhu Yennawar

Hi, thanks. This is Madhu on for Marc. We just had a question on, sort of when you're thinking of disclosing other products that you are internally developing that leverage your controlled release technology. Thanks.

Greg Divis

Yeah, thank you. I think it's a great question, because we certainly know how important it is as we move through a potential approval and launch, the, what's next question will certainly come about. And I would describe it this way. We've done quite a bit of planning and haven't even initiated some early work on what we would characterize as what's next beyond FT218, but I don't think we're at a place where we'll discuss specifics at this stage.

I mean, we're very focused on executing against the current regulatory and launch readiness strategy, which is very important for us. But I think as you think about it, right, in potential future areas for, you know, expansion, you can think about in the form of lifecycle management, you can think about, you know, whether it's a pipeline in the product, you can think about our leveraging technology, our technology platform, both in SLEEP or in relevant adjacencies from that standpoint is, kind of a couple of legs of the stool, if you will, in terms of how we think about going what's next.

But I would say, at this stage, we remain very focused on 218, while we plan and begin to do a little work on the other aspects of our portfolio, and at the right time we'll come forward and provide some more insights to our shareholders for sure. Thank you.

Madhu Yennawar

Thanks.

Operator

Thank you. Our next questions come from the line of David Sherman with Lifesci Capital. Please proceed with your questions.

David Sherman

Hi, guys. I was wondering if you could talk a little bit more about how you're planning to engage with non-prescribers in an effort to expand the existing oxybate prescriber base. And then I was curious to hear a little bit more about how you're planning to, kind of engage and advertise to consumers down the road if it's approved.

Greg Divis

Richard, do you want to go first?

Richard Kim

Yeah, sure. Thanks for the question, David. So as far as non-prescribers, we know that, sort of within any sort of given a year, there's around [4,000 to 4,500] physicians who prescribe oxybate. So, we believe that's relatively concentrated. So, to your question around non-prescribers, to be candid, I think the initial thrust of our focus will be on current prescribers of oxybates, who have the experience, but because of the proposition of a once-nightly FT218, where I think you're going is, we do believe that there is an opportunity to expand the treater base going forward as well.

So, you know, I think what we see is, interest has grown in the narcolepsy class with other new novel therapies who have come to the marketplace. So, we intend to, sort of capture some of this momentum. And just, you know, we're – I think, also, we're not going to be too specific around who's going to be invited to some of our speaker programs going forward as well. And as far as, sort of how to, sort of connect with a lot of the patients that are out there, we believe that the patient voice is really critically important in the treatment of narcolepsy, as there really aren't, as you know, markers, blood markers, or scans that really helped assess the impact of this disease.

So, you know, our commitment is really to, sort of focus on getting the appropriate education through the venues that patients seek information today. And we think there's really good opportunities for us to get out there because the narcolepsy community is in general, pretty active online. So that really, digital communication provides a very focused opportunity for us to reach out and make sure that the proper education and information is out there on what we're doing in narcolepsy and upon approval for once-nightly FT218 as well.

Greg Divis

Yeah, David, just one additional comment to Richard's, you know, comments around market expansion or prescriber expansion. I want to differentiate those a little bit, only because we believe within the current prescriber audience of these 4,000 plus per year, and, you know, and those who are, you know, within that subset to prescribe a lot more, there is a fairly reasonable sized cohort of patients, you know, in every practice is a little bit different, but in aggregate, that are sodium oxybate eligible as defined by those current prescribers who aren't going on sodium oxybate, as Richard described a little earlier, whether that's because the physician has decided not to treat them, or the patient has decided not to go on it, the predominant reason is dosing related. So, in that category, we believe there's expansion opportunities within the current prescriber base, which makes it even that much more efficient for us accordingly.

David Sherman

Okay. Thanks for taking my question.

Operator

Thank you. Our next questions come from the line of Robin Garner with Craig-Hallum. Please proceed with your questions.

Robin Garner

Hi, good morning, and thanks for taking my question. You shared some new patient insights earlier in the call, for context can you share with us a ballpark of how many patients you've been able to engage during your market research?

Richard Kim

Yeah, thanks Robin. We, you know, patient market research is one of the interesting things that we do here as well. And I would say in general, what we've seen is, we've been able to engage with hundreds of physicians, patients and payers, we don't always sort of break out the exact numbers of what we've done there. But it's fair to, sort of say that it's more than it's dozens upon dozens of patients. And then what we've also done is, also done individual conversations as well, to get more qualitative perspective.

So – and going forward, we will continue to do this. Not only through market research, but our engagement through patient advocacy and other sources as well. So, I can say, from my perspective, the feedback from the payer work that we've done, if it's in market research, speaking to advocacy groups or individuals is generally pretty consistent. And I think, even though that there are some individual needs to patients out there as well. So, hopefully, that gives you some of the perspective from what we do in a patient research.

Greg Divis

Yeah. And Robin, I'll just add one more comment to that to Richards, and that is, you know, in particular, as time continues to go and the market continues to evolve, we're doing robust research. And it is a combination of both qualitative insights, as Richard described, but statistically and market research based [quant studies] that are robust, and, you know, appropriately designed and with demographics that are meant to represent, you know, our target audience and geographically dispersed accordingly. So, we try to get, you know, [quant work] that's large to give us the right views and not make decisions based on very, very small sample sizes, but on large robust work products.

Robin Garner

Okay, thank you for that. And then just lastly, will you be presenting any new data points at the SLEEP Congress?

Greg Divis

So just to be clear, are we presenting any new data at the SLEEP Congress is what you asked?

Robin Garner

Yes, that's right.

Greg Divis

Yeah. Okay, Jen, do you want to answer that.

Jennifer Gudeman

Yes, I do. Hi, Robin, thank you for your question. So, the new data that is being presented are post hoc analyses and this is data that we think is really relevant for clinicians to understand. So the abstracts have been published for the SLEEP Congress. And our three post talks are looking at efficacy stratified by subgroups. So, in T1, and T2, looking at efficacy by the subgroups of stimulant use or no stimulant use, and also examining the weight loss that occurred with FT218.

And, as I mentioned in my opening remarks, the consistency of benefit that is seen with FT218 underscores just how robust these findings are, and how consistent the efficacy is. And so, we look forward to having that full presentation in just a month's time.

Robin Garner

Okay, thank you.

Greg Divis

Thanks, Robin.

Operator

Thank you. Our next questions come from the line of Oren Livnat with HC Wainwright. Please proceed with your questions.

Oren Livnat

Hi, guys, can you hear me?

Greg Divis

Yeah, hi Oren, good morning.

Oren Livnat

Good morning. I just want to return back to the review process, you know, with the caveats, you know, we understand you can't comment on anything you can't comment on, but I'm getting a lot of questions as we get closer towards the PDUFA regarding, you know, any unknowns, obviously, your tolerability profile looked really good in phase 3, yeah, at least as good as [IRM]. But people are asking me what do we know or what did you already submitted with regards to the safety or risks around your drug delivery technology in general, specifically, I'm getting asked about those stumping work you've done or food effect work you've done and how that might factor into, you know, the benefit risk calculation? And then also just in the review, on the manufacturing front, I think in the past, you've mentioned bridging studies that, you know, need or plan to do, can you just remind us is that just for your backup domestic supplier for post approval, or, you know, and how [confident are you] the FDA can inspect your original European manufacturer in time? Thanks.

Greg Divis

Yeah, great questions. You know, as it relates to the technology itself, although I would say that this formulation is unique on its own to a certain extent, the technology has been approved in the prior product [indiscernible] it is a beta blocker, commercialized by another product, another company, in the past.

So, the technology has been through, and if you will, an FDA process, so to speak, from that perspective, although, you know, again, this is a, you know, an application of that technology in that process, with, you know, with its, you know, tailored to, you know, sodium oxybate in that regard, but I would say that, as it relates to the – all of the non-clinical work that we had to do in our submission.

Again, we believe it's robust, it's complete, whether that's our food effect data or otherwise. And the work we provided to, you know, validate, you know, this formulation and how this formulation performs in different settings that are required relative to our NDA. We feel really good about our submission. And obviously, that includes, you know, the drug interaction data that we provided, as well, as part of our NDA submission.

As it relates to our CMC, yeah, you know, we have a primary supplier who has been making this product for well over five years. We filed with over three years of stability data, during the review process we'll tick over four years actually of stability data. So, they've been making it, you know, at this scale for quite some time.

So, we feel we have a robust manufacturer who's been doing it for a long time. But we also recognize we wanted to have another source and a backup source. We've done all that work. We've completed those bridging studies, if you will, and that will be an action that will occur post approval, as you referenced.

Oren Livnat

And with regards to access to your European facility given, you know, COVID dynamics. You know, [indiscernible].

Greg Divis

Yeah, sorry. Again, that, you know, we've seen some of the recent guidance from the FDA that has recently come out about how they'll, you know, prioritize inspections. The limited number, you know, less than one half of 1% or so that they claim are facilities that didn't get inspected tied to a review over the last 18 months that they needed to inspect. That being said, this facility was recently inspected, just prior to the pandemic. And with no observations, [indiscernible], if you will, we've done all of our work to prepare for any sort of PAI with our partner, our CMO. So, at this stage, I would say there's nothing more to say on at this point. And if anything comes up, we'll certainly update accordingly. But we see no reason that PAI would be determined at this point. But you know, again, we have to work and see how the NDA process unfolds.

Oren Livnat

All right, appreciate it. Thanks.

Operator

Thank you. Our next questions come from the line of Matt Kaplan with Ladenburg Thalmann. Please proceed with your questions.

Unidentified Analyst

Oh, hi. This is [Raymond] in for Matt. Thanks for taking our questions and congrats on all the progress so far. Maybe just the question on the market research, you mentioned that there were high levels of treatment refusals and high discontinuations after treatment starts. And you said, the second dosing as a main issue, but can you provide any color on any other sources of refusals and discontinuation and how FT218 might be positioned to capitalize on it? And my other question is just any updates you can provide on the switch study enrollment? Thanks.

Greg Divis

Yeah. Richard, do you want to start with the first one? And maybe Jen, take the second?

Richard Kim

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Sure. No problem. Thanks, [Raymond]. So yeah, as far as the research is concerned, you know, we often focus on the inconvenience of getting up during the middle of the night for a second dose for the twice-nightly oxybate. But beyond that, there's a lot of other concerns that go on around, you know, the fear of waking up a partner, the leaving out your medications out at the nights and with kids running around the house.

So, there's a lot of stress on these patients that we find from the research in regards to more than just getting up during the middle of the night. And I think what we generally sort of see there is, it's not easy. Also, a lot of – some of the patients have now gone to adjusting their dose that is called asymmetric dosing to maybe take more of her dose earlier on and less later on during the middle of the night. So, I think there's a lot of factors that continue to go on there with these patients that go beyond just the perceived inconvenience of the second dose.

And I'll pass it over now to Jen on the second part of your question.

Jennifer Gudeman

Thank you, Richard. And thank you for the question, Raymond. So, we are now at just about 60 patients or approximately a 20% increase from our last call. We've got a number who are in the screening process right now. So, we're looking to add to that overall number. We're also continuing to activate sites. And of course, all of this is happening still in the remainder of the backdrop of a worldwide pandemic. There's also the unique aspect with FT218 because it is not yet FDA approved is considered a schedule one medication, which necessitates patients having to come in once a month to pick up the medication.

What we're really pleased with in regard to this open label switch study are the insights that we're gathering and the primary purpose of course, is long-term safety and tolerability. And we're also seeing in addition to good results there, sustained efficacy with FT218 as well. And then lastly, it's preliminary, but the feedback that we're getting in regard to the preferred dosing regimen once or twice-nightly has been extremely positive for once-nightly FT218.

Unidentified Analyst

Thanks.

Operator

Thank you. There are no further questions at this time. I would like to turn the call back over to Greg Divis for any closing comments.

Greg Divis

Thank you again, and thank you everyone for your questions. In closing, to say I'm proud of every team member's contribution is to where we are today would be an understatement. It's been a very, very busy few months. But it's also exciting to see us closing in on the PDUFA date, and wrapping up our preparations for the next chapter in our company's history. And I just want to reiterate, and rest assured that this entire team is working very hard every day to deliver the best possible results for all key stakeholders. That includes patients and providers, but also importantly, so includes our shareholders and we'll continue to keep you apprised of our progress. And with that, we thank you for joining the start of the week and the start your day with us and wish you a great rest of the day. Thank you.

Operator

Thank you for your participation. This does conclude today's teleconference. You may disconnect your lines at this time. Have a great day.

EXHIBIT G

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Pharmacokinetics of FT218, a Once-Nightly Sodium Oxybate Formulation in Healthy Adults

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ABSTRACT

Purpose: FT218 is an investigational, once-nightly, modified-release formulation of sodium oxybate (SO). SO effectively treats excessive daytime sleepiness and cataplexy in patients with narcolepsy. Current approved SO formulations, at effective doses of 6, 7.5, and 9 g, require twice-nightly divided dosing, with the first dose taken at bedtime and the second 2.5–4 h later. The purpose of the following studies was to evaluate the pharmacokinetic properties, safety profile, and tolerability of FT218 in healthy adults.

Methods: Four crossover, single-dose studies were conducted. The first was a pilot study (n = 16) that compared 3 prototype formulations of FT218 4.5 g to twice-nightly SO 4.5 g (2 divided doses of 2.25 g); the second, a dose-proportionality study (n = 20) that evaluated FT218 4.5, 7.5, and 9 g; the third, a relative bioavailability study (n = 28) that compared FT218 6 g with twice-nightly SO 6 g (2 divided doses of 3 g); and the fourth, a food-effect study (n = 16) of FT218 6 g.

Results: In the pilot study, FT218 prototype 2 had a lower C_{max}, lower plasma concentration 8 h after dosing (C_{8h}), similar exposure (AUC), and comparable interperson variability to twice-nightly SO 4.5 g. Exploratory pharmacodynamic data indicated similar sleep quality and morning alertness between FT218 and twice-nightly SO. Prototype 2 was selected for further development. In the dose-proportionality study, FT218 had dose proportionality for C_{max} and slightly more than dose proportionality for AUC. The relative bioavailability study confirmed that FT218 6 g had lower C_{max} and C_{8h} than twice-nightly SO 6 g but equivalent AUC and comparable variability. In the food-effect study, FT218 6 g had longer t_{max} (1 h later), lower C_{max} (67%), and decreased AUC (86%) in fed versus fasted states. For all studies, adverse events with FT218 were mostly mild or moderate in severity, nonserious, and known to be associated with SO. Most common adverse events included somnolence, dizziness, and nausea. Safety profiles of FT218 and twice-nightly SO at 4.5 and 6 g were similar.

Implications: Once-nightly FT218 at 4.5 and 6 g had lower overall C_{max} and C_{8h} and similar exposure and variability compared with twice-nightly SO. FT218 was generally well tolerated and comparable to twice-nightly SO. (*Clin Ther*. xxxx;xxx:xxx) © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: clinical study, narcolepsy, pharmacokinetic properties, sodium oxybate.

INTRODUCTION

Narcolepsy is a chronic sleep disorder characterized by symptoms of excessive daytime sleepiness, cataplexy, sleep paralysis, hypnagogic and hypnopompic hallucinations, disrupted nocturnal sleep, and/or dysregulated rapid eye movement sleep.[1,2] Prevalence in the United States and Europe ranges from 0.03% to 0.05%.[3,4] Approximately 70% of patients with narcolepsy have narcolepsy type 1 (NT1), which is characterized by the presence of cataplexy and is associated with low or undetectable levels of the neurotransmitter orexin/hypocretin in cerebral spinal fluid (CSF), selective loss of orexin/hypocretin-producing neurons in the lateral hypothalamus, and the human leucocyte antigen allelic mutation *HLA-DQB1*06:02* in 95% of individuals with NT1, suggesting an autoimmune origin.[1,5,6] Narcolepsy

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type 2 (NT2) is characterized by the absence of cataplexy and mostly normal orexin/hypocretin levels in the CSF; the underlying pathophysiology of NT2 remains unclear.[7,8]

Sodium oxybate (SO), the sodium salt of γ-hydroxybutyrate (GHB), is one of the primary treatments for NT1 and NT2. Although its mechanism of action in narcolepsy is not clearly defined, SO is thought to reduce nocturnal sleep disruption and promote daytime wakefulness through activation of γ-aminobutyric acid B receptors in the central nervous system.[5,9] The efficacy and tolerability of SO, as well as its positive impact on health-related quality of life, have been established via extensive study in clinical trials in patients with narcolepsy.[10–13]

Twice-nightly SO and the newly approved twice-nightly mixed-salts formulation of SO are the only medications approved in the United States to treat both excessive daytime sleepiness and cataplexy in children and adults with narcolepsy.[9,10,14,15] SO* (at recommended total doses of 6–9 g nightly) is administered twice nightly in divided doses because of its short $t_{½}$ of <1 h; the first dose is typically taken before bedtime and the second dose 2.5–4 h later, requiring the patient and/or caregiver to wake in the middle of the night. Moreover, this twice-nightly dosing regimen may be associated with increased adverse events (AEs) in the middle of the night (eg, falls).

FT218 is an investigational, once-nightly, modified-release formulation of SO. FT218 possesses an innovative delivery system that contains thousands of microparticles, composed of controlled-release pellets (which have a modified systemic release) and immediate-release pellets. We report the findings from 4 Phase I clinical studies investigating the pharmacokinetic properties, safety profile, and tolerability of FT218 in healthy adults.

PARTICIPANTS AND METHODS

Study Designs

The pilot study, dose-proportionality study, relative bioavailability study, and food-effect study were conducted in Groningen, Netherlands, and Gières, France.

* Trademark: Xyrem® (Jazz Pharmaceuticals, Dublin, Ireland).

Pilot Study

The pilot study was a randomized, open-label, crossover study to evaluate the pharmacokinetic properties, safety profile, and tolerability of 3 formulations of FT218 (prototypes 1, 2, and 3) compared with twice-nightly SO. Participants were randomized 1:1:1:1 to a single 4.5-g dose of each formulation of FT218 or 4.5 g twice-nightly SO (given as two 2.25-g doses 4 h apart) in 4 different sequential orders separated by a washout period of ≥3 days.

Dose-Proportionality Study

This was an open-label, single-dose, 3-sequential-period study to assess the pharmacokinetic properties, safety profile, and tolerability of single-dose FT218 (optimized prototype selected from the pilot study) 4.5, 7.5, and 9 g, and to estimate dose proportionality. Participants received 3 separate single doses of FT218 (without titration) in a sequential order of 4.5, 7.5, and 9 g with a minimum 7-day washout period between doses.

Relative Bioavailability Study

The relative bioavailability study was a randomized, open-label, crossover study to evaluate the relative bioavailability of FT218 compared with twice-nightly SO. Participants were randomized 1:1 to a single dose of 6 g FT218 or 6 g twice-nightly SO (given as two 3-g doses 4 h apart) with a washout period of ≥3 days between treatments. For the pilot, dose-proportionality, and relative bioavailability studies, FT218 or the first dose of twice-nightly SO was administered at approximately 9:00 PM, 2 h after a standardized dinner (1251 kcal, 19.6 g of protein, 25.5 g of fat, and 54.9 g of carbohydrate).

Food-Effect Study

The food-effect study was an open-label, 2-period, crossover, single-dose study to assess the effect of food on the pharmacokinetic properties of single-dose FT218 6 g. Participants were randomized 1:1 to single-dose FT218 6 g after a 10-hour overnight fast (fasted state) or 30 min after a standardized, high-fat breakfast (fed state; 50% total content of meal consisting of fat and 800–1000 kcal, of which 150 kcal was derived from protein, 250 kcal derived from carbohydrate, and 500–600 kcal derived from

fat) with a minimum 3-day washout between study periods.

For all studies, FT218 was administered orally as a powder reconstituted as a suspension in 50−70 mL of water. Twice-nightly SO was administered orally as a 500-mg/mL solution diluted in 60 mL of water in divided doses given 4 h apart.[10] All treatments were administered under investigator supervision and were followed by a hospitalization period of 16−36 h.

Participants

Individuals eligible for study enrollment were men or women (white/non-Hispanic or Latino) 18−65 years of age who weighed ≥60 kg with a body mass index of 18−28 kg/m^2 and were considered healthy by comprehensive clinical assessment (detailed medical history and complete physical examination). All participants had normal supine blood pressure and heart rate, ECG findings, laboratory parameters, and dietary habits and were nonsmokers (or able to abstain from smoking during the clinical inpatient period). Women were required to be nonpregnant and nonlactating, and all participants had to use adequate forms of contraception if sexually active. Specific exclusion criteria across studies included succinic semialdehyde dehydrogenase deficiency, sleep apnea, suicidal ideation, migraine, symptomatic hypotension, asymptomatic postural hypotension, use of renal or hepatic-clearing medication within 30 days of study start, use of vitamins (such as St. John's wort) within 21 days of study start, positive drug screen result, or alcohol use. All participants provided written informed consent for participation, and studies were approved by the local institutional review board or independent ethics committee. Studies were performed in accordance with the Declaration of Helsinki.

Blood Sampling

Pilot Study

In the pilot study, for FT218 treatment, blood samples were collected from all participants before dosing and at 30 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, and 12 h after dosing. For twice-nightly SO treatment, the same time points were used for the first dose (omitting the 2.5-hour collection), with an additional collection 20 min after the second dose (at 4 h 20 min).

Dose-Proportionality Study

In the dose-proportionality study, blood samples were collected before dosing; at 10, 20, and 30 min after dosing; and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, and 14 h after dosing.

Relative Bioavailability Study

In the relative bioavailability study, for FT218 treatment, blood samples were collected from all participants before dosing; at 10, 20, and 30 min after dosing; and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, and 14 h after dosing. The same time points were used in reference to the first dose of twice-nightly SO, omitting the 3.5-hour collection; there were 2 additional collections at 10 and 20 min after the second dose of twice-nightly SO (at 4 h, 10 min, and at 4 h 20 min).

Food-Effect Study

In the food-effect study, during the fed and fasted study periods, blood samples were collected before dosing; at 10, 20, and 30 min after dosing; and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, and 14 h after dosing.

Analytical Methods

In each of the four studies, at each sampling time point, 4−6 mL of blood was drawn (via indwelling intravenous catheter or direct venipuncture) in a heparinized tube and centrifuged at 1500g for 5 min at 4 °C within 30 min of blood draw. At least 2 mL of the top layer of plasma was transferred into 2 prelabeled polypropylene tubes, each containing at least 1000 µL of plasma and frozen at −70 °C (+/−15 °C) within 2 h.

Blood samples were sent for analysis to Eurofins/ADME Bioanalyses (Vergèze, France). Concentrations of GHB in sodium heparinized human plasma were assayed according to an analytical method validated by Eurofins/ADME Bioanalyses. The method involves a liquid−liquid extraction followed by LC-MS/MS with a calibration range of 0.2 µg/mL as the lower limit of quantitation to 150 µg/mL as the upper limit of quantitation. Quality control principles were applied throughout the performance of the studies. All study samples were analyzed with analytical runs that complied with acceptance ranges for the quality control samples. Frozen quality control samples at 3 times the lower limit of quantitation (0.6 µg/mL),

0.5 times the upper limit of quantitation (75 μg/mL), and 0.8 times the upper limit of quantitation (120 μg/mL) GHB concentration levels were used. The quality control concentration levels covered the study sample concentration range of 0.204−143 μg/mL. Incurred sample reanalysis was approximately 98%, met the acceptance criteria, and indicated the robustness of the analytical method.

Pharmacokinetic parameters were calculated using noncompartmental analysis with Kinetica software, version 4.3 (Thermo Electron Corporation, Philadelphia, Pennsylvania) or WinNonlin software (Certara/Pharsight Corporation, Princeton, New Jersey).

Pharmacokinetic Analysis

Evaluated pharmacokinetic parameters were estimated from the plasma concentration time data for plasma GHB and included C_{max}, t_{max}, concentration 8 h after administration (C_{8h}), AUC_{0-8}, $AUC_{0-\infty}$, and AUC_{0-t}). AUC was calculated using log-transformed data (logarithmic trapezoid method).

Leeds Sleep Evaluation Questionnaire and Actigraphy

In the pilot study, pharmacodynamic effects were explored using the Leeds Sleep Evaluation Questionnaire (LSEQ; getting to sleep, quality of sleep, awake following sleep, behavior following wakening)[16] and actigraphy (sleep time >8 h).

Safety Monitoring

Safety evaluations included AE reporting, physical examination, and monitoring of vital signs and clinical laboratory values. It was prespecified that participants who vomited after study drug intake were excluded from the primary analysis.

Statistical Analysis

Statistical analyses were performed using SAS statistical software, version 9.3 or 9.4 (SAS Institute Inc, Cary, North Carolina). Descriptive statistics with no formal statistical analysis were used for safety parameters, general analysis of pharmacokinetic parameters in all studies, and LSEQ scores and actigraphy in the pilot study. Variability of concentrations of FT218 and twice-nightly SO were compared in terms of SD. Bioequivalence was analyzed using the two 1-sided test procedure on log-transformed data for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and was defined as 90% CIs for ratios of geometric means falling within the 80%−125% range. Dose proportionality was assessed using the power model[17] with slope estimate and 90% CI for dose-normalized pharmacokinetic data. Sensitivity analyses were performed using ANOVA on log-transformed normalized data.

RESULTS

Demographic Characteristics and Participant Disposition

Table I gives the demographic characteristics and disposition of the study participants. The pilot study included 16 participants (8 men and 8 women), with a mean (SD) age of 39.5 (11.9) years. There were no study discontinuations due to AEs.

The dose-proportionality study included 20 individuals (12 men and 8 women), with a mean (SD) age of 45.5 (12.5) years. All participants completed the 4.5- and 7.5-g periods of the study, and 12 of 20 participants (60.0%) completed the 9-g period. The study was stopped by the sponsor after a serious AE (SAE) of somnolence in 1 individual (described below) after 12 participants were given the 9-g dose level without titration. One individual was withdrawn owing to a positive drug screen.

The relative bioavailability study included 28 individuals (10 men and 18 women), with a mean (SD) age of 27 (9) years. Overall, 26 of 28 participants completed both study phases per protocol, and the remaining 2 participants withdrew prematurely owing to AEs.

The food-effect study included 16 individuals (10 men and 6 women), with a mean (SD) age of 32 (13) years. A total of 15 of 16 participants completed the study per protocol. One individual discontinued participation in the study because of vomiting after receiving FT218 in the fasted state. Two individuals were also excluded from the pharmacokinetic analysis set because of vomiting.

Pharmacokinetic Properties

Pilot Study

Each of the 3 FT218 formulations exhibited an extended-release profile with t_{max} at approximately 2 h, followed by a gradual decline in plasma GHB

Table I. Demographic and clinical characteristics of the study participants.

Characteristic	Pilot Study (n = 16)	Dose-Proportionality Study (n = 20)	Relative Bioavailability Study (n = 28)	Food-Effect Study (n = 16)
Sex, No. (%)				
Male	8 (50.0)	12 (60.0)	10 (35.7)	10 (62.5)
Female	8 (50.0)	8 (40.0)	18 (64.3)	6 (37.5)
Age, mean (SD), y	39.5 (11.9)	45.5 (12.5)	27 (9)	32 (13)
Race, No. (%)				
White	14 (87.5)	NR	28 (100)	16 (100)
Black	1 (6.3)	NR	0	0
Other	1 (6.3)	NR	0	0
Height, mean (SD), cm	167.8 (8.1)	171.8 (7.0)	177 (7)	179 (9)
Weight, mean (SD), kg	66.5 (11.2)	70.9 (10.5)	73.0 (8.8)	75.4 (9.5)
BMI, mean (SD), kg/m^2	23.5 (2.7)	23.9 (2.1)	23.2 (2.5)	23.5 (2.0)

BMI = body mass index; NR = not reported.

concentration (Table II and Figure 1). C_{max} for the 3 FT218 formulations was lower than the global C_{max} of twice-nightly SO (mean [SE] C_{max} was 43 [6] μg/mL for prototype 1, 46 [5] μg/mL for prototype 2, 30 [4] μg/mL for prototype 3, and 66 [7] μg/mL for twice-nightly SO). Mean (SE) $AUC_{0-\infty}$ was 189 (28) h*mg/mL for prototype 1, 210 (28) h·μg/mL for prototype 2, 153 (22) h*mg/mL for prototype 3, and 214 (27) h·μg/mL for twice-nightly SO. C_{8h} values were numerically lower for the 3 FT218 formulations (mean [SE] prototype 1, 6.85 [2.1]; prototype 2, 7.40 [1.6]; prototype 3, 8.33 [1.9] μg/mL) relative to twice-nightly SO (mean [SE], 9.24 [3.2] μg/mL).

Prototype 2 was selected for further optimization and used in the remainder of the studies because it exhibited pharmacokinetic characteristics closest to the desired target profile, with higher C_{max} compared with other prototypes and $AUC_{0-\infty}$ comparable to that of twice-nightly SO.

For each LSEQ domain and sleep time >8 h, there appeared to be no clinically meaningful differences between the FT218 prototypes and twice-nightly SO;

Table II. Pharmacokinetic properties in the pilot study.

Parameter	FT218 4.5 g			
	Type 1 (n = 12)	Type 2 (n = 12)	Type 3 (n = 12)	Twice-Nightly SO 4.5 g (n = 12)
C_{max}, mean (SE), μg/mL	43 (6)	46 (5)	30 (4)	66 (7)
$AUC_{0-\infty}$, mean (SE), h·μg/mL	189 (28)	210 (28)	153 (22)	214 (27)
C_{8h}, mean (SE), μg/mL	6.85 (2.09)	7.40 (1.63)	8.33 (1.93)	9.24 (3.15)

C_{8h} = plasma concentration 8 h after dosing; SO = sodium oxybate.

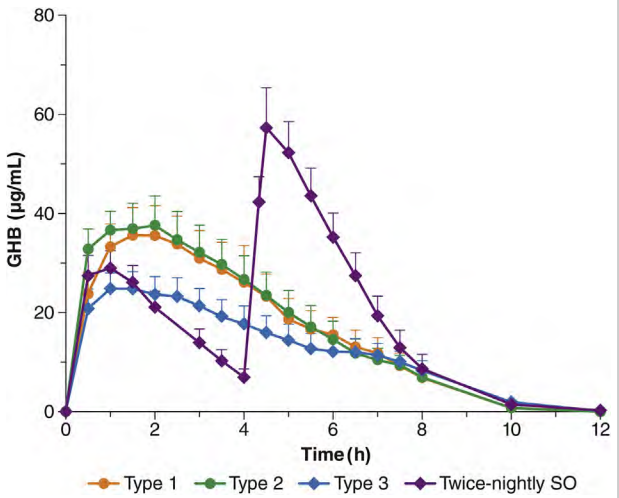

Figure 1. Mean plasma concentrations of γ-hydroxybutyrate (GHB) over time after twice-nightly sodium oxybate (SO) or 3 formulations of FT218 in the pilot study. Errors bars indicate SEs.

however, there was no formal statistical analysis of these data, and this study was not powered to find any differences (Supplemental Figure I).

Dose-Proportionality Study

At all 3 doses of FT218, mean pharmacokinetic properties exhibited similar overall profiles (Table III and Figure 2). The t_{max} was reached after approximately 1.5−2 h followed by a gradual decline in GHB concentration. Mean (SD) C_{max} increased with increasing doses of FT218 (42.9 [15.8] µg/mL at 4.5 g, 72.0 [23.3] µg/mL at 7.5 g, and 84.5 [28.6] µg/mL at 9 g). Similarly, mean (SD) $AUC_{0-\infty}$ increased with increasing doses of FT218 (191 [94.7] h·µg/mL at 4.5 g, 358 [170] h·µg/mL at 7.5 g, and 443 [202] h·µg/mL at 9 g). Mean (SD) C_{8h} also increased with increasing doses of FT218 (4.8 [5.01] µg/mL at 4.5 g, 19.7 [19.9] µg/mL at 7.5 g, and 25.5 [24.8] µg/mL at 9 g). Moreover, the variability of the concentrations was similar.

Using the power method,[18] the estimated slope of C_{max} was 1.02 (90% CI, 0.76−1.28), indicating dose proportionality, and the estimated slope of $AUC_{0-\infty}$ was 1.34 (90% CI, 1.19−1.48), which indicated that dose-dependent increase in $AUC_{0-\infty}$ was slightly more than proportional. These results were consistent with ANOVA sensitivity analyses.

Relative Bioavailability Study

Once-nightly FT218 6 g had equivalent exposure with a lower overall C_{max} than twice-nightly SO at a total dose of 6 g (Table IV and Figure 3). Mean (SE) $AUC_{0-\infty}$ of FT218 6 g (273 [27] h·µg/mL) met bioequivalence criteria compared with $AUC_{0-\infty}$ of twice-nightly SO 6 g (259 [22] h·µg/mL). Mean (SE) C_{max} of FT218 6 g (64.6 [5] µg/mL) was lower (below bioequivalence criteria) than overall C_{max} of twice-nightly SO 6 g (70.9 [4] µg/mL). Mean (SE) AUC_{0-8} of FT218 6 g (267 [27] h·µg/mL) also met bioequivalence criteria compared with AUC_{0-8} of twice-nightly SO 6 g (248 [18] h·µg/mL). Mean (SE)

Table III. Pharmacokinetic properties in the dose-proportionality study.

Parameter	FT218 4.5 g (n = 20)	FT218 7.5 g (n = 20)	FT218 9 g (n = 11)
t_{max}, median (range), h	1.71 (0.33−4)	1.5 (0.33−7)	2 (0.5−4)
C_{max}, mean (SD), µg/mL [CV]	42.9 (15.8) [37]	72.0 (23.3) [32]	84.5 (28.6) [34]
$AUC_{0-\infty}$, mean (SD), h·µg/mL [CV]	191 (94.7) [50]	358 (170) [48]	443 (202) [46]
AUC_{0-8}, mean (SD), h·µg/mL [CV]	174 (96.3) [55]	320 (148) [46]	379 (154) [41]
C_{8h}, mean (SD), µg/mL [CV]	4.76 (5.01) [37]	19.7 (19.9) [101]	25.5 (24.8) [97]

C_{8h} = plasma concentration 8 h after dosing.

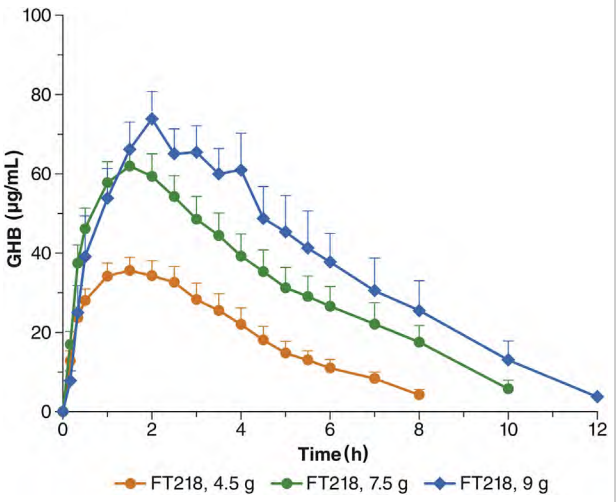

Figure 2. Mean plasma concentrations of γ-hydroxybutyrate (GHB) over time after 3 dose levels of FT218 in the dose-proportionality study. Error bars indicate SEs.

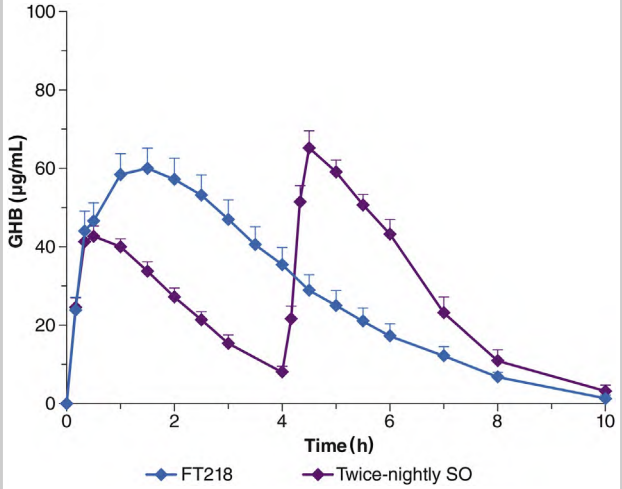

Figure 3. Mean plasma concentrations of γ-hydroxybutyrate (GHB) over time after FT218 or twice-nightly sodium oxybate (SO) in the relative bioequivalence study. Error bars indicate SEs.

Table IV. Pharmacokinetic properties in the relative bioavailability study.

Parameter	FT218 6 g (n = 26)	Twice-Nightly SO 6 g (First Dose) (n = 27)
t_{max}, median (range), h	1.50 (0.3–3.5)	0.50 (0.3–2.0)
C_{max}, mean (SE), µg/mL [CV]	64.6 (5) [40]	70.9 (4) [28]
$AUC_{0-\infty}$, mean (SE), h·µg/mL [CV]	273 (27) [51]	259 (22) [44]
AUC_{0-8}, mean (SE), h·µg/mL [CV]	267 (27) [51]	248 (18) [39]
C_{8h}, mean (SE), µg/mL [CV]	6.6 (1) [108]	10.7 (3) [145]

C_{8h} = plasma concentration 8 h after dosing; SO = sodium oxybate.

C_{8h} for FT218 6 g (6.6 [1] µg/mL) was lower (below equivalence criteria) than C_{8h} of twice-nightly SO 6 g (10.7 [3] µg/mL). Interpatient variability between the 2 treatments was similar for all pharmacokinetic parameters.

Food-Effect Study

FT218 had lower C_{max} in the fed versus the fasted state, and exposure met bioequivalence criteria (Table V, Figure 4, and Supplemental Figure 2). Mean t_{max} was 1 h longer in the fed versus the fasted state (1.5 vs 0.5 h). Mean (SE) C_{max} in the fed state (64.0 [5] µg/mL) was lower than in the fasted state (90.5 [4] µg/mL) and was below the bioequivalence 80%–125% no-effect boundaries (mean fed:fasted ratio, 66.7%; 90% CI, 58.2%–76.5%). Mean (SE) $AUC_{0-\infty}$ in the fasted state (267 [24] h·µg/mL) was slightly higher than in the fed state (242 [24] h·µg/mL), but the 90% CIs were within the 80%–125% no-effect boundaries for bioequivalence (mean fed:fasted ratio, 86.1%; 90% CI, 80.0%–92.7%).

Table V. Pharmacokinetic properties in the food-effect study.

Parameter	FT218 6 g	
	Fed (n = 14)	Fasted (n = 13)
t_{max}, median (range), h	1.5 (0.5–2.5)	0.53 (0.33–1)
C_{max}, mean (SE), μg/mL [CV]	64.0 (5) [27.3]	90.5 (4) [17.5]
$AUC_{0-\infty}$, mean (SE), h·μg/mL [CV]	242 (24) [36.5]	267 (24) [32]
AUC_{0-8}, mean (SE), h·μg/mL [CV]	239 (23) [35.5]	266 (23) [31.2]
C_{8h}, mean (SE), μg/mL [CV]	2.09 (1) [150.5]	1.43 (1) [142.7]

C_{8h} = plasma concentration 8 h after dosing.

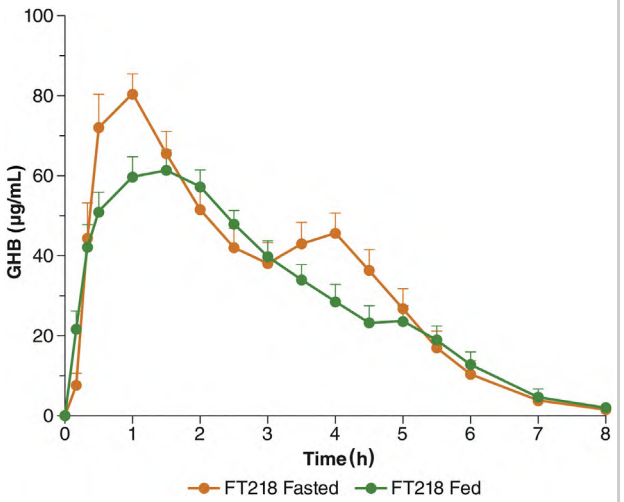

Figure 4. Mean plasma concentrations of γ-hydroxybutyrate (GHB) over time after FT218 administration in fasted or fed participants in the food-effect study. Error bars indicate SEs.

Safety and Tolerability

Pilot Study

Four participants reported a total of 5 AEs (Table VI). All AEs were mild to moderate in severity, with no SAEs or AEs leading to study discontinuation. AEs were comparable between the 3 prototypes of FT218 and twice-nightly SO.

Dose-Proportionality Study

Thirteen participants (65%) reported a total of 31 AEs (Table VI). The incidence of AEs increased with increasing doses. Eight AEs (mainly headache [n = 5/8]) were experienced by 7 of 20 participants (35%) during the 4.5-g period, 7 AEs (mainly gastrointestinal disorders [n = 4/7]) were experienced by 4 of 20 participants (20%) during the 7.5-g period; and 16 AEs (mainly gastrointestinal disorders [n = 8/16]) were experienced by 6 of 12 participants (50%) during the 9-g period. One of these, a nervous system disorder (sedation), was an SAE. This SAE was most likely a result of treatment at 9 g without subsequent continuous titration through the lower doses of FT218; however, even without titration, AEs at the 9-g dose only occurred in 50% of participants and were mainly mild to moderate in severity. All AEs were resolved before the end of the study.

Relative Bioequivalence Study

The incidence and types of AEs were similar between the FT218 and twice-nightly SO groups, and most were known SO-related AEs (Table VI). The most common AE during both treatments was somnolence, and all AEs were mild or moderate in severity. There were no SAEs during the study. Two participants withdrew from the study after experiencing AEs, including 1 event of nausea after FT218 treatment and 1 event of flulike symptoms after twice-nightly SO treatment.

Food-Effect Study

The frequency of AEs was higher in the fasted versus the fed state (58 AEs in all 16 participants [100%, with 54 potentially related to study treatment] in the fasted state and 32 AEs in 13 participants [86.7%, 31 potentially related to study treatment] in the fed state) (Table VI). This finding was primarily driven by an increase in gastrointestinal disorders (37.5% in the fasted state vs 13.3% in the fed state; most commonly nausea and vomiting) and nervous system

Table VI. Number (percentage) of participants experiencing ≥1 AE.

AE	Pilot Study				Dose-Proportionality Study			Relative Bioavailability Study		Food-Effect Study	
	FT218 Type 1 4.5 g (n = 15)	FT218 Type 2 4.5 g (n = 14)	FT218 Type 3 4.5 g (n = 15)	Twice-Nightly SO 4.5 g (n = 15)	FT218 4.5 g (n = 20)	FT218 7.5 g (n = 20)	FT218 9 g (n = 12)	FT218 6 g (n = 27)	Twice-Nightly SO 6 g (n = 27)	Fasted State 6 g (n = 16)	Fed State 6 g (n = 15)
Somnolence/ sedation					0	0	2 (16.7)	9 (33.3)	6 (22.2)	13 (81.3)	10 (66.7)
Dizziness								1 (3.7)	4 (14.8)	7 (43.8)	3 (20.0)
Headache	0	0	0	1 (6.7)	4 (20.0)	1 (5.0)	2 (16.7)	1 (3.7)	3 (11.1)	4 (25.0)	2 (13.3)
Feeling drunk				0	0	1 (5.0)	1 (8.3)	3 (11.1)	2 (7.4)	4 (25.0)	4 (26.7)
Nausea	0	0	0	1 (6.7)	0	1 (5.0)	2 (16.7)	3 (11.1)	2 (7.4)	6 (37.5)	1 (6.7)
Vomiting					0	1 (5.0)	3 (25.0)			3 (18.8)	1 (6.7)
Abdominal discomfort					0	1 (5.0)	0				
Abdominal pain					1 (5.0)	0	0				
Diarrhea					0	1 (5.0)	2 (16.7)				
Gastroenteritis	0	0	1 (6.7)	0	1 (5.0)	0	0				
Fatigue										3 (18.8)	1 (6.7)
Rhinitis								0	3 (11.1)		
Pharyngitis	1 (6.7)	0	0	0	1 (5.0)	0	0				
Flulike syndrome	1 (6.7)	0	0	0							
Hyperhidrosis					0	0	1 (8.3)	1 (3.7)	3 (11.1)		

AE = adverse event; SO = sodium oxybate.

disorders (all participants in the fasted state vs 80.0% in the fed state; most commonly somnolence and dizziness). All events were mild or moderate in severity, and no SAEs were reported.

DISCUSSION

Disturbed nocturnal sleep is a prominent feature of narcolepsy.[1–3] Although SO is an effective treatment for narcolepsy symptoms of cataplexy and excessive daytime sleepiness, it does not fully address disrupted nocturnal sleep through sleep consolidation because current formulations of SO have a short $t_{½}$ and require twice-nightly dosing.[10,19,20] Patients must wake in the middle of the night to take the second dose 4 h after going to sleep.[10] Therefore, a once-nightly formulation of SO with similar efficacy and tolerability to current twice-nightly formulations of SO could fulfill an unmet need in the treatment of narcolepsy.

FT218 is an investigational modified-release formulation of SO. It represents a potential once-nightly SO formulation for the treatment of narcolepsy. In all Phase I studies, FT218 had a uniform pharmacokinetic profile that supported once-nightly dosing with adequate C_{max}, short t_{max}, plasma GHB concentration maintained throughout the night, and gradual decline to lowest levels by 8−10 h after dosing (ie, the time when most patients wake up in the morning). Moreover, FT218 was well tolerated at all doses and had a favorable safety profile. Most AEs were mild or moderate in severity at all doses (4.5−9 g), even without titration before receiving the highest dose. AE reporting by participants receiving FT218 was consistent with the known AEs of SO, the most common being somnolence, dizziness, and nausea.[10,13,18,21,22]

In the pilot study, although all 3 prototypes had similar pharmacokinetic attributes, prototype 2 was selected for subsequent studies (including a recently completed Phase III efficacy and safety study [NCT02720744]) because it had pharmacokinetic properties closest to current twice-nightly SO formulations. In addition to supporting once-daily dosing, FT218 had dose proportionality for C_{max} and only slightly more than dose proportionality for exposure as measured by AUC. GHB plasma concentrations were greater in the fasted versus fed state for C_{max} and only slightly greater for overall exposure (AUC).

In direct comparison to twice-nightly SO, FT218 had bioequivalent exposure at the 4.5- and 6-g doses. C_{max} for FT218 was lower than that for twice-nightly SO, as were GHB C_{8h} concentrations. Indirect comparison to twice-nightly SO from the published literature suggests that FT218 may have a more predictable pharmacokinetic profile with ascending doses (dose-proportional increase in C_{max} and slightly more than dose-proportional increase in $AUC_{0-\infty}$ [an approximate 2.3-fold increase in plasma GHB concentration with a 2-fold dose increase]). Twice-nightly SO treatment produces a 3.7-fold increase in plasma GHB concentration with a 2-fold dose increase,[10,23,24] indicating nonlinear clearance and necessitating weight-based dosing in pediatric populations.[23] Moreover, the pharmacokinetic profile of FT218 suggests that food may have less of an effect on GHB concentrations, particularly overall exposure, than twice-nightly SO. In a study of healthy volunteers treated with twice-nightly SO, significant differences were observed for t_{max}, C_{max}, and $AUC_{0-\infty}$, with C_{max} values >2-fold higher in the fasted versus fed states.[21] In the present studies, this difference was reflected by second-dose t_{max} and C_{max} (relatively fasted state at 6 h after eating) being higher than first-dose t_{max} and C_{max} (relatively fed state at 2 h after eating) with twice-nightly SO. The increase in C_{max} observed with the second dose of twice-nightly SO (ie, the relatively fasted state) and associated AEs could potentially lead some patients to eat during the night before taking their second dose to avoid AEs associated with high C_{max} further disrupting nocturnal sleep.

The results suggest that the pharmacokinetic profile of FT218 supports once-nightly dosing, which eliminates the risks associated with having to wake up in the middle of the night to take the second dose. FT218 may also offer other clinical benefits over twice-nightly SO in patients with narcolepsy.

Once-nightly dosing in itself should have a positive effect on disrupted nocturnal sleep, allowing a full 8 h of consolidated nocturnal sleep. Although LSEQ scores in the pilot study suggest improvement in all participant-reported sleep domains, no conclusions can be drawn from these results owing to the intensive blood sampling schedule in the protocol, and clinical confirmation is needed from Phase III studies.

A temporal relationship has been observed between incidence of AEs and C_{max} with twice-nightly SO. Data from a new mixed-salts formulation of twice-nightly SO indicated a positive relationship between incidence of nausea and vomiting with higher C_{max}.[25] The single C_{max} with FT218 that is lower than those of twice-nightly SO may translate into fewer C_{max}-associated AEs, an outcome that requires confirmation in Phase III studies.

It could be postulated that a modified-release formulation of SO would have higher morning concentrations of GHB than a shorter-acting, twice-nightly formulation and might therefore be associated with more morning somnolence. However, the current studies indicate that 8-hour GHB levels with FT218 are slightly lower than with twice-nightly SO, and in the pilot study, there was no observable difference between FT218 and twice-nightly SO in the "awake following sleep" domain of the LSEQ.

FT218 produced dose proportionality in the GHB concentration. This predictable dosing profile may avoid the weight-based dosing currently needed in children and adolescents treated with twice-nightly SO.

Finally, pharmacokinetic parameters of FT218 were affected to a lesser extent in relation to food intake compared with those of twice-nightly SO. Thus, variability of efficacy with FT218 when administered with food may not be a clinical concern.

In summary, the pharmacokinetic profile of FT218 supports once-nightly dosing and addresses the important issue of sleep consolidation in patients with narcolepsy by avoiding the need for middle-of-the-night dosing.

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CONFLICTS OF INTEREST

Avadel Pharmaceuticals was involved in the study design, analysis, interpretation of data, decision to publish, and the preparation of the manuscript. DS and CT authors are employees of Avadel Pharmaceuticals. JD is a former employee of and current consultant to Avadel Pharmaceuticals.

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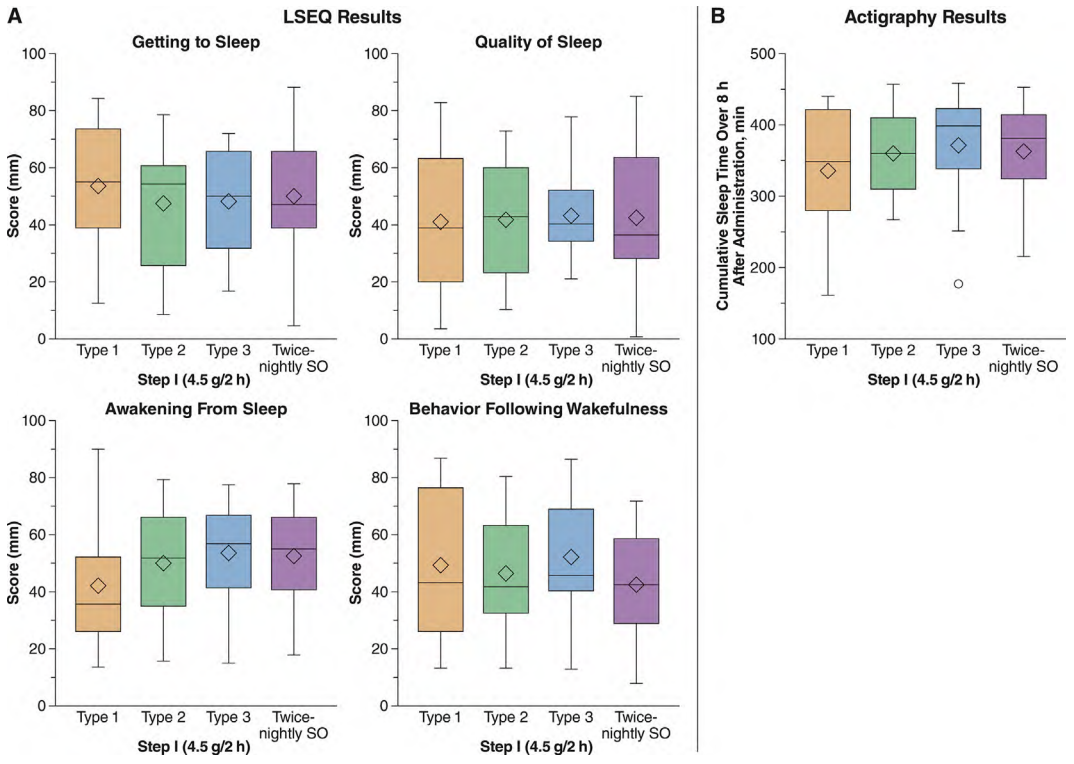
APPENDIX



Supplemental Figure 1. Exploratory pharmacodynamic evaluations in the pilot study: (A) Leeds Sleep Evaluation Questionnaire (LSEQ) and (B) actigraphy results.

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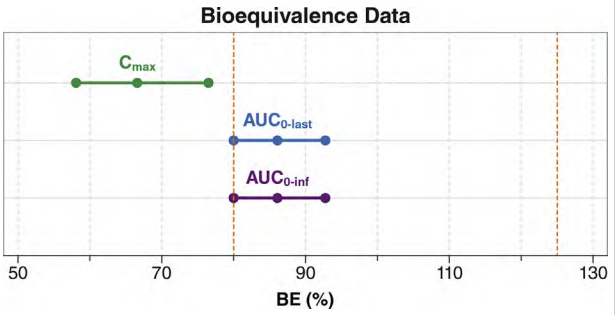

Supplemental Figure 2. Bioequivalence data of fed versus fasted states in the food-effect study. C_{max}, 90% CIs below 80%–125% bioequivalence boundaries; $AUC_{0\text{-}inf}$, 90% CIs within 80%–125% bioequivalence boundaries. $AUC_{0\text{-}inf}$, AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$, AUC from time 0 to last measurable concentration; C_{max}, maximum concentration.

EXHIBIT H

US010272062B2

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

(10) **Patent No.: US 10,272,062 B2**
(45) **Date of Patent: Apr. 30, 2019**

(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.

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

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

(65) **Prior Publication Data**

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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.

(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61K 9/16	(2006.01)
A61K 9/50	(2006.01)
A61K 31/19	(2006.01)
A61K 31/22	(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.

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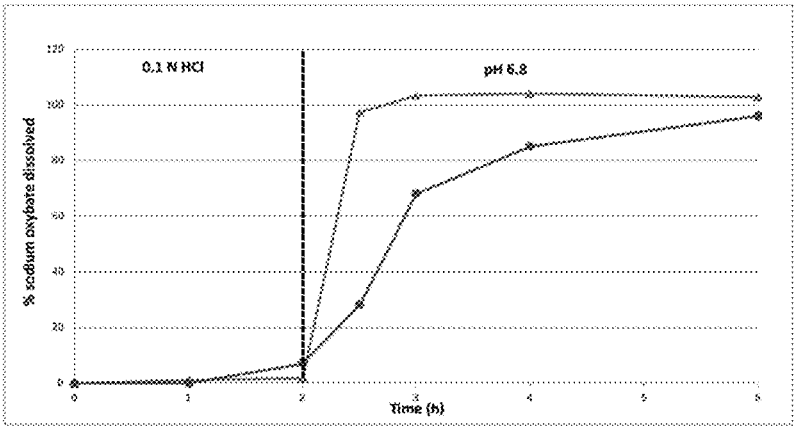
(57) **ABSTRACT**

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

89 Claims, 46 Drawing Sheets



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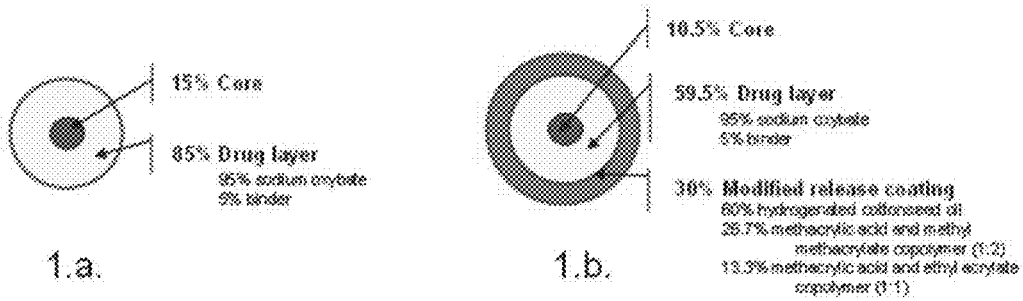

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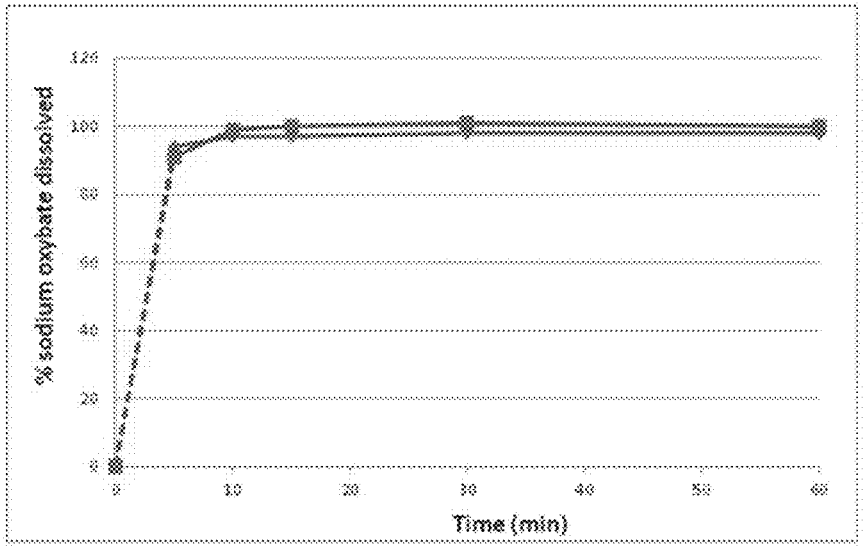

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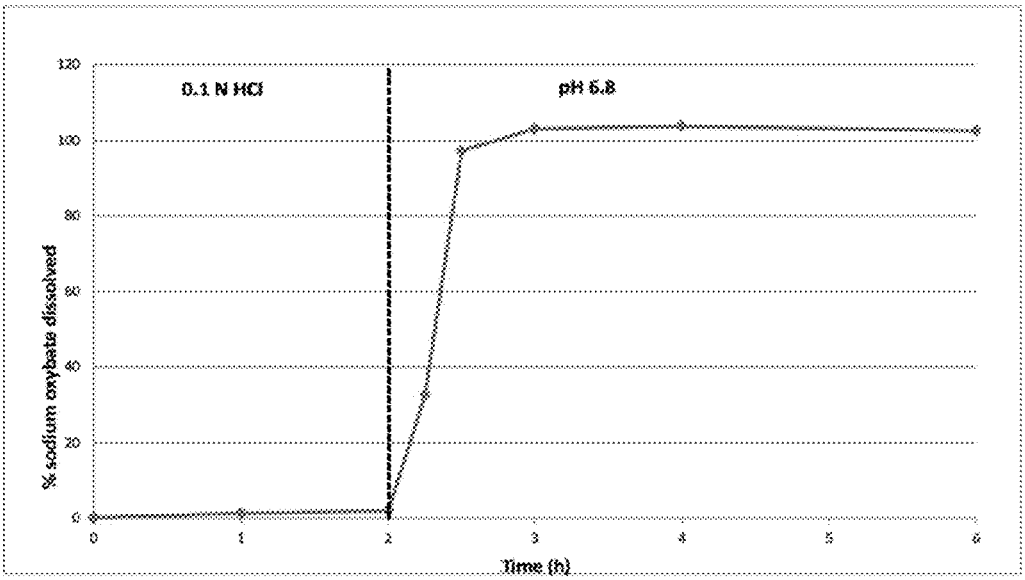

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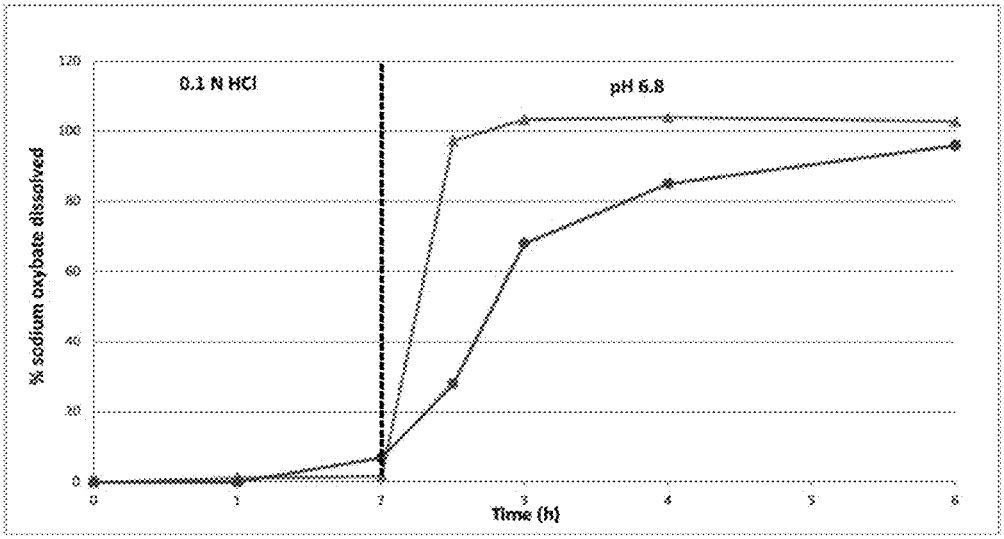

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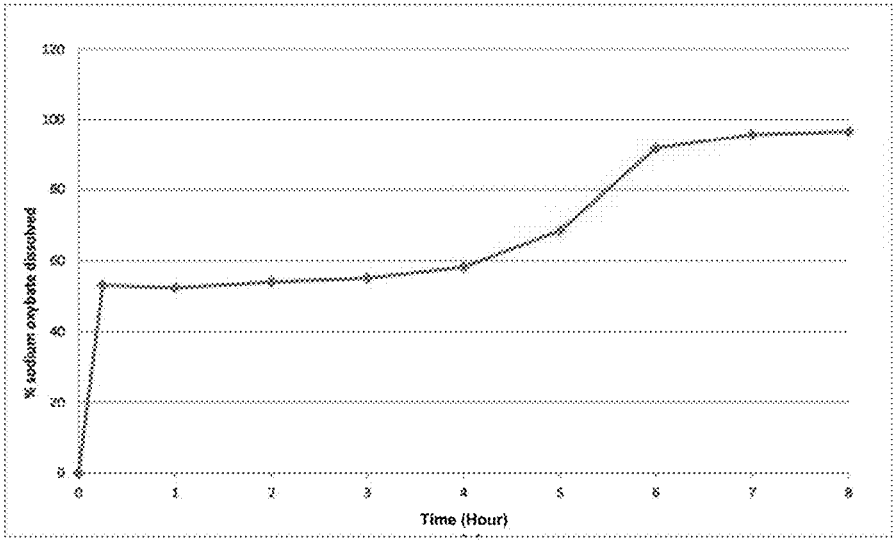

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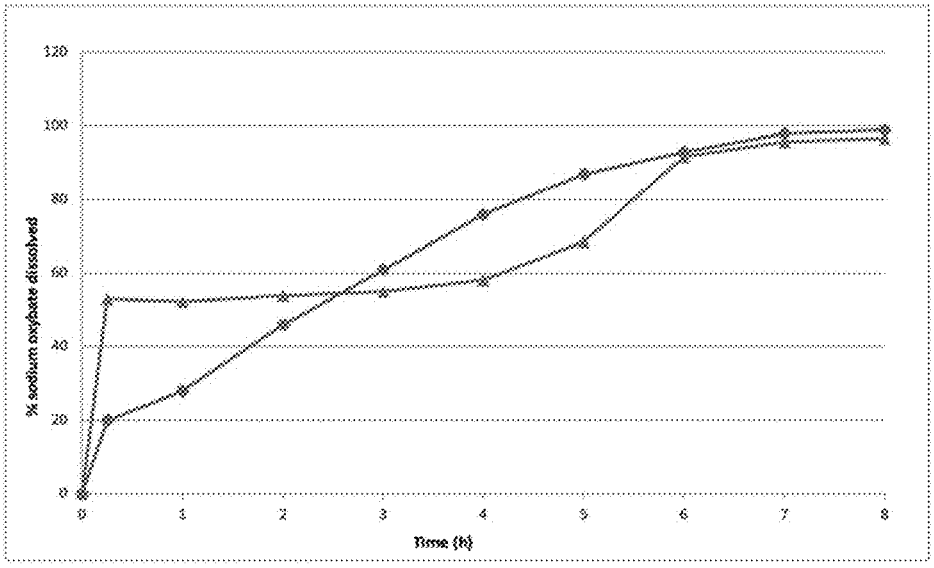

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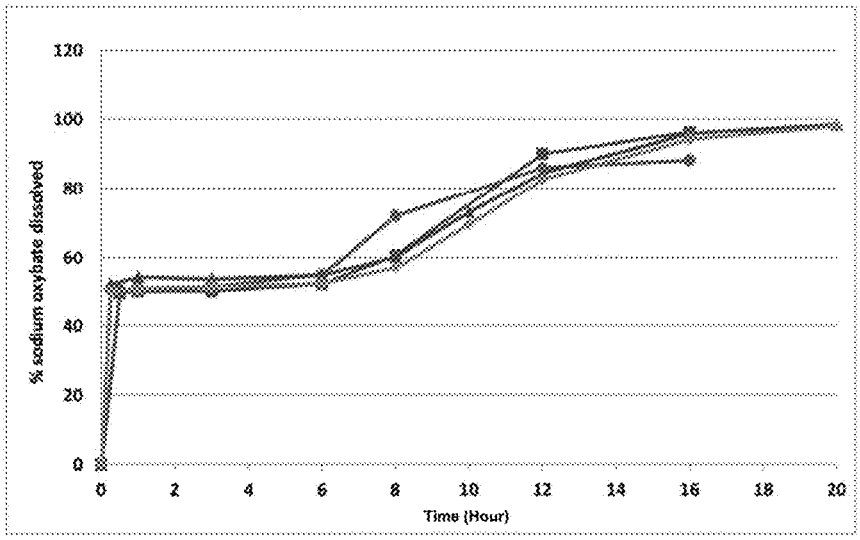

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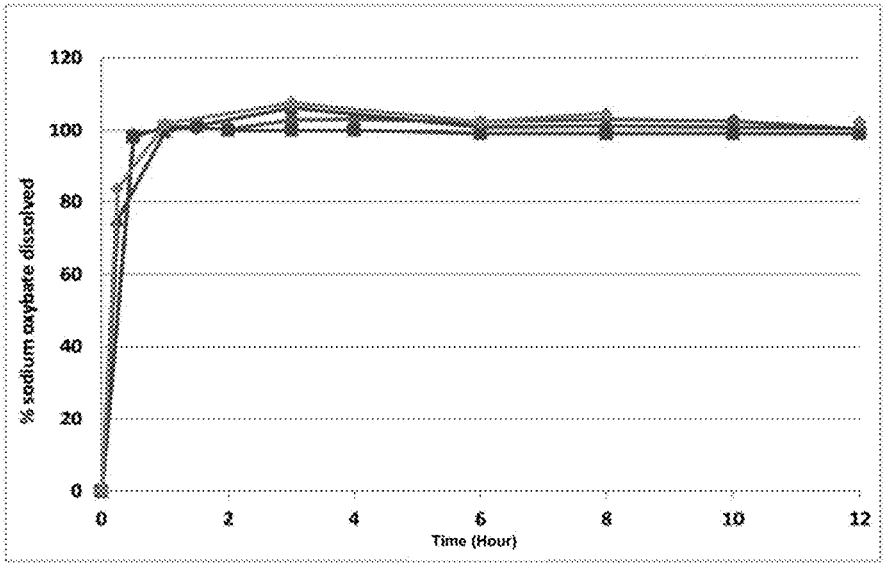

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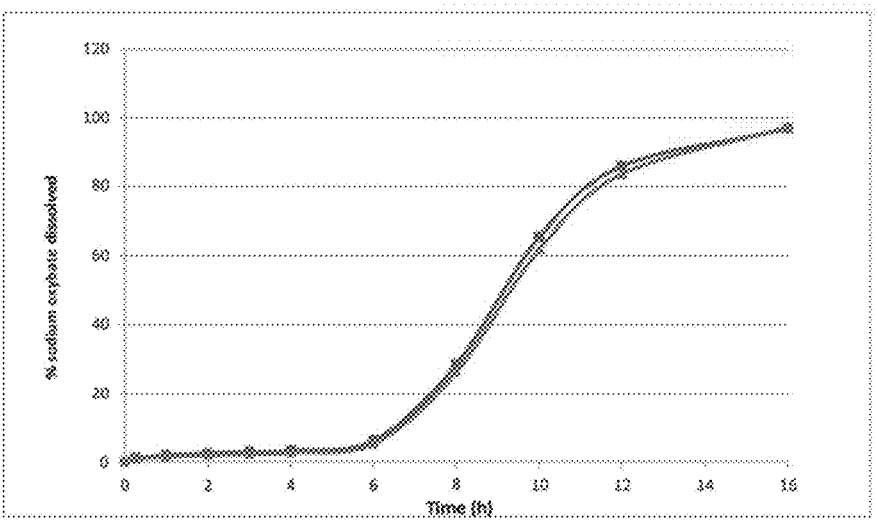

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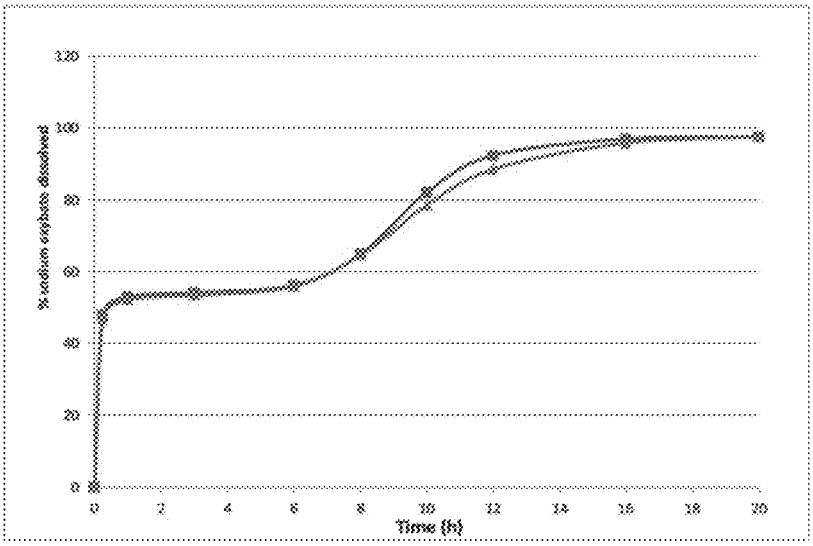

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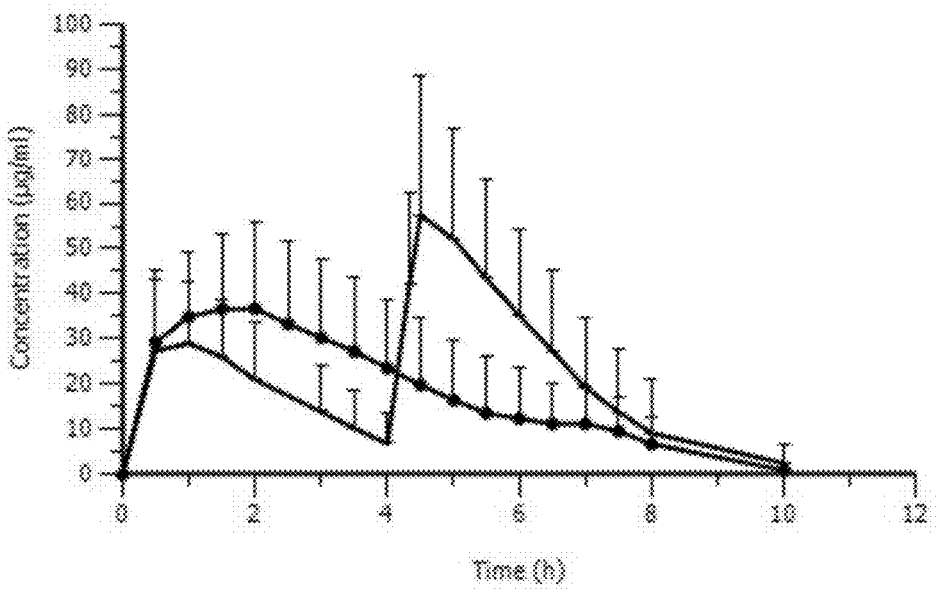

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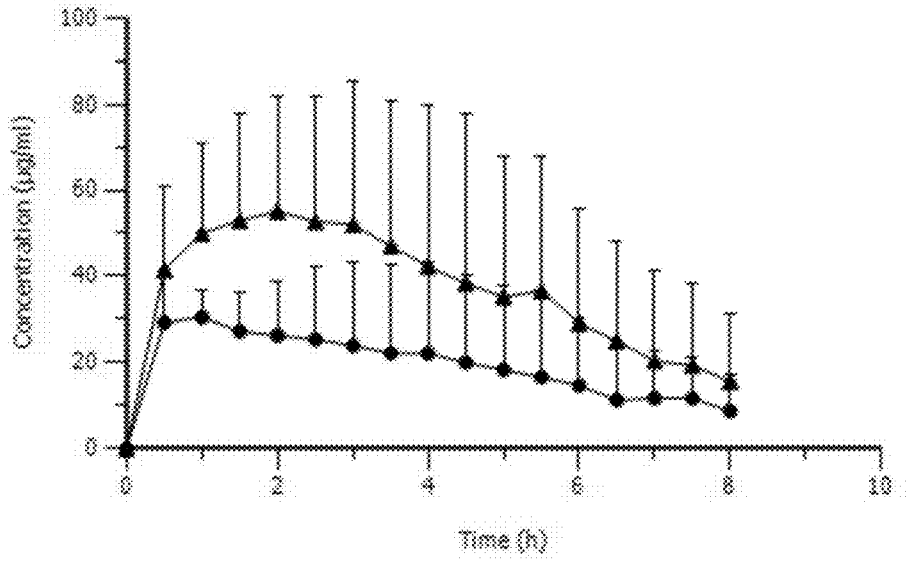

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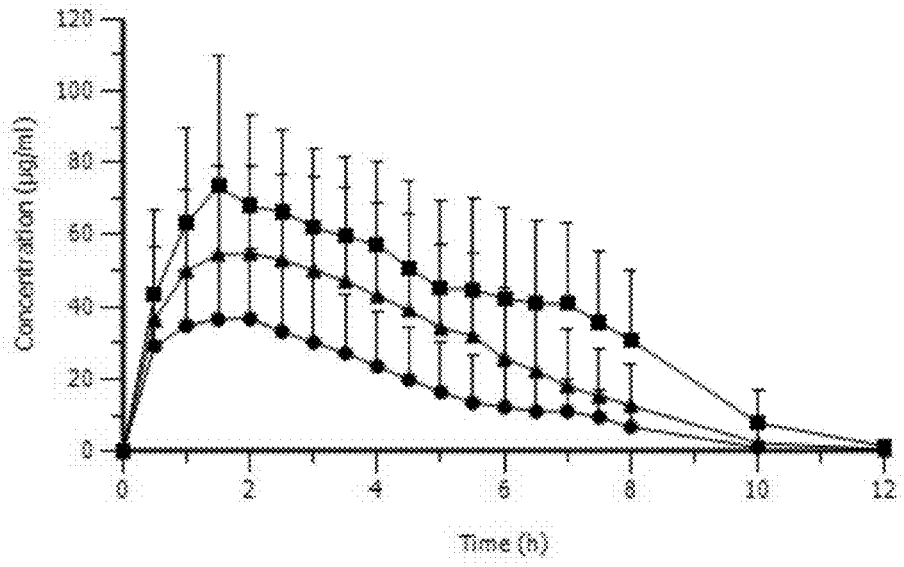

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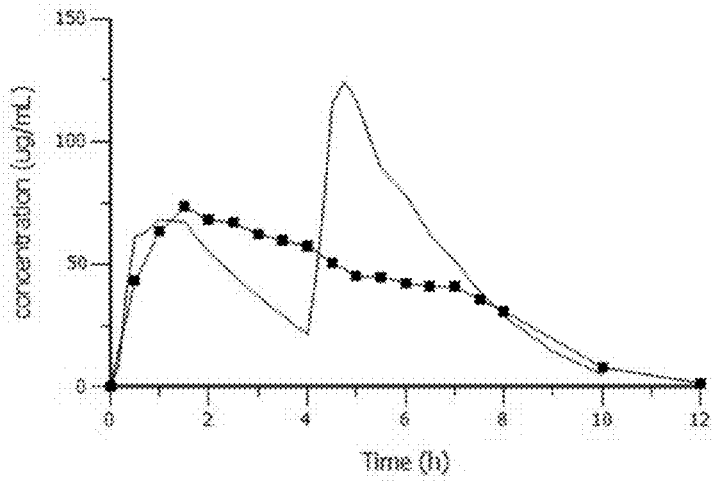

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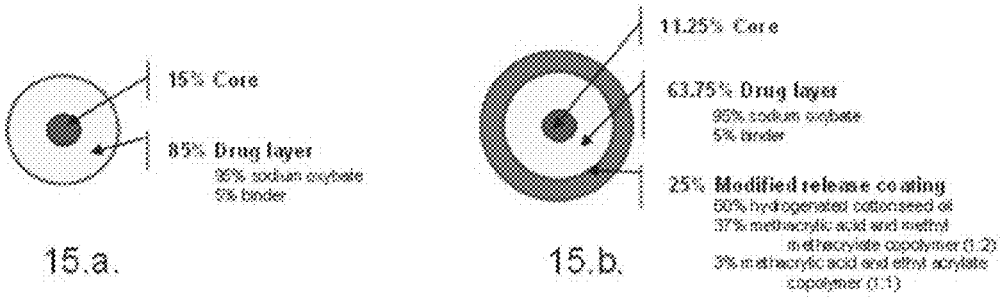

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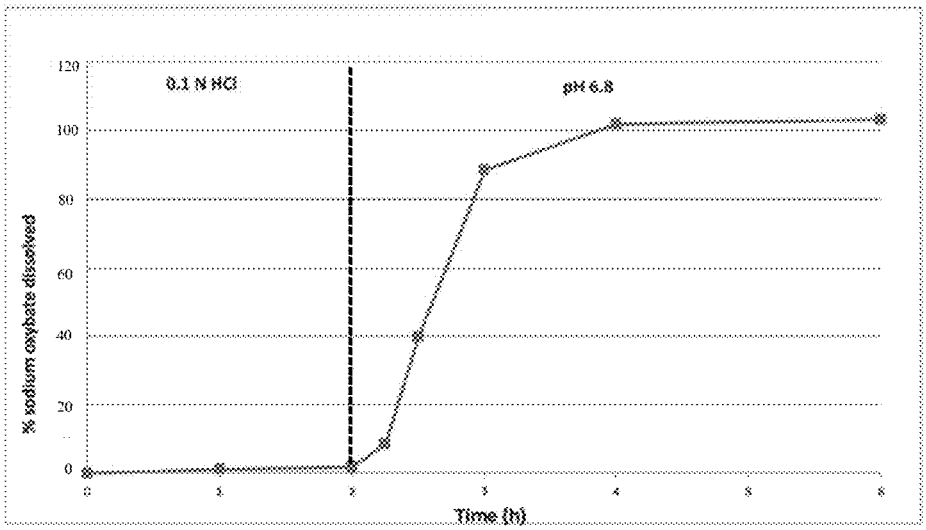

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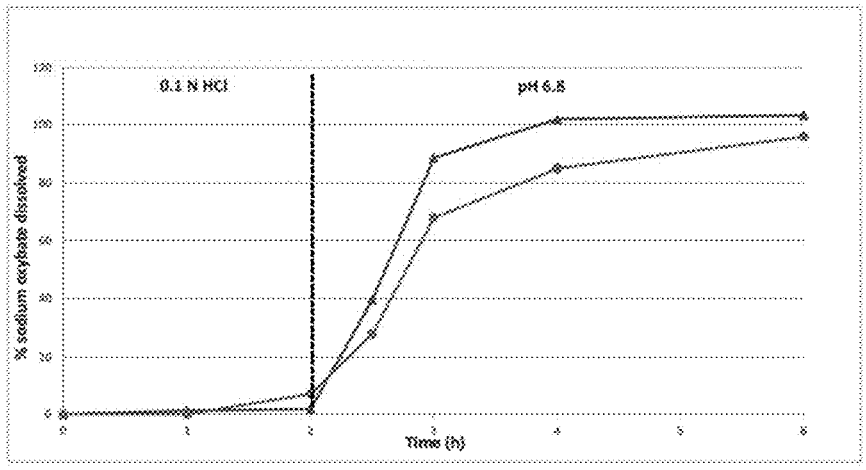

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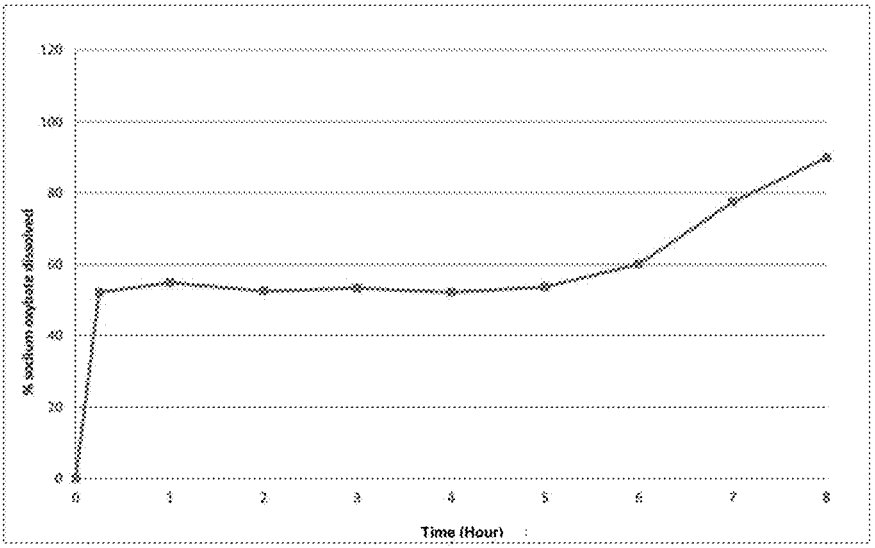

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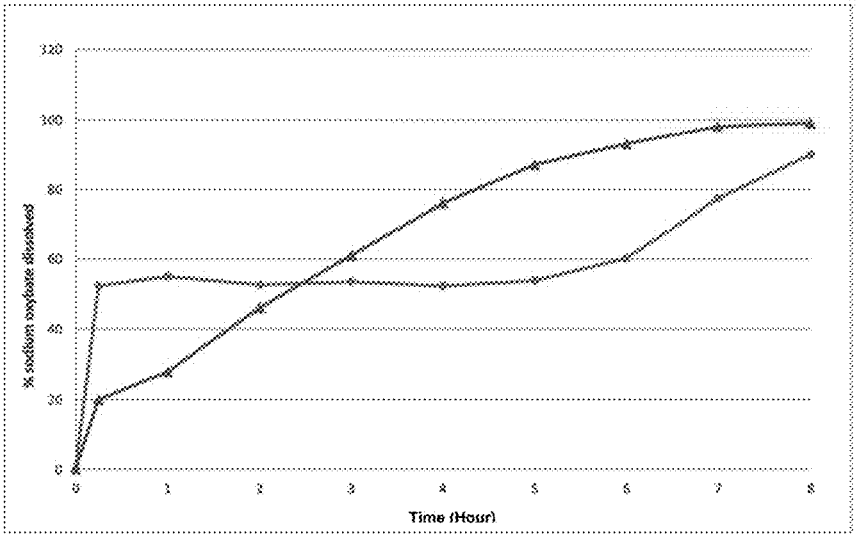

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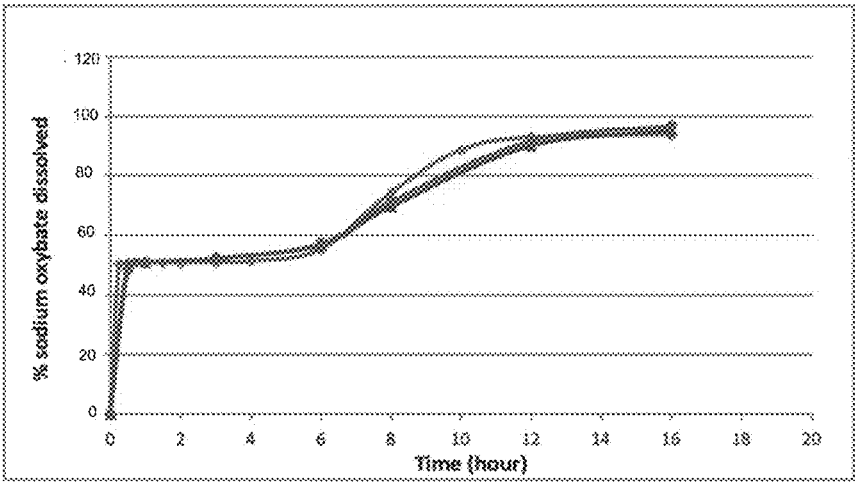

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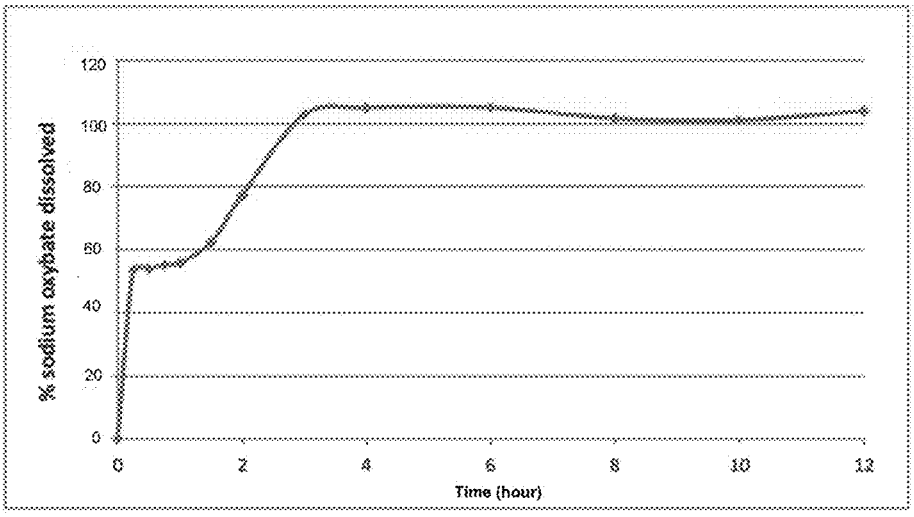

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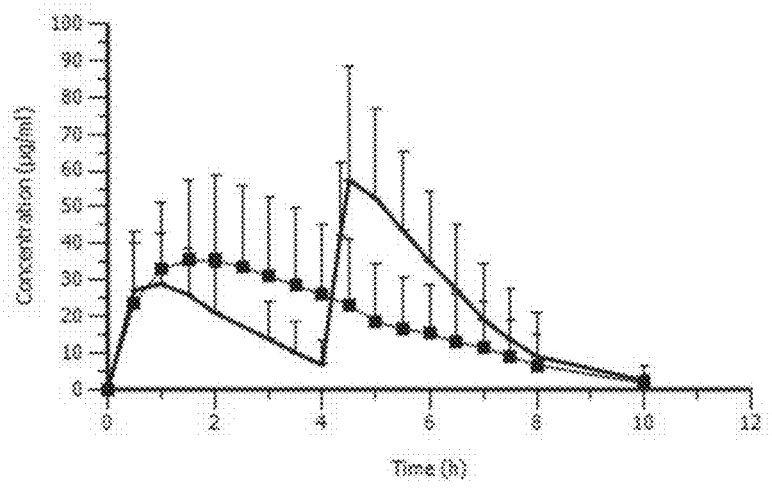

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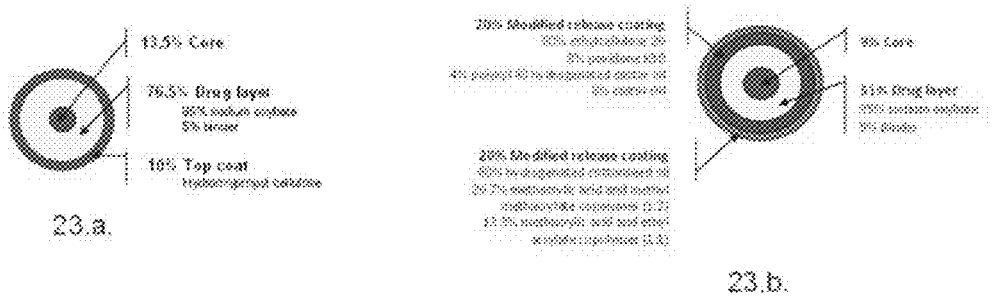

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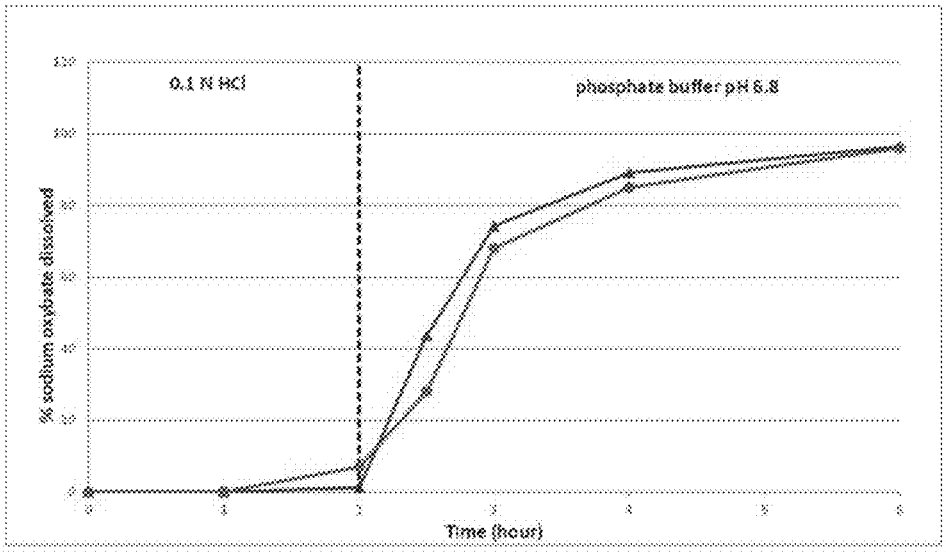

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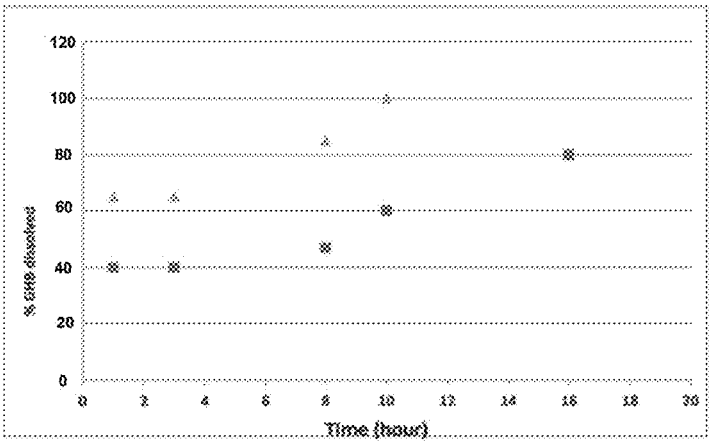

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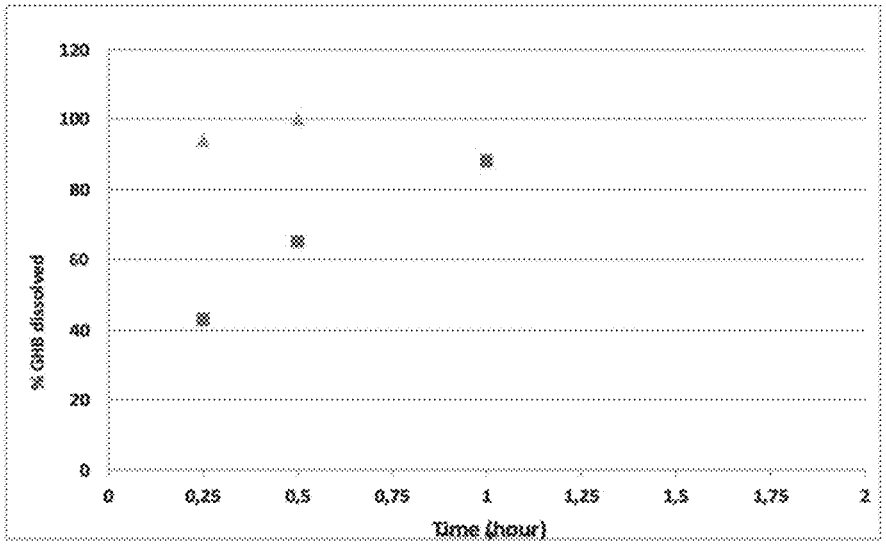

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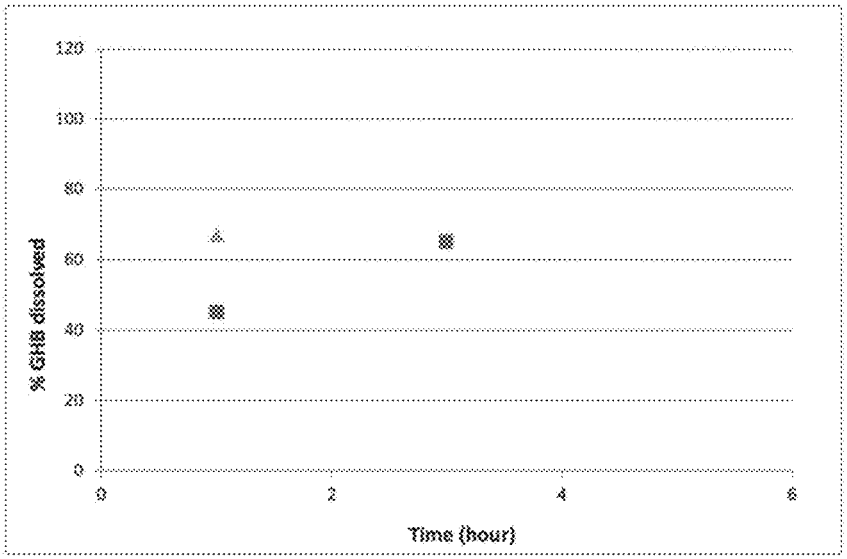

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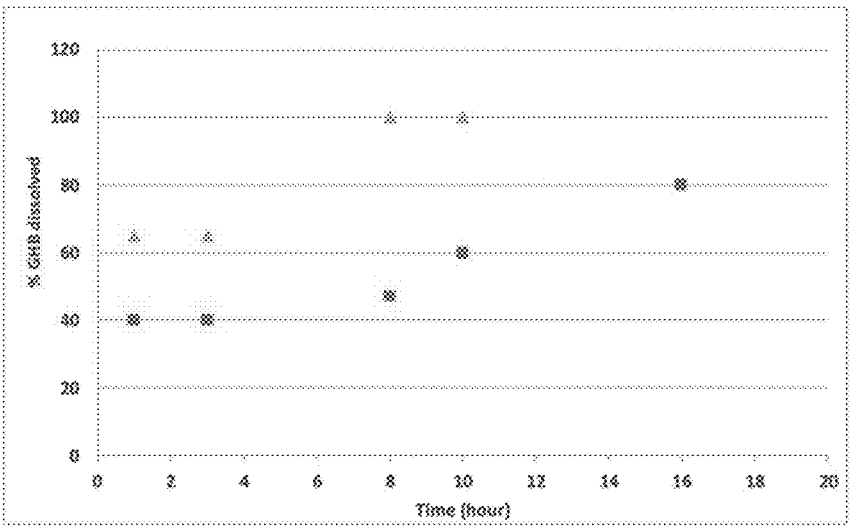

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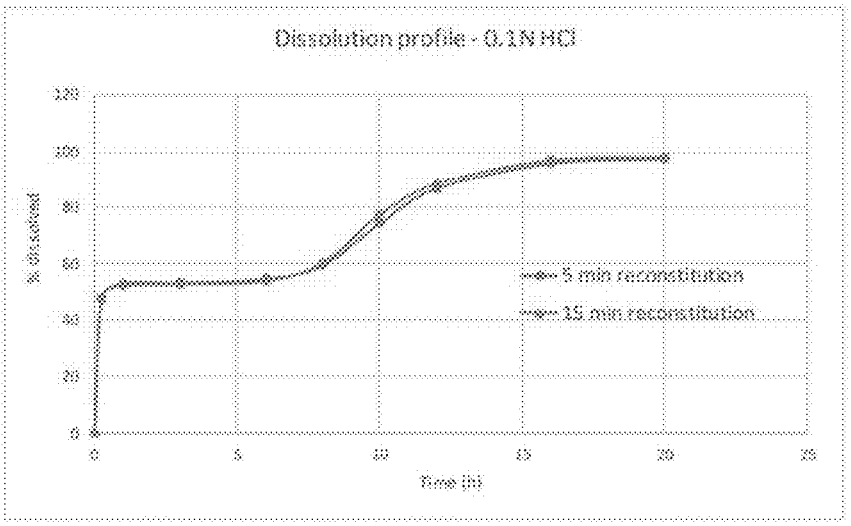

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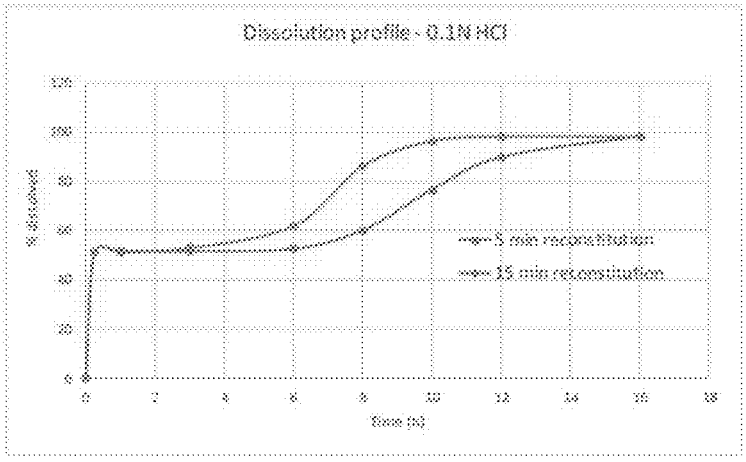

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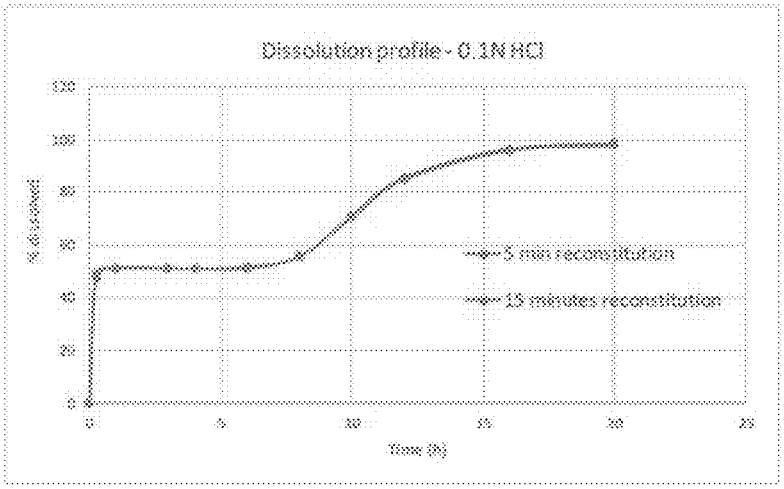

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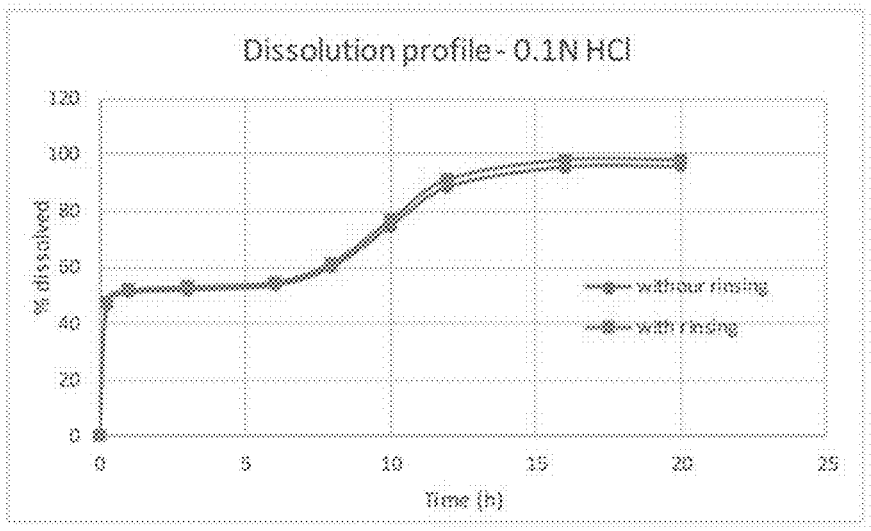

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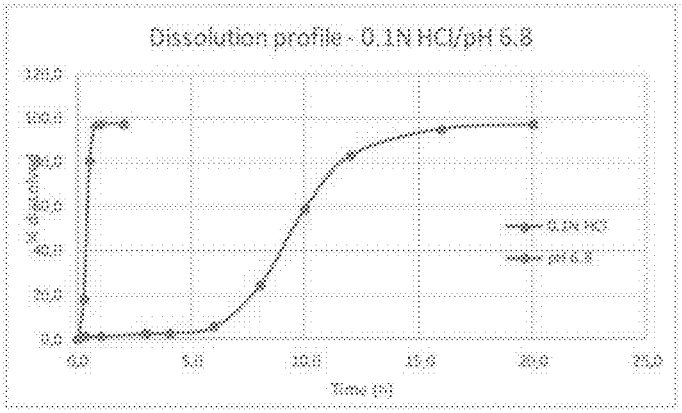

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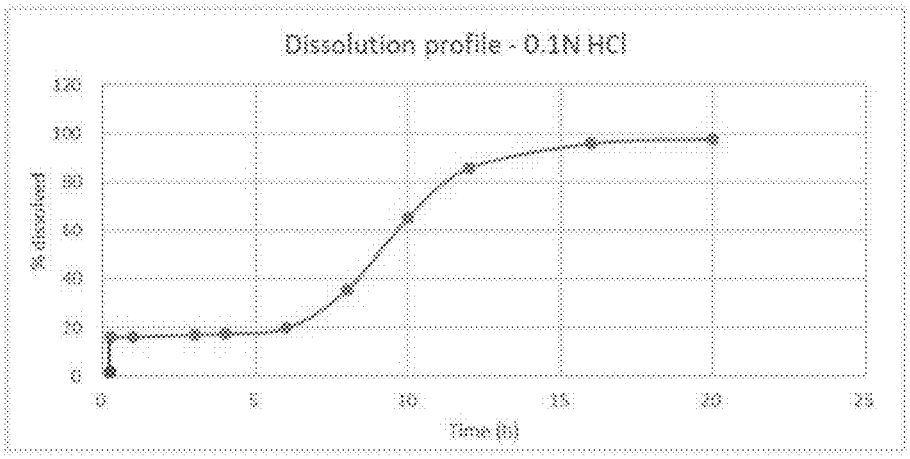

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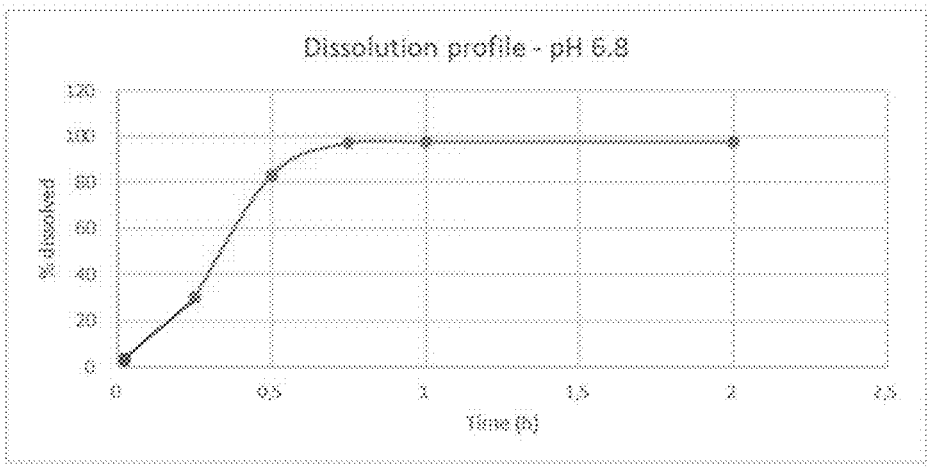

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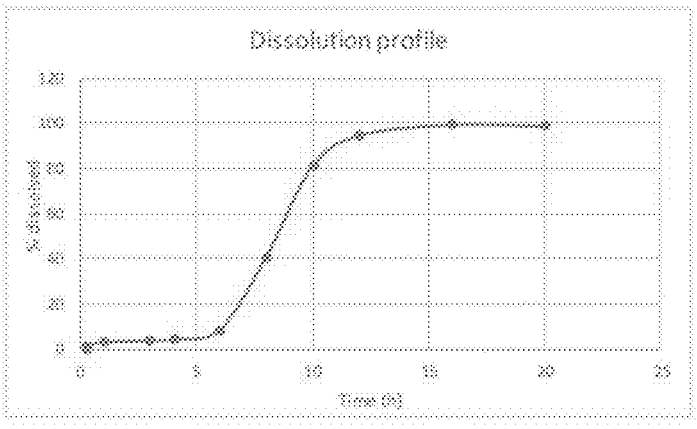

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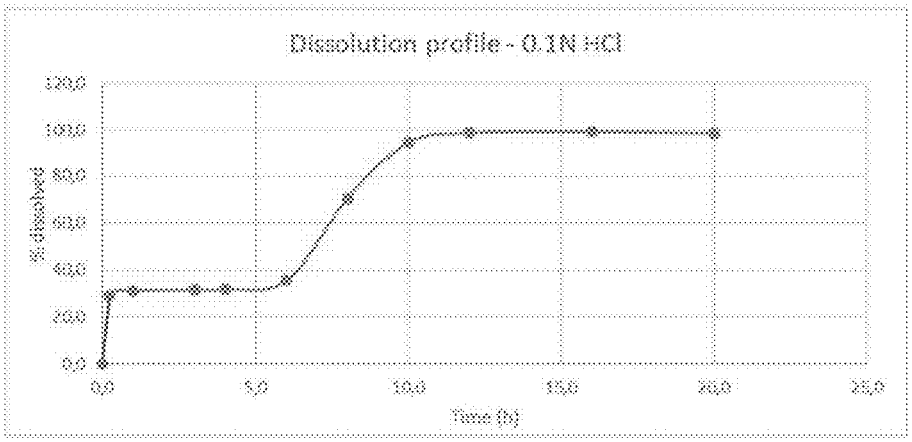

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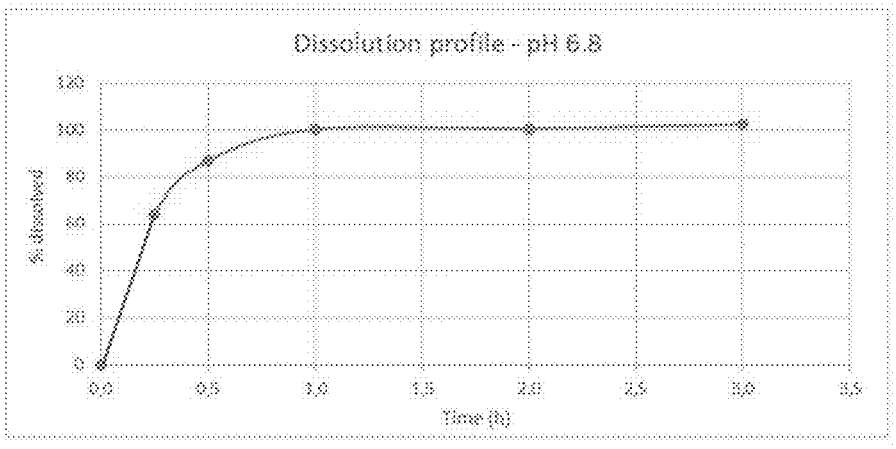

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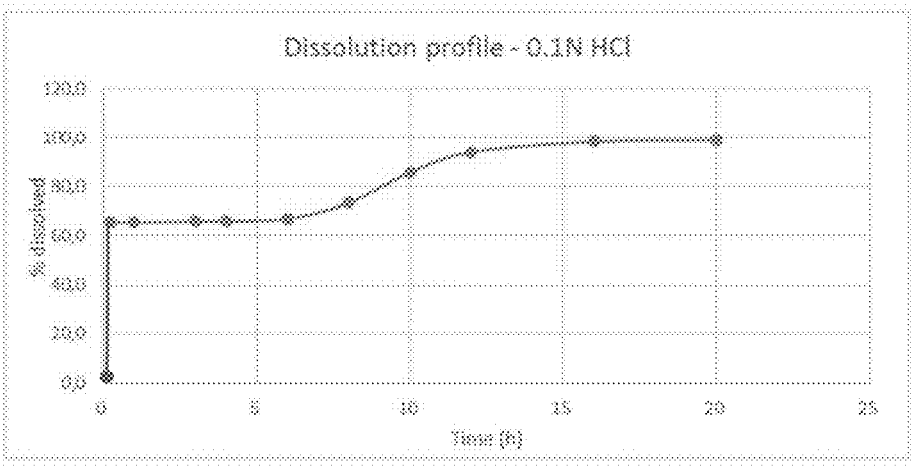

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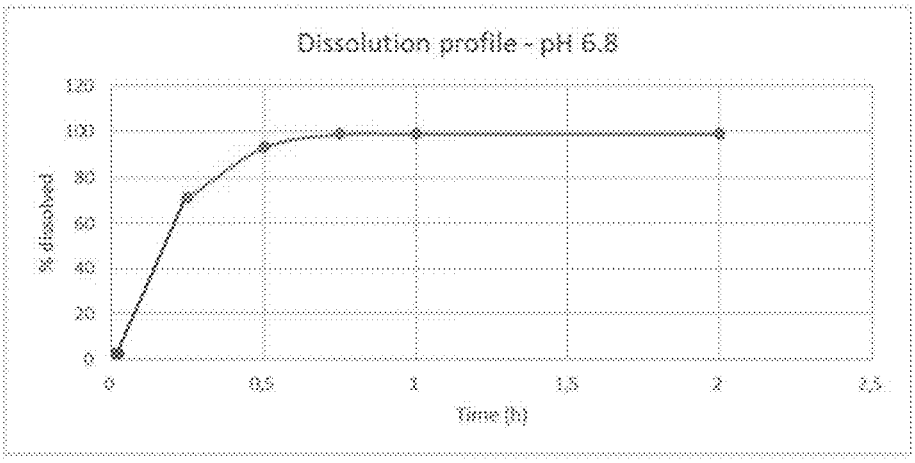

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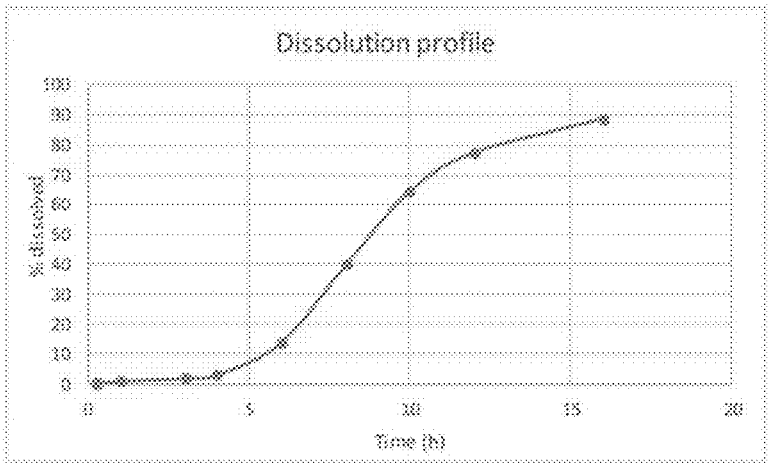

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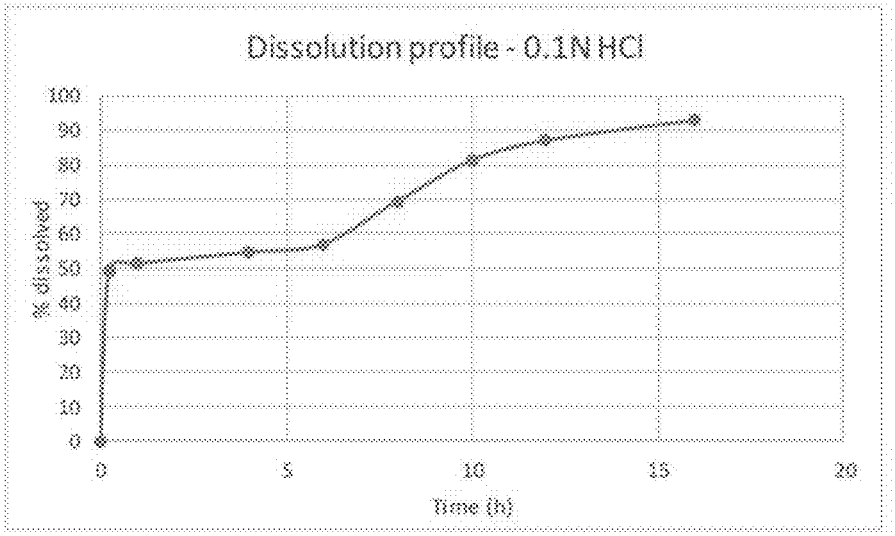

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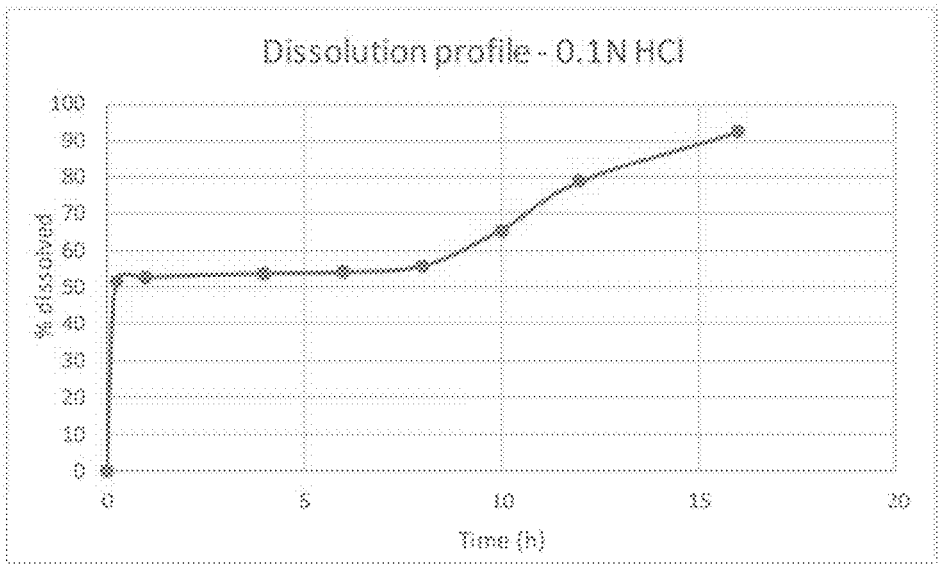

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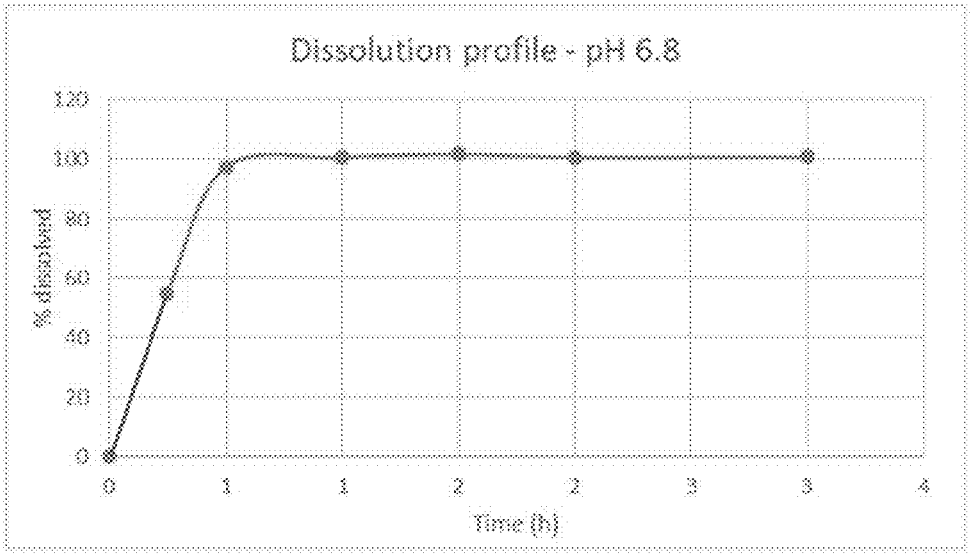

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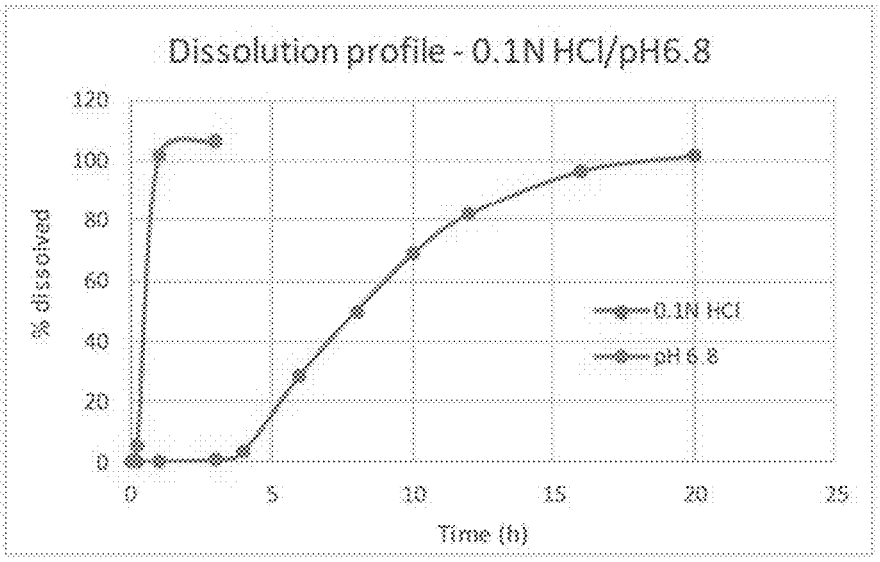

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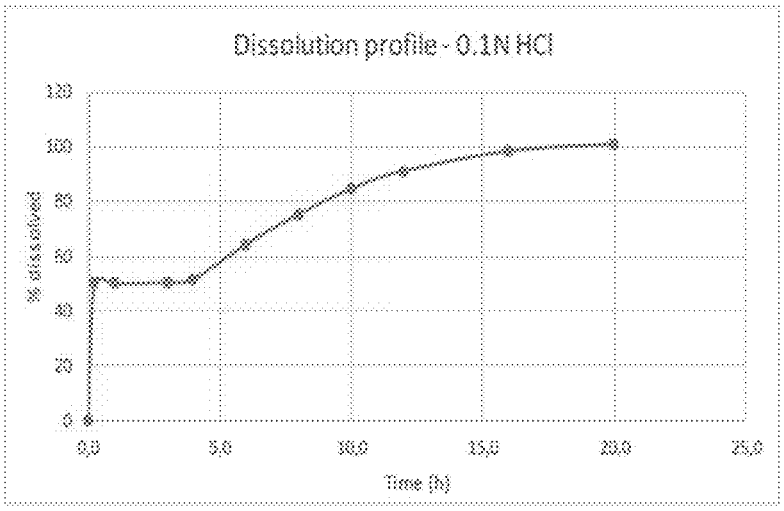

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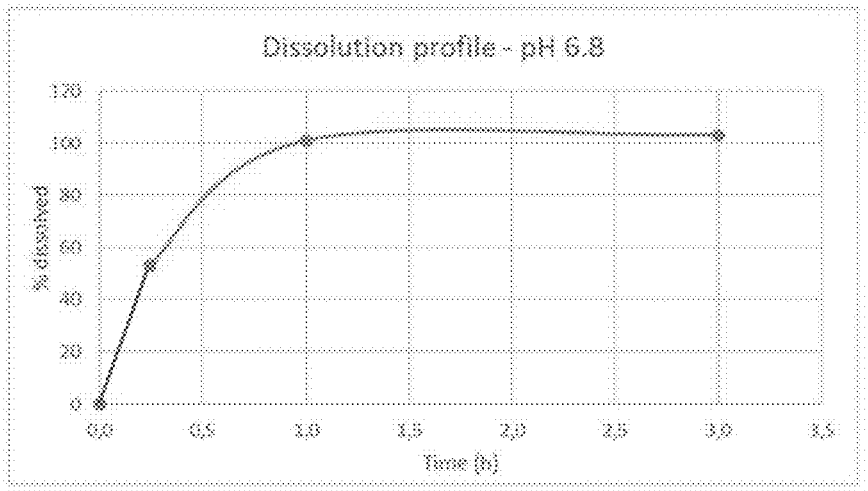

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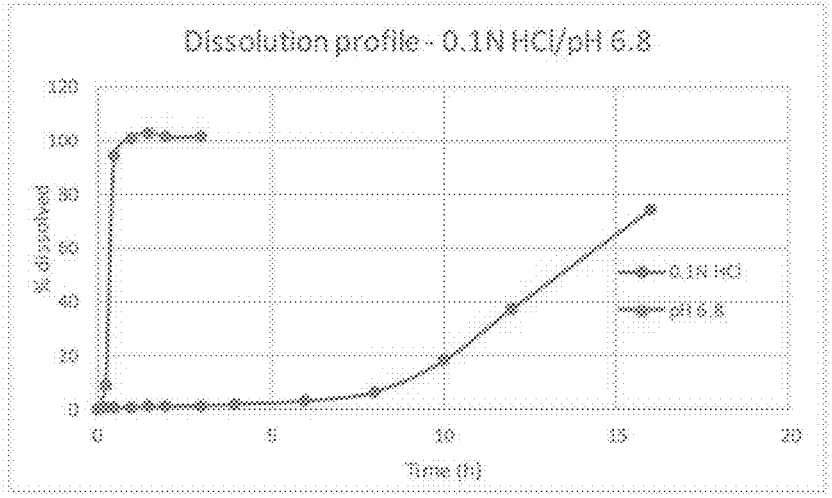

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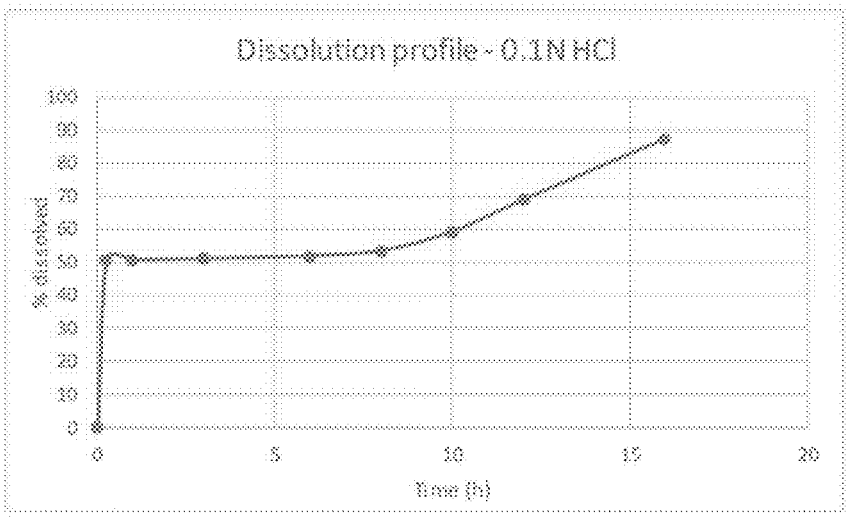

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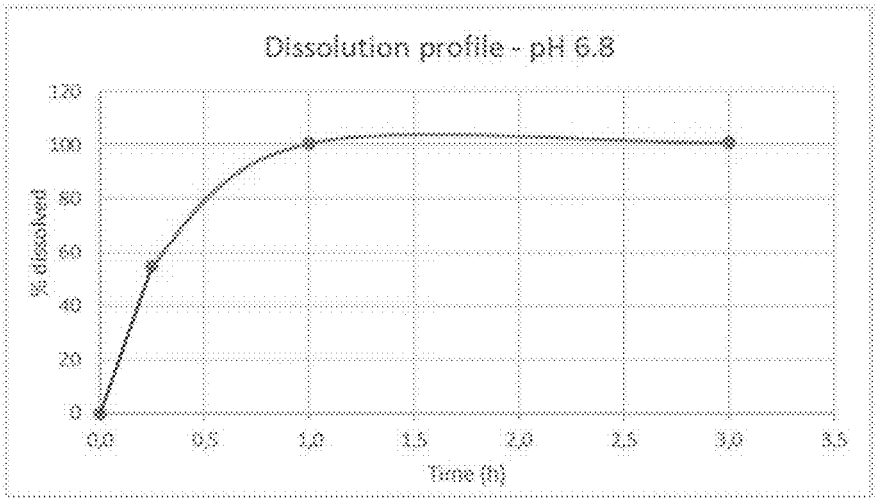

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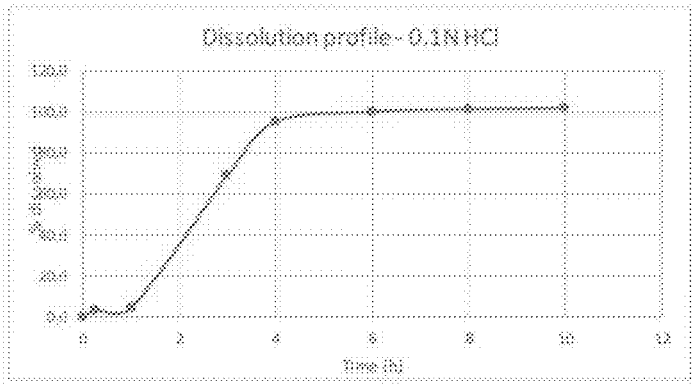

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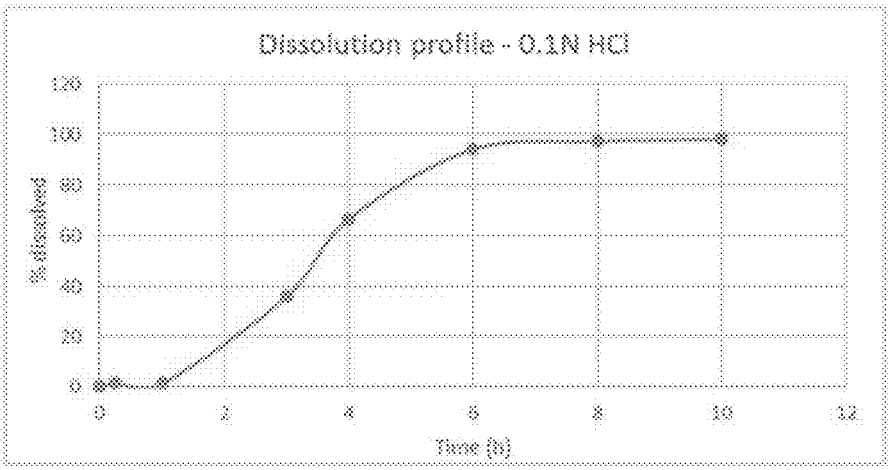

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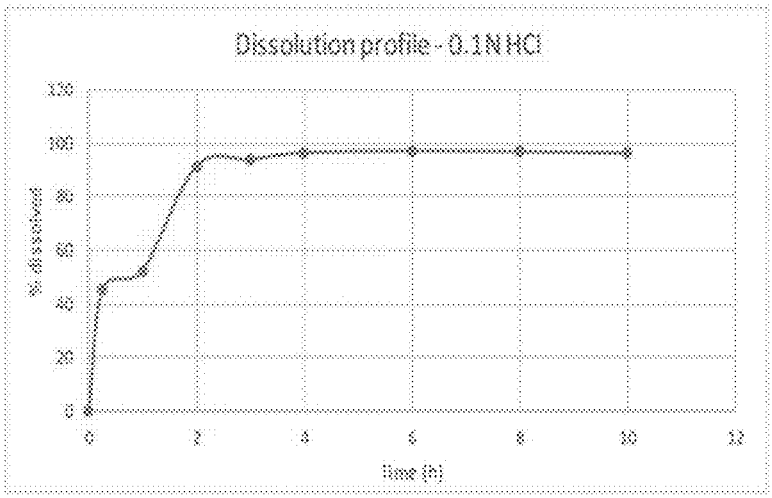

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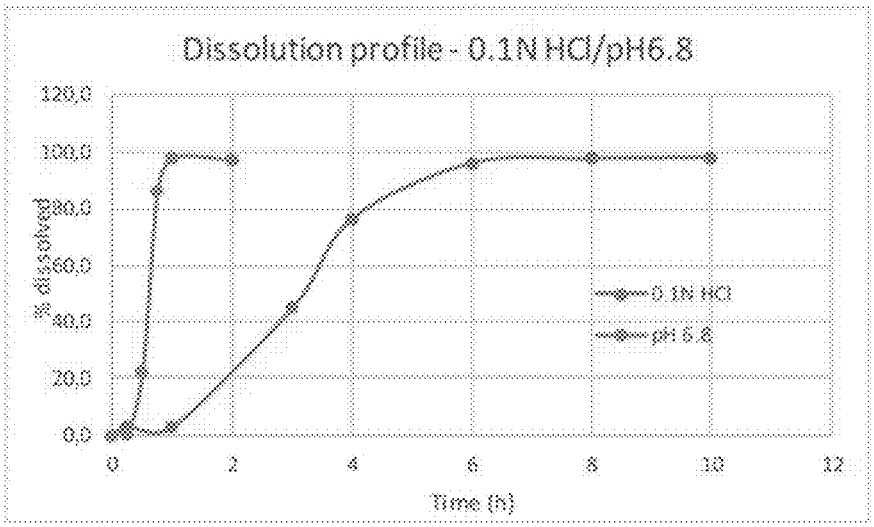

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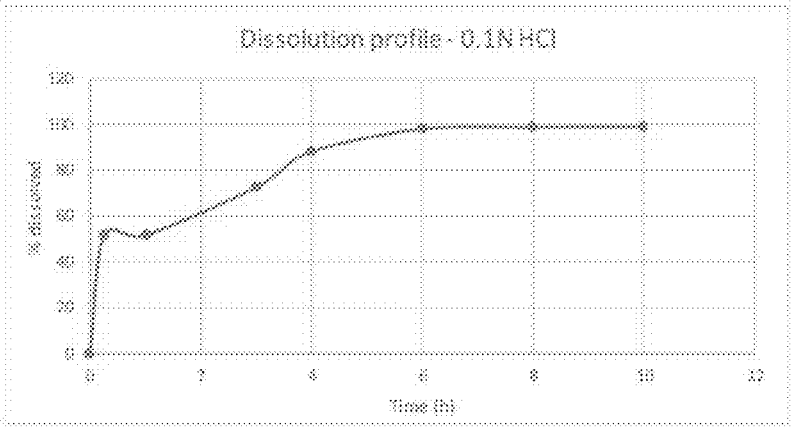

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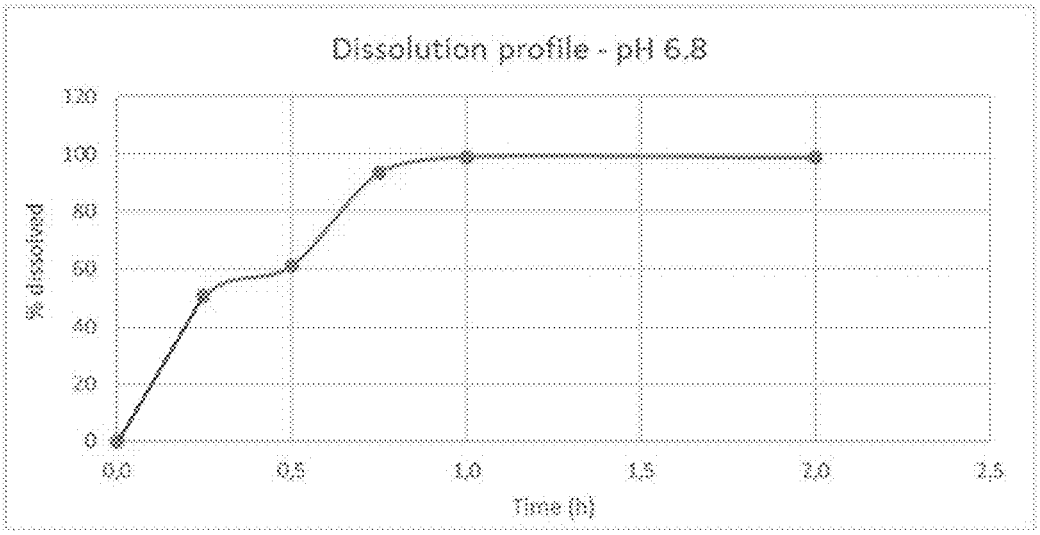

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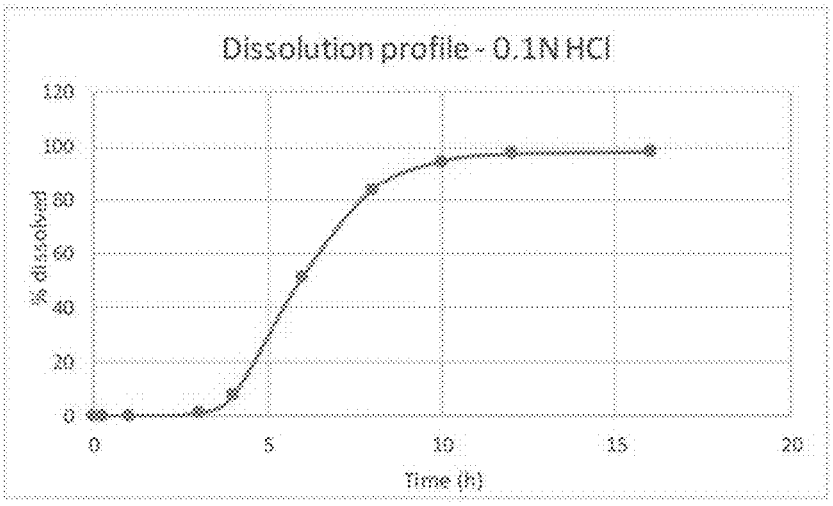

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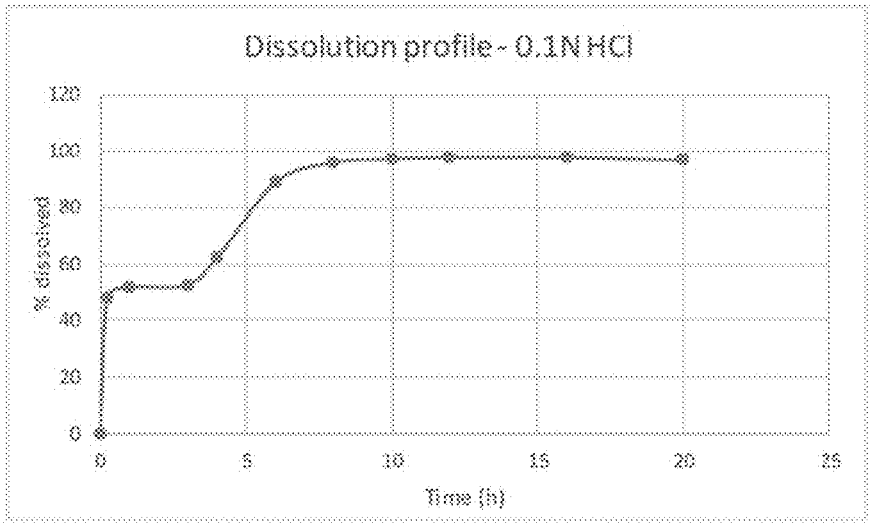

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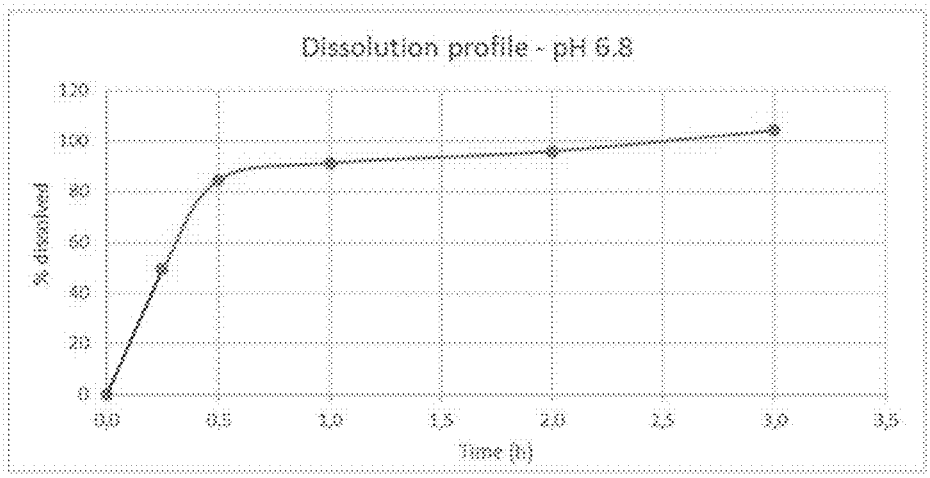

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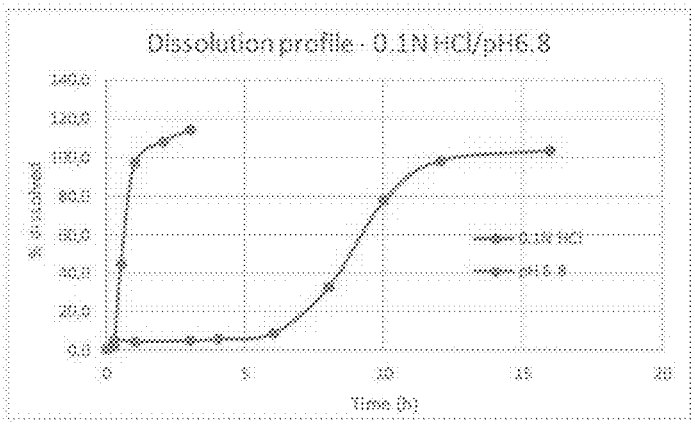

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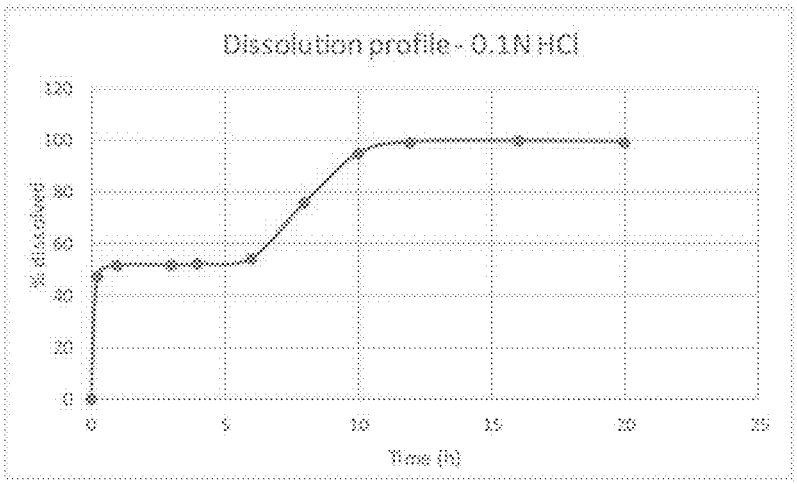

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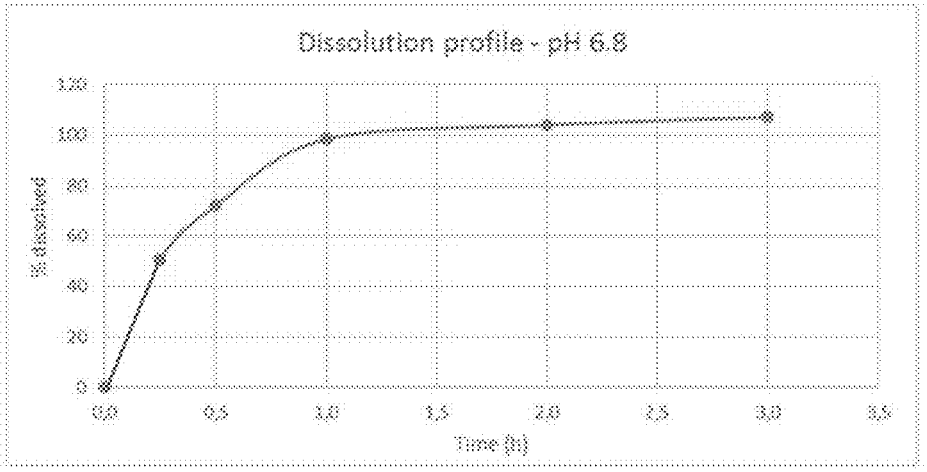

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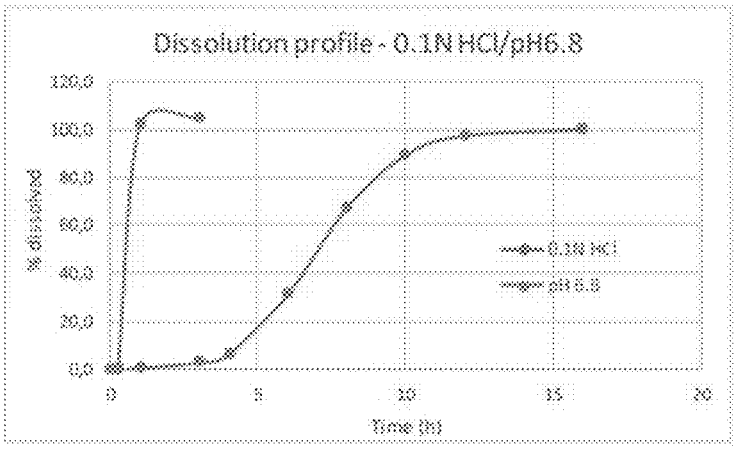

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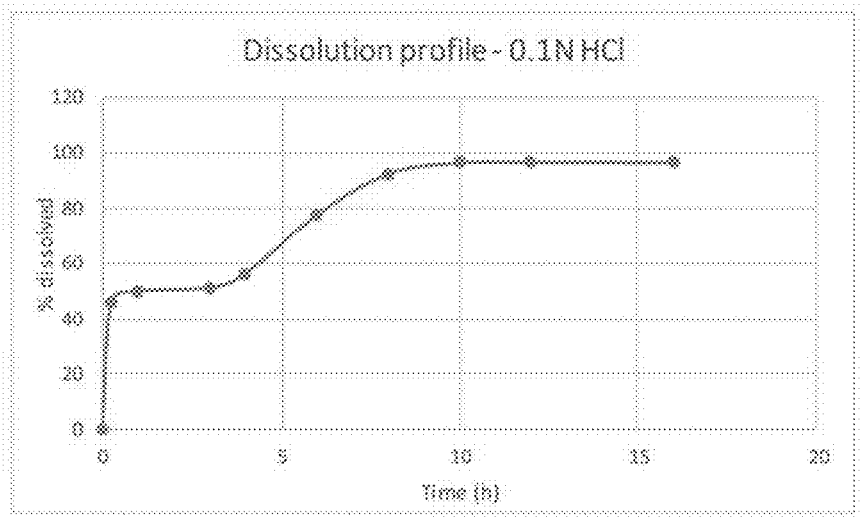

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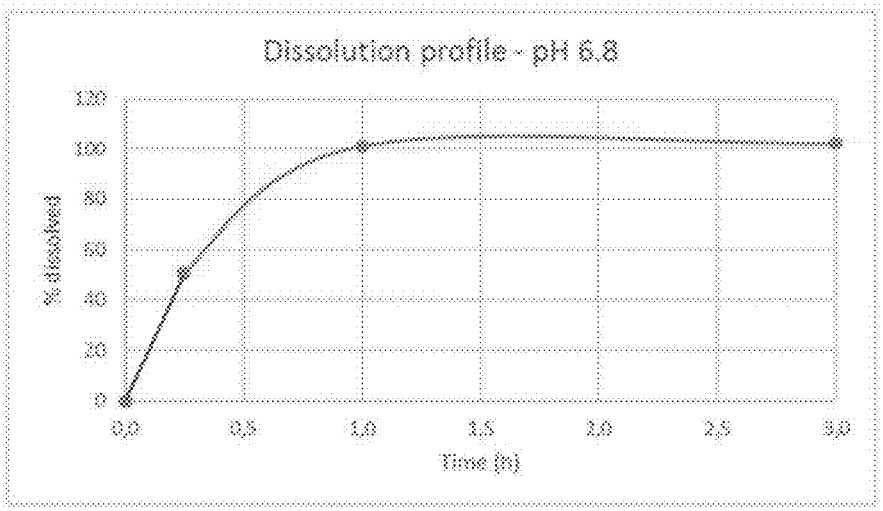

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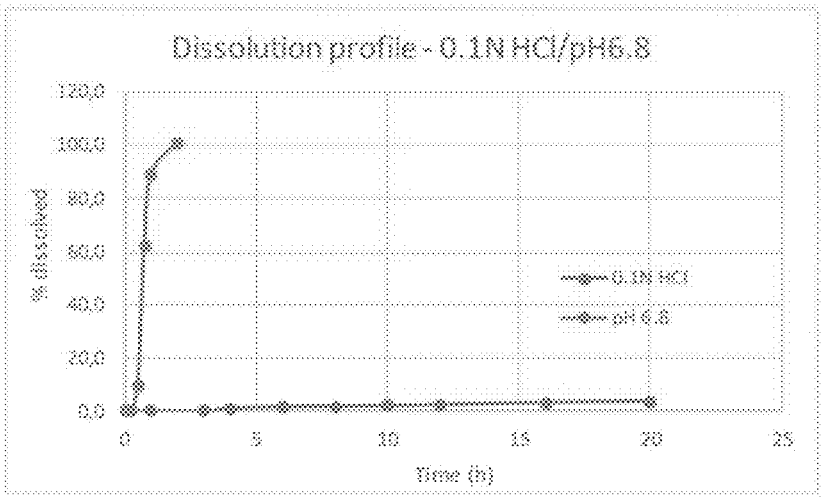

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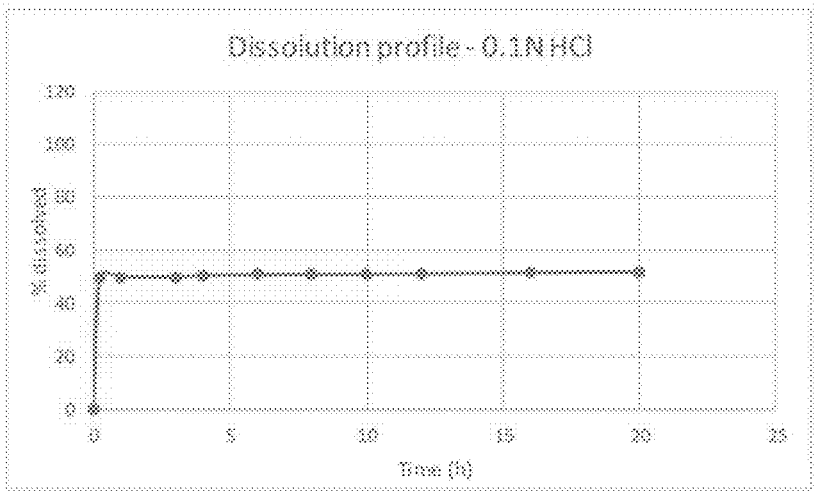

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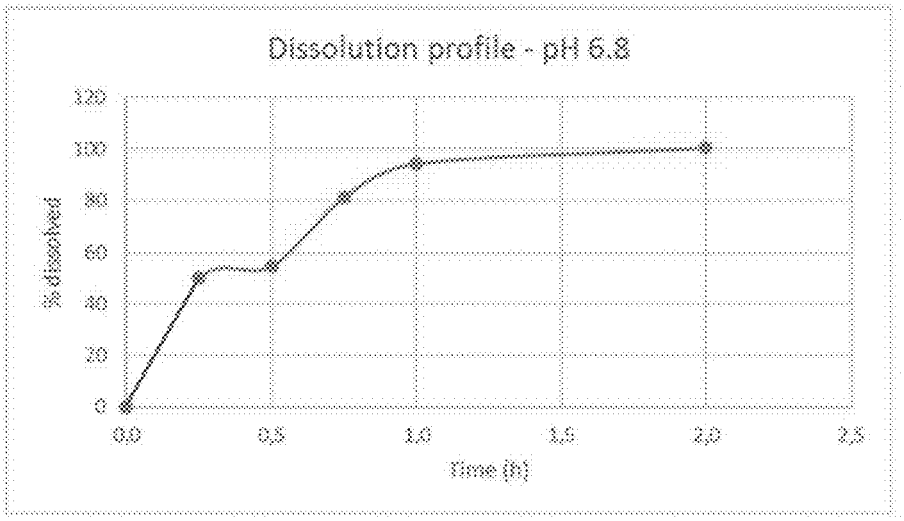

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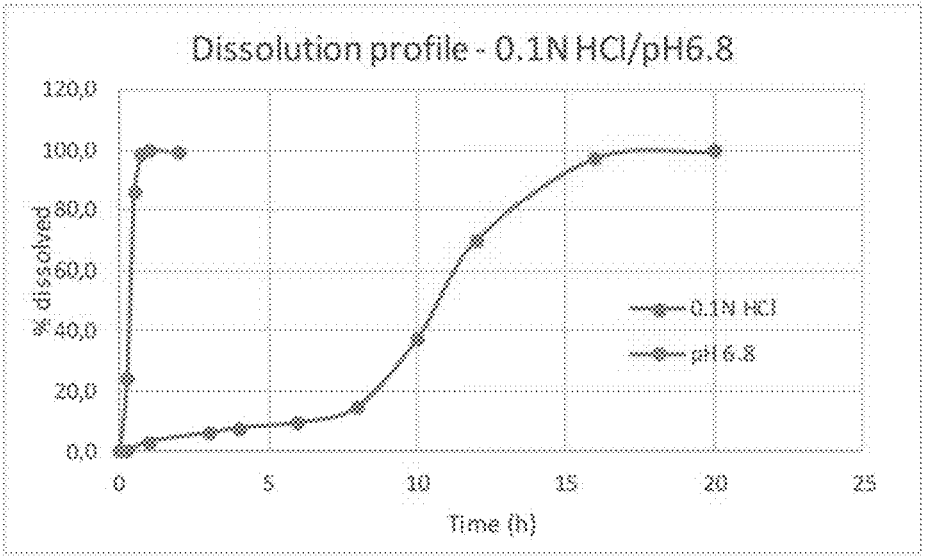

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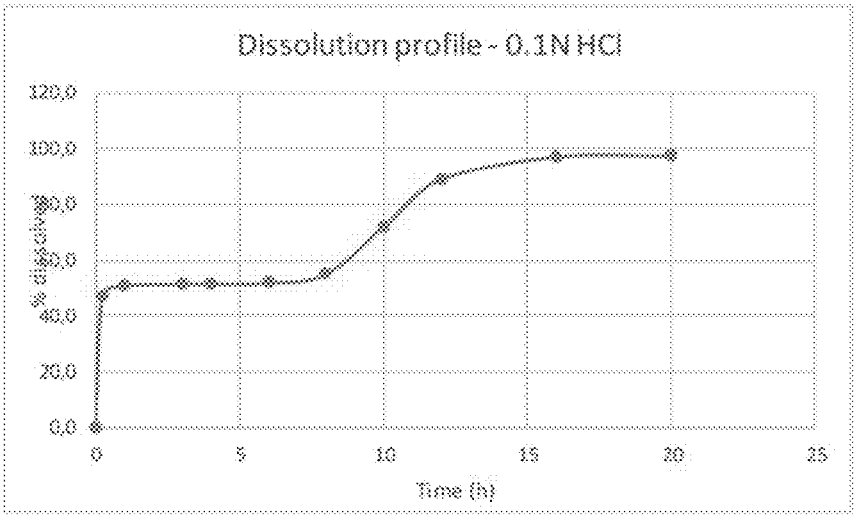

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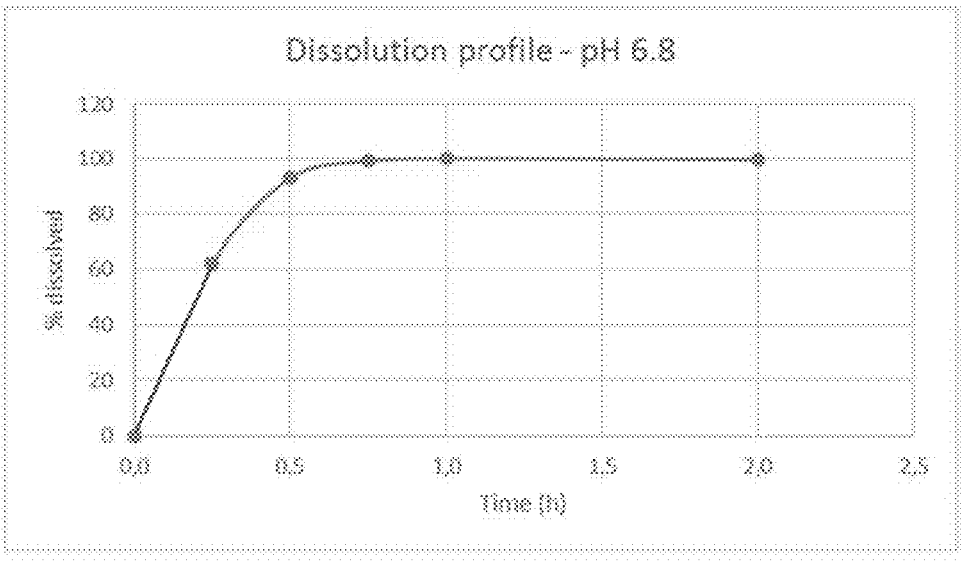

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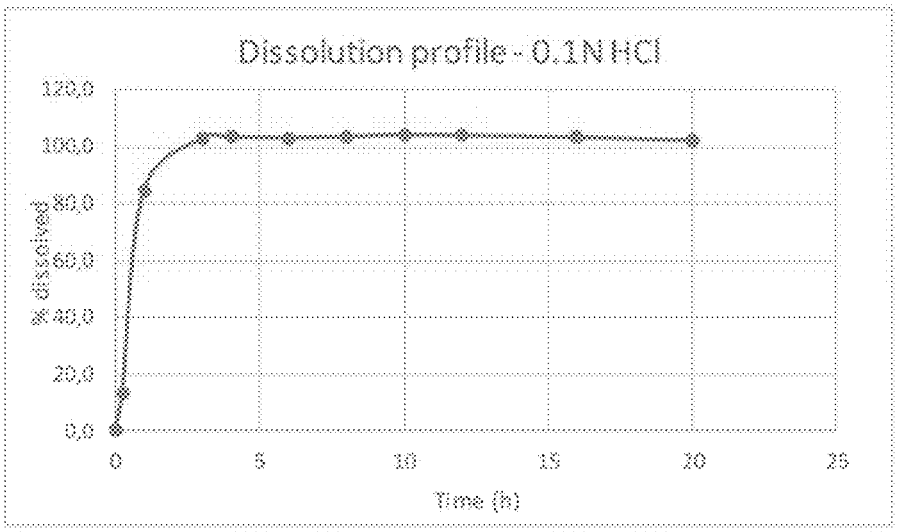

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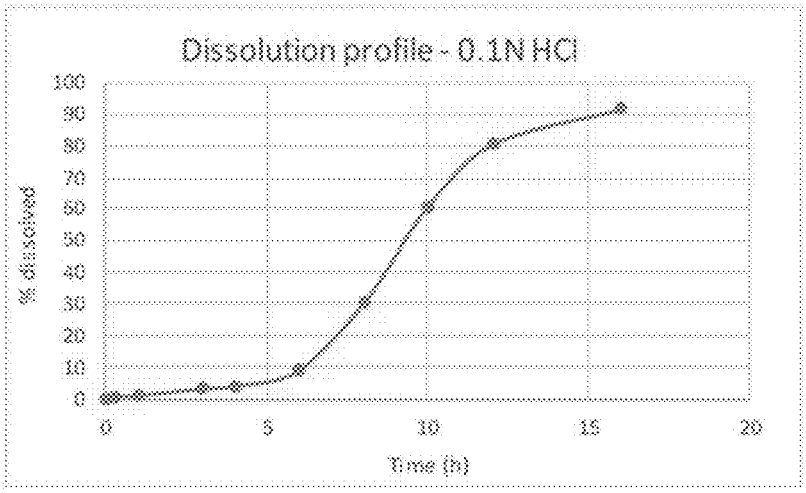

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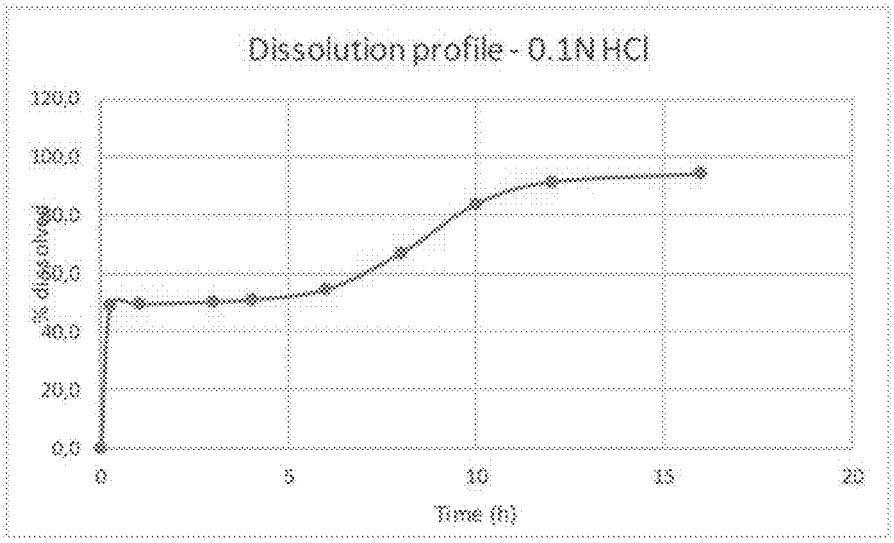

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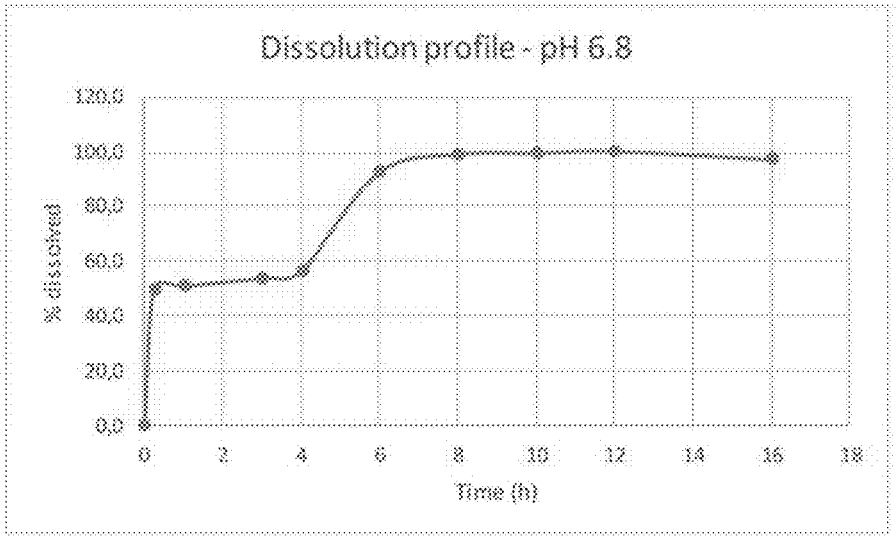

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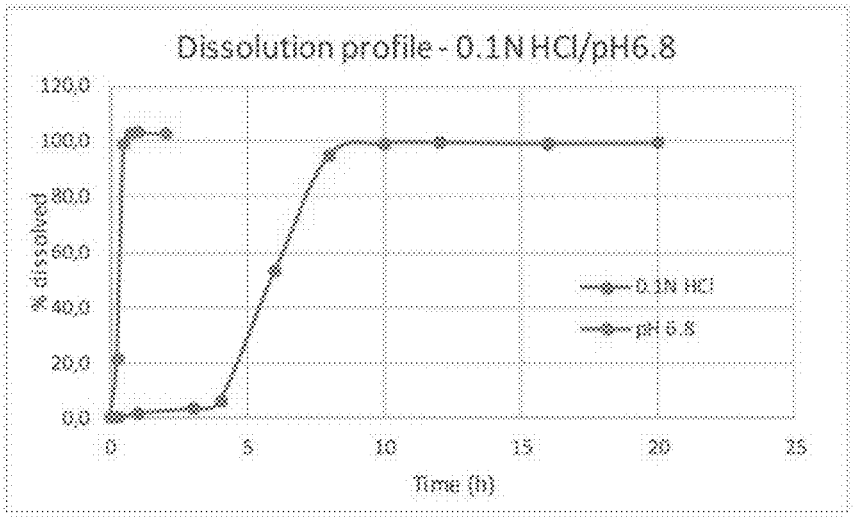

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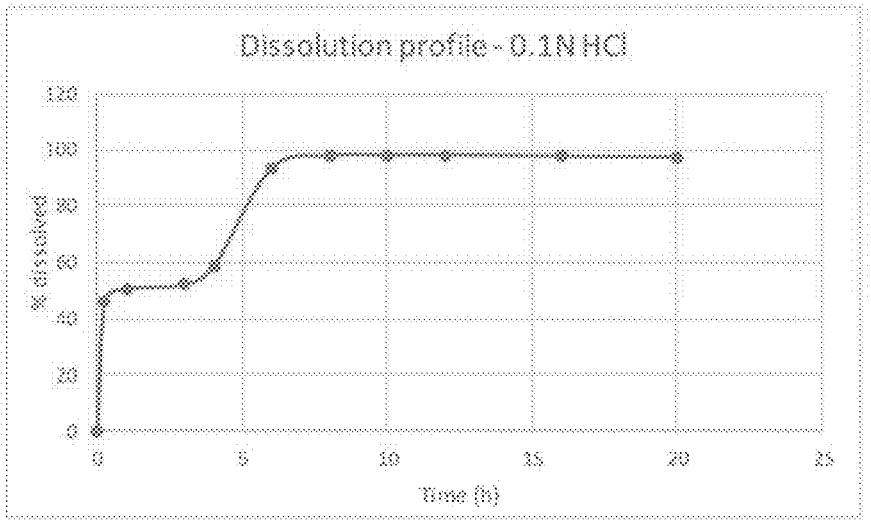

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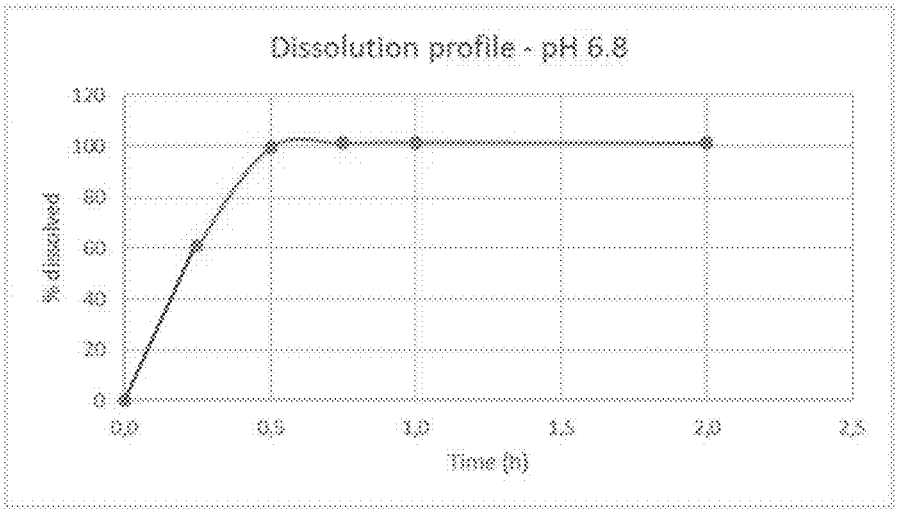

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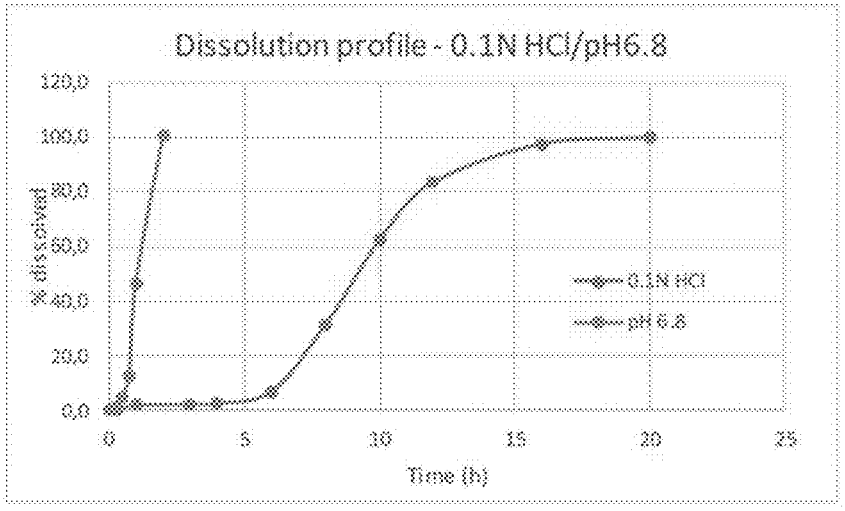

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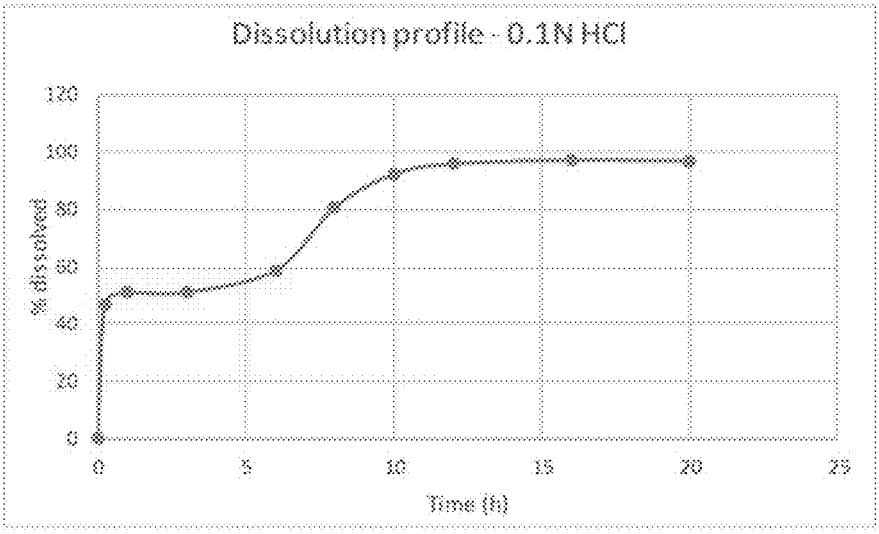

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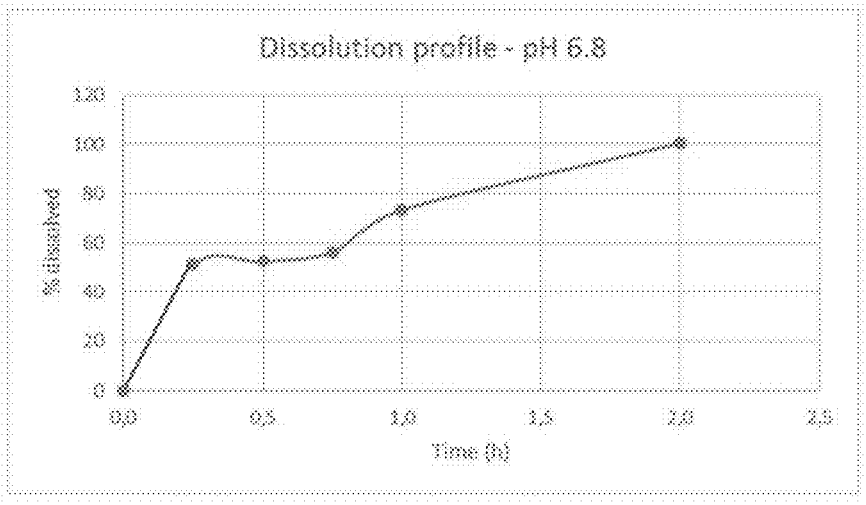

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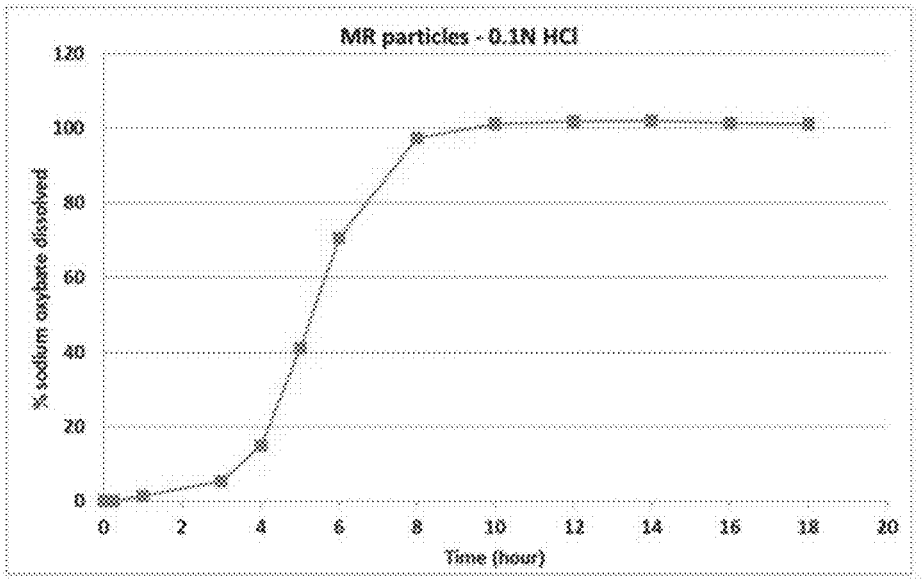

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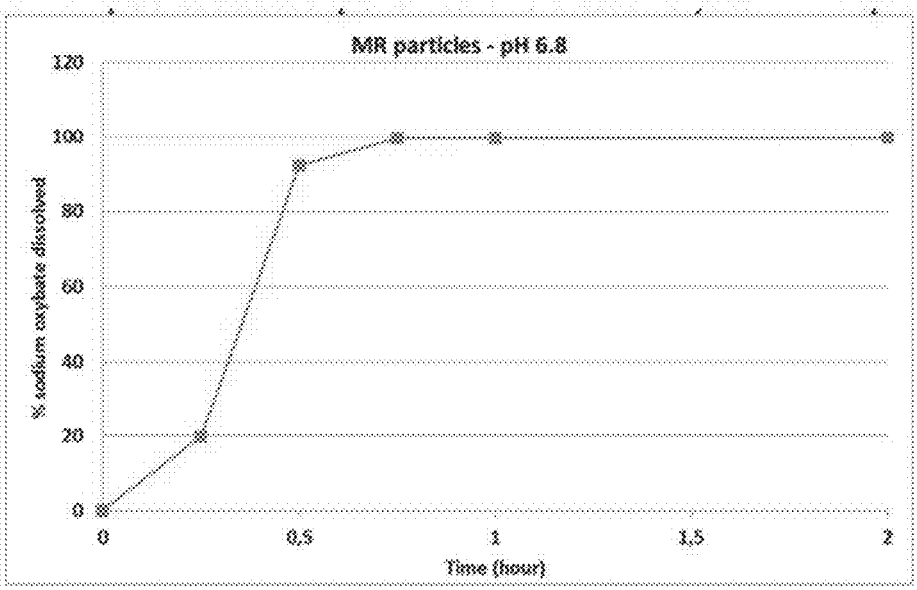

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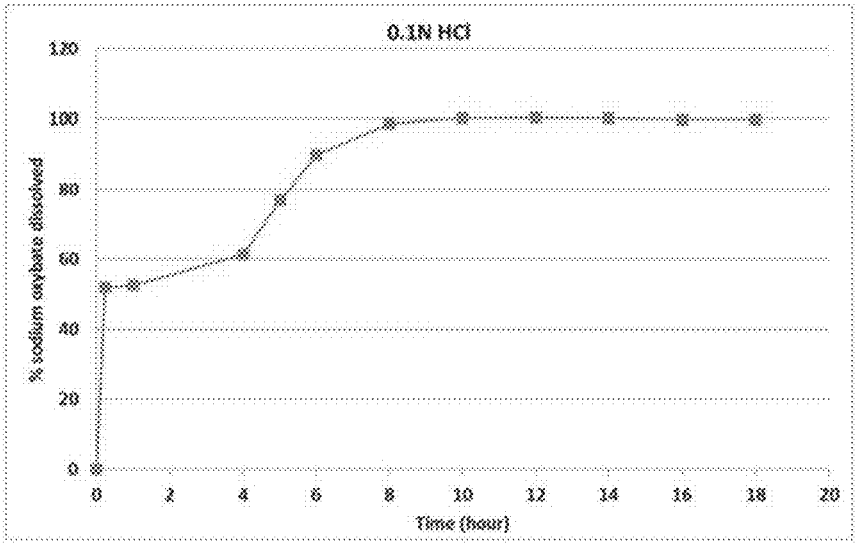


Figure 84

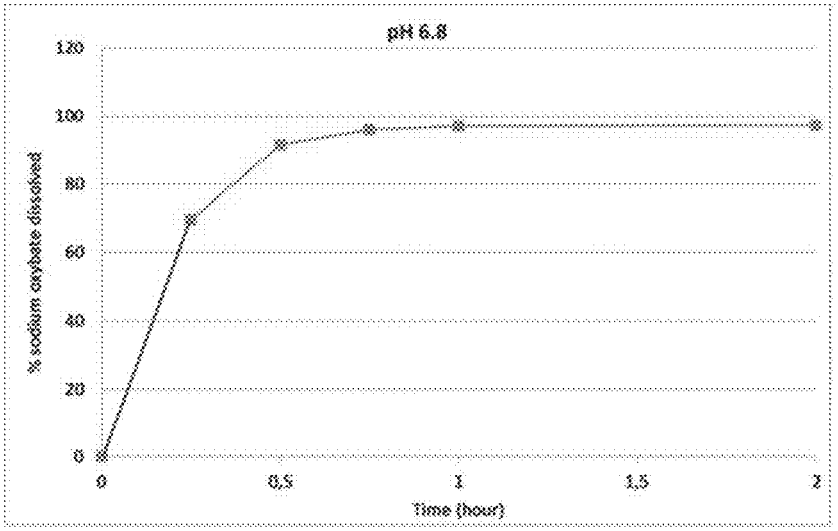


Figure 85

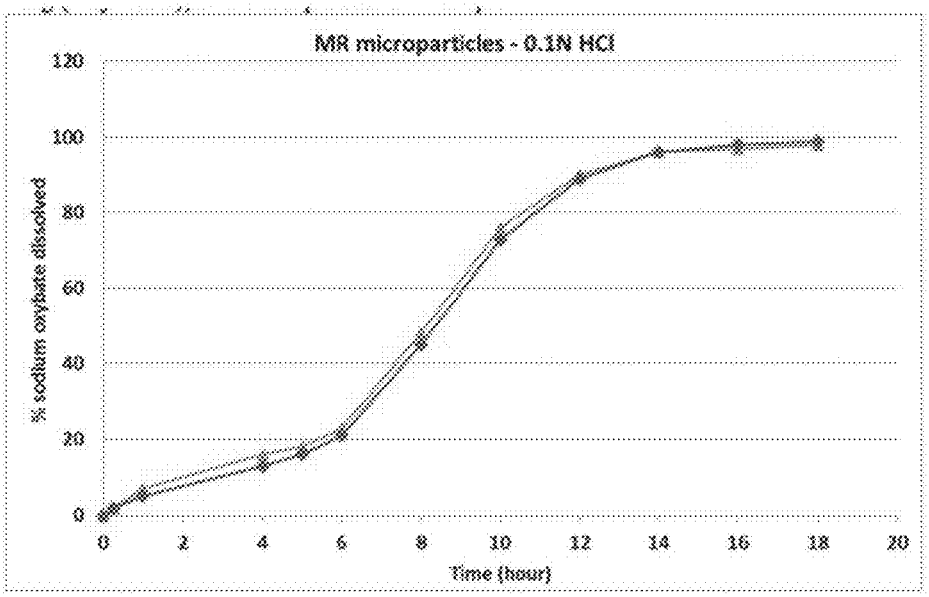


Figure 86

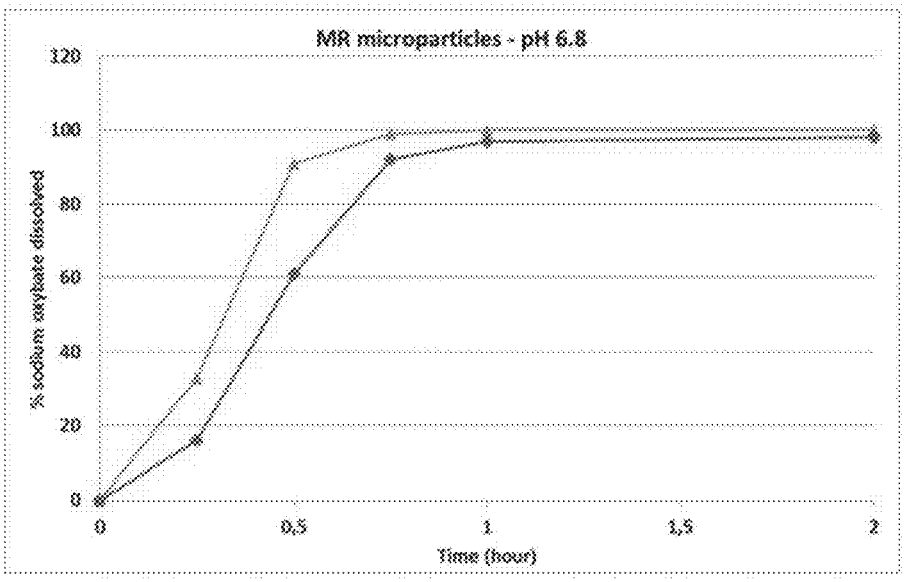


Figure 87

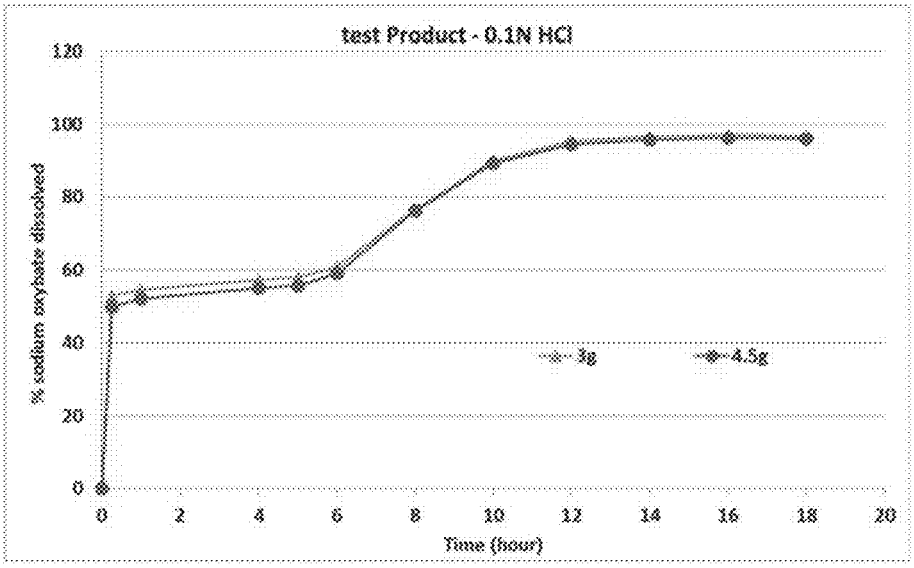


Figure 88

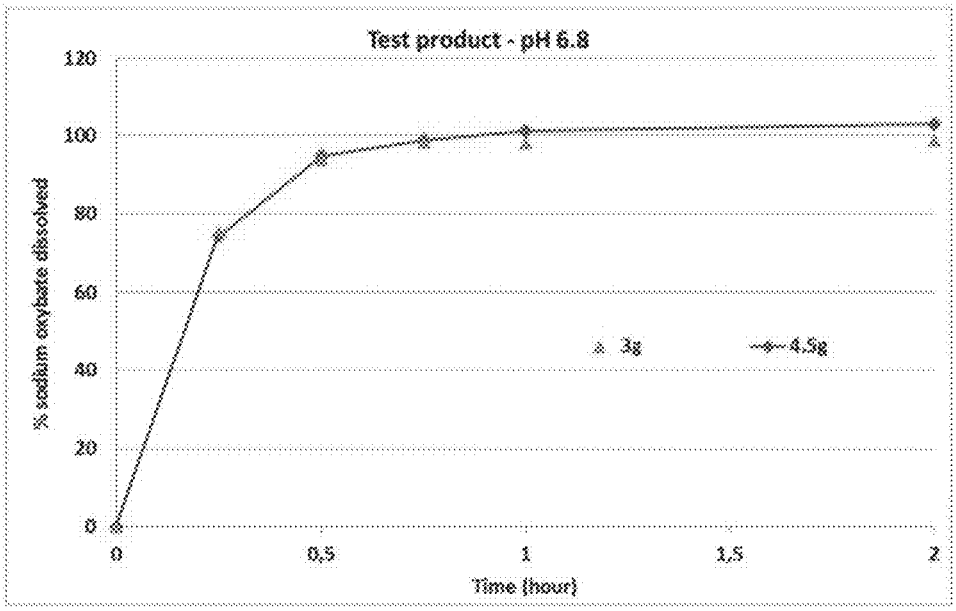

Test product - pH 6.8
% sodium oxybate dissolved
120
100
80
60
40
20
0
0
0,5
1
1,5
2
Time (hour)
3g
4.5g

Figure 89

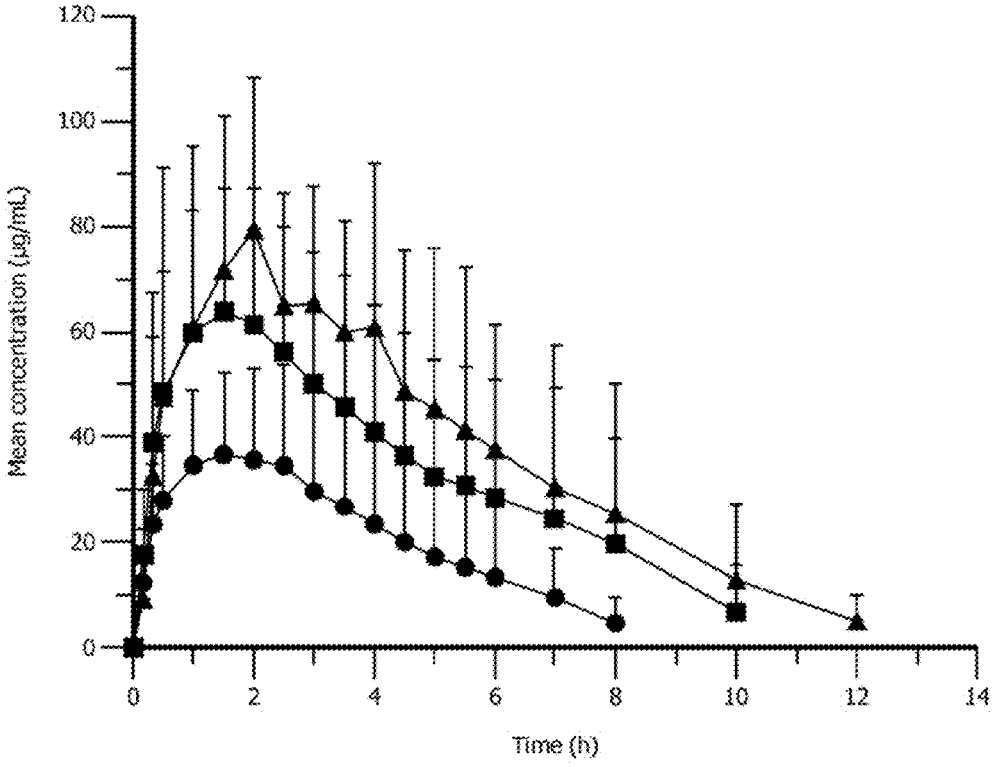

120
100
80
60
40
20
0
Mean concentration (µg/mL)
0
2
4
6
8
10
12
14
Time (h)

Figure 90

MODIFIED RELEASE GAMMA-HYDROXYBUTYRATE FORMULATIONS HAVING IMPROVED PHARMACOKINETICS

PRIOR APPLICATIONS

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

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

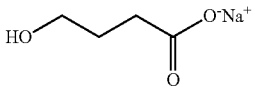
BACKGROUND

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:

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
			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

-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)
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

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
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

-continued

Mean GHB Concentrations (ug/mL)

	Period			
Time Point (Hr)	1 DR1-w/ Acid	2 DR1-No Acid	3 IR	4 DR2
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-hydroxybu-

tyrate, 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 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.

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=1).

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 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.

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_{8h}) 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 65/3 5 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, mix-

tures 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 carragenan 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 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™)

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™ S 100 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™ S 100 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™ S 100 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 Buden-

heim) 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 from Huber).

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™ A1 5 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 copo-

lymers 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™ S 100 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™ S 100 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™ S 100 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™ S 100 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™ S 100 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 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

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 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.

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-hydroxybu-

tyrate, 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 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.

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™ 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.

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 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 microparticles 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 (0.1 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

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 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

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

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

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
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
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

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)
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 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 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 Hydro-

genated 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

TABLE 4c-continued

Qualitative Finished Composition

Component	Function	Quantity per 4.5 g dose (g)
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
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 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.

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)
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_{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
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 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

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™ 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.

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
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

TABLE 8d-continued

Quantitative Composition of Finished Formulation of Example 8.1

Component	Function	Quantity per 4.5 g dose (g)
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

TABLE 8e-continued

Qualitative Composition of Finished Formulation of Example 8.2

Component	Function	Quantity per 4.5 g dose (g)
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

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. 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 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.

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

TABLE 9a-continued

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
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

TABLE 9b-continued

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
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 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.

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

TABLE 9c-continued

Time (h)	% dissolved 5 min reconstitution time	% dissolved 15 min reconstitution time
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 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.

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
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 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.

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

TABLE 11f-continued

Time (hour)	% dissolved
4.0	4
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 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.

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

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 carragenan 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

TABLE 11j-continued

Time (hour)	% dissolved in 0.1N HCl
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

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 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.

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
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

TABLE 14d-continued

Time (hour)	% dissolved in 0.1N HCl
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 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.

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 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%)

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 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.

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 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.

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

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 carragenan 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
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 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.

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

TABLE 16g-continued

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	0.033
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 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.

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™ 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.

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

TABLE 16l-continued

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	0.033
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 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.

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™ S100

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
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 carragenan 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 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)

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

TABLE 17h-continued

Dissolution profile in 0.1N HCl	
Time (h)	% dissolved
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 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.

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
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

TABLE 18d-continued

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 ®
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.

The invention claimed is:

1. A modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the immediate release portion comprises particles of gamma-hydroxybutyrate, and the modified release portion comprises particles of gamma-hydroxybutyrate coated with a coating comprising:

a polymer carrying free carboxylic groups, and

a hydrophobic compound having a melting point equal or greater than 40° C., wherein the modified release formulation is suitable for administration only once nightly.

2. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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.

3. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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.

4. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the polymer carrying free carboxylic groups has a pH trigger from 5.5 to 6.97.

5. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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.

6. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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.

7. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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.

8. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein:

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.

9. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the hydrophobic compound is present at a weight ratio of 0.4 to 4 to the polymer carrying free carboxylic groups.

10. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the coating of the particles of gamma-hydroxybutyrate, in the modified release portion is from 10 to 50% by weight of said particles.

11. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the formulation comprises 4.5 g, 6.0 g, 7.5 g, or 9.0 g of gamma-hydroxybutyrate.

12. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the gamma-hydroxybutyrate is a pharmaceutically acceptable salt of gamma-hydroxybutyric acid.

13. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

14. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 40/60 to 60/40.

15. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the particles of gamma-hydroxybutyrate in the immediate release portion have a mean diameter from 150 to 400 microns, and the particles of gamma-hydroxybutyrate in the modified release portion have a mean diameter from 200 to 800 microns.

16. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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 0.05 M 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 0.1 N 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 0.1 N hydrochloric acid for 2 hours then switched to 950 mL 0.05 M monobasic potassium phosphate buffer adjusted to pH 6.8 at a temperature of 37° C. and a paddle speed of 75 rpm.

17. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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 0.1 N 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 0.1 N 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 0.1 N 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.

18. The modified release formulation of gamma-hydroxybutyrate of claim **1**, 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 0.1 N 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 0% 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.

19. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein a 7.5 g dose of the formulation has 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.

20. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the formulation has 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.

21. The modified release formulation of gamma-hydroxybutyrate of claim **11**, wherein the formulation has 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.

22. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of a half dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

23. The modified release formulation of gamma-hydroxybutyrate of claim **11**, wherein the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of a half dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

24. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein a 4.5 g dose achieves a mean C_{8h} from 3.5 to 9.0 microgram/mL when administered once approximately two hours after a standardized evening meal; a 6 g dose achieves a mean C_{8h} from 6.3 to 16.7 microgram/mL when administered once approximately two hours after a standardized evening meal; and a 7.5 g dose achieves a mean C_{8h} from 13.0 to 40.3 microgram/mL when administered once approximately two hours after a standardized evening meal.

25. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein 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, 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.

26. The modified release formulation of gamma-hydroxybutyrate of claim **11**, wherein 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, 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.

27. The modified release formulation of gamma-hydroxybutyrate of claim **1** in a dosage form selected from the group consisting of tablets, powders and capsules.

28. The modified release formulation of gamma-hydroxybutyrate of claim **27**, wherein the dosage form is a powder.

29. The modified release formulation of gamma-hydroxybutyrate of claim **28**, further comprising from 1.2% to 15% of an acidifying agent and from 1% to 15% a suspending or viscosifying agent.

30. The modified release formulation of gamma-hydroxybutyrate of claim **1** in an amount effective to treat narcolepsy Type 1 or Type 2, wherein said treatment of narcolepsy comprises reducing excessive daytime sleepiness, reducing the frequency of cataplectic attacks, or a combination thereof.

31. The modified release formulation of gamma-hydroxybutyrate of claim **1** in an amount effective to induce sleep for eight consecutive hours.

32. A modified release formulation of gamma-hydroxybutyrate comprising immediate release and modified release portions, wherein the immediate release portion comprises particles of gamma-hydroxybutyrate, and the modified release portion comprises particles of gamma-hydroxybutyrate coated with a coating comprising:

a polymer carrying free carboxylic groups, and

a hydrophobic compound having a melting point equal or greater than 40° C., wherein the modified release formulation comprises 4.5 grams or more of gamma-hydroxybutyrate.

33. The modified release formulation of gamma-hydroxybutyrate of claim **32**, 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.

34. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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.

35. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the polymer carrying free carboxylic groups has a pH trigger from 5.5 to 6.97.

36. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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.

37. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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.

38. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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.

39. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein:

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.

40. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the hydrophobic compound is present at a weight ratio of 0.4 to 4 to the polymer carrying free carboxylic groups.

41. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the coating of the particles of gamma-hydroxybutyrate in the modified release portion is from 10 to 50% by weight of said particles.

42. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the formulation comprises 4.5 g, 6.0 g, 7.5 g, or 9.0 g of gamma-hydroxybutyrate.

43. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the gamma-hydroxybutyrate is a pharmaceutically acceptable salt of gamma-hydroxybutyric acid.

44. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 10/90 to 65/35.

45. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the ratio of gamma-hydroxybutyrate in the immediate release portion and the modified release portion is from 40/60 to 60/40.

46. The modified release formulation of gamma-hydroxybutyrate of claim 32, wherein the particles of gamma-hydroxybutyrate in the immediate release portion have a mean diameter from 150 to 400 microns, and the particles of gamma-hydroxybutyrate in the modified release portion have a mean diameter from 200 to 800 microns.

47. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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 0.1 N 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 0.1 N 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.

48. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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 0.1 N 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 0.1 N 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 0.1 N 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.

49. The modified release formulation of gamma-hydroxybutyrate of claim 32, 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 0.1 N 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.

50. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein a 7.5 g dose of the formulation has 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.

51. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the formulation has 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.

52. The modified release formulation of gamma-hydroxybutyrate of claim **42**, wherein the formulation has 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.

53. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of a half dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

54. The modified release formulation of gamma-hydroxybutyrate of claim **42**, wherein the formulation achieves a median T_{max} within 150 minutes of the median T_{max} of a half dose of an immediate release liquid solution of sodium oxybate, when administered approximately two hours after a standardized evening meal.

55. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein a 4.5 g dose achieves a mean C_{8h} from 3.5 to 9.0 microgram/mL when administered once approximately two hours after a standardized evening meal; a 6 g dose achieves a mean C_{8h} from 6.3 to 16.7 microgram/mL when administered once approximately two hours after a standardized evening meal; and a 7.5 g dose achieves a mean C_{8h} from 13.0 to 40.3 microgram/mL when administered once approximately two hours after a standardized evening meal.

56. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein 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, 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.

57. The modified release formulation of gamma-hydroxybutyrate of claim **42**, wherein 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, 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.

58. The modified release formulation of gamma-hydroxybutyrate of claim **32** in a dosage form selected from the group consisting of tablets, powders and capsules.

59. The modified release formulation of gamma-hydroxybutyrate of claim **58**, wherein the dosage form is a powder.

60. The modified release formulation of gamma-hydroxybutyrate of claim **59**, further comprising from 1.2% to 15% of an acidifying agent and from 1% to 15% a suspending or viscosifying agent.

61. The modified release formulation of gamma-hydroxybutyrate of claim **32** in an amount effective to treat narcolepsy Type 1 or Type 2, wherein said treatment of narcolepsy comprises reducing excessive daytime sleepiness, reducing the frequency of cataplectic attacks, or a combination thereof.

62. The modified release formulation of gamma-hydroxybutyrate of claim **32** in an amount effective to induce sleep for eight consecutive hours.

63. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the modified release formulation comprises 4.5 grams of gamma-hydroxybutyrate.

64. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the modified release formulation comprises 6.0 grams of gamma-hydroxybutyrate.

65. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the modified release formulation comprises 7.5 grams of gamma-hydroxybutyrate.

66. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the modified release formulation comprises 9.0 grams of gamma-hydroxybutyrate.

67. The modified release formulation of gamma-hydroxybutyrate 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.

68. The modified release formulation of gamma-hydroxybutyrate of claim **32**, 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.

69. The modified release formulation of gamma-hydroxybutyrate of claim **1**, wherein the modified release portion does not contain particles of gamma-hydroxybutyrate having a coating comprising ethylcellulose.

70. The modified release formulation of gamma-hydroxybutyrate of claim **32**, wherein the modified release portion does not contain particles of gamma-hydroxybutyrate having a coating comprising ethylcellulose.

71. A formulation of gamma-hydroxybutyrate comprising:
an immediate release portion comprising particles of gamma-hydroxybutyrate; and
a modified release portion comprising particles of gamma-hydroxybutyrate having a coating comprising:
a polymer carrying free carboxylic groups; and
a hydrophobic compound having a melting point equal to or greater that 40° C.,
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 modified release portion does not contain particles of gamma-hydroxybutyrate having a coating comprising ethylcellulose,

wherein the formulation comprises an amount of gamma-hydroxybutyrate equivalent to from 3.0 to 12.0 grams 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.

72. The formulation of claim **71**, wherein the weight ratio of the hydrophobic compound to the polymer carrying free carboxylic groups is from 0.4 to 4.

73. The formulation of claim **71**, wherein the polymer carrying free carboxylic groups has a pH trigger from 5.5 to 6.97.

74. The formulation of claim **71**, wherein the free carboxylic groups are ionized at pH 7.5.

75. The formulation of claim **71**, 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.

76. The formulation of claim **71**, 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.

77. The formulation of claim **71**, wherein:

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.

78. The formulation of claim **71**, further comprising:

a suspending or viscosifying agent; and

an acidifying agent.

79. The formulation of claim **78**, wherein:

the suspending or viscosifying agent is selected 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, medium viscosity 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, benzoic acid, and mixtures thereof.

80. The formulation of claim **78**, 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 is present at 1 to 15% by weight of the formulation; and

the acidifying agent is malic acid or tartaric acid and is present at 1.2 to 15% by weight of the formulation.

81. The formulation of claim **71**, wherein the formulation comprises gamma-hydroxybutyrate in the form of sodium oxybate.

82. The formulation of claim **71**, 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.

83. The formulation of claim **71**, 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.

84. The formulation of claim **71**, 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.

85. The formulation of claim **71**, wherein a dose of the formulation achieves a mean C_{6h} or mean C_{7h} greater than, and a mean $_{10h}$ 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.

86. The formulation of claim **71**, 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.

87. The formulation of claim **71**, 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, and

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.

88. The formulation of claim **71**, 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.

89. The formulation of claim **71**, 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 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm;

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 0.1N hydrochloric acid at a temperature of 37° C. and a paddle speed of 75 rpm; and

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.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 10,272,062 B2
APPLICATION NO. : 15/655924
DATED : April 30, 2019
INVENTOR(S) : Claire Mégret et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 113, Line 24, Claim 18: "0%" should read --60%--.

Signed and Sealed this
Thirtieth Day of July, 2019

Andrei Iancu
Director of the United States Patent and Trademark Office

EXHIBIT I

REFINITIV STREETEVENTS

EDITED TRANSCRIPT

Q4 2020 Avadel Pharmaceuticals PLC Earnings Call

EVENT DATE/TIME: MARCH 09, 2021 / 1:30PM GMT

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PRESENTATION

Operator

Greetings. Welcome to the Avadel Pharmaceuticals Fourth Quarter and Full Year 2020 Earnings Call. (Operator Instructions) Please note, this conference is being recorded.

I will now turn the conference over to your host, Tom McHugh. You may begin.

Thomas S. McHugh ***Avadel Pharmaceuticals plc - Senior VP & CFO***

Good morning, and thank you for joining us on our conference call. This morning, we issued our full year and fourth quarter financial results news release. The release can be accessed on our website, www.avadel.com.

As a reminder, before we begin, the following presentation includes several matters that constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those contemplated in such forward-looking statements. These risks include risk that products in the development stage may not achieve scientific objectives or milestones or meet stringent regulatory requirements; uncertainties regarding market entry and acceptance of products; and the impact of competitive products and pricing. These and other risks are described more fully in Avadel's public filings under the Exchange Act, included in the Form 10-K for the year ended December 31, 2019, which was filed on March 16, 2020, and subsequent SEC filings.

Except as required by law, Avadel undertakes no obligation to update or revise any forward-looking statements contained in this presentation to reflect new information, future events or otherwise.

On the call with me today are Greg Divis, our Chief Executive Officer; Richard Kim, our Chief Commercial Officer; and Dr. Jennifer Gudeman, our VP of Medical and Clinical Affairs.

At this time, I'll turn the call over to Greg.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Thank you, Tom. Good morning, everyone, and thank you for joining us on our fourth quarter 2020 conference call.

I will begin with several updates on our business outlook, highlighting the significant progress made and key milestones achieved over the past several months. Jennifer will then offer an overview of the progress we've made with our scientific communications for FT218, including the upcoming presentation of secondary and post-hoc data from REST-ON, which we are all excited for as it builds upon the primary endpoint data presented last year. Richard, who just recently joined as our Chief Commercial Officer, will provide his early views on where we are from a launch readiness perspective, including his initial insights into our commercialization and launch planning for

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FT218 and his near-term priorities as we move closer to the PDUFA date and a potential FDA approval. Finally, Tom will provide a review of the financial results for the quarter, and we will conclude with a Q&A session.

With that as an outline for the call, let's get started.

Overall, I am very proud of and pleased with the progress we have made over the last 12 months. We continue the transformation of Avadel, while successfully executing the clinical development and the regulatory filing strategy for our lead program, FT218, an extended-release once-nightly formulation of sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy.

It was just a year ago that we were completing our pivotal Phase III REST-ON study of FT218, just prior to the pandemic taking hold. Since then, and despite the COVID-19 challenges we have all faced, we announced in late April, the positive topline results from the REST-ON study, including that FT218 met all 3 co-primary efficacy endpoints at all 3 doses, demonstrating highly significant clinically meaningful improvements compared to placebo and was well tolerated with low rates of commonly known sodium oxybate adverse reactions.

We completed the additional work for in preparation of the NDA filing for FT218, including a successful pre-NDA meeting in Q3 that was followed up with the full NDA submission to the FDA in December. And just last week, announced that the FDA notified us in a day 74 letter that the NDA for FT218 was accepted and assigned a PDUFA target action date of October 15, 2021.

We are pleased with the overall response and the limited comments that the agency has provided to date. The acceptance of the submission supports our confidence in our NDA and overall regulatory filing strategy. In addition, through this stage of the review, we have not been asked to provide a Paragraph IV certification against any Orange Book-listed patents. Furthermore, based on the proposed label and data package we've submitted as part of the NDA for FT218, we have no reason to believe we should be asked to do so.

As we advance and execute our business plan and priorities, the same success breeds success is beginning to ring true for Avadel. The full promise of FT218's profile is now coming into view as we deliver the positive REST-ON data, confirmed the significant commercial opportunity with our market insights, including the clear patient and physician preference for once-nightly FT218. And now on the heels of FDA acceptance of our NDA with our strong conviction in our regulatory filing strategy, we are positioned to deliver on our mission of liberating patients with narcolepsy from middle of the night dosing and creating significant and deserved value for our shareholders. The momentum we are experiencing in the market is real and it is profound from key opinion leaders to patient groups, to our newest team members. The growing level of interest in once-nightly FT218 and Avadel is rapidly accelerating and is attracting the best of the best as we prepare to disrupt this 18-year-old, multibillion-dollar market to the potential benefits of patients, health care providers and our shareholders.

With that setting of the stage, let's get into a little bit more detail on some of these highlights. To begin, I'm pleased to turn the call over to Dr. Jennifer Gudeman, who joined our team at the end of last year and is overseeing all medical and clinical affairs activities and is already making a tremendous impact. Jennifer, the floor is yours.

Jennifer Gudeman

Thanks, Greg. It's great to have the opportunity to update everyone on today's call regarding the exciting work we are doing to expand awareness of the FT218 program, and most importantly, the unequivocal clinical benefits FT218 has proven in our pivotal trial.

Since joining Avadel toward the end of last year, I have come to fully appreciate the tremendous body of work that has been completed to date, much of which has formed the basis for the NDA submission. Now in 2021, we are leveraging these data and generating additional insights to engage the medical community on the potential of this investigational once-nightly oxybate formulation. While we have previously focused on the primary endpoints with our pivotal trial, REST-ON, we have also completed 10 Phase I PK studies in more than 250 healthy volunteers, which have affirmed the predictable PK profile and adds to the body of evidence supporting the safety of FT218.

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We also recently initiated an open-label extension and switch study known as RESTORE. Collectively, there is a substantial amount of data we will be presenting this year and beyond, and RESTORE will only add to this already strong foundation. Our efforts will ensure physicians understand that FT218, if approved, will liberate patients from unnecessary middle of the night dosing.

Looking first at REST-ON, we announced last April, the top line results, which reported that FT218 met all 3 co-primary efficacy endpoints compared to placebo for all 3 doses evaluated: 6 grams, 7.5 grams and 9 grams. These results were highly statistically significant with all p-values less than 0.001 and clinically meaningful, as assessed by the maintenance of wakefulness test, clinical global impression improvement and mean weekly cataplexy attacks. Notably, improvements across these endpoints were demonstrated at week 3 with the lowest dose of 6 grams. Furthermore, multiple sensitivity analyses of the primary endpoints were completed, affirming the positive results.

Adding to the strength of these primary endpoints, we are also very pleased that the secondary endpoints and post-hoc analyses further substantiate the robust findings from REST-ON with additional measures of improvement in daytime sleepiness and improvements in disturbed nocturnal sleep, which we believe is key for patients living with narcolepsy. These data provide us an excellent platform for a robust publication plan that we are already executing upon. We are excited to announce that 8 abstracts we've submitted have officially been accepted to be presented at AAN in April and the Sleep Meeting in June. We look forward to sharing these new secondary endpoints and key post-hoc data from the REST-ON trial once permitted under the embargo rules set by the conferences.

Earlier this month, we announced publishing pharmacokinetic data in a leading international peer-reviewed journal, Clinical Therapeutics, reviewing 4 of the clinically relevant PK studies from our Phase I program. These data provide a solid understanding of FT218's unique PK profile, including the demonstration of dose proportionality and a limited food effect. Taking it a step further, I'd also say that these data support our belief that the design and formulation of FT218 are ideal to enable once-nightly dosing of sodium oxybate.

This follows the publication we supported last quarter in Sleep Medicine authored by Dr. Avidan and Dr. Kushida, which systematically reviewed the nearly 20 years of data for twice-nightly sodium oxybate, finding no evidence of increased cardiovascular risk, including hypertension. These publications are just the beginning. We are hard at work with notable thought leaders in the narcolepsy space and will soon have many more publications to share with the medical community.

Let's turn now to RESTORE. As a reminder, this study is not required for FDA approval. While it is early, we are pleased with initial investigator and patient feedback, including a tolerability profile consistent with that of REST-ON. Importantly, no patients have withdrawn from RESTORE due to adverse reactions. Lastly, we are also asking patients who have previously been on twice-nightly sodium oxybate, which dosing regimen they prefer and we are very pleased with the preliminary feedback thus far, which we look forward to sharing in the future. RESTORE underscores Avadel's commitment to patients and this therapeutic area. We fully intend to continue generating meaningful data to improve patient care.

It's now my pleasure to introduce Richard, who shares my excitement at how the positive data generated with FT218 could translate to disrupting the narcolepsy treatment market and improving the lives of patients living with this chronic and debilitating condition. Richard, the floor is yours.

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Thank you, Jennifer. And let me say how great it is to join everyone on the call today. Even though it was just last month that I joined Avadel, I have been speaking with Greg and members of the team for several months prior, and keeping track of the company's significant progress at the end of 2020, with Jennifer's hiring and the submission of the NDA. As I continue to do my diligence on the company, I became convinced that, if approved, once-nightly FT218 would become a game-changing therapy for patients suffering from narcolepsy. And I could not pass up the opportunity to be part of the Avadel team.

Now since joining, I've had the chance to review the incredibly strong foundation of data and research guiding our launch preparations. We have tapped into key claims and prescription databases that will allow us to look at the narcolepsy market at various points in time and longitudinally. Additionally, to date, we have conducted over a dozen large market research initiatives, with hundreds of physicians,

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patients, caregivers, office staff and peer groups who represent over 175 million covered lives. The knowledge about narcolepsy that we have already amassed, really gives us confidence that we are making launch decisions based on a deep understanding of the market.

Now let me share some of the more striking insights about the current level of treatment dissatisfaction in the oxybate marketplace. Almost half of all patients refused twice-nightly sodium oxybate when offered by a physician. This is primarily due to the requirement of taking the second dose in the middle of the night. About 60% of patients report dose adjusting their twice-nightly sodium oxybate outside physician direction. This sense occur when patients take more at bed time unless at the required second dose 2.5 to 4 hours later. And almost 60% of patients report negative treatment outcomes. From this research and other work that we have done, it's clear that there is still significant unmet need that is not being well addressed with current oxybate treatment. As such, if approved, once-nightly FT218 has the potential to gain market-leading share in the oxybate class.

Our team has been busy, and we have already begun to build a critical components for our launch, like safely and efficiently distributing FT218, if approved, through the REMS, patient services hub and specialty pharmacy network. Our pricing research to date and the framework for our payer discussions have centered on ensuring that FT218 is not considered convenience play, but rather that once-nightly dosing should lead to meaningful outcomes for patients.

With the data from REST-ON and additional clinical studies that Jennifer described, we also have a very strong foundation for promotional claims and messages if FT218 is approved. Additionally, key operational work for targeting, field force sizing, data integration and much more is well underway.

And finally, one more key area of preparation that has been really impressive is the patient focus and the work that has been done with advocacy groups, like the Narcolepsy Network, Wake Up Narcolepsy and Project Sleep. As ultimately, we only succeed when patients do. In short, the team is making significant progress. And now with the October 15 PDUFA date, we are taking our work to the next level.

This brings me to our goal to successfully build out a world-class commercial team and be ready to launch once-nightly FT218, if approved by the FDA. Now I've been privileged to launch several products that made a significant difference to patient care, predominantly in specialty and orphan diseases. Now each product launch has its own unique set of challenges and opportunities that I've had the benefit of learning from. Whether that was building a team from scratch, dealing with entrenched competitors or shifting a treatment paradigm. All those learnings and experience of each new team member will collectively be leveraged to support our potential launch of once-nightly FT218.

With the progress made to date and the actions required to realize our launch vision, my immediate priorities are to further build out internal capabilities within the commercial team, with my immediate focus on market access, patient services and marketing teams. As Greg mentioned, we are attracting exceptionally talented people to join us, and we are very excited about how our team is shaping up.

Second, to continue to hone our launch strategy and resources. We will invest disproportionately in the most critical parts of our launch. But at the same time, due to the concentrated nature of the customer base, unlike primary care or larger specialty markets, we anticipate not having to dilute our resources to cover a large prescriber audience.

Last but maybe most important is our overall company commitment as we will continue to speak with physicians, patient advocacy groups and payers and ensure that we hear the customer voice about what they need from a new therapy. This is exactly what FT218 is really about, delivering a new option, if approved, that can be transformative for people suffering from narcolepsy. Well, if you can't tell, I am really excited, as it isn't often that a new product has the potential to offer a significant advancement in patient care for an established multibillion-dollar market. I look forward to providing updates about our progress on future calls.

Now I will turn the call back over to Tom to provide an overview of our financial results for the quarter. Tom, over to you.

Thomas S. McHugh ***Avadel Pharmaceuticals plc - Senior VP & CFO***

Thanks, Richard. During 2020, we completed several important actions to strengthen our balance sheet and position the company to prepare for the approval of FT218, and if approved, its launch. In that regard, we received $177.5 million of net proceeds from financing

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activities in the first half of the year and also sold our sterile injectable drug portfolio for $42 million on June 30. As a result of that sale, we did not report revenue or cost of products in the second half of 2020.

R&D expenses were $5.3 million in the fourth quarter of 2020 compared to $7.8 million in the fourth quarter of 2019. The $2.5 million year-over-year decrease was primarily due to the completion of the REST-ON study during the first quarter 2020 as well as lower headcount due to the restructuring activities initiated during 2019.

SG&A expenses were $9 million in the fourth quarter of 2020 compared to $7.7 million in the fourth quarter of 2019. The $1.3 million year-over-year increase is a result of a number of factors, including FT218 NDA preparation and submission costs, FT218 commercial launch planning costs and higher stock-based compensation.

Net loss for the fourth quarter of 2020 was $11.3 million or $0.19 per diluted share compared to a net loss of $2.7 million or $0.07 per diluted share in the prior year. The increase in net loss and diluted loss per share is primarily the result of the year-over-year decrease in revenue, which was partially offset by lower overall operating expenses. In addition, our diluted share count increased by approximately 21 million shares year-over-year due primarily to the financing activities completed during the first half of the year.

Our full year tax benefit was $12.1 million, or a 238% effective rate. This was largely driven by a $9 million benefit resulting from the passage of the Coronavirus Aid, Relief and Economic Security Act, or the CARES Act.

And as I mentioned a moment ago, we significantly strengthened the balance sheet and ended the year with $221.4 million of cash, cash equivalents and marketable securities compared to $64.2 million at December 31, 2019. The year-over-year increase was due in large part to $177.5 million of net proceeds from the financing activities, plus $25.5 million of proceeds received during 2020 from the sale of the sterile injectable drug portfolio. We expect to collect the remaining $16.5 million of the total $42 million sale transaction value in the first half of 2021.

The cash proceeds received in 2020 were partially offset by approximately $49 million of net cash used in operations. We believe our cash, cash equivalents and marketable securities will support the expected financial requirements to complete the NDA review process, compile additional supporting scientific data to position FT218 in the market and ramp up our launch preparation for FT218.

I will now turn the call back over to Greg.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Thanks, Tom, and thanks, team. Before I provide my closing comments, why don't we open the call up for Q&A. And operator, if you could do that, that would be great.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question is from Ami Fadia with SVB Leerink.

Eason Lee ***SVB Leerink LLC, Research Division - Associate***

This is Eason Lee on for Ami. Maybe 2 quick ones, please. First, just how much read through would you say the FT218 NDA acceptance provides in terms of whether a 30-month stay is now off the table? And then maybe second, in terms of orphan drug exclusivity, maybe remind us what is the arguments and data you guys have put forth by which FT218 should get this? And help us think about the time lines for when this exclusivity could be granted relative to the October 15 PDUFA?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. Thanks, and appreciate the question. Again, the comment relative to read through on NDA acceptance and relative to 30-month stay, the question we get quite often, and clearly, there's some views who believe that, that decision point is an important confirmatory decision on the part of the FDA. Again, we're very pleased having accomplished and achieved and surpassed that milestone, and we're

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very pleased what I would describe generally as the nature of the commentary and feedback we've received to date as our NDAs under review.

We've also been very clear that we are not just asking for a carve-out, right? We have generated our own data as we've shared publicly. We have provided that data to the FDA, including our proposed labeling, even before NDA submission, which has helped guide our strategy. So because we view the first 60-day period as a period of review of completeness, not necessarily of substance, we believe that some of these matters could very well be arbitrated post this acceptance as the NDA review gets into the heart of the data that's been submitted.

That being said, it could very well have been arbitrated already. A decision could have been made. What we've always said is that we certainly are very confident in our regulatory strategy, and we're very confident, in particular, as we continue to advance through this review process. That being said, we won't speak to the affirmative on this matter definitively until the FDA does, which we would expect to be at the approval date. The only caveat to that would be is if something changes relative to the strategy and the FDA has required us to do something different, then we will clearly communicate that as urgently as we possibly can.

So again, I think that we're very comfortable and confident in our strategy. We're very pleased with the kind of passing the first milestone, and we'll continue to execute and prosecute the NDA accordingly.

With regards to orphan drug, from our perspective, again, we were granted orphan drug designation on really the plausible hypothesis that once-nightly FT218 could be clinically superior to the reference product. From a submission perspective, although we won't go into details, we've provided and have completed our own robust rationale for confirmation of this exclusivity, which includes data we generated to support our position, both relative to our product and the twice-nightly product as well. We recognize, as you noted, this is a matter of review and that will be arbitrated and decided by the agency at or around the time of approval. Our experience would be that, that decision comes somewhere 30 to 90 days or so post-approval, where your exclusivity decisions are made and the Orange Book is appropriately updated accordingly. So that's our current assumptions. There's always exceptions to those things, but that's how we're thinking about it today. So I appreciate the question.

Operator

Our next question is from Paul Matteis with Stifel.

Nathaniel Tower

This is for Tower on for Paul. Can you just give us a little bit more color on to your thoughts on sales force sizing and potential SG&A ramp as we approach potential launch for FT218.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Sure. Why don't I turn the sales force sizing question over to Richard, and then maybe Tom can comment a little bit on kind of SG&A ramp?

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Yes. Thanks for the question, Nate. So as far as sales force sizing is concerned, we're clearly doing the analytics into it now. The one thing I'll say since joining the team is the narcolepsy marketplace, definitely within the oxybate class is a relatively concentrated market. We know that there's only about 4,000 prescribers of current oxybate therapies in the country today, and which about 1,600 physicians make up 80% of the total prescription. So we're still looking at things. It's a little too early for us to make a call on the size, but we know that it's relatively concentrated, and we don't need a huge field force. But I think the other thing that we'll be looking at is other services that we will add in addition to the sales team to really be customer-facing.

So I don't anticipate it being huge, not in the hundreds and probably more in the -- less in that range. But once again, we'll be updating that over time as well. And for the SG&A, I'll pass it over to Tom.

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Thomas S. McHugh ***Avadel Pharmaceuticals plc - Senior VP & CFO***

Yes. So with SG&A, as I mentioned, we had $9 million of SG&A in the fourth quarter. We haven't provided specific guidance around OpEx for 2021. But listen, I think what you can expect is that we're going to step-up from that level as we proceed through the year, quarter-over-quarter. Our spending will be more heavily weighted towards second half of the year, particularly as we approach PDUFA date.

Operator

Our next question is from David Amsellem with Piper Jaffray.

David A. Amsellem ***Piper Sandler & Co., Research Division - MD & Senior Research Analyst***

So a couple of questions on the commercial landscape. And I guess, what we're seeing now is conversion of patients to -- from Xyrem to Xywav. And to the extent that, that continues, how do you think about your ability to then get these patients from the low-sodium product to FT218? I mean, do you -- asking in another way, do you think that these patients will prove to be sticky? And what's your market research telling you about propensity to switch from low sodium twice a night to high sodium once a night? So that's question number one.

Then number two, Jazz has been contracting aggressively on the payer front. So I guess with that in mind, is that something we should presume you're going to be equally or more aggressive? And what kind of ramifications does that have for your gross to net spread? I know it's early to talk about, but wanted to at least get some qualitative color from you.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Thanks, David. Richard, feel free to start and I'll provide any other comments when you're finished?

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Yes, sure. Dave, thanks for the question. So as far as our competitors sort of conversion from the sodium oxybate twice-nightly to the mixed salt twice-nightly, I'm not sure how I sort of view their early success. They clearly had some patients convert. But if we really think about this, there's really been no clinical benefit for that conversion that's going on. There are a lot of drivers. There's been a lot of marketing and efforts that have gone on. There is a lower co-pay for commercial patients for the mixed salt formulation.

But as far as the stickiness of sort of patients to your question, what our market research shows us unequivocally is that patients when given an option, really see the most important attribute of a new therapy being a once-nightly formulation. It really addresses a lot of the issues that they currently have, as I noted in some of my prepared remarks. And going from a sodium oxybate to mixed salt twice-nightly really does nothing to change the treatment paradigm with the exception of sodium. So the fact that patients are changing, actually, we see it as a good sign for us, knowing that patients who may have been on therapy of twice-nightly sodium oxybate for years are potentially willing to change therapy, we actually see as a potential upside.

And as far as your question about contracting is concerned, obviously, it's a little too early for us to get into our contracting strategy discussion. But the one thing we will absolutely make sure we do with payers is ensure that they understand fully that FT218 is not a convenience play, but it is absolutely an opportunity to look at potentially improving outcomes for patients as well. We believe that by focusing the discussion on the clinical benefit of FT218, that is absolutely our best leverage point. And yes, there may be some work that has to be done with contracting. But by keeping our clinical profile front and center, we believe that is our absolute best leverage with payers.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Just additional comment, David, if I may, just on the pricing, and that is clearly, I think from a pricing perspective, we're only seeing favorable trends relative to the opportunity for us, right, in terms of what's happening on a list basis. We saw pitolisant take a 14-plus percent increase at the end of last year. We saw the twice-nightly product take 8.5% in January. Those things clearly are putting the average kind of net price that we can calculate in the marketplace at a higher level than we had previously estimated. And at the end of the day, we understand that the price to pay -- to play is going to be the price to play, right?

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So if there's a net price at a specific plan that's going to be required for us to be there to create access, then we're going to have to do that to create access. And our goal, again, is to ensure that we're, as Richard noted, defending our proposition relative to some true benefits clinically and for the patient of once-nightly. And there'll be -- and some payers, there'll be pricing matters that we're going to have to resolve and some perhaps not. But I think your comment that it's a bit early, is correct, but we certainly understand that there's going to be a net price in the marketplace at specific payers that we're going to have to meet to get into the category.

David A. Amsellem ***Piper Sandler & Co., Research Division - MD & Senior Research Analyst***

Okay. Yes, that's helpful. If I may sneak in a follow-up. Do you think you can capture oxybate-naive patients? Your competitors talked about getting some Xywav patients who are oxybate naive. So is that something that you think is realistic on a meaningful scale?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Richard, do you want to start?

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Yes, sure. David, it's a great question. So our focus is really going to be predominantly focused on the unmet need with the patients who have been exposed to twice-nightly sodium oxybate. However, we do know from our market research, there is a significant amount of patients who are eligible for oxybate, 60% of patients who are eligible for current oxybate therapy are not going on it. As I mentioned in my prepared remarks, half of the patients who are offered this through -- from their physicians don't take it. So there is a great opportunity there as well. However, I think our immediate focus will really be on those who have been exposed to twice-nightly oxybate. But absolutely that opportunity for patients who have not even taken or taken that initial dose is an opportunity for us as we build this launch going forward.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. Just -- maybe just an additional add-on to it, if I may. And that is, we've heard the feedback from the other companies in the marketplace about market expansion opportunities, primarily driven by comorbidities. And in our research project, we confirm some of those numbers talking to those physicians who are treating sodium oxybate today. And I think that's the important point to make is that when we're talking to hundreds of physicians, we're talking to physicians who are actively prescribing sodium oxybate today. And at the same point in time, actively deciding not to treat specific patients in the marketplace perhaps for reasons the other company has referenced. But also, as we've learned in our research, equally as much, if not more, due to the fact of the dosing-related challenges.

So I think what's good here is that, as Richard described, the highly concentrated marketplace with a small discrete number of prescribers, the opportunity to take share and expand the opportunity sits within that same universe.

Operator

And our next question is from François Brisebois with Oppenheimer.

François Daniel Brisebois ***Oppenheimer & Co. Inc., Research Division - MD & Senior Analyst***

Richard, I think the first one would be for you. I was just wondering your thoughts when you did your diligence here on the importance of really the market penetration prior to, maybe not as much the authorized generics in '23 potentially, but especially in 2026 with the regular generics. Any thoughts there through your due diligence would be helpful?

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Yes, François, thanks for the question. So yes, obviously, we do keep in -- we keep our forward-looking thoughts about us as we prepare for the launch of FT218 as well. I think the one thing I would say when multisource generics can come into the market potentially in 2026 is at the end of the day, it is still going to be a twice-nightly regimen that is done. What we know about the narcolepsy marketplace is people step through their therapies moderately quickly as well. So first and foremost, we believe that the value proposition of once-nightly FT218 and the clinical benefits associated with that are a really significant offering this marketplace.

Even if we get in a situation where there is penetration from twice-nightly generics in the future, those step-throughs are still through a potential for a twice-nightly. And we believe that even though it may alter some of the opportunity, it significantly still doesn't really

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change the value proposition to patients. So at the end of the day, when I've done my diligence, I really do believe that the once-nightly is such a potentially game-changing therapy for patients that if we do our job with peers, we help them along this journey as well. But also when patients realize it's still a twice-nightly, we still think that there is significant opportunity even after the multisource generics may enter the marketplace as well.

François Daniel Brisebois ***Oppenheimer & Co. Inc., Research Division - MD & Senior Analyst***

Okay. Great. No, that's helpful. And then I wanted to ask just in terms of -- I know all the focus here is on FT218 but any thoughts as you're going through this about maybe growing the pipeline? Or is this still FT218 first, second and third priority at Avadel?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. Frank, great question. And again, I think we've been, obviously, as we've described over the last couple of years, incredibly focused on executing on the 218 program, and that hasn't changed by any stretch of the imagination. But I would say that we've begun and have done work relative to kind of the what's next question. And we're not going to obviously do that without -- we're not going to do anything that we think will compromise the focus on FT218 because it is really the catalyst to help drive the kind of what's next strategy.

But that being said, I would say there's -- a few legs of that stool that we've begun and have done quite a bit of analysis on and even a little bit of very early work that we're just not prepared to discuss at this stage. But I think whether it's the concept of a pipeline in a product from formulation development to life cycle management or other indications, certainly, that's a leg to the stool. Certainly, the application of our technology is an opportunity for us in the future, given it's our technology and our rights, whether that's strategically in an overlapped marketplace or a very close adjacency.

And then I guess the third leg would obviously be [DNL] to leverage the infrastructure. But let's be clear, I think the focus has to be 218. And then from there, how do we build around that to allow us to define what's next? And I think as time goes on, we'll certainly talk more about what that is as we get further down the path from that standpoint. I just think we're just not prepared to discuss it in detail right now.

Operator

Our next question is from David Sherman with LifeSci Capital.

David A. Sherman ***LifeSci Capital, LLC, Research Division - Senior Analyst & Director of Research***

I was just wondering if you can give any more detail on what we might see at AAN and some of the other medical meetings? I assume sleep transitions is probably something that we're going to be seeing, but just any more color on data relating to like sleep architecture or EEG power analysis or anything like that would be helpful?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Thanks, David. Jennifer, do you want to take that?

Jennifer Gudeman

Yes, absolutely. Thank you so much for the question. Your assumption is absolutely correct. Starting at a big picture point of view, we have 7 secondary endpoints that were part of the statistical analysis plan so we will be presenting those, including in point such as the Epworth Sleepiness scale, where we assess the subjective improvement in terms of patient sleepiness. A big focus though for us will certainly be on sleep architecture and looking at improvements in the shifts for patients who are treated with FT218.

As I mentioned in my prepared remarks, disturbed nocturnal sleep is an area that we really want to focus in on with FT218. I think it's been an area that has been minimized to a certain degree. And I'm not going to get ahead of sharing the actual data that we'll be presenting, but I'll just reiterate that we are very pleased with the results and look forward to sharing them.

Operator

Our next question is from Matt Kaplan with Ladenburg Thalmann.

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Matthew Lee Kaplan ***Ladenburg Thalmann & Co. Inc., Research Division - MD & Head of Healthcare Equity Research***

Congrats on the NDA acceptance. Just want to dig in a little bit more to the RESTORE study and what you hope to show with that? And I guess, is there chance that the patients that end up in that study could transition to commercial patients?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. Thanks, Matt. Jen, you want to start with that as well?

Jennifer Gudeman

Yes, absolutely. So just a quick reminder for all. RESTORE is not required or -- as part of our FDA approval. Our main focus with RESTORE is on long-term safety, tolerability and efficacy. And it's early, but we are pleased with what we are seeing. I mentioned the fact that the tolerability profile remains consistent and that there have been no withdrawals due to adverse reactions.

And Greg, do you want to comment on the transition topic?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. I think just to add a couple of other comments. I think the data we're generating is really, really important for us, right, because it's going to help inform health care practitioners how to switch patients. It's going to talk about patients who are on a stable dose of twice-nightly and moved into what dose of the once-nightly product, right? And again -- and then we're going to get some feedback, as Jen noted, in terms of patients' preference and experience. And I think all of those are really important data points to generate that, that as we go on, we'll communicate publicly around as we advance the study through the balance of this year. And I would say, again, as Jen noted, we're -- early on, we're very pleased with it.

In terms of what we can expect post-approval? There certainly is the opportunity as that study ramps up, that will create the opportunity for patients to move into a transition window and onto commercial drug from that standpoint as we get into that phase of our launch. So -- but we're very pleased with what we've seen early on, and we'll continue to chop wood and execute against it and look forward to sharing more as we go. Thanks, Matt.

Matthew Lee Kaplan ***Ladenburg Thalmann & Co. Inc., Research Division - MD & Head of Healthcare Equity Research***

Okay. And then one other question maybe for Richard. I guess what's your initial research showing with respect to the unmet need of sodium oxybate patients -- current patients? And specifically, how many patients are coming off drug, I guess, in the first 6 months due to, I guess, issues with the current offerings?

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Yes. Thanks, Matt. Great question. So as I mentioned before in my prepared remarks, there is a significant unmet need. Half the patients not actually wanted to take twice-nightly sodium oxybate when prescribed by their physician. Interesting, 60% of the patients dose adjusting when their physician hasn't even talked to them about that, mostly because of the concern of taking that second dose 2.5 to 4 hours after their initial dose during the middle of the night. But what our research does show us is about 1/4 of patients who are taking twice nightly sodium oxybate discontinue after the first month, and about half have discontinued by the end of the first year.

So to me, especially that first month metric really tells me there is some significant challenges with how patients are accepting these twice-nightly sodium oxybate. So it's a tremendous opportunity, and we absolutely believe that once-nightly FT218 may be able to provide some -- address some of that unmet need that patients and physicians are facing today.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. And I'll just add to that. I think the other part of that research that says that there's actually more patients that these treaters are not putting on sodium oxybate, I think is equally as emblematic of the challenges associated with the twice-nightly product, right? It manifests itself both in terms of discontinuations and it manifests itself in terms of those who decide not to go on, as Richard noted. So those are both opportunities for us. And again, as we stated before, this is all within that highly concentrated marketplace that we described. So thanks, Matt.

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Operator

Our next question is from Robin Garner with Craig-Hallum.

Robin Thai Garner Kalley ***Craig-Hallum Capital Group LLC, Research Division - Senior Research Analyst***

A lot of great questions today. Just wanted to ask, are there any key learnings from commercializing the injectables portfolio that you could apply to FT218?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. I would say not really, Robin. It's just a different channel. And it's much more of a commodities marketplace given that, although at times, we may have been only 1 or 1 or 2 agents in the marketplace, it got to as many as 11. So it was really a price-driven concentrated purchasing channel in the GPO sector. So not really related and commercially only required about half of a person to manage. So very different from that standpoint.

Robin Thai Garner Kalley ***Craig-Hallum Capital Group LLC, Research Division - Senior Research Analyst***

Okay. Another -- my final question is just a big part of the untapped market is the number of undiagnosed patients with only 50,000 being diagnosed. In a disease of 2 decades of history with therapy available, how do you expand this market, which would significantly rise all boats in this market?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Richard, would you care to offer your 2 weeks of insight on that, and I'm happy to add on top of it.

Richard Kim ***Avadel Pharmaceuticals plc - Chief Commercial Officer***

Absolutely, Greg. And thanks for the question, Robin. Yes. No, I think for us, all things will come in time as well. I mean we are going to be absolutely laser-focused on converting patients who have already experienced twice-nightly sodium oxybate treatment initially. We talked about the other opportunity that Greg said about all these patients who have been considered for treatment within that concentrated treater base that are sitting there as well. That's really the low-hanging fruit for us.

But I guess what I've always experienced in my past, Robin, is as new innovative therapies come to the marketplace, to your point, it just raises the entire level of awareness in this category. So I think that will come over time. But what I will say is, at the beginning, that really will not be our initial focus. But I think having a great new innovative therapy like once-nightly FT218 really well creates some more attention in this marketplace. And over time, I think that other untapped, underdiagnosed marketplace will continue -- will potentially grow as well into more meaningfully diagnosed patients as well. So great question and something that we are definitely thinking about for the future as well.

Operator

(Operator Instructions) Our next question is from Oren Livnat with H.C. Wainwright.

Oren Gabriel Livnat ***H.C. Wainwright & Co, LLC, Research Division - MD & Senior Healthcare Analyst***

If I could just circle all the way back and follow-on to the 1 of the first questions about orphan exclusivity. Even conservatively assuming you don't get orphan exclusivity, can you just speak to the pick-a-fence senses that exist around FT218 now and that you continue to build, whether it be patents or just inherent difficulties around formulating and manufacturing the product, maybe duplicating your particular PK profile?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes, Oren, thanks. Again, I think as a company, it was the first to innovate a modified-release GHB formulation that could demonstrate the clinical effect in the single once-nightly dosing. You should assume that we have taken all the steps to protect that from an intellectual property standpoint as extensively and as broadly as we can, both in the U.S. and abroad, from that standpoint.

So we already have a handful of patents that have been issued and that are Orange Book listable, for sure. There is many, many more that are in and under review at the USPTO. And I would just say that it is our expectation that we'll have a robust patent estate that just

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doesn't protect, if you will, the uniqueness of this formulation, but not only our formulation, but GHB derived drugs, whether it's pro-drugs, alternate salts, not only the formulation, but how that formulation performs from release profiles, PK, so on and so forth.

So again, we're very pleased with how that's been executed to date, and we've spent a lot of time over the last 1.5 years, defending how we're going to navigate Orange Book-listed patents. And in the future, we'll have our own and others will have to likely do that, navigate over ours.

Oren Gabriel Livnat ***H.C. Wainwright & Co, LLC, Research Division - MD & Senior Healthcare Analyst***

Okay. And just 1 quick one. Sorry if I missed it. You mentioned the RESTORE study a few times. I think you actually gave us a number of patients enrolled in that last quarter in 3Q like 29. I'm just wondering, is there any update to that now? Or should we just hold on until we see updates in the future?

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Yes. I mean, again, we're not so focused on enrollment. It's going to be something we'll continue to update. We've almost doubled that number. I think we're just a little right -- approaching 50 right now since the last time we updated. I think we updated at 27. So anyway, that's where we are at this stage. And now we're seeing our sites ramp-up in terms of beyond RESTORE -- our REST-ON sites. So we're really pleased with the momentum we're seeing coming out of the holidays, despite kind of the COVID-related challenges. So at this stage, we've got good momentum going there, and we'll update as we go forward.

Operator

Thank you. Ladies and gentlemen, we have reached the end of the question-and-answer session. I will now turn the call over to Greg Divis for closing remarks.

Gregory J. Divis ***Avadel Pharmaceuticals plc - CEO & Director***

Thanks, everybody. I know this has been a bit of a long call. I appreciate all the questions and the opportunity to introduce some of our new team members here. But maybe just wrap up on a couple of comments, right? Because we're really -- the momentum we're building right now is really profound, right, whether it's from the progress we've made on the regulatory front with our now acceptance and PDUFA date. And specifically, what we believe the confidence in our regulatory filing strategy that will enable us to navigate any third-party related challenges with regards to FT218. We're very pleased on that front.

And again, as we sit here today through the review process, we've not been asked to certify against any Orange Book-listed patents, and we do not believe there's a reason to do so. Jennifer covered some of the data, but clearly, our data stands on its own, whether it's primary data you've all seen, the secondary post-hoc and adverse reaction data, you'll see more of coming up this year. It is unequivocal and has the potential to be the best-in-class treatment. And that very much demonstrates itself when we share that data even on a blinded basis, along with a blinded target product profile in our market research to patients and physicians who quickly conclude that once-nightly FT218, if approved, is something very unique and different and has the potential to be the preferred treatment of choice both for currently treated oxybate patients and untreated eligible oxybate patients as well.

And I would say the last thing that I'll comment on is that all of this momentum is really resulting in us being able to attract really great new team members, whether it's Richard and Jennifer as new leaders to the organization, but the breadth and depth of the quality of folks who are raising their hand to want to come, be a part of this opportunity to introduce this breakthrough treatment for patients who, unfortunately, from a patient perspective, have had very limited options for nearly 2 decades, it's really great. And we're really excited about what the team is going to look like as we go forward.

So we're very focused in terms of bringing FT218 to patients and to do all we have to do to ensure we command a meaningful and potential market-leading share of this highly dynamic, highly valuable multibillion-dollar marketplace. And again, as we noted earlier, our mission is to help liberate patients with narcolepsy from the middle of the night dosing and make sure we're doing all we can to create significant and deserved shareholder value.

So I'm very proud of the work the team has done. We're here in large part because of all of the work they've done, along with the

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dedication and support to physicians and patients alike. And we remain committed and focused and, quite frankly, relentless in doing all we can to ensure we deliver the best outcome for all stakeholders, patients, providers and our shareholders.

So we look forward to providing you more updates as we go along, including sharing our data here coming up next month. And with that, I thank you for joining our call. Stay safe, be healthy, and have a great rest of the day. Thank you.

Operator

And this concludes today's conference, and you may disconnect your lines at this time. Thank you for your participation.

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