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**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

**SUPERNUS PHARMACEUTICALS, INC.,**

**Plaintiff,**

**v.**

**ACTAVIS INC., WATSON  
LABORATORIES, INC. – FLORIDA,  
ACTAVIS PHARMA, INC., WATSON  
LABORATORIES, INC., and ANDA, INC.,**

**Defendants.**

**Civil Action No. \_\_\_\_\_**

**COMPLAINT FOR PATENT  
INFRINGEMENT**

**(Filed Electronically)**

**COMPLAINT**

Plaintiff Supernus Pharmaceuticals, Inc. (“Supernus”) by its undersigned attorneys, for its Complaint against defendants Actavis Inc. (“Actavis”), Watson Laboratories, Inc. – Florida (“Watson Florida”), Actavis Pharma, Inc. (“Actavis Pharma”), Watson Laboratories, Inc. (“Watson Laboratories”), and Anda, Inc. (“Anda”) (collectively, “Defendants”) herein allege as follows:

**NATURE OF THE ACTION**

1. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, involving United States Patent No. 7,722,898 (“the

'898 patent”) and United States Patent No. 7,910,131 (“the ’131 patent”), attached hereto as Exhibits A and B, respectively.

### **THE PARTIES**

2. Plaintiff Supernus is a corporation organized and existing under the laws of Delaware, having its principal place of business at 1550 East Gude Drive, Rockville, Maryland 20850.

3. Upon information and belief, Actavis is a corporation organized under the laws of Nevada and operating at its principal place of business at 400 Interspace Parkway, Parsippany, NJ 07054. Upon information and belief, Actavis is in the business of, *inter alia*, the development, manufacture, marketing, sale, and distribution of generic pharmaceutical products throughout the United States—including throughout the State of New Jersey—through its various subsidiaries, including Watson Florida, Actavis Pharma, Watson Laboratories, and Anda.

4. Upon information and belief, Watson Florida is a company organized and existing under the laws of Florida and operating at its principal place of business at 4955 Orange Drive, Davie, Florida 33314. Upon information and belief, Watson Florida (formerly known as Andrx Pharmaceuticals, Inc.) is wholly-owned by Andrx Corporation, which is wholly-owned by defendant Actavis. Upon information and belief, Watson Florida acts at the direction of, under the control of, and for the direct benefit of Actavis and is controlled and/or dominated by Actavis. Upon information and belief, Actavis and Watson Florida have at least one officer and/or director in common.

5. Upon information and belief, Watson Florida is in the business of: (i) developing generic pharmaceutical products for sale throughout the United States, including throughout the State of New Jersey; and (ii) preparing and filing Abbreviated New Drug Applications

(“ANDAs”) seeking U.S. Food and Drug Administration (“FDA”) approval to market generic drugs throughout the United States.

6. Upon information and belief, Watson Florida filed ANDA No. 205444 (“the Watson ANDA”) with the FDA seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of generic oxcarbazepine extended-release tablets, containing 150 mg, 300 mg, and 600 mg of oxcarbazepine (“the Watson Product”).

7. Upon information and belief, Actavis Pharma is a corporation organized under the laws of Delaware and operating at its principal place of business at 400 Interspace Parkway, Parsippany, NJ 07054. Actavis Pharma was formerly known as Watson Pharma, Inc. Upon information and belief, Actavis Pharma is wholly-owned by defendant Actavis. Upon information and belief, Actavis Pharma acts at the direction of, under the control of, and for the direct benefit of Actavis and is controlled and/or dominated by Actavis.

8. Upon information and belief, Actavis Pharma is in the business of marketing, selling, and distributing generic pharmaceutical products throughout the United States, including throughout the State of New Jersey. Actavis Pharma is registered as a manufacturer and wholesale drug distributor in the State of New Jersey under the registration number 5003854.

9. Upon information and belief, Watson Laboratories is a corporation organized under the laws of Nevada and operating at its principal place of business at 400 Interspace Parkway, Parsippany, NJ 07054. Upon information and belief, Watson Laboratories is wholly-owned by defendant Actavis. Upon information and belief, Watson Laboratories acts at the direction of, under the control of, and for the direct benefit of Actavis and is controlled and/or

dominated by Actavis. Upon information and belief, Actavis and Watson Laboratories have at least one officer and/or director in common.

10. Upon information and belief, Watson Laboratories is in the business of marketing, selling, and distributing generic pharmaceutical products throughout the United States, including throughout the State of New Jersey.

11. Upon information and belief, Actavis sells its generic pharmaceutical products throughout the United States, including in New Jersey, “primarily under the ‘Watson Laboratories’, ‘Watson Pharma’ and ‘Actavis Pharma’ labels.” *See* Actavis, Inc. Form 10-K for the Year Ended December 31, 2012 at 8.

12. Upon information and belief, Anda is a corporation organized and existing under the laws of Florida and operating at its principal place of business at 2915 Weston Road, Weston, FL 33331. Upon information and belief, Anda is wholly-owned by defendant Actavis. Upon information and belief, Anda acts at the direction of, under the control of, and for the direct benefit of Actavis and is controlled and/or dominated by Actavis. Upon information and belief, Actavis and Anda have at least one officer and/or director in common.

13. Upon information and belief, Anda distributes Actavis’ generic drug products to independent pharmacies, alternate care providers (hospitals, nursing homes, and mail-order pharmacies), pharmacy chains, and physicians’ offices throughout the United States, including distribution to entities in New Jersey. Anda is registered as a manufacturer and wholesale drug distributor in the State of New Jersey under the registration number 5003858.

#### **JURISDICTION AND VENUE**

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

15. This Court has personal jurisdiction over Actavis because, *inter alia*: (i) Actavis's principal place of business is located in New Jersey; (ii) Actavis, together with its subsidiaries, has committed, induced, or contributed to acts of patent infringement in New Jersey; (iii) Actavis is doing business in New Jersey and maintains continuous and systematic contacts with this judicial district; (iv) Actavis has submitted to the jurisdiction of this Court in at least nine prior New Jersey actions (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-3038; *Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084;<sup>1</sup> *Depomed, Inc. v. Actavis Elizabeth LLC, et al.*, Civil Action No. 12-1358; *Noven Pharms. v. Watson Labs., Inc., et al.*, Civil Action No. 11-5997;<sup>2</sup> *Shire LLC, et al. v. Amneal Pharms. LLC, et al.*, Civil Action No. 11-3781; *King Pharms. Inc., et al. v. Actavis, Inc., et al.*, Civil Action No. 09-6585; *Shire LLC v. Actavis South Atlantic, LLC, et al.*, Civil Action No. 09-479; *King Pharms. Inc., et al. v. Actavis, Inc., et al.*, Civil Action No. 07-5041; *Sanofi-Aventis U.S. LLC, et al. v. Actavis Totowa LLC, et al.*, Civil Action No. 07-3142); and (v) Actavis has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in at least one prior New Jersey action (*Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084).

16. This Court has personal jurisdiction over Actavis Pharma because, *inter alia*: (i) Actavis Pharma's principal place of business is located in New Jersey; (ii) Actavis Pharma, together with Actavis, Watson Florida, Watson Laboratories, and Anda, has committed, induced, or contributed to acts of patent infringement in New Jersey; (iii) Actavis Pharma is doing business in New Jersey and maintains continuous and systematic contacts with this judicial

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<sup>1</sup> Watson Pharmaceuticals, Inc. submitted to the jurisdiction of this Court on July 6, 2012. Watson Pharmaceuticals, Inc. thereafter changed its name to Actavis Inc.

<sup>2</sup> Watson Pharmaceuticals, Inc. submitted to the jurisdiction of this Court on November 4, 2011. Watson Pharmaceuticals, Inc. thereafter changed its name to Actavis Inc.

district; (iv) Actavis Pharma has submitted to the jurisdiction of this Court in at least six prior New Jersey actions (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-3038); *Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084;<sup>3</sup> *Abbott Labs., et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 10-3241;<sup>4</sup> *Teva Neuroscience, Inc., et al. v. Watson Pharma, Inc., et al.*, Civil Action No. 10-5078;<sup>5</sup> *Duramed Pharms. v. Watson Pharma, Inc.*, Civil Action No. 07-5941;<sup>6</sup> *Hoffman La-Roche Inc., et al. v. Cobalt Pharms. Inc., et al.*, Civil Action No. 07-4539;<sup>7</sup> (v) Actavis Pharma has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in at least one prior New Jersey action (*Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084); and (vi) Actavis Pharma is registered as a manufacturer and wholesale drug distributor in the State of New Jersey under the registration number 5003854.

17. This Court has personal jurisdiction over Watson Laboratories because, *inter alia*: (i) Watson Laboratories' principal place of business is located in New Jersey; (ii) Watson Laboratories, together with Actavis, Watson Florida, Actavis Pharma, and Anda, has committed, induced, or contributed to acts of patent infringement in New Jersey; (iii) Watson Laboratories is doing business in New Jersey and maintains continuous and systematic contacts with this judicial district; (iv) Watson Laboratories has submitted to the jurisdiction of this Court in at least ten prior New Jersey actions (*Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action

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<sup>3</sup> Watson Pharma, Inc. submitted to the jurisdiction of this Court on July 6, 2012. Watson Pharma, Inc. thereafter changed its name to Actavis Pharma, Inc.

<sup>4</sup> Watson Pharma, Inc. submitted to the jurisdiction of this Court on May 3, 2010. Watson Pharma, Inc. thereafter changed its name to Actavis Pharma, Inc.

<sup>5</sup> Watson Pharma, Inc. submitted to the jurisdiction of this Court on December 23, 2010. Watson Pharma, Inc. thereafter changed its name to Actavis Pharma, Inc.

<sup>6</sup> Watson Pharma, Inc. submitted to the jurisdiction of this Court on March 3, 2008. Watson Pharma, Inc. thereafter changed its name to Actavis Pharma, Inc.

<sup>7</sup> Watson Pharma, Inc. submitted to the jurisdiction of this Court on September 1, 2011. Watson Pharma, Inc. thereafter changed its name to Actavis Pharma, Inc.

No. 12-3084; *Warner Chilcott Co. v. Watson Labs., Inc.*, Civil Action No. 12-2928; *Janssen Pharms., Inc., et al. v. Watson Labs., Inc., et al.*, Civil Action No. 08-5103; *Duramed Pharms. v. Watson Pharma, Inc, et al.*, Civil Action No. 07-5941; *Hoffman La-Roche Inc., et al. v. Cobalt Pharms. Inc., et al.*, Civil Action No. 07-4539; *Sanofi-Aventis, et al. v. Watson Pharms., Inc., et al.*, Civil Action No. 07-443; *Warner Chilcott Co. v. Watson Pharms., Inc., et al.*, Civil Action No. 07-4697; *Novartis Corp. et al. v. Watson Labs., Inc., et al.*, Civil Action No. 06-1130; *Schering Corp. v. Zydus Pharms., USA, Inc., et al.*, Civil Action No. 06-4715; *Warner Chilcott Co. v. Watson Pharms., Inc., et al.*, Civil Action No. 06-3491); and (v) Watson Laboratories has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in at least one prior New Jersey action (*Auxilium Pharms., Inc., et al. v. Watson Labs., Inc. et al.*, Civil Action No. 12-3084).

18. This Court has personal jurisdiction over Watson Florida because, *inter alia*: (i) Watson Florida, together with Actavis, Watson Laboratories, Actavis Pharma, and Anda, has committed, induced, or contributed to acts of patent infringement in New Jersey; (ii) Watson Florida directly or indirectly through agents, including Actavis, Actavis Pharma, Watson Laboratories, and/or Anda, regularly does or solicits business in New Jersey and/or derives substantial revenue from services or things used or consumed in New Jersey; (iii) Watson Florida is doing business in New Jersey and maintains continuous and systematic contacts with this judicial district; (iv) Watson Florida has submitted to the jurisdiction of this Court in at least six prior New Jersey actions (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-3038; *Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida*, Civil Action No. 13-1669; *Depomed, Inc. v. Actavis Elizabeth LLC, et al.*, Civil Action No. 12-1358; *Warner Chilcott Co., et al. v. Watson Labs., Inc. – Florida*, Civil Action No. 11-5989; *Abbott Labs., et al. v.*

*Watson Labs., Inc. – Florida, et al.*, Civil Action No. 10-3241; *Mallinckrodt Inc. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 10-6424); and (v) Watson Florida has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in at least one prior New Jersey action (*Astrazeneca AB, et al. v. Watson Labs., Inc. – Florida, et al.*, Civil Action No. 13-1669).

19. This Court has personal jurisdiction over Anda because, *inter alia*: (i) Anda, together with Actavis, Watson Laboratories, Actavis Pharma, and Watson Florida, has committed, induced, or contributed to acts of patent infringement in New Jersey; (ii) Anda directly or indirectly through agents, including Actavis, Actavis Pharma, Watson Laboratories, and/or Watson Florida, regularly does or solicits business in New Jersey and/or derives substantial revenue from services or things used or consumed in New Jersey; (iii) Anda transacts business, performs work, and contracts to supply services or products in New Jersey; (iv) Anda is doing business in New Jersey and maintains continuous and systematic contacts with this judicial district; (v) Anda has availed itself of the rights, benefits, and privileges of this Court by asserting counterclaims in at least one prior New Jersey action (*Celgene Corp., et al. v. Natco Pharma Ltd., et al.*, Civil Action No. 10-5197); and (vi) Anda is registered as a manufacturer and wholesale drug distributor in the State of New Jersey under the registration number 5003858.

20. Actavis' Form 10-K, filed with the U.S. Securities and Exchange Commission on February 28, 2013, states that its research and development efforts relating to generic products are being conducted in, *inter alia*, Elizabeth, New Jersey.

21. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and (c), and § 1400(b).



**FACTS AS TO ALL COUNTS**

22. Supernus owns New Drug Application (“NDA”) No. 202810, which was approved by the FDA for the manufacture and sale of oxcarbazepine extended-release tablets, 150 mg, 300 mg, and 600 mg, which Supernus markets under the name Oxtellar XR<sup>TM</sup>.

23. Oxtellar XR<sup>TM</sup> is an antiepileptic drug indicated for: (i) adjunctive therapy in the treatment of partial seizures in adults; and (ii) adjunctive therapy in the treatment of partial seizures in children 6 to 17 years of age.

24. The ’898 patent, entitled “Modified-Release Preparations Containing Oxcarbazepine and Derivatives Thereof” was duly and legally issued by the United States Patent and Trademark Office on May 25, 2010, to Supernus upon assignment from inventors Padmanabh P. Bhatt, Argaw Kidane, and Kevin Edwards. Supernus owns, all rights, title, and interest in the ’898 patent.

25. The ’131 patent, entitled “Method of Treating Seizures Using Modified Release Formulations of Oxcarbazepine” was duly and legally issued by the United States Patent and Trademark Office on March 22, 2011, to Supernus upon assignment from inventors Padmanabh P. Bhatt, Argaw Kidane, and Kevin Edwards. Supernus owns, all rights, title, and interest in the ’131 patent.

26. Pursuant to 21 U.S.C. § 355(b)(1), the ’898 patent and the ’131 patent are listed in FDA’s publication titled “Approved Drug Products with Therapeutic Equivalence Evaluations” (commonly known as the “*Orange Book*”) as covering Oxtellar XR<sup>TM</sup>.

27. Upon information and belief, Defendants worked in concert to prepare, submit, and file the Watson ANDA to FDA under § 505(j) of the Federal Food, Drug, and Cosmetic Act (“FDCA”) (codified at 21 U.S.C. § 355(j)), seeking approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Watson Product and included a

“paragraph IV” certification seeking approval before the expiration of the ’898 patent and the ’131 patent.

28. 21 U.S.C. § 355(j)(2)(B)(iv)(II) requires that a letter notifying a patent holder of the filing of an ANDA containing a paragraph IV certification “include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.” Likewise, 21 C.F.R. § 314.95(c)(6) requires that such a letter include “[a] detailed statement of the factual and legal basis of the applicant’s opinion that the patent is not valid, unenforceable, or will not be infringed.” The detailed statement must include “(i) [f]or each claim of a patent alleged not to be infringed, a full and detailed explanation of why the claim is not infringed” and “(ii) [f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation.” 21 C.F.R. § 314.95(c)(6)(i)-(ii).

29. On or about June 25, 2013, Watson purportedly sent a letter pursuant to § 505(j)(2)(B)(iv) of the FDCA and 21 C.F.R. § 314.95 regarding the Watson Product (the “Watson Notice Letter”).

30. The Watson Notice Letter does not include any non-infringement contentions for claims 1-3, 6-8, 10, 11, 13, 14, or 17-20 of the ’898 patent. The Watson Notice Letter also does not include any non-infringement contentions for claims 1-3, 6-8, 10, 11, 13, 14, or 16-24 of the ’131 patent.

31. The Watson Notice Letter included an Offer of Confidential Access (“OCA”) purportedly pursuant to 21 U.S.C. § 355(j)(5)(C). Plaintiff objected to certain provisions of Watson’s OCA as unreasonable and in violation of 21 U.S.C. 355(j)(5)(C)(i)(III).

**FIRST COUNT**  
**(Defendants Infringement of the '898 Patent)**

32. Plaintiff repeats and re-alleges each of the foregoing Paragraphs as if fully set forth herein.

33. Upon information and belief, Defendants seek FDA approval for the manufacture, use, marketing, sale, and/or distribution of the Watson Product.

34. Upon information and belief, Defendants included a paragraph IV certification to the '898 patent to obtain approval to engage in the commercial manufacture, use, sale, offer for sale and/or importation of Watson's Product before the expiration of the '898 patent.

35. Upon information and belief, Defendants will commercially manufacture, use, sell, offer for sale, and/or import Watson's Product upon, or in anticipation of, FDA approval.

36. The submission and filing of ANDA No. 205444 with a paragraph IV certification to the '898 patent for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the Watson Product before the expiration of the '898 patent is an act of infringement by Defendants of one or more claims of the '898 patent under 35 U.S.C. § 271(e)(2)(A).

37. Defendants' commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the Watson Product that is the subject of ANDA No. 205444 will infringe one or more claims of the '898 patent under 35 U.S.C. § 271(a), 35 U.S.C. § 271(b) and/or 35 U.S.C. § 271(c).

38. Defendants' infringement of the '898 patent has caused and will cause Supernus to suffer irreparable harm. Defendants' infringement will continue unless enjoined by the Court. Supernus has no adequate remedy at law and thus preliminary and permanent injunctions are appropriate to prohibit Defendants from infringing the '898 patent.

39. Upon information and belief, as of the date of the Watson Notice Letter, Defendants were aware of the existence of the '898 patent—as well as the statutory provisions and regulations set forth in 21 U.S.C. § 355 and 21 C.F.R. § 314.95—and acted without a reasonable basis for believing that they would not be liable for infringement of the '898 patent, thus rendering this case “exceptional” under 35 U.S.C. § 285.

**SECOND COUNT**  
**(Defendants' Infringement of the '131 Patent)**

40. Plaintiff repeats and re-alleges each of the foregoing Paragraphs as if fully set forth herein.

41. The submission and filing of ANDA No. 205444 with a paragraph IV certification to the '131 patent for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the Watson Product before the expiration of the '131 patent is an act of infringement by Defendants of one or more claims of the '131 patent under 35 U.S.C. § 271(e)(2)(A).

42. The commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the Watson Product by Defendants will infringe, directly and/or indirectly (including by inducement and/or contributory infringement) one or more claims of the '131 patent under 35 U.S.C. § 271(a), 35 U.S.C. § 271(b) and/or 35 U.S.C. § 271(c).

43. Defendants' infringement of the '131 patent has caused and will cause Supernus to suffer irreparable harm. Defendants' infringement will continue unless enjoined by the Court. Supernus has no adequate remedy at law and thus preliminary and permanent injunctions are appropriate to prohibit Defendants from infringing the '131 patent.

44. Upon information and belief, as of the date of the Watson Notice Letter, Defendants were aware of the existence of the '131 patent—as well as the statutory provisions

and regulations set forth in 21 U.S.C. § 355 and 21 C.F.R. § 314.95—and acted without a reasonable basis for believing that they would not be liable for infringement of the '131 patent, thus rendering this case “exceptional” under 35 U.S.C. § 285.

**PRAYER FOR RELIEF**

WHEREFORE, Plaintiff respectfully requests the following relief:

- i. A Judgment declaring that the '898 patent is valid and enforceable;
- ii. A Judgment declaring that, pursuant to 35 U.S.C. § 271(e)(2)(A), the submission to the FDA and filing of ANDA No. 205444 with a paragraph IV certification to obtain approval for the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Watson's Product was an act of infringement of the '898 patent by Defendants;
- iii. A Judgment declaring that, pursuant to 35 U.S.C. § 271(e)(2)(A), 35 U.S.C. § 271(a), 35 U.S.C. § 271(b) and/or 35 U.S.C. § 271(c), the commercial manufacture, use, sale, offer for sale and/or importation into the United States of Watson's Product prior to the expiration of the '898 patent, including any regulatory extensions, will constitute an act of infringement by Defendants;
- iv. An Order that, pursuant to 35 U.S.C. §§ 271(e)(4)(A), 281, and 283, the effective date of any approval of Watson's Product shall be no earlier than the date on which the '898 patent expires, including any regulatory extensions;
- v. A Judgment pursuant to 35 U.S.C. §§ 271(e)(4)(B), 281, and 283, preliminarily and permanently enjoining Defendants and their officers, agents, servants, employees, and attorneys, and those persons in active concert or participation or privity with them or any of them, from engaging in the commercial manufacture, use, sale, offer for sale, and/or

- importation in the United States of the product that is the subject of ANDA No. 205444 until the expiration of the '898 patent, including any regulatory extensions;
- vi. A Judgment awarding Supernus damages or other monetary relief, pursuant to 35 U.S.C. §§ 271(e)(4)(C) and 284, if Defendants commercially manufacture, use, sell, offer to sell, and/or import any product that is the subject of ANDA No. 205444 that infringes the '898 patent;
  - vii. A Judgment declaring that infringement of the '898 patent is willful if Defendants commercially manufacture, use, sell, offer to sell, and/or import any product that is the subject of ANDA No. 205444 that infringes the '898 patent;
  - viii. A Judgment declaring that the '131 patent is valid and enforceable;
  - ix. A Judgment declaring that, pursuant to 35 U.S.C. § 271(e)(2)(A), the submission to the FDA and filing of ANDA No. 205444 with a paragraph IV certification to obtain approval for the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Watson's Product was an act of infringement of the '131 patent by Defendants;
  - x. A Judgment declaring that, pursuant to 35 U.S.C. § 271(e)(2)(A), 35 U.S.C. § 271(a), 35 U.S.C. § 271(b) and/or 35 U.S.C. § 271(c), the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Watson's Product prior to the expiration of the '131 patent, including any regulatory extensions, will constitute an act of infringement by Defendants;
  - xi. An Order that, pursuant to 35 U.S.C. §§ 271(e)(4)(A), 281, and 283, the effective date of any approval of Watson's Product shall be no earlier than the date on which the '131 patent expires, including any regulatory extensions;

- xii. A Judgment pursuant to 35 U.S.C. §§ 271(e)(4)(B), 281, and 283, preliminarily and permanently enjoining Defendants and their officers, agents, servants, employees, and attorneys, and those persons in active concert or participation or privity with them or any of them, from engaging in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the product that is the subject of ANDA No. 205444 until the expiration of the '131 patent, including any regulatory extensions;
- xiii. A Judgment awarding Supernus damages or other monetary relief, pursuant to 35 U.S.C. §§ 271(e)(4)(C) and 284 if Defendants commercially manufacture, use, sell, offer to sell, and/or import any product that is the subject of ANDA No. 205444 that infringes the '131 patent;
- xiv. A Judgment declaring that infringement of the '131 patent is willful if Defendants commercially manufacture, use, sell, offer to sell, and/or import any product that is the subject of ANDA No. 205444 that infringes the '131 patent;
- xv. A Judgment declaring that, pursuant to 35 U.S.C. § 285, this is an exceptional case and awarding Supernus its attorneys' fees and costs;
- xvi. Such other and further relief as this Court may deem just and proper.

Dated: August 7, 2013

Respectfully submitted,

By: s/ Charles M. Lizza

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**CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1**

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter in controversy is not the subject of any other action pending in any court or of any pending arbitration or administrative proceeding.

Dated: August 7, 2013

Respectfully submitted,

By: s/ Charles M. Lizza

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# **EXHIBIT A**



US007722898B2

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

(10) **Patent No.:** US 7,722,898 B2  
(45) **Date of Patent:** May 25, 2010

- (54) **MODIFIED-RELEASE PREPARATIONS CONTAINING OXCARBAZEPINE AND DERIVATIVES THEREOF**
- (75) Inventors: **Padmanabh P. Bhatt**, Rockville, MD (US); **Argaw Kidane**, Montgomery Village, MD (US); **Kevin Edwards**, Lovettsville, VA (US)
- (73) Assignee: **Supernus Pharmaceuticals, Inc.**, Rockville, MD (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.: 11/734,874
- (22) Filed: **Apr. 13, 2007**
- (65) **Prior Publication Data**  
US 2007/0254033 A1 Nov. 1, 2007  
**Related U.S. Application Data**
- (60) Provisional application No. 60/794,837, filed on Apr. 26, 2006.
- (51) **Int. Cl.**  
**A61K 9/22** (2006.01)
- (52) **U.S. Cl.** ..... 424/468
- (58) **Field of Classification Search** ..... None  
See application file for complete search history.
- (56) **References Cited**

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(57) **ABSTRACT**

Controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration are disclosed. The inventive compositions comprise solubility-and/or release enhancing agents to provide tailored drug release profiles, preferably sigmoidal release profiles. Methods of treatment comprising the inventive compositions are also disclosed.

**20 Claims, 14 Drawing Sheets**

FIGURE 1

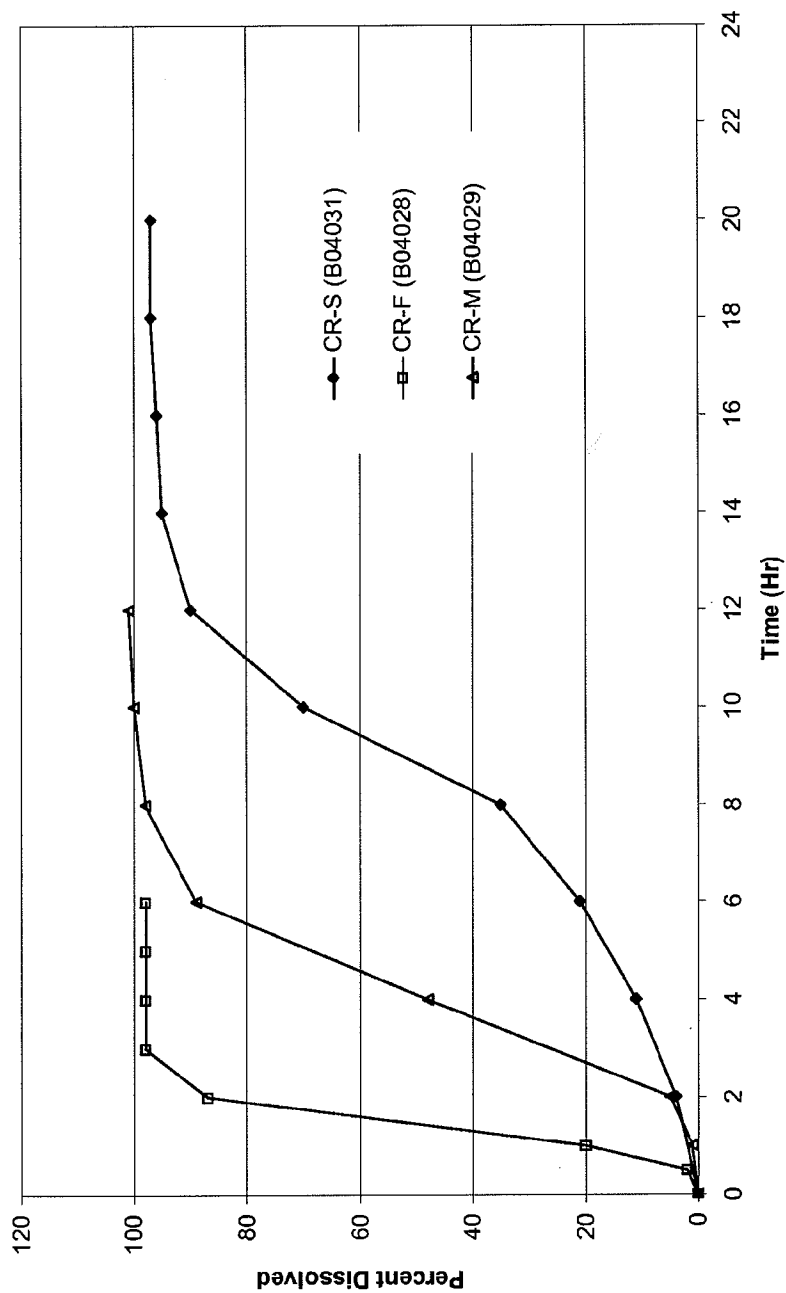


FIGURE 2

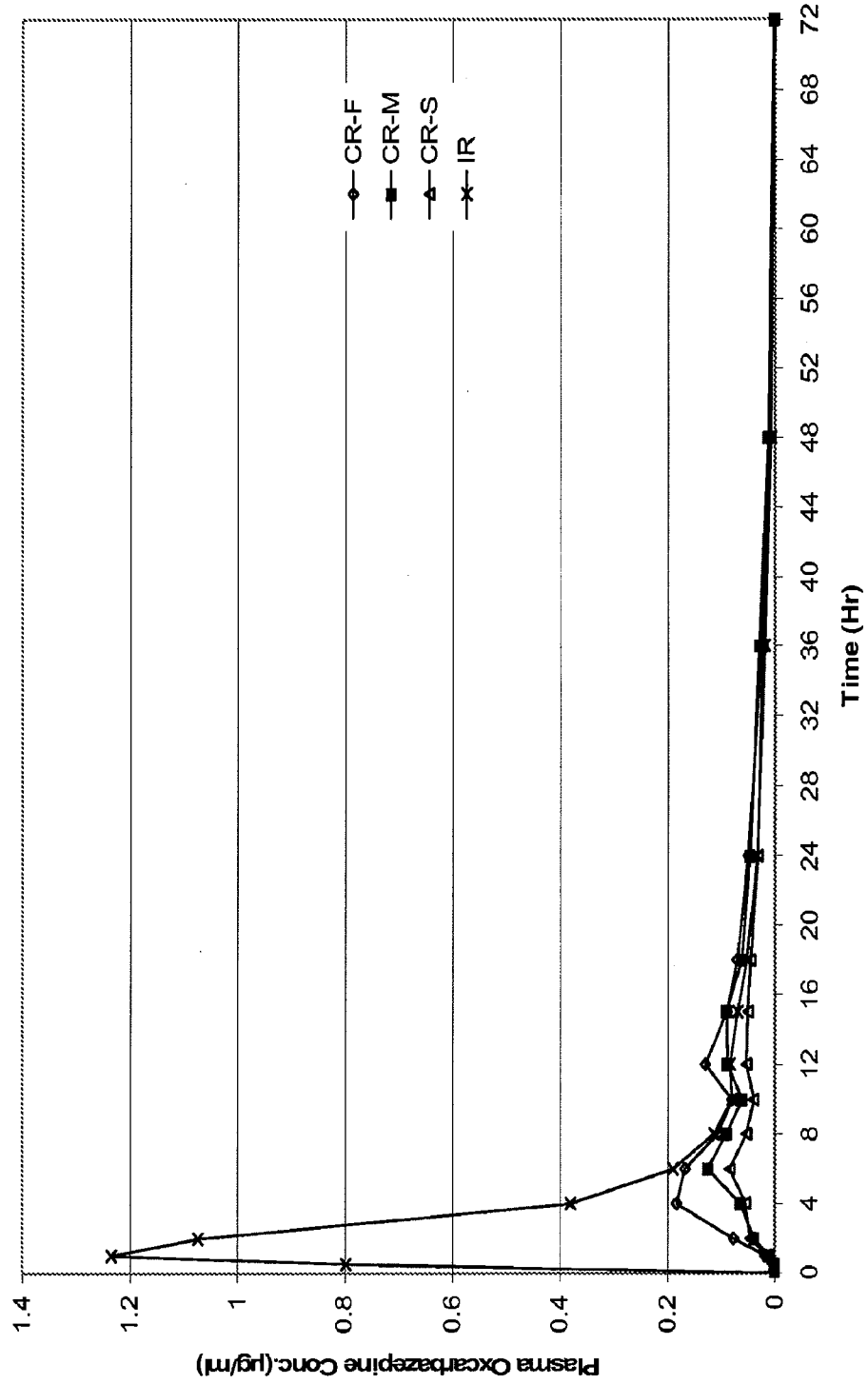


FIGURE 3

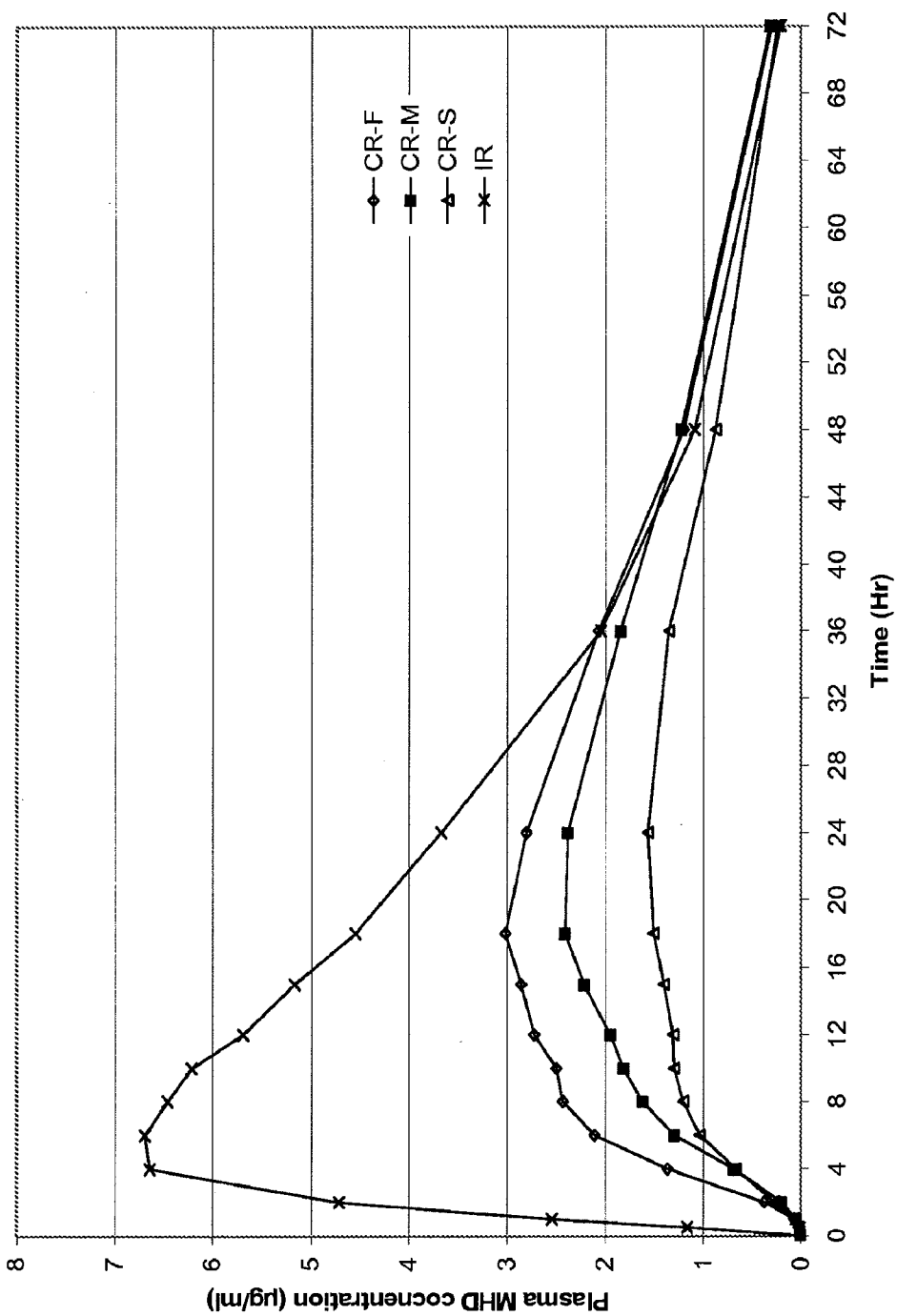


FIGURE 4

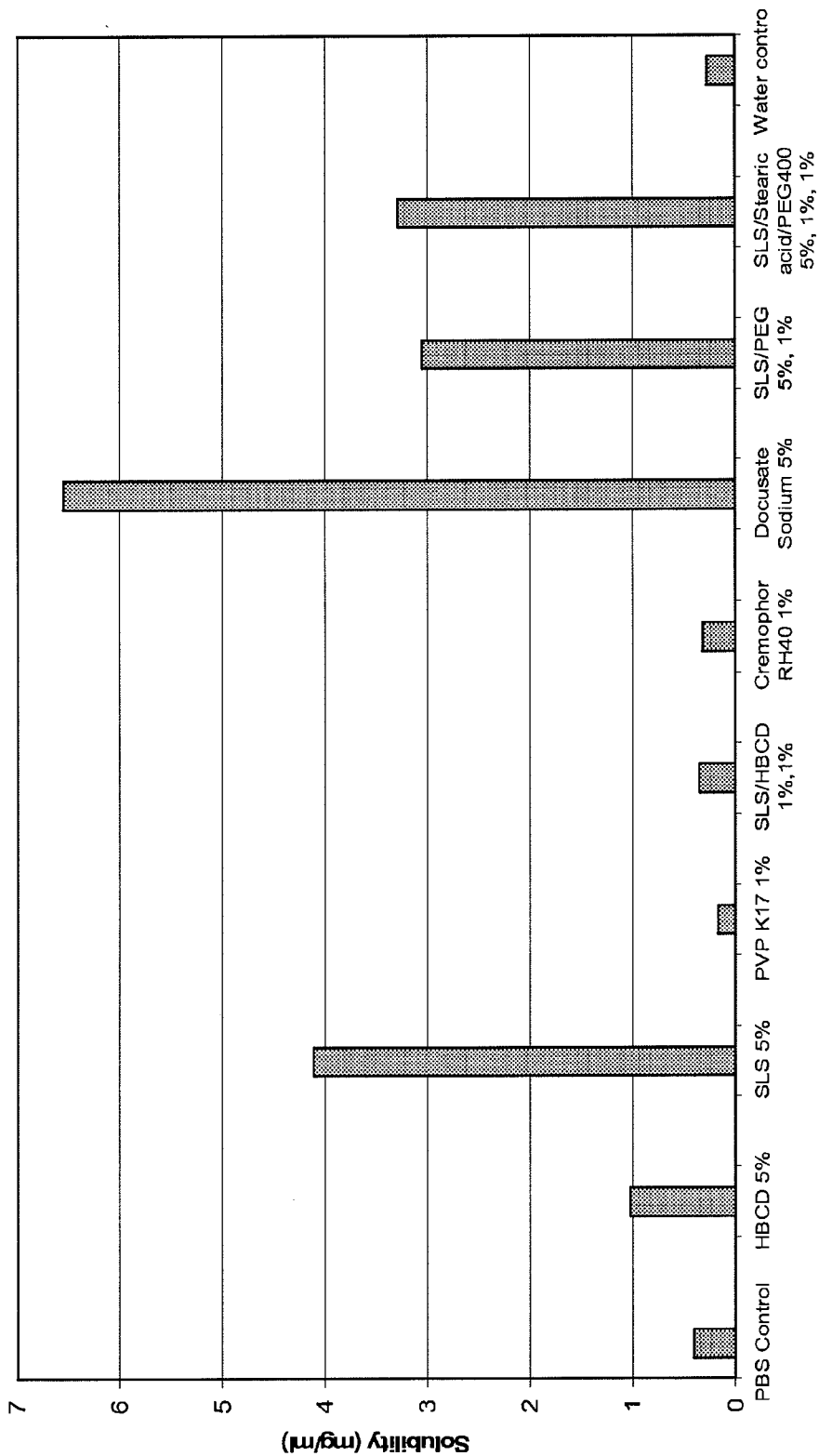


FIGURE 5

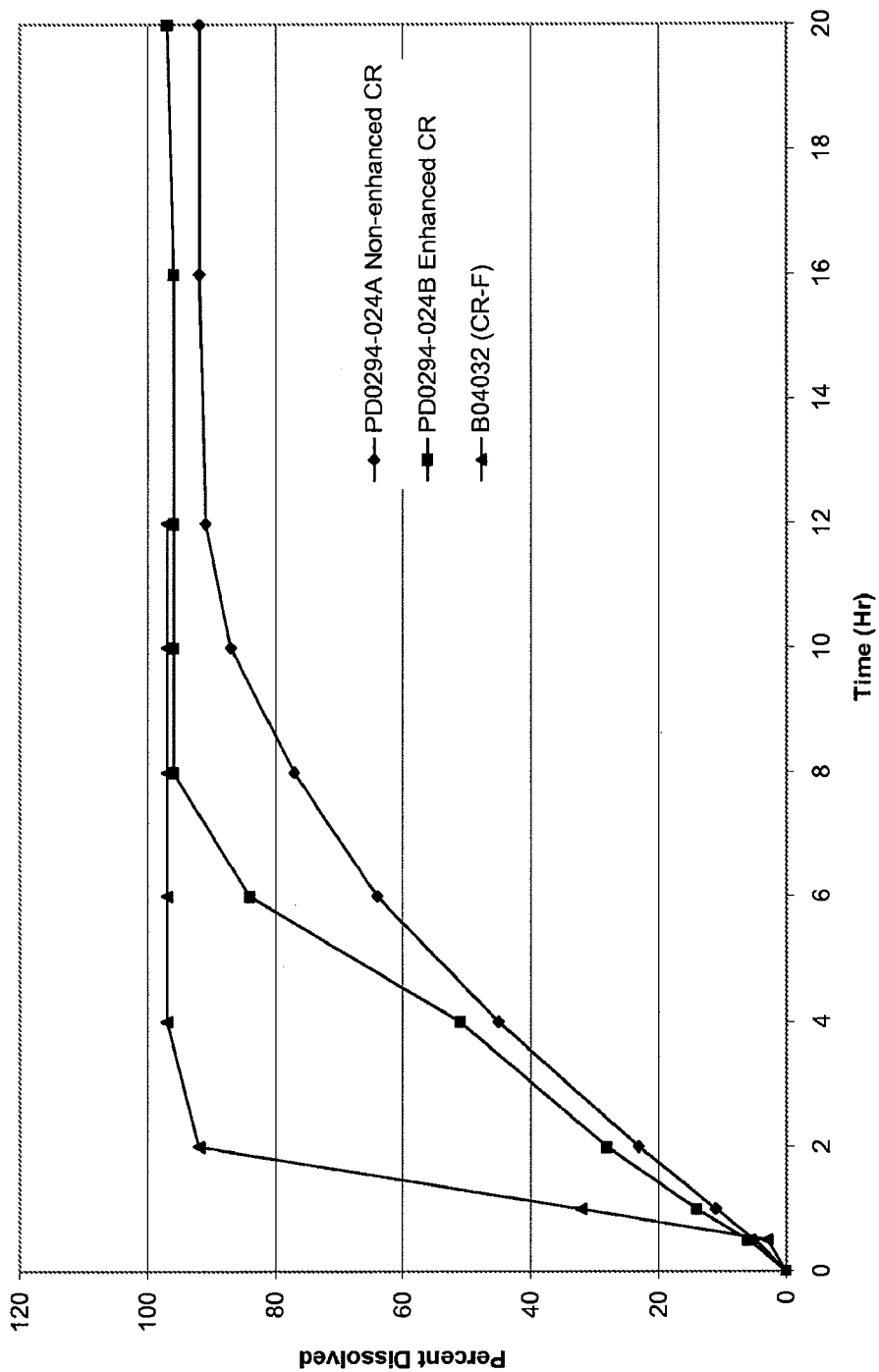




FIGURE 6

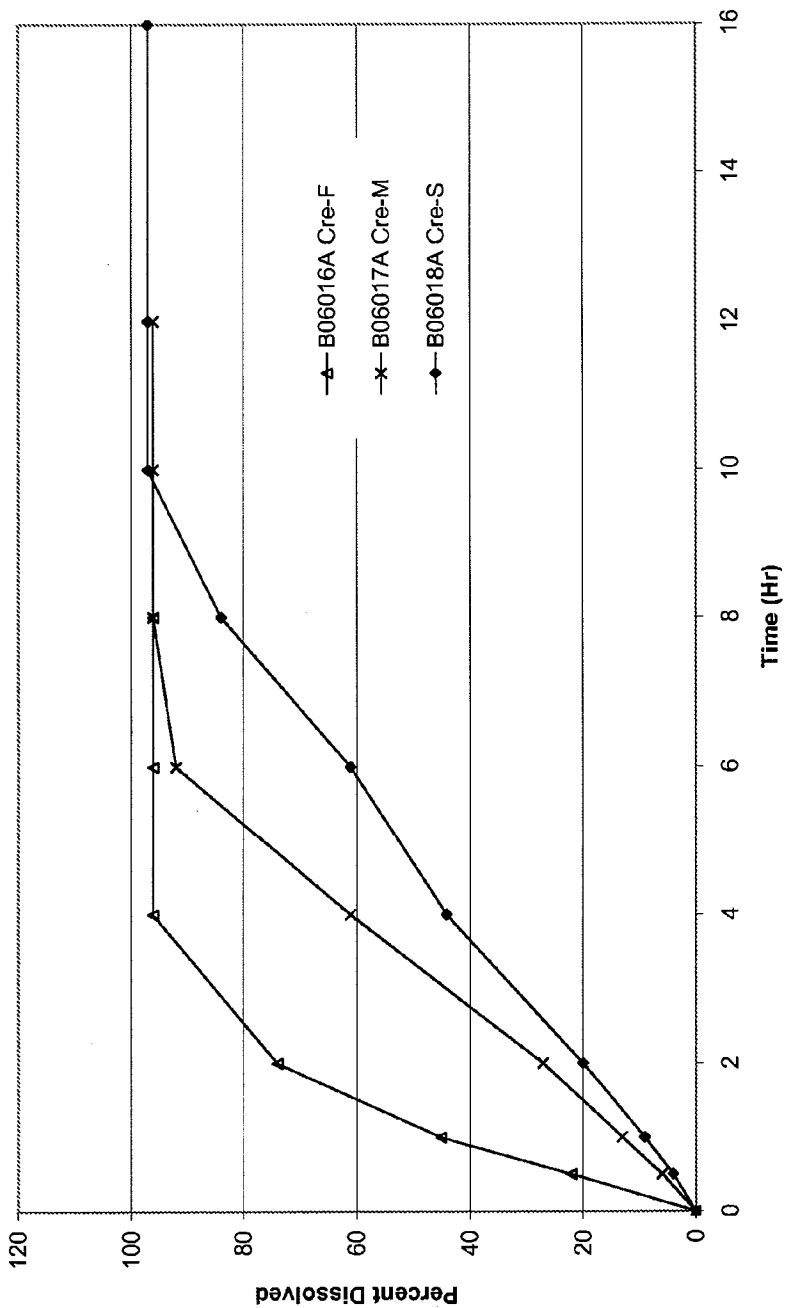


FIGURE 7

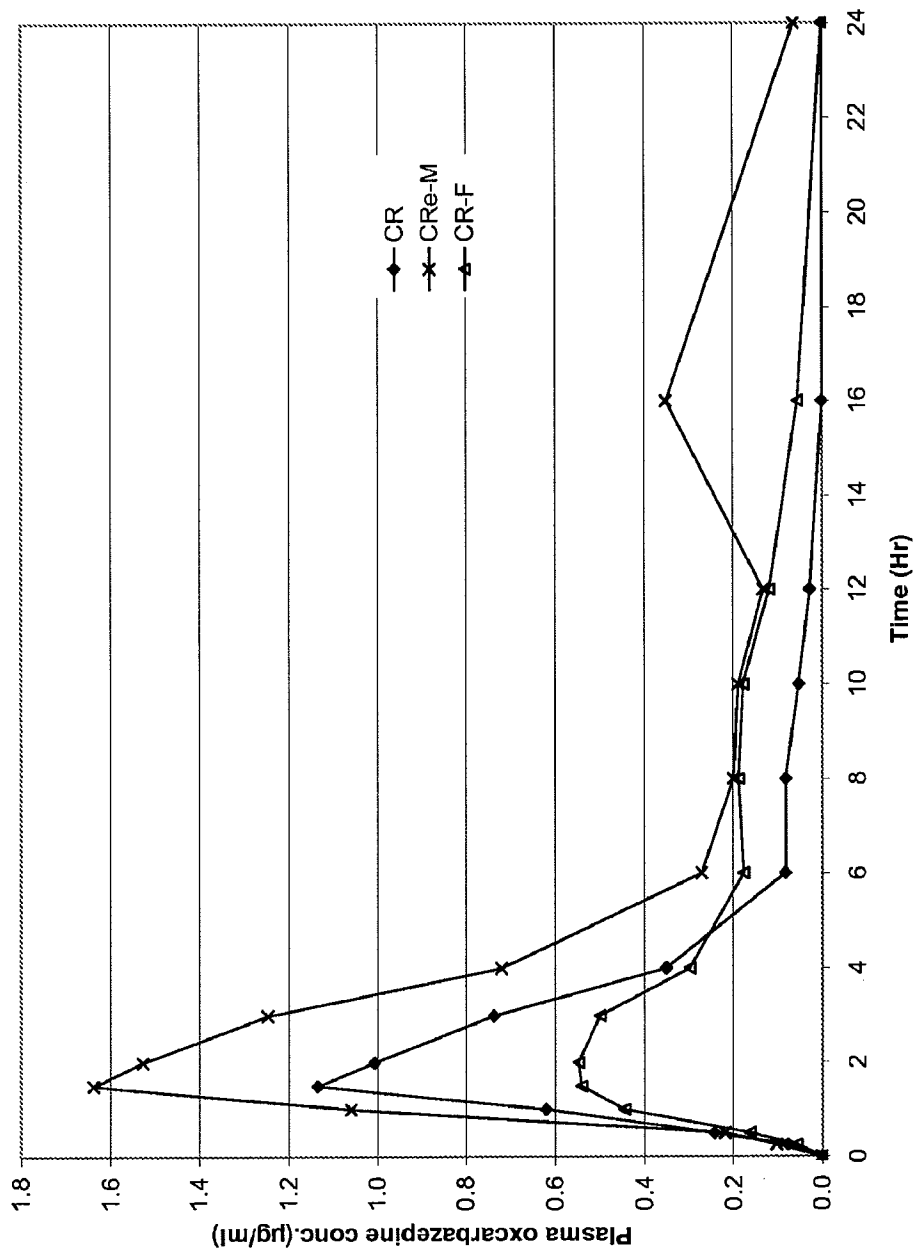


FIGURE 8

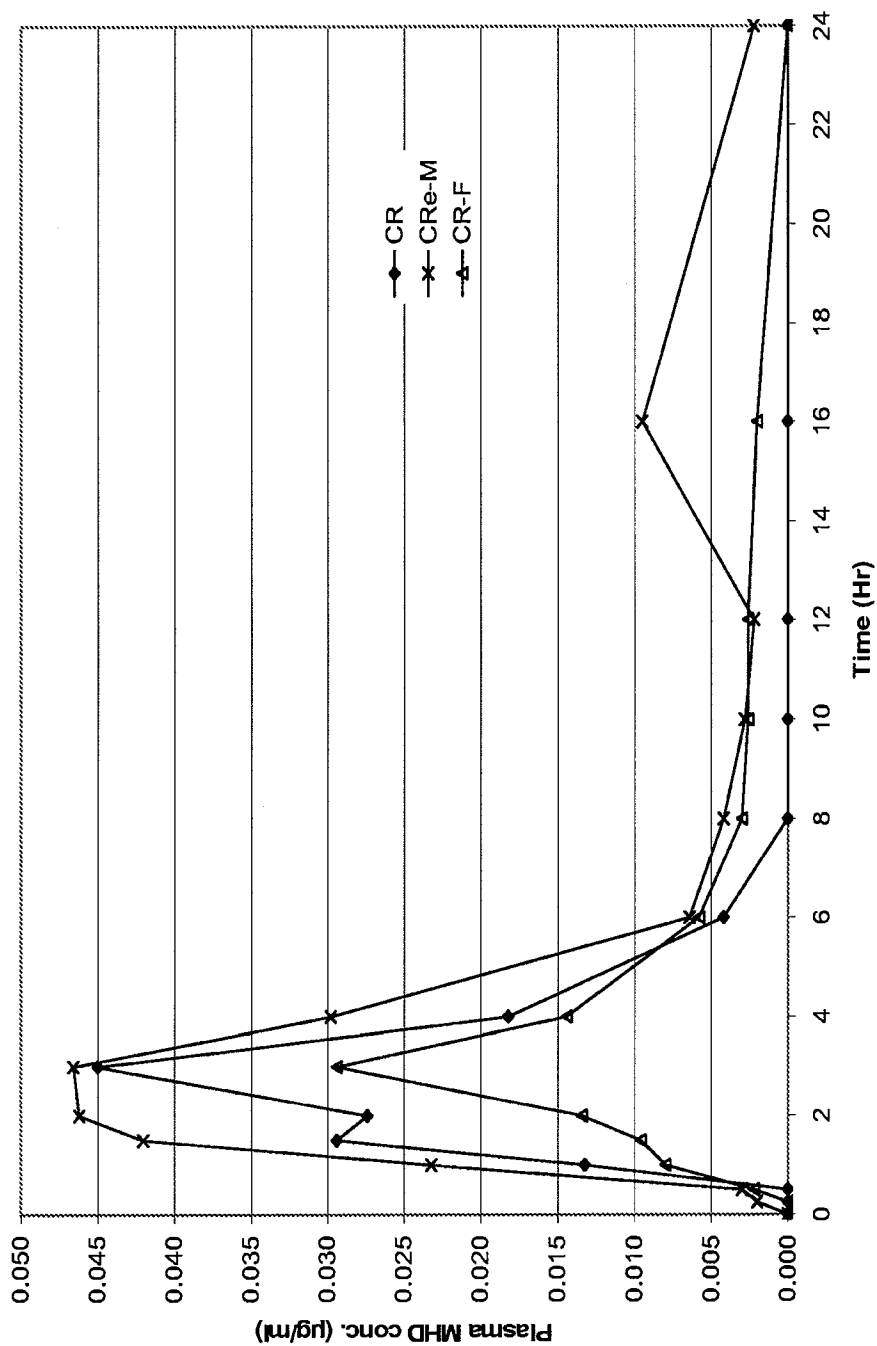


FIGURE 9

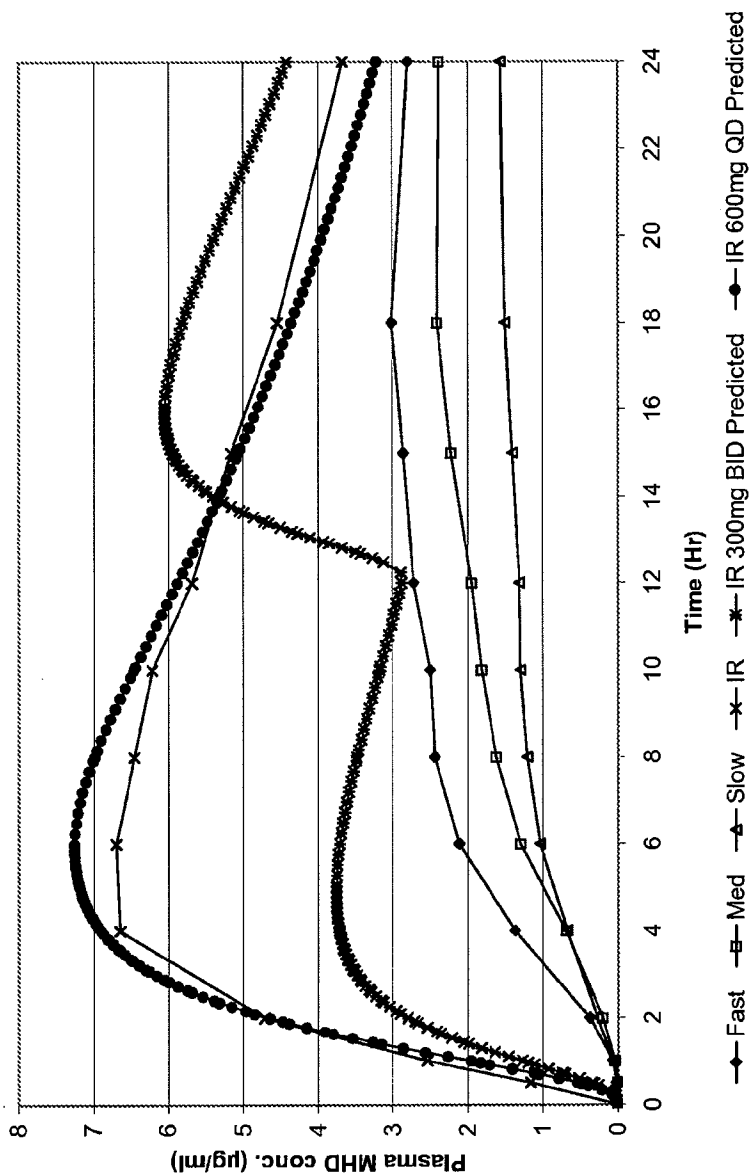


FIGURE 10

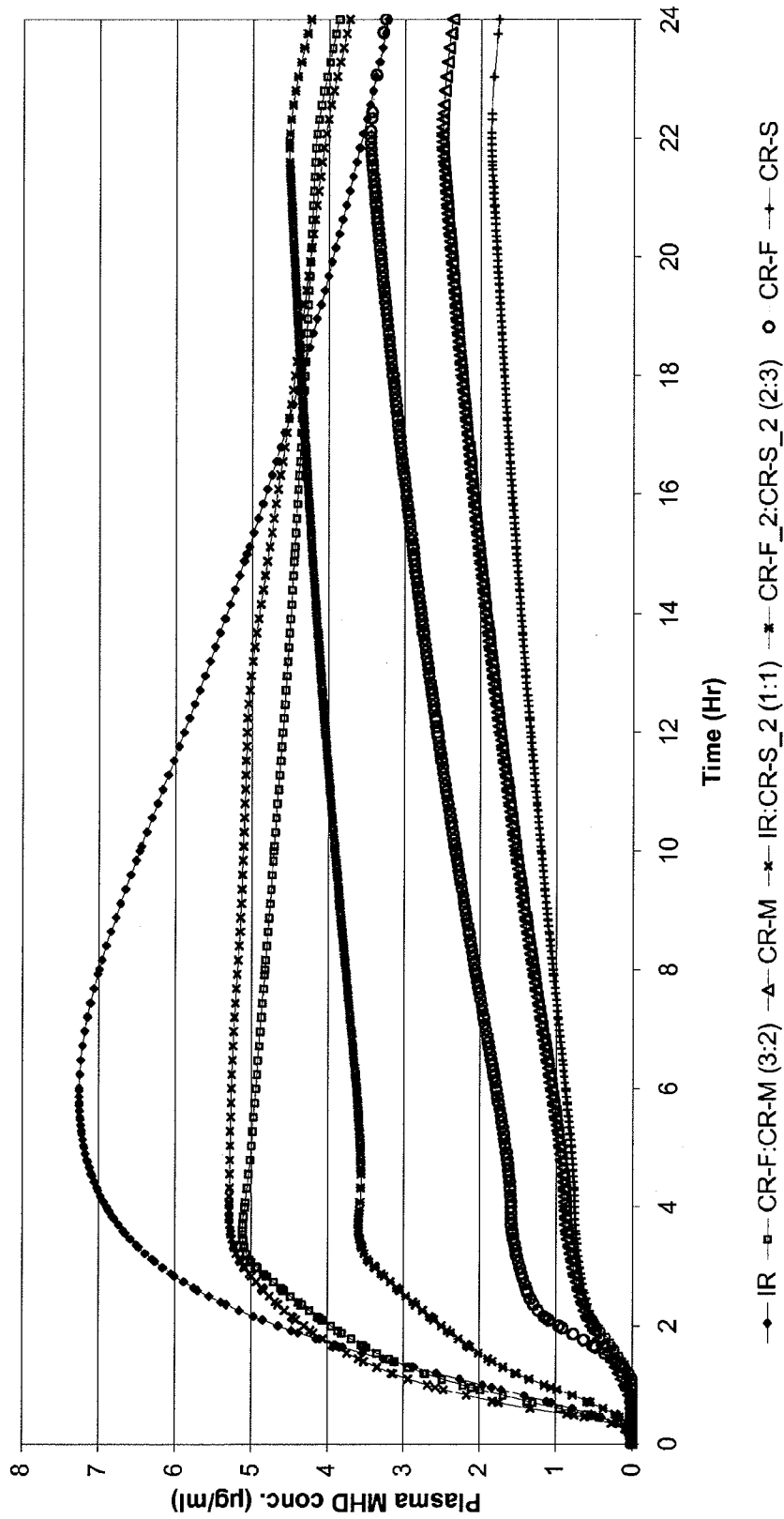


FIGURE 11

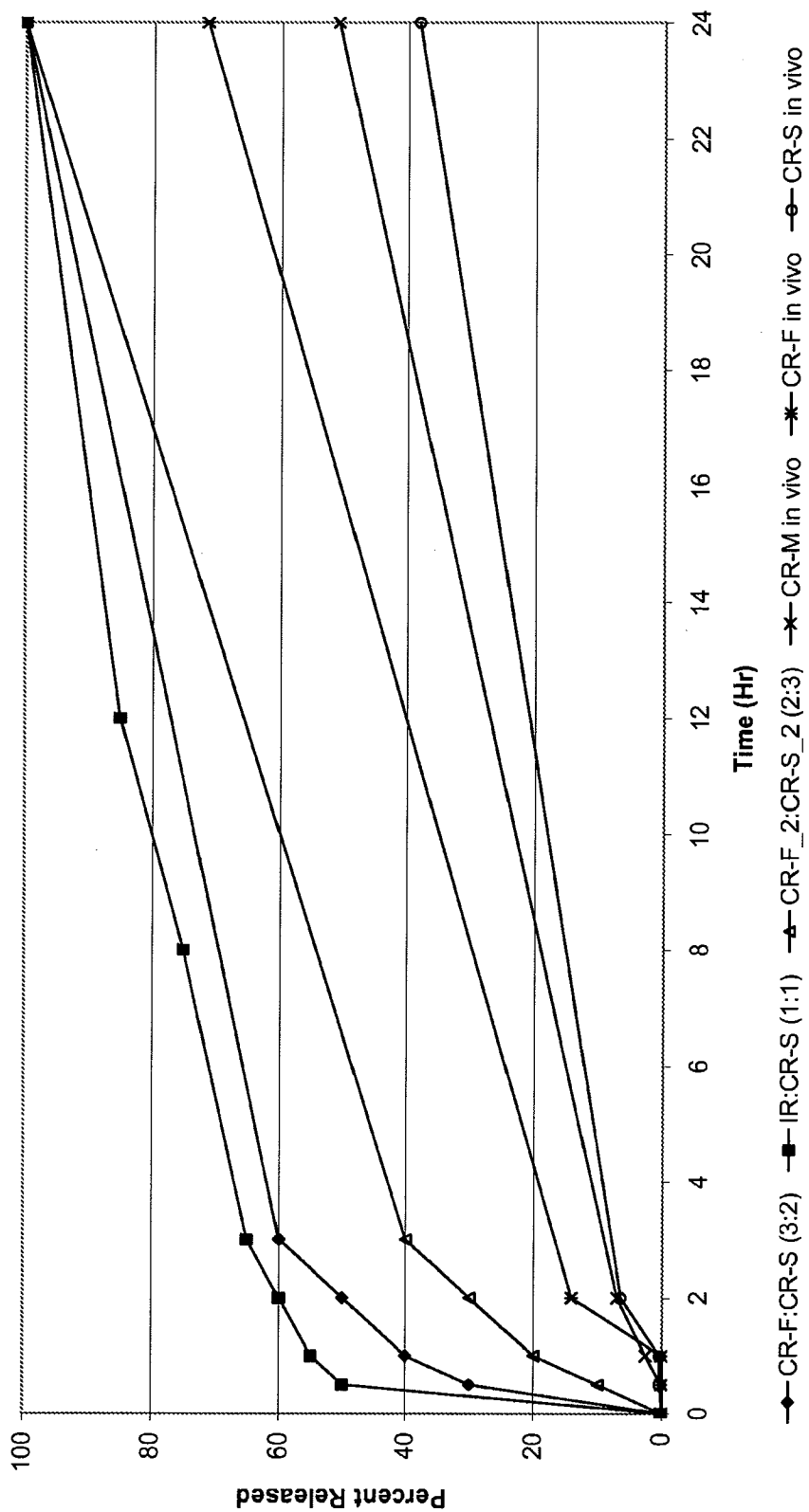


FIGURE 12

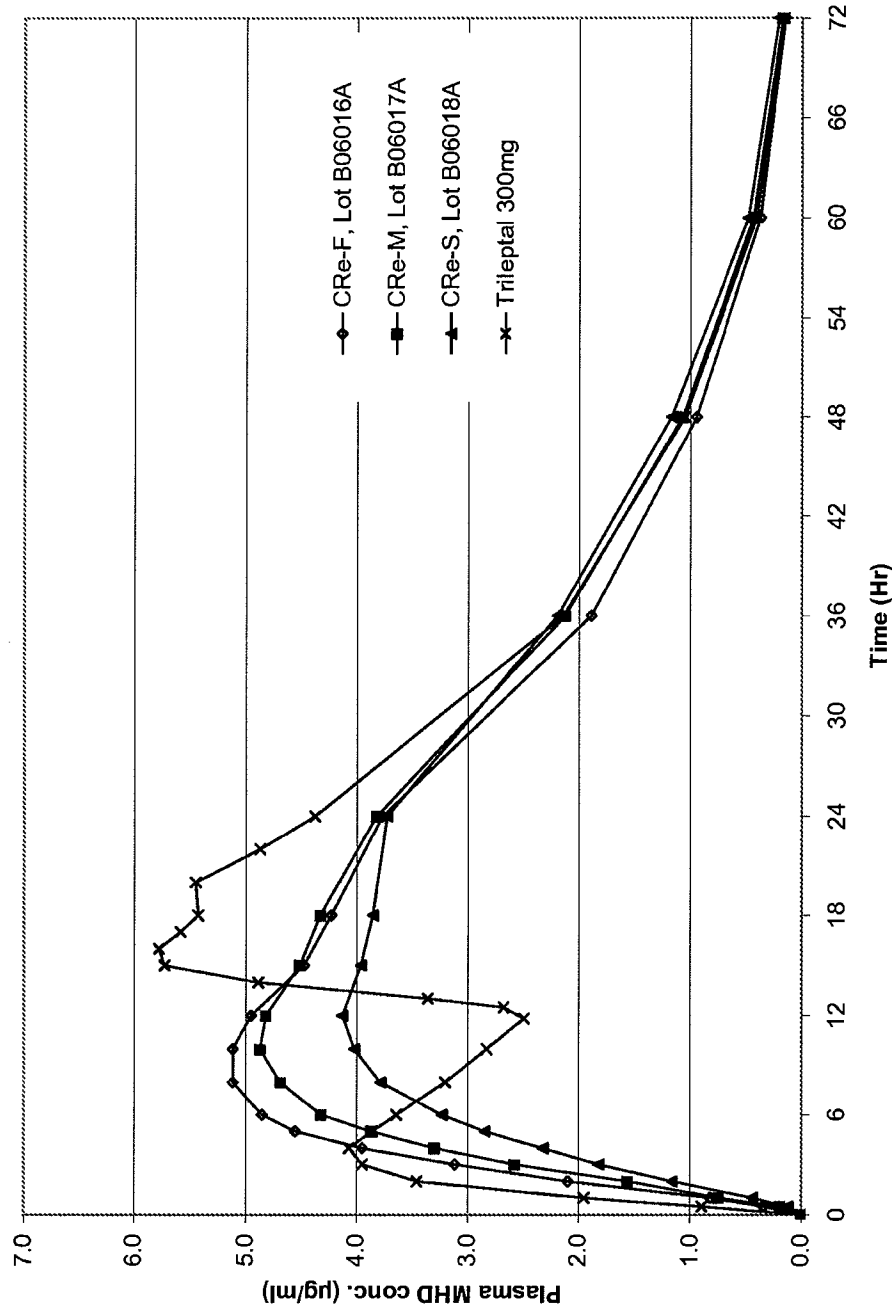


FIGURE 13

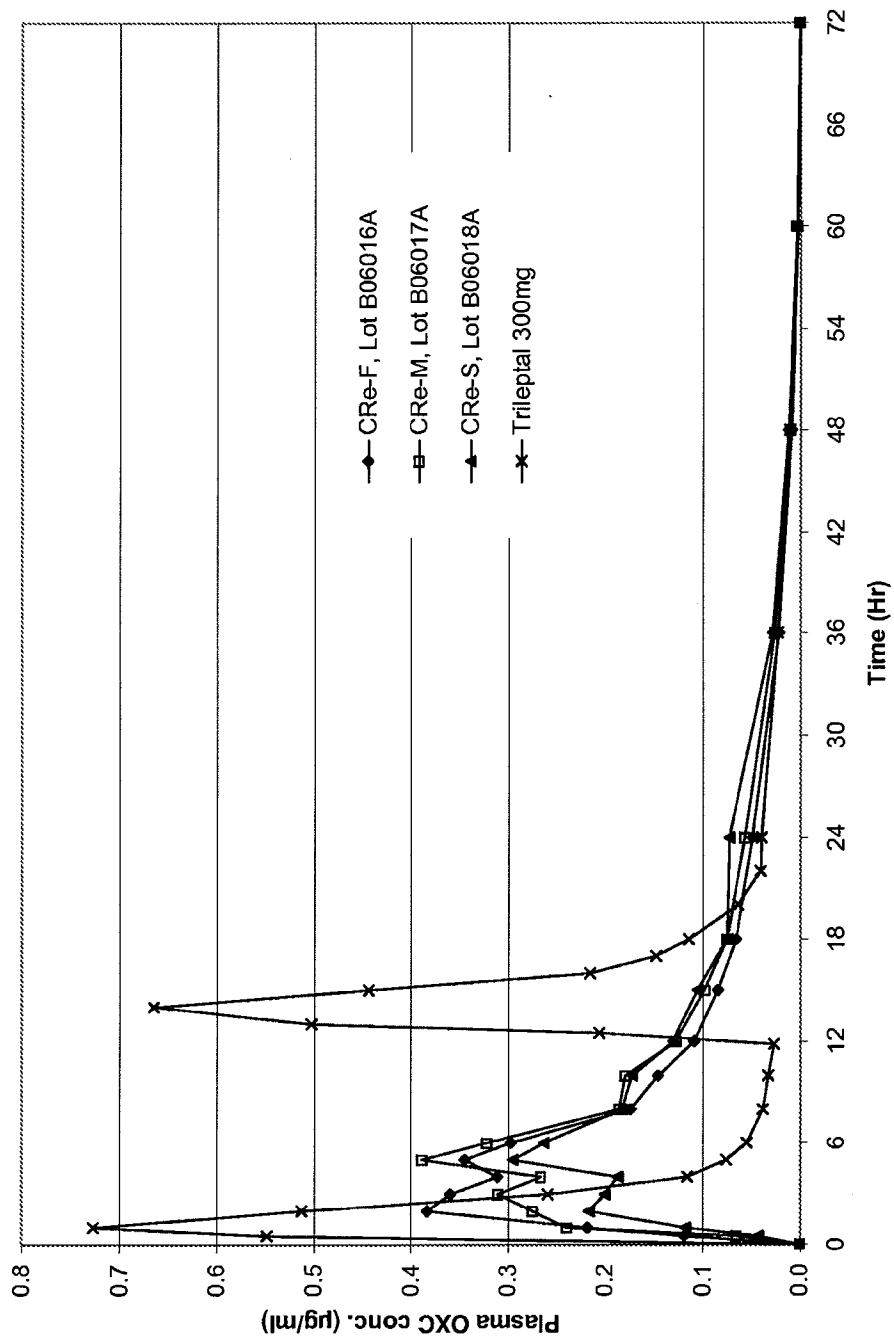
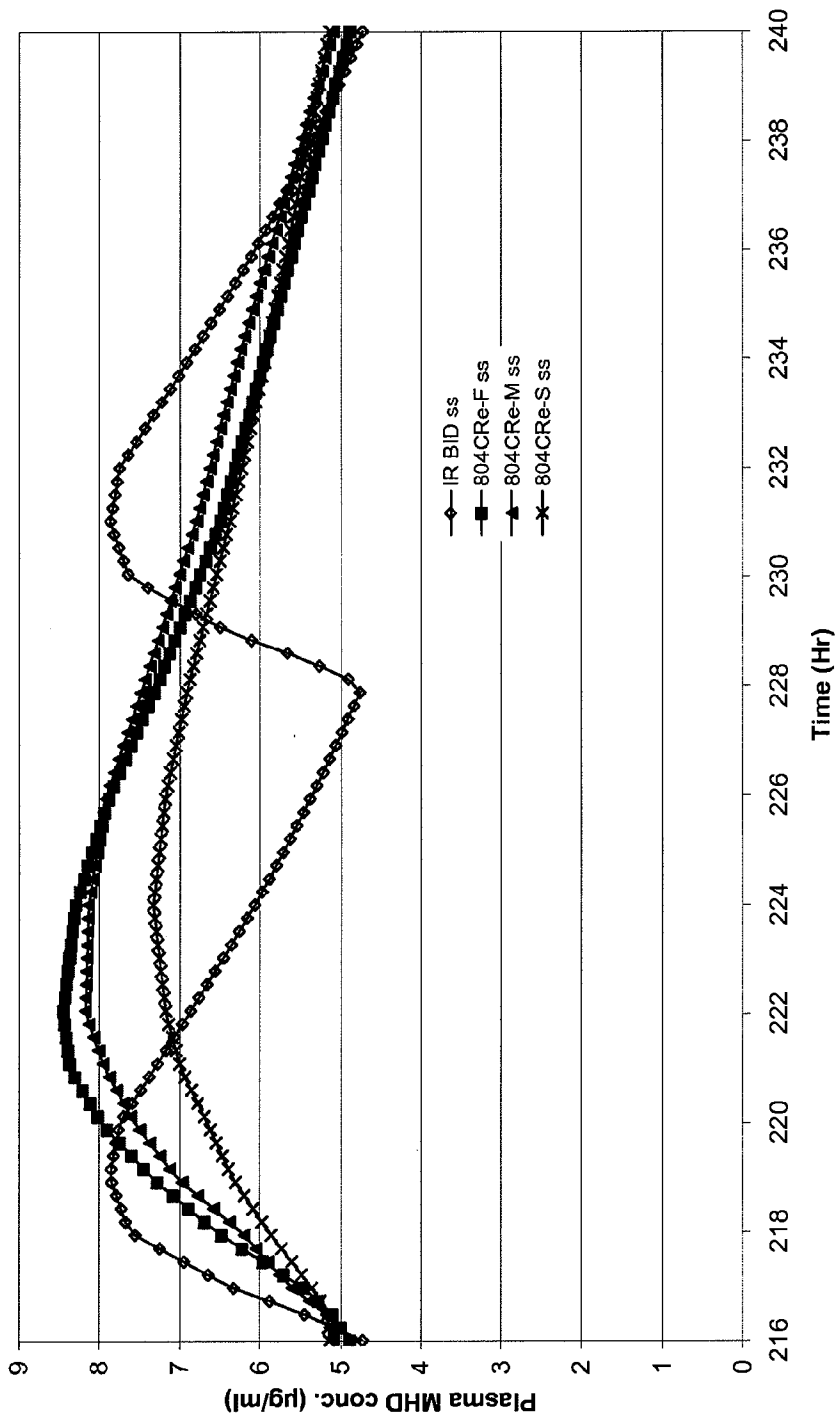




FIGURE 14



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**MODIFIED-RELEASE PREPARATIONS  
CONTAINING OXCARBAZEPINE AND  
DERIVATIVES THEREOF**

**CROSS REFERENCE TO RELATED  
APPLICATIONS**

This application claims priority to U.S. Provisional Application No. 60/794,837, filed Apr. 26, 2006, the disclosure of which is incorporated herein by reference in its entirety.

**FIELD OF THE INVENTION**

The present invention is directed to controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration.

**BACKGROUND OF THE INVENTION**

Oxcarbazepine belongs to the benzodiazepine class of drugs and is registered worldwide as an antiepileptic drug. Oxcarbazepine is approved as an adjunct or monotherapy for the treatment of partial seizures and generalized tonic-clonic seizures in adults and children. An immediate-release (IR) formulation of oxcarbazepine is currently on the market under the trade name Trileptal® and is administered twice a day to control epileptic seizures. Such immediate release compositions provide the drug to the patient in a manner that result in a rapid rise of the plasma drug concentration followed by a rapid decline. This sharp rise in drug concentration can result in side effects, and make multiple daily administration of the drug necessary in order to maintain a therapeutic level of the drug in the body. The need for a controlled-release dosage form for drugs taken chronically such as oxcarbazepine and derivatives is self-evident. Patient compliance is greatly improved with controlled-release (CR) dosage forms that are taken, for example, once-a-day. Also, there are significant clinical advantages such as better therapeutic efficacy as well as reduced side effects with controlled-release dosage forms.

Oxcarbazepine and its derivatives contemplated in this invention are poorly soluble in water. Due to their poor solubility, their release from a sustained release dosage form is rather incomplete. Whereas the in vitro release of oxcarbazepine is dependent on the dissolution method, including the dissolution media used, it has been found through in silico modeling that the release of oxcarbazepine in vivo from a traditional sustained-release dosage form is relatively low. This results in reduced bioavailability of the drug making the dosage form ineffective in providing a therapeutically effective concentration in the body. This poses a serious challenge to the successful development of sustained-release dosage forms for oxcarbazepine and its derivatives.

The rate of drug release from a dosage form has a significant impact on the therapeutic usefulness of the drug and its side effects. Hence, drug release profiles must be customized to meet the therapeutic needs of the patient. An example of a customized release profile is one that exhibits a sigmoidal release pattern, characterized by an initial slow release followed by fast release which is then followed by slow release until all of the drug has been released from the dosage form.

Sustained-release dosage forms for oxcarbazepine and derivatives have been described in the art. For example, Katzhendler et al. (U.S. Pat. No. 6,296,873) describes sustained-release delivery systems for carbamazepine and its derivatives. Katzhendler et al. teaches that a zero-order release profile is achieved for carbamazepine and derivatives

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through the use of hydrophilic and hydrophobic polymers. Zero-order (constant) release was achieved using high molecular weight hydroxypropyl methyl cellulose (HPMC) along with some optional hydrophobic excipients. A similar approach is taught by Shah et al. (US Patent Application 20020169145). Franke et al. (US Patent Application 20040142033) discloses sustained-release formulations of oxcarbazepine that are characterized by the release of 55%-85% of the drug in 15 minutes, and up to 95% in 30 minutes. According to the authors, such release profiles provide adequate sustained-release to achieve once-a-day administration of oxcarbazepine. However, the solubility and bioavailability of the drug from these enhanced preparations suitable for once-a-day administration. The prior art does not teach how to make preparations of oxcarbazepine and derivatives characterized by sigmoidal release profiles.

**SUMMARY OF THE INVENTION**

It is an object of this invention to provide controlled-release formulations of oxcarbazepine for once-a-day administration. The composition of this invention is administered once-a-day and yet meets the therapeutic need of the patient. It is another object of this invention to improve the bioavailability of oxcarbazepine and derivatives thereof. It is yet another object of this invention to meet the therapeutic need of the patient without causing "spikes" in blood drug concentration that may lead to toxicity. It is yet another object of this invention to keep the blood concentration of the drug within the therapeutic window. It is yet another object of this invention to minimize the fluctuation between the  $C_{max}$  and  $C_{min}$  that is typical of many immediate-release and sustained-release preparations.

Many, if not all, of these objectives may be achieved in this invention through formulations that comprise both solubility-enhancing agents and release-promoting agents, and are characterized by release profiles that meet the requirement for once-a-day administration. The objectives may also be achieved through the combination of a multiplicity of units with different release profiles in one dosage unit. Minipellets/granules/tablets, which can be mixed in a certain ratio, provide a dosage form that meets the above stated therapeutic objectives.

This invention also pertains to multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the drug at a rate that is different from the rate of release from another layer. In multi-layer tablets, each layer may or may not be coated.

All of the advantages that stem from once-daily administration of a drug apply to the compositions of this invention. Some of the specific advantages of this invention may be: reduced fluctuation between  $C_{max}$  and  $C_{min}$  during the course of treatment and hence better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

**BRIEF DESCRIPTION OF THE DRAWINGS**

FIG. 1 shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no solubility/release enhancer. The profiles show a non-zero order release with a lag. The  $T_{80\%}$ s (time for 80% of the dose to be released in vitro) for the CR-F, CR-M, and CR-S formulations were 2 Hrs, 5 Hrs and 11 Hrs, respectively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

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FIG. 2 shows the human pharmacokinetic (PK) profiles with respect to oxcarbazepine for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. 3 shows the PK profiles with respect to the metabolite of oxcarbazepine (MHD) for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. 4 shows the solubility results of oxcarbazepine with selected excipients.

FIG. 5 shows the dissolution profiles of oxcarbazepine CR formulations with solubility enhancer (CRE), without solubility enhancer (CR) and a "fast formulation" (CR-F) developed in Example 1. The time to dissolve 80% of the drug ( $T_{80}$ ) for CRE, CR, and CR-F are 5-6 Hrs, 8 Hrs, and 1.5 Hrs, respectively.

FIG. 6 shows the dissolution profiles for the fast (CRE-F), medium (CRE-M), and slow (CRE-S) oxcarbazepine formulations containing solubility/release enhancers. The  $T_{80}$ s for the CRE-F, CRE-M, and CRE-S are 1.5 Hrs, 5 Hrs, and 8 Hrs, respectively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. 7 shows the canine pharmacokinetic profiles with respect to oxcarbazepine, comparing the enhanced formulation (CRE) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. 8 shows the canine pharmacokinetic profiles with respect to MHD, comparing the enhanced formulation (CRE) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. 9 shows the PK profiles shown in FIG. 8 with in silico predicted PK profile for a twice-a-day 300 mg IR.

FIG. 10 shows in silico predicted PK profiles for various in vitro release profiles.

FIG. 11 shows the in silico predicted in vivo release profiles for the systems in FIG. 10.

FIG. 12 shows human plasma concentration vs. time profiles with respect to MHD of the three Oxcarbazepine CR formulations in Example 4 (CRE-F, CRE-M, CRE-S) and Trileptal® as an IR control, dosed BID.

FIG. 13 shows human plasma concentration vs. time profiles with respect to the oxcarbazepine of the three Oxcarbazepine CR formulations in Example 4 (CRE-F, CRE-M, CRE-S) and Trileptal® as an IR control, dosed BID.

FIG. 14 shows the in silico predicted steady-state plasma profiles for the three exemplary formulations (CRE-F, CRE-M, and CRE-S) described in Example 4.

#### DETAILED DESCRIPTION OF THE INVENTION

It is the object of this invention to provide controlled-release oxcarbazepine formulations suitable for once-a-day administration. It is an additional object of the invention to incorporate a combination of solubility-enhancing excipients and/or release-promoting agents into the formulations to enhance the bioavailability of oxcarbazepine and its derivatives. Such compositions are referred to as enhanced formulations.

Oxcarbazepine was formulated to provide release profiles characterized by slow release initially, followed by rapid release and then followed by another period of slow release. Such a release profile is known to those skilled in the art as sigmoidal. Oxcarbazepine formulations with sigmoidal release profiles were tested in human pharmacokinetic (PK)

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studies. Based on the human data, improvements were made to the formulations by incorporating solubility enhancers and/or release-promoting excipients (such formulation are referred to as enhanced formulations). The enhanced formulations were tested in canine models and were surprisingly found to provide significant increase in bioavailability of oxcarbazepine compared to formulations containing no solubility/release enhancing excipients.

The incorporation of solubility enhancing agents in formulations containing poorly soluble drugs such as oxcarbazepine has a profound effect on the in vivo solubility and hence bioavailability of the drugs. Enhancing the solubility of oxcarbazepine results in an increase in its bioavailability and hence in better therapeutic performance of the drug. A combination of solubility and release promoters is contemplated in this invention. Preferable release promoting agents are pH dependent polymers, also known as enteric polymers. These materials are well known to those skilled in the art and exhibit pH dependent solubility such that they dissolve at pH values higher than about 4.0, while remaining insoluble at pH values lower than 4.0. Solubilizers function by increasing the aqueous solubility of a poorly soluble drug. When a formulation containing both the enteric polymer and solubilizer is exposed to an aqueous media of pH higher than 4.0, the enteric polymer dissolves rapidly leaving a porous structure, resulting in increased contact surface between the aqueous medium and the poorly soluble drug. This increased surface area enhances the efficiency of the solubilizer(s), and hence, the overall solubility and release rate of the drug is enhanced to a point where it impacts the availability of the drug for systemic absorption in patients.

Excipients that function as solubility enhancers can be ionic and non-ionic surfactants, complexing agents, hydrophilic polymers, pH modifiers, such as acidifying agents and alkalinizing agents, as well as molecules that increase the solubility of poorly soluble drug through molecular entrapment. Several solubility enhancers can be utilized simultaneously. All enteric polymers that remain intact at pH value lower than about 4.0 and dissolve at pH values higher than 4.0, preferably higher than 5.0, most preferably about 6.0, are considered useful as release-promoting agents for this invention.

Suitable pH-sensitive enteric polymers include cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic monoester copolymer, methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc. These may be used either alone or in combination, or together with the polymers other than those mentioned above. Preferred enteric polymers are the pharmaceutically acceptable methacrylic acid copolymers. These copolymers are anionic polymers based on methacrylic acid and methyl methacrylate and, preferably, have a mean molecular weight of about 135000. A ratio of free carboxyl groups to methyl-esterified carboxyl groups in these copolymers may range, for example, from 1:1 to 1:3, e.g. around 1:1 or 1:2. Such polymers are sold under the trade name Eudragit™ such as the Eudragit L series e.g. Eudragit L 12.5™, Eudragit L 12.5P™, Eudragit L 100™, Eudragit L 100-55™, Eudragit L-30D™, Eudragit L-30 D-55™, the Eudragit S™ series e.g. Eudragit S 12.5™, Eudragit S 12.5P™, Eudragit S100™. The release promoters are not limited to pH dependent polymers. Other hydrophilic molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can be also be used for the same purpose.

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The release-promoting agent can be incorporated in an amount from 10% to 90%, preferably from 20% to 80% and most preferably from 30% to 70% by weight of the dosage unit. The agent can be incorporated into the formulation either prior to or after granulation. The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.

Solubilizers preferred in this invention include surface active agents such as sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, Tweens® and Spans (PEO modified sorbitan monoesters and fatty acid sorbitan esters), poly(ethylene oxide)-polypropylene oxide-poly(ethylene oxide) block copolymers (aka Pluronic™); complexing agents such as low molecular weight polyvinyl pyrrolidone and low molecular weight hydroxypropyl methyl cellulose; molecules that aid solubility by molecular entrapment such as cyclodextrins, and pH modifying agents, including acidifying agents such as citric acid, fumaric acid, tartaric acid, and hydrochloric acid; and alkalinizing agents such as meglumine and sodium hydroxide.

Solubilizing agents typically constitute from 1% to 80% by weight, preferably from 1% to 60%, more preferably from 1% to 50%, of the dosage form and can be incorporated in a variety of ways. They can be incorporated in the formulation prior to granulation in dry or wet form. They can also be added to the formulation after the rest of the materials are granulated or otherwise processed. During granulation, solubilizers can be sprayed as solutions with or without a binder.

This invention also contemplates controlled-release formulations comprising oxcarbazepine that release the drug at variable rates in the GI tract. It is also an object of this invention to design a drug delivery system to deliver drug at a very low rate early, followed by a relatively increased rate. It is another object of this invention to provide a drug release profile that is characterized by an immediate-release followed by a modified-release, such as extended-release (XR) or delayed-release (DR). These types of release profiles ensure that the  $C_{max}$  (maximum concentration of the drug in blood/plasma) is kept within the therapeutic window while extending the maintenance of an effective drug level in the body. The goal of this invention is to develop a controlled-release pharmaceutical composition of oxcarbazepine that provides steady-state blood levels of MHD, an active metabolite of oxcarbazepine, at a concentration of about 2  $\mu\text{g}/\text{ml}$  to about 10  $\mu\text{g}/\text{ml}$ . In the preferred embodiment, steady-state blood  $C_{max}$  levels of MHD fall in the range of about 6  $\mu\text{g}/\text{ml}$  to about 10  $\mu\text{g}/\text{ml}$ , and  $C_{min}$  levels of MHD fall in the range of about 2  $\mu\text{g}/\text{ml}$  to about 5  $\mu\text{g}/\text{ml}$ . Reduced fluctuation between  $C_{max}$  and  $C_{min}$  during the course of treatment results in a better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

The desired drug release pattern contemplated by this invention is achieved by using "matrix" polymers that hydrate and swell in aqueous media, such as biological fluids. As these polymers swell, they form a homogenous matrix structure that maintains its shape during drug release and serves as a carrier for the drug, solubility enhancers and/or release promoters. The initial matrix polymer hydration phase results in slow-release of the drug (lag phase). Once the polymer is fully hydrated and swollen, the porosity of the matrix increases due to the leaching out of the pH-dependent release promoters, and drug is released at a faster rate. The rate of the drug release then becomes constant, and is a function of drug diffusion through the hydrated polymer gel.

Thus, the release vs. time curve is characterized by at least two slopes: one slope for the lag phase where drug release rate

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is low and a second slope where drug release is faster. The slope of the rising part of the release vs. time curve can be customized as to match the rate at which the drug is eliminated from the body. A desired release profile can be achieved by using swellable polymers alone or in combination with binders, such as gelling and/or network forming polymers.

The water-swellable, matrix forming polymers useful in the present invention are selected from a group comprising cellulosic polymers, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose such as microcrystalline cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose; alginates, gums such as guar and xanthan gums; cross-linked polyacrylic acid derivatives such as Carbomers (aka Carbopol™) available in various molecular weight grades from Noveon Inc. (Cincinnati, Ohio); carageenan; polyvinyl pyrrolidone and its derivatives such as crospovidone; polyethylene oxides; and polyvinyl alcohol. Preferred swellable polymers are the cellulosic compounds, HPMC being the most preferred.

The swellable polymer can be incorporated in the formulation in proportion from 1% to 50% by weight, preferably from 5% to 40% by weight, most preferably from 5% to 20% by weight. The swellable polymers and binders may be incorporated in the formulation either prior to or after granulation. The polymers can also be dispersed in organic solvents or hydro-alcohols and sprayed during granulation.

It is yet another aspect of this invention to prepare formulations of oxcarbazepine that combine multiple modified-release "units," each "unit" prepared according to any one or more of the above-disclosed dosage forms, to provide for a customized release profile.

The modified-release units comprise minipellets/granules/tablets etc., each with unique release profiles, that can be mixed in a certain ratio to provide a dosage form that meets the above-stated therapeutic objectives. Alternatively, multiple modified release units may be formed into of multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the active compound at a rate that is different from the rate of release of the active ingredient from another layer. In multi-layer tablets, each layer may optionally be coated with controlled-release polymer(s). The combination dosage forms can exhibit release profiles that comprise any/all possible combinations of immediate release (IR), delayed release (DR), and extended release (XR) formulations. Pellets/granules/tablets or each layer of a single tablet may optionally be coated.

Various hydrophobic excipients can be used to modify the hydration rate of the dosage unit when exposed to water or aqueous media. These excipients retard the wetting of the dosage unit and hence modify the release of the active agent. Hydrophobic excipients suitable for this invention are represented by, but not limited to, glyceryl monostearate, mixtures of glyceryl monostearate and glyceryl monopalmate (Myvaplex, Eastman Fine Chemical Company), glycerylmonooleate, a mixture of mono, di and tri-glycerides (ATMUL 84S), glycerylmonolaurate, glyceryl behenate, paraffin, white wax, long chain carboxylic acids, long chain carboxylic acid esters and long chain carboxylic acid alcohols.

Examples of saturated straight chain acids, useful with the invention, are n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid and melissic acid. Also useful are unsaturated monoolefinic straight chain monocarboxylic acids. Examples of these are oleic acid, gadoleic acid

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and erucic acid. Also useful are unsaturated (polyolefinic) straight chain monocarboxylic acids such as linoleic acid, linolenic acid, arachidonic acid and behenic acid. Useful branched acids include, for example, diacetyl tartaric acid.

Examples of long chain carboxylic acid esters include, but are not limited to: glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate (Myverol 18-92, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monogadoleate (Myverol 18-99, Eastman Fine Chemical Company); acetylated glycerides such as distilled acetylated monoglycerides (Myvacet 5-07, 7-07 and 9-45, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); d-alpha tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures of mono- and diglyceride esters such as Atmul (Humko Chemical Division of Witco Chemical); calcium stearyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactylic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglycerol citrate; stearyl heptanoate; cetyl esters of waxes; cetearyl octanoate; C<sub>10</sub>-C<sub>30</sub> cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters. In addition, waxes can be useful alone or preferably in combination with the materials listed above. Examples of these are white wax, paraffin and carnauba wax.

Drug, polymers, and other excipients are typically combined and wet granulated using a granulating fluid. However, other methods of forming granules such as slugging, and roller compaction can also be used to manufacture matrix granules. Matrix tablets can also be made by direct compression. In wet granulation, typical granulating fluids are: water, a mixture of water and alcohol, anhydrous alcohol. Wet granules can be made in any granulating device such as mixers, high shear granulators, and fluid bed granulators. Granules can be dried in appropriate drying equipment such as fluid bed dryers, ovens, microwave dryers etc. Granules can also be air-dried. Dried granules can be milled using appropriate milling device to achieve a particular particle size distribution. Granules can be filled in to capsules, or blended with other excipients and tableted on a tablet press. Granules can also be packaged into sachets for sprinkle application. Other excipients used to aid tableting are well known to those skilled in the art and include magnesium stearate, talc, cabosil etc. Granules and tablets can, optionally, be coated to further modify release rates. Furthermore, formulations can also optionally contain dyes.

Optionally, but preferably, the tablet composition can contain one or more lubricants, which may be added to assure proper tableting. Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic

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acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and other waxes, including but not limited to, beeswax, carnauba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol. The lubricant, when present, is typically included in an amount of from about 0.1 wt. % to about 20 wt. % of the composition, preferably from about 1 to about 10 wt. %, and more preferably about 0.3 to about 3.0 wt. %.

The oxcarbazepine dosage can be formulated into tablets, granules, and pellets. The steps involved in the manufacturing of these dosage forms are well known to those skilled in the art. Briefly, tablets can be compressed from directly compressible blend containing the active or pre-formed granules. The tablets can be coated or not coated. The coating may optionally impart modification of release. Granules can be made by high shear granulation or fluid bed processing. The granules may or may not be coated. Pellets can be manufactured by drug layering on inert carriers such as sugar spheres. Pellets can also be manufactured by extrusion/spheronization process. The pellets may or may not be coated. Coated pellets and granules can be filled into capsules.

Formulations of this invention can also be made in pelletized forms, which can be filled into capsules or dispensed in sachets for sprinkle application. Each pellet is composed of the drug, swellable polymer(s) and other excipients that aid the processing. Pellets can be prepared in one of the many ways that are known by those skilled in the art. These include, for example, extrusion/spheronization and roller compaction (slugging). In the extrusion/spheronization technique, drug is mixed with swellable polymer(s), such as cellulosic polymers and other excipients. The blend is then granulated in a high shear granulator. The wet mass is then passed through an extruder and spheronized using a spheronizer. The pellets are then dried in an oven or fluid bed processor. The dried pellets are either processed further or encapsulated without further processing.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The invention now will be described in particularity with the following illustrative examples; however, the scope of the present invention is not intended to be, and shall not be, limited to the exemplified embodiments below.

## EXAMPLES

### Example 1

#### Oxcarbazepine Formulations with Sigmoidal Release Profiles

Table 1 provides the formula composition of oxcarbazepine controlled-release preparations with sigmoidal release profiles. Granules were prepared by high shear granulation using anhydrous ethanol as the granulating liquid. All ingredients, except for magnesium stearate, were charged in to VG-65/10 M high shear granulator. The dry powders are blended by running the blade for 3 minutes, after which time the anhydrous ethanol was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10 M was started

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and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules were screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The blend was then tableted on a rotary tablet press.

TABLE 1

Formula composition of Oxcarbazepine CR formulations with changing slope			
Ingredients	SLI 530 CR-F (Fast)	SLI530 CR-M (Medium)	SLI530 CR-S (Slow)
Oxcarbazepine	60	60	60
Comprol 888ATO	9.5	7	—
Prosolv HD90	9.8	20.3	15
Kollidon 25	10	—	—
Kollidon 90	—	3	—
Methocel E5 Prem. LV	—	—	10
Methocel K4M Premium CR	—	—	5
Carbopol 971P	10	9	9
Mg Stearate	0.5	0.5	0.5
FD&C Red #40	—	—	0.5
FD&C Blue #1	0.2	—	—
FD&C Yellow #6	—	0.2	—
Anhydrous Ethanol	*	*	*
Total	100	100	100

\*Removed during processing

FIG. 1 shows the dissolution profiles of three exemplary oxcarbazepine CR formulations (CR-F, CR-M, and CR-S). The profiles exhibited non-zero order release.

## Example 2

## Human Pharmacokinetic Evaluation of Oxcarbazepine CR Formulations from Example 1

The three formulations from the Example 1 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 600 mg) was used as a control reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 2 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. 2 and 3.

TABLE 2

Pharmacokinetic parameters of the three exemplary formulations in example 1 and immediate release reference product.				
PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal™ IR
T <sub>max</sub> (Hr)	6.5	8.4	9.1	1.4
C <sub>max</sub> (ug/mL)	0.248	0.146	0.103	1.412
AUC <sub>last</sub> (Hr * ug/mL)	3.0	2.5	1.7	5.7
Rel BA	53%	44%	30%	100%

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## Example 3

## Solubility Enhancers Screening

The solubility of oxcarbazepine in the presence of excipients was evaluated as follows:

Excipients were dissolved in phosphate buffer to make solutions with concentrations shown in Table 3. One gram of oxcarbazepine was then mixed with 19 µm of the excipient solution. The mixture was rocked overnight at room temperature and then filtered using 0.22 µm filter. The filtrates were analyzed by HPLC. The solubility results are given in Table 3 and FIG. 4.

TABLE 3

Solubility of Oxcarbazepine in the presence of excipients		
Excipients	Excipient conc. (% w/w)	Solubility (mg/mL)
Phosphate Buffer Control	NA	0.4009
Hydroxypropyl beta-cyclodextrin (HBCD)	5	1.0218
Sodium Lauryl Sulfate (SLS)	5	4.1113
Kollidon 17	1	0.1717
SLS/HBCD	1, 1	0.3489
Cremonophor RH40	1	0.3140
Docusate Sodium	5	6.5524
SLS/Polyethylene Glycol 400 (PEG400)	5, 1	3.0516
SLS/Stearic Acid/PEG400	5, 1, 1	3.2821
De-ionized Water	NA	0.2733

## Example 4

## Formulation of Enhanced Dosage Forms

Tables 4 and 5 provide the composition of the formulation containing solubility- and release-enhancing agents. Granules were manufactured by high shear granulation using water as the granulating liquid. All ingredients, except for magnesium stearate, were charged into a VG-65/10 M high shear granulator. The dry powders were blended by running the blade for 3 minutes, upon which time water was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10 M was started and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules are screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The resulting blend was then tableted on a rotary tablet press. Dissolution profiles for these formulations are shown in FIGS. 5 and 6.

TABLE 4

Percent Composition of Enhanced (CR-M) and non-Enhanced (CR) Prototypes		
Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
Oxcarbazepine	60	60
Prosolv SMCC50	10	25
PVP K25	5	5

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TABLE 4-continued

Percent Composition of Enhanced (CR-M) and non-Enhanced (CR) Prototypes		
Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
HPMC K4M premium	10	10
SLS	5	0
Eudragit L100-55	10	0
Magnesium Stearate	0.5	0.5

TABLE 5

Percent Composition for the three exemplary enhanced formulations: CR-F, CR-M, and CR-S.			
Formulation	% PD0294-046 CR-F	% PD0294-051 CR-M	% PD0294-054 CR-S
Oxcarbazepine	60	60	60
Prosolv SMCC50	15	10	5
PVP K25	5	5	5
HPMC K4M premium	5	10	15
SLS	5	5	5
Eudragit L100-55	10	10	10
Magnesium Stearate	0.5	0.5	0.5

Example 5

Canine PK Studies on Formulations from Example 4. Table 4 and Example 1. (SLI530CR-F)

Six male beagle dogs were dosed orally with the formulations in the order given in Table 6. Blood was drawn over a 24 Hr period and blood samples were analyzed by HPLC. A noncompartmental analysis of the data was used to generate  $T_{max}$ ,  $C_{max}$ ,  $AUC_{last}$  and  $AUC_{inf}$ . Relative Bioavailability was calculated in Excel using the  $AUC_{last}$  and  $AUC_{inf}$  for the CRf formulation as the control. The PK profiles for oxcarbazepine and 10-hydroxycarbazepine are given in FIGS. 7 and 8.

TABLE 6

Prototypes tested in dogs			
Phase	Test Article	SLI Lot #	Dose (mg)
1	Oxcarbazepine CR	PD0294-024A	600
2	Oxcarbazepine CR	PD0294-024B	600
3	Oxcarbazepine CR-F	B04032	600

TABLE 7

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine			
Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CR-M) PD0294-024B	Fast CR (CR-F) B04032
$T_{max}$	1.5	1.8	1.7
$C_{max}$	1.20	1.72	0.7

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TABLE 7-continued

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine			
Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CR-M) PD0294-024B	Fast CR (CR-F) B04032
$AUC_{last}$	3.44	7.98	3.41
$AUC_{inf}$	3.74	11.09	4.01
Rel $BA_{last}$	101%	234%	100%
Rel $BA_{inf}$	93%	276%	100%

Example 6

In Silico Modeling of Various Release Profiles of Oxcarbazepine XR

In silico modeling was carried out for various hypothetical systems. Results are shown in FIGS. 9-11.

Example 7

Human Pharmacokinetic Evaluation of Solubility Enhanced Oxcarbazepine CR Formulations from Example 4

The three solubility enhanced prototypes from the Example 4 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 300 mg) given BID was used as a reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 8 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. 12 and 13.

TABLE 8

Pharmacokinetic parameters of the three exemplary solubility enhanced formulations in Example 4 and Trileptal™				
PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal™ BID
$T_{max}$ (Hr)	9	11	14	16
$C_{max}$ (ug/mL)	5.32	5.14	4.40	6.23
$AUC_{last}$ (Hr * ug/mL)	160.3	161.3	148.9	167.1
Rel BA	96%	97%	89%	100%

What is claimed is:

1. A pharmaceutical formulation for once-a-day administration of oxcarbazepine comprising a homogeneous matrix comprising:

- (a) oxcarbazepine;
- (b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
- (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
- (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhy-

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droxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers.

2. The formulation of claim 1, wherein the surface active agents comprise sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, polyethylene oxide (PEO) modified sorbitan monoesters, fatty acid sorbitan esters, polyethylene oxide-polypropylene oxide-(poly(ethylene oxide)) block copolymers, or combinations thereof.

3. The formulation of claim 1, wherein the cellulosic polymers are selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose.

4. The pharmaceutical formulation of claim 1, wherein the release promoting agent is incorporated in an amount from 10% to 90% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

5. The pharmaceutical formulation of claim 4, wherein the release promoting agent is incorporated in an amount from 30% to 70% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

6. The pharmaceutical formulation of claim 1, wherein the amount of oxcarbazepine is effective to produce a steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2  $\mu\text{g}/\text{ml}$  to about 10  $\mu\text{g}/\text{ml}$ .

7. The pharmaceutical formulation of claim 1 wherein the formulation is effective in minimizing fluctuations between  $C_{min}$  and  $C_{max}$  of monohydroxy derivative of oxcarbazepine.

8. The pharmaceutical formulation of claim 7, which provides  $C_{max}$  levels of monohydroxy derivative of oxcarbazepine in the range of about 6  $\mu\text{g}/\text{ml}$  to about 10  $\mu\text{g}/\text{ml}$  and  $C_{min}$  levels of monohydroxy derivative of oxcarbazepine in the range of about 2  $\mu\text{g}/\text{ml}$  to about 5  $\mu\text{g}/\text{ml}$ .

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9. The formulation of claim 1, wherein the amount of oxcarbazepine is 600 mg.

10. The pharmaceutical formulation of claim 1 in the form of pellets, tablets, granules or capsules.

11. The formulation of claim 10 in the form of tablets.

12. The formulation of claim 11, wherein each tablet comprises 600 mg of oxcarbazepine.

13. The formulation of claim 1, wherein the matrix-forming polymer is present in the amount of 1% to 50% by weight of the formulation.

14. The formulation of claim 1, further comprising a lubricant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and waxes.

15. The formulation of claim 1, wherein the wax is selected from the group consisting of beeswax, camuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol.

16. The formulation of claim 12 wherein the lubricant is incorporated in an amount of from 0.1% to 20% by weight of the formulation.

17. The pharmaceutical formulation of claim 1, wherein the polymer having pH-dependent solubility remains intact at pH values of below 4 and dissolves at pH values of more than 4.

18. The pharmaceutical formulation of claim 1, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 5.

19. The pharmaceutical formulation of claim 1, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 6.

20. The formulation of claim 1 comprising HPMC and polyvinyl pyrrolidone as matrix-forming polymers; sodium lauryl sulfate as the agent that enhances the solubility of oxcarbazepine, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)) as the release promoting agent.

\* \* \* \* \*



# **EXHIBIT B**



US007910131B2

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

(10) **Patent No.:** **US 7,910,131 B2**  
(45) **Date of Patent:** **\*Mar. 22, 2011**

(54) **METHOD OF TREATING SEIZURES USING MODIFIED RELEASE FORMULATIONS OF OXCARBAZEPINE**

(75) **Inventors:** **Padmanabh P. Bhatt**, Rockville, MD (US); **Argaw Kidane**, Montgomery Village, MD (US); **Kevin Edwards**, Lovettsville, VA (US)

(73) **Assignee:** **Supernus Pharmaceuticals, Inc.**, Rockville, MD (US)

(\*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 170 days.

This patent is subject to a terminal disclaimer.

(21) **Appl. No.:** **12/230,276**

(22) **Filed:** **Aug. 27, 2008**

(65) **Prior Publication Data**

US 2009/0004263 A1 Jan. 1, 2009

**Related U.S. Application Data**

(63) Continuation of application No. 11/734,874, filed on Apr. 13, 2007, now Pat. No. 7,722,898.

(60) Provisional application No. 60/794,837, filed on Apr. 26, 2006.

(51) **Int. Cl.**  
**A61K 9/20** (2006.01)

(52) **U.S. Cl.** ..... **424/464**

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

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*Primary Examiner* — Michael G Hartley

*Assistant Examiner* — Paul Dickinson

(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP; Stephen B. Maebius; Sunit Talapatra

(57) **ABSTRACT**

Controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration are disclosed. The inventive compositions comprise solubility- and/or release enhancing agents to provide tailored drug release profiles, preferably sigmoidal release profiles. Methods of treatment comprising the inventive compositions are also disclosed.

**24 Claims, 14 Drawing Sheets**

FIGURE 1

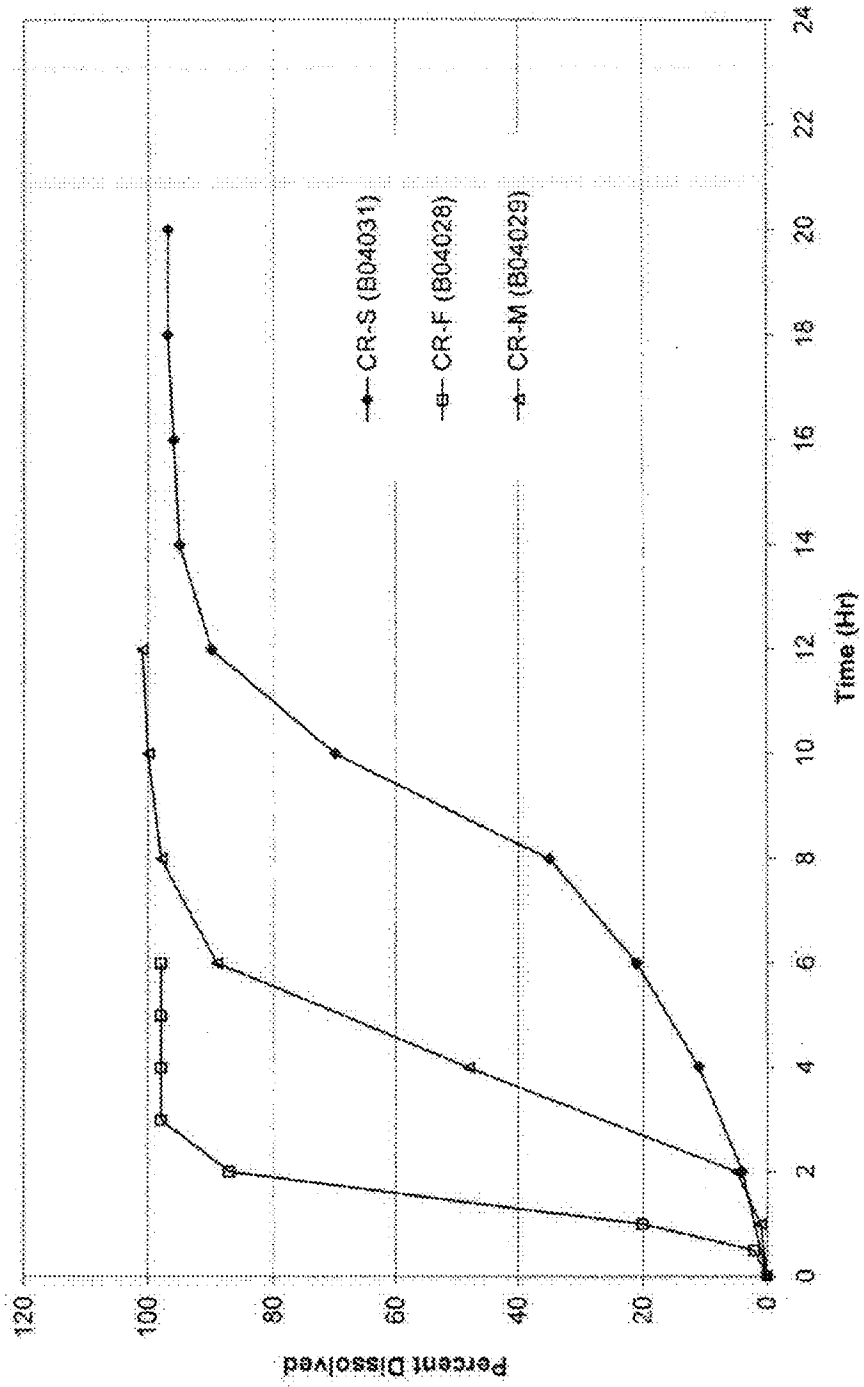


FIGURE 2

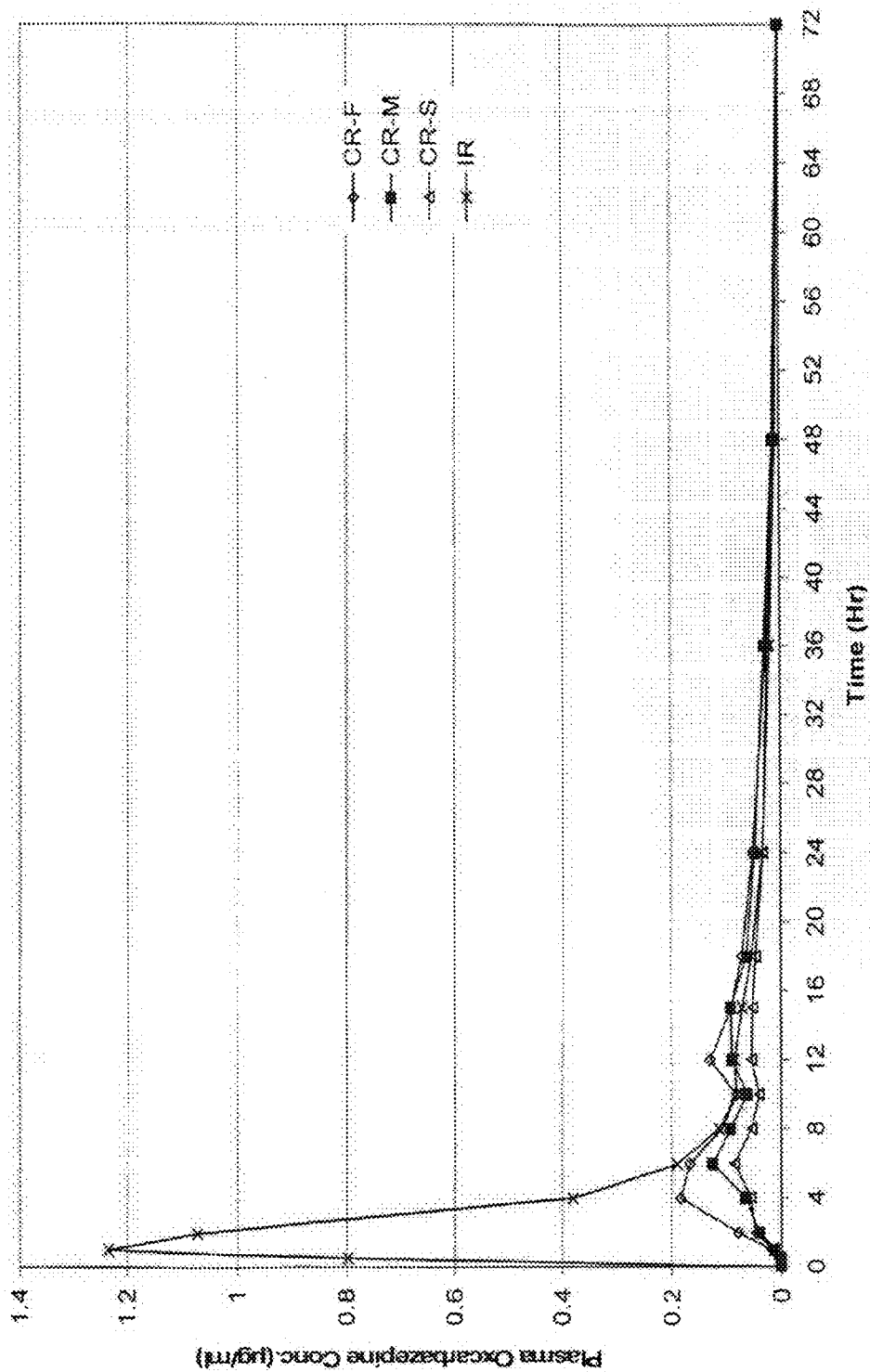


FIGURE 3

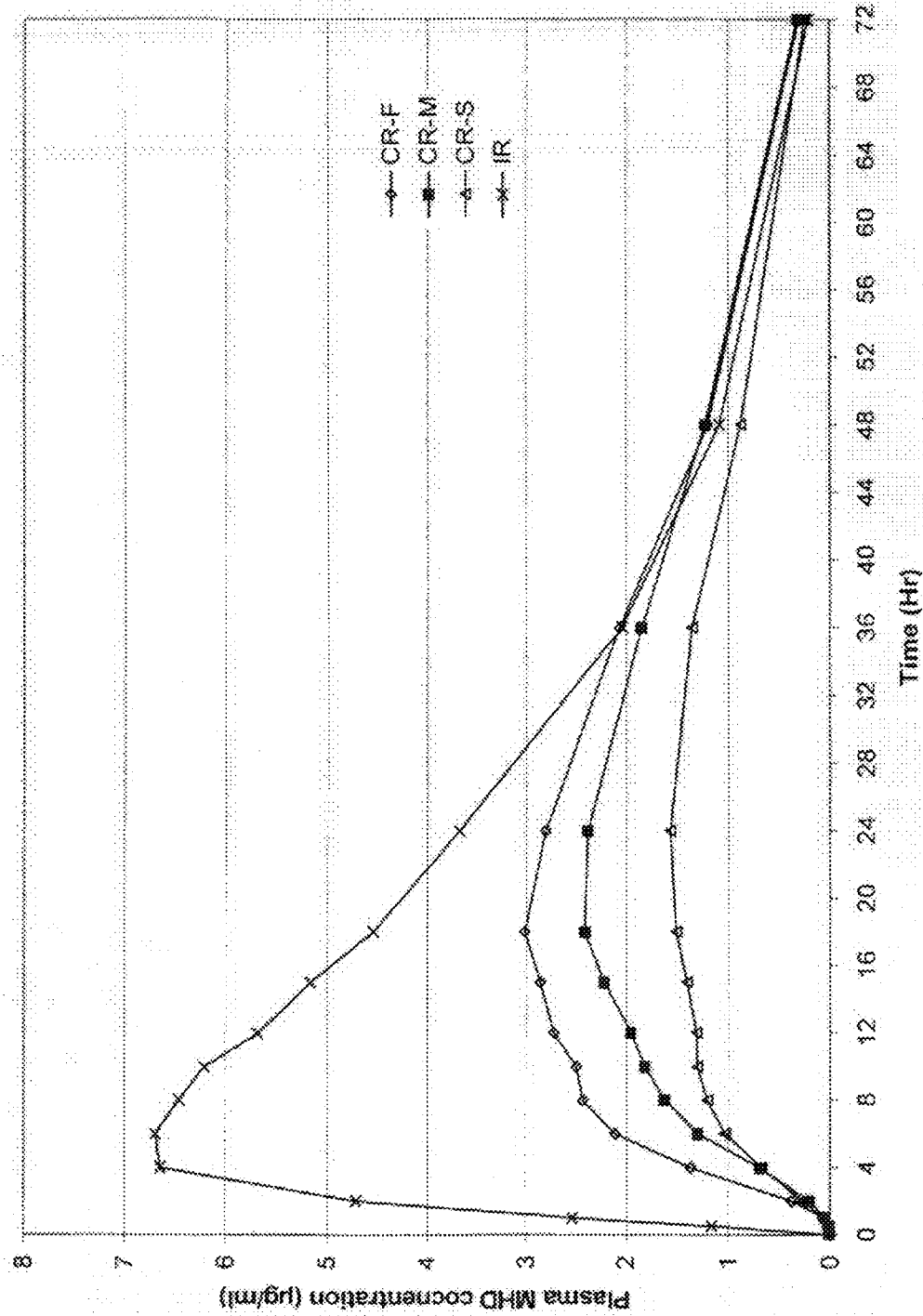


FIGURE 4

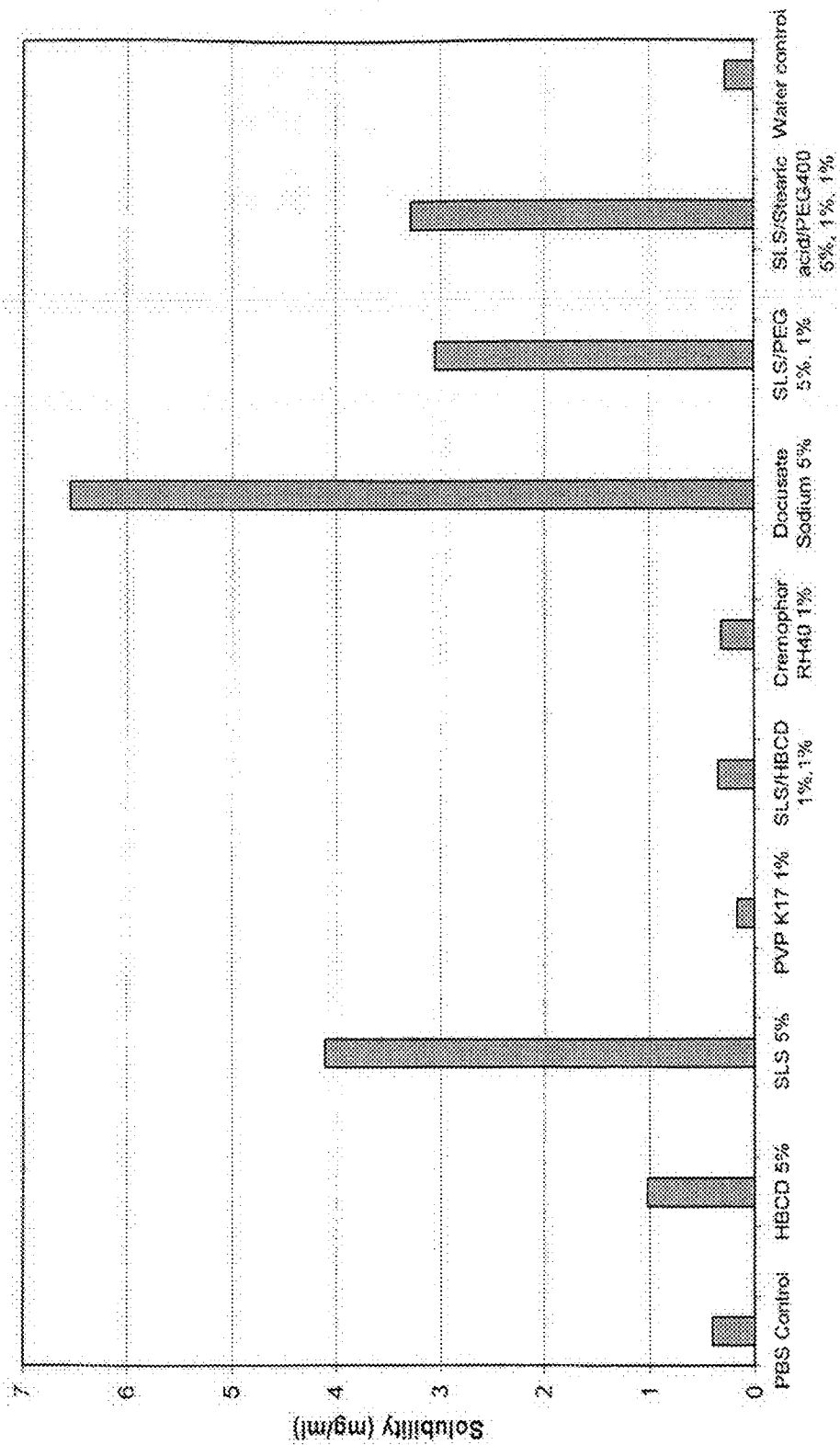


FIGURE 5

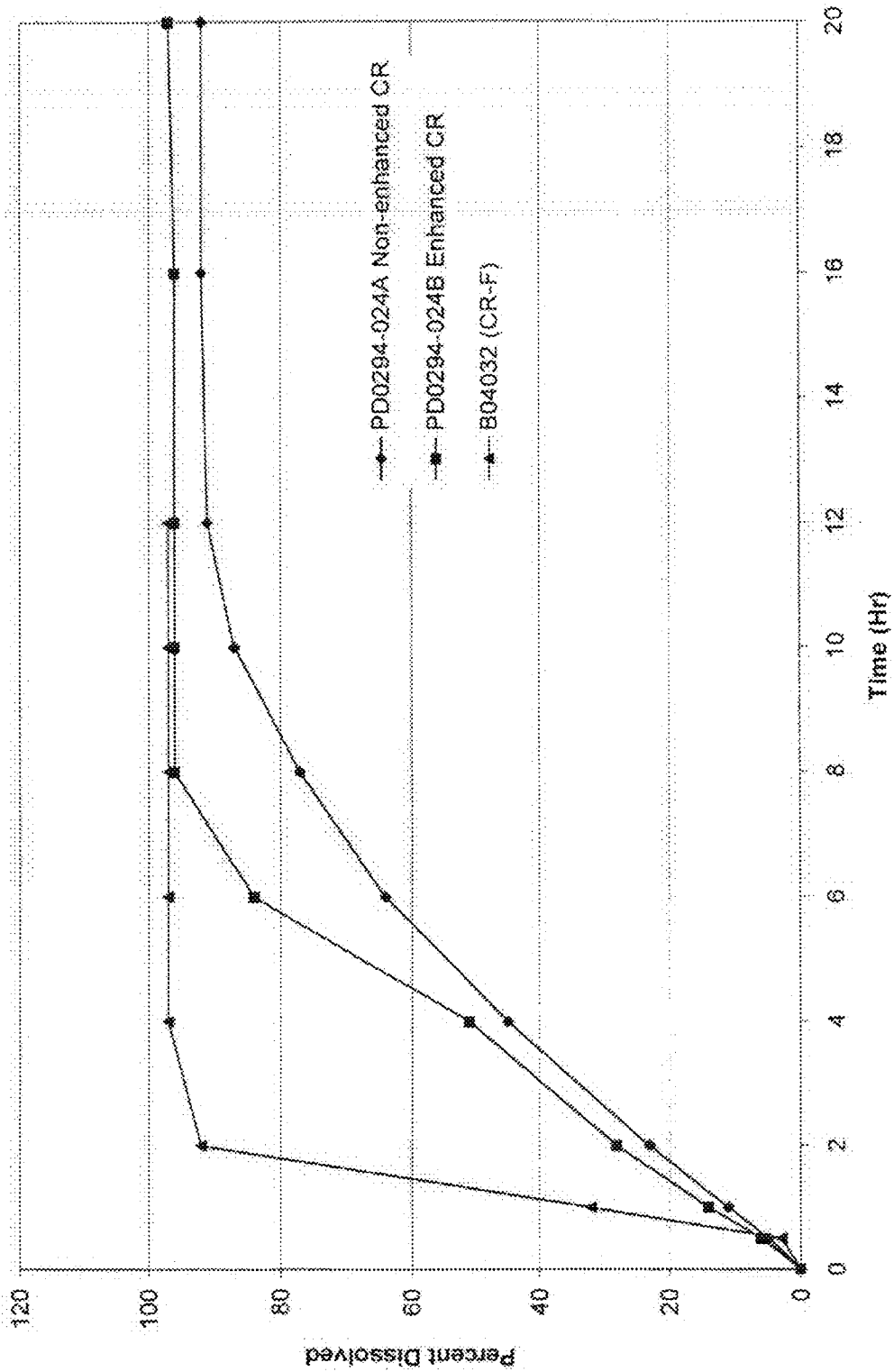


FIGURE 6

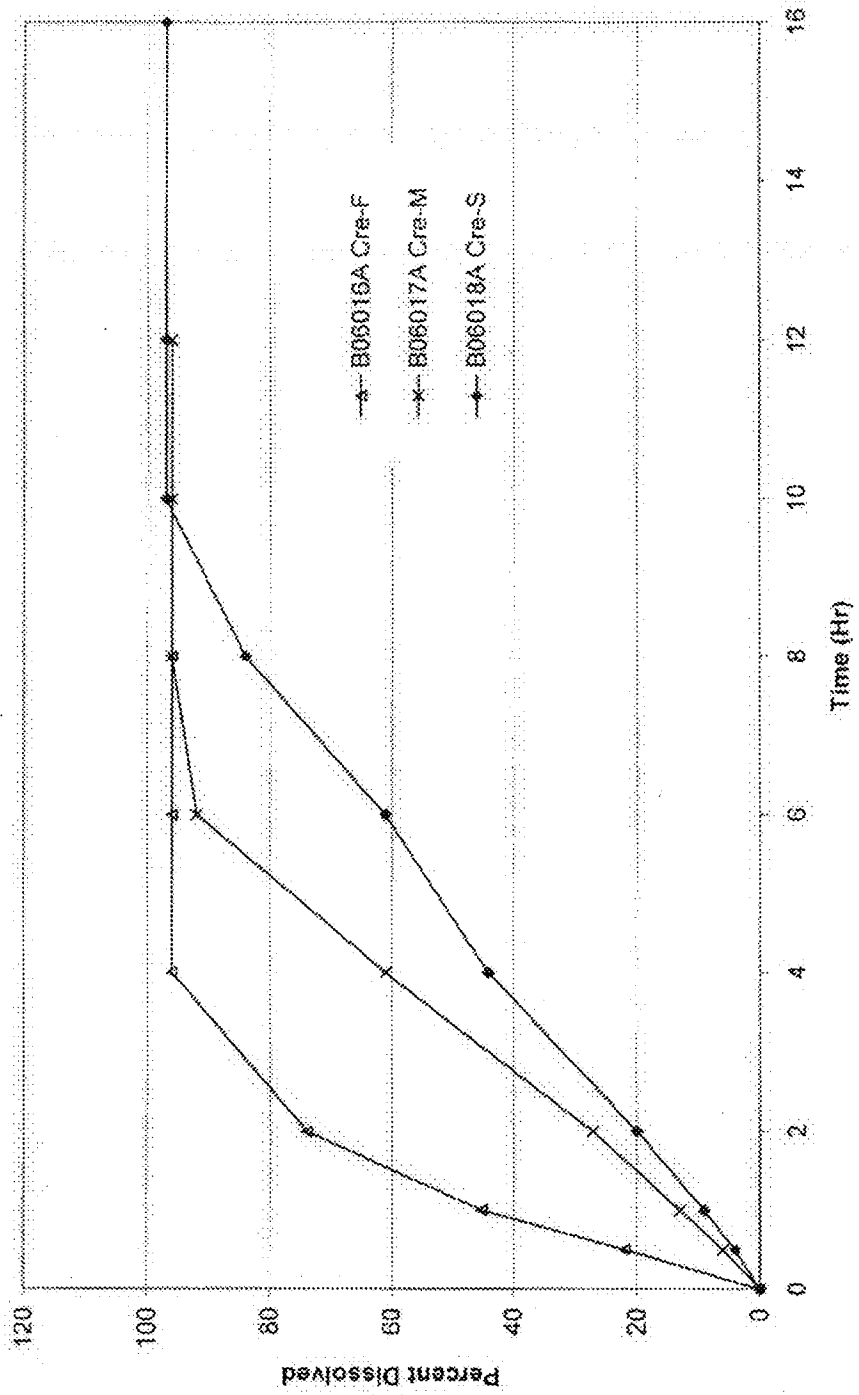




FIGURE 7

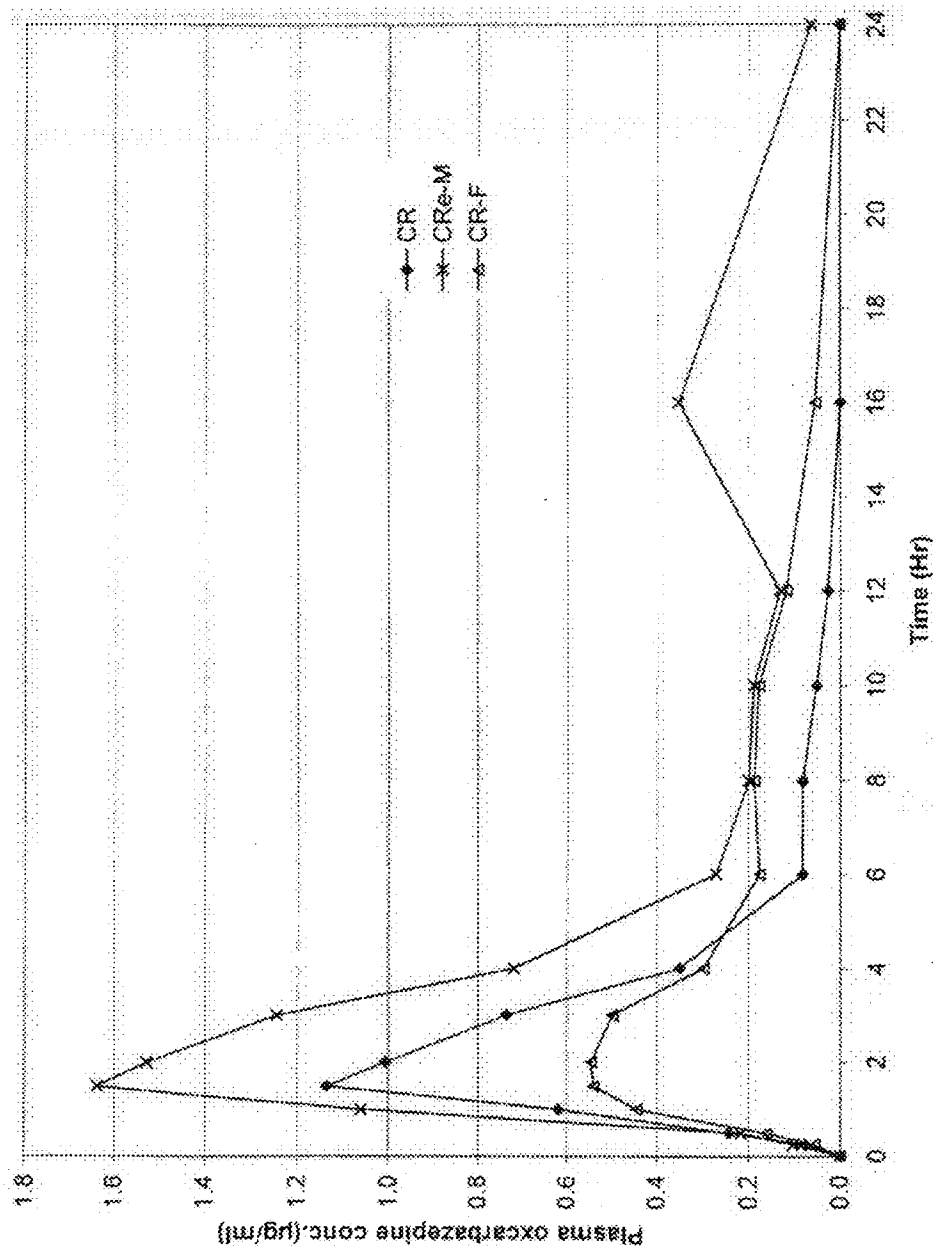


FIGURE 8

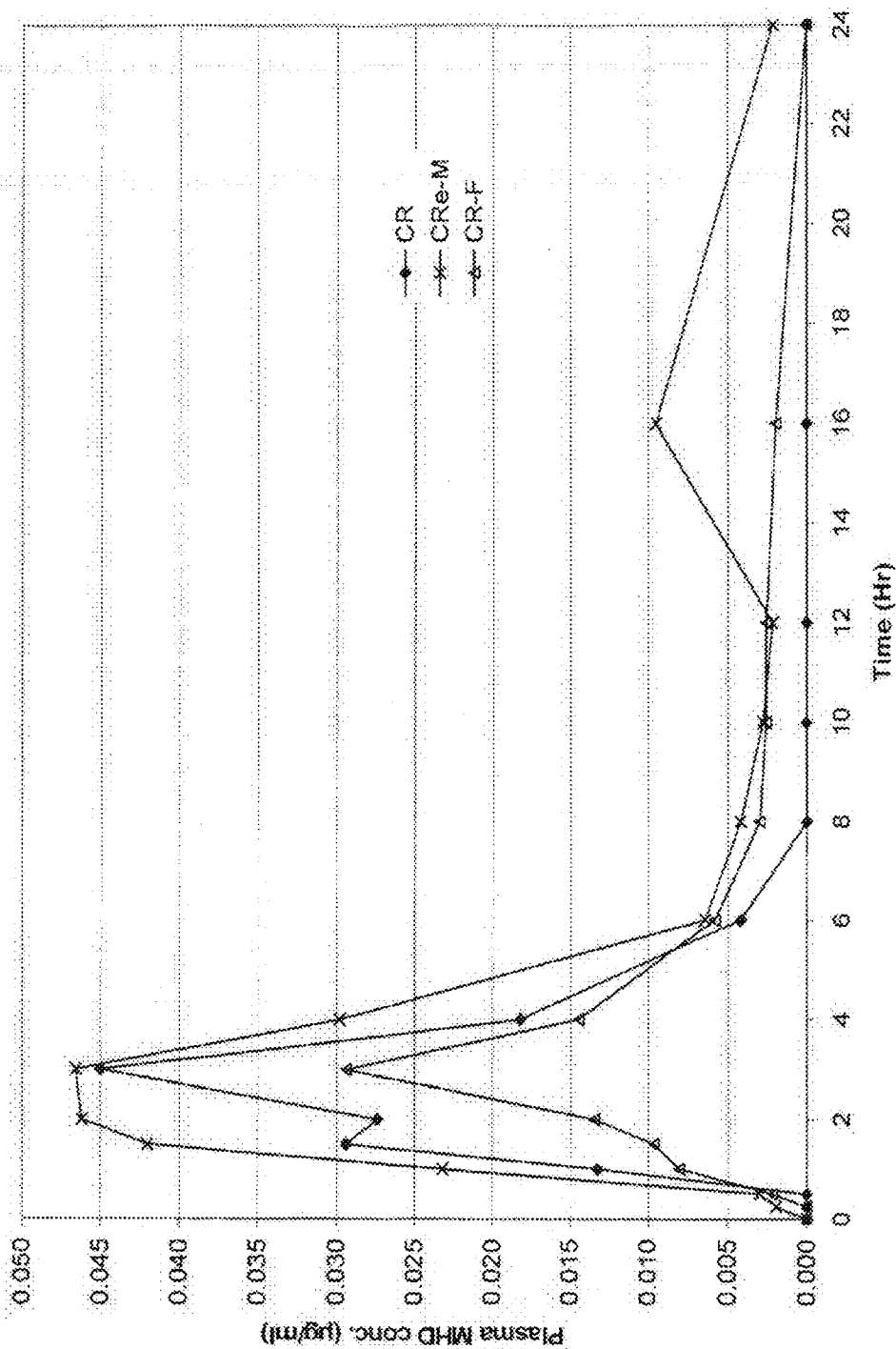


FIGURE 9

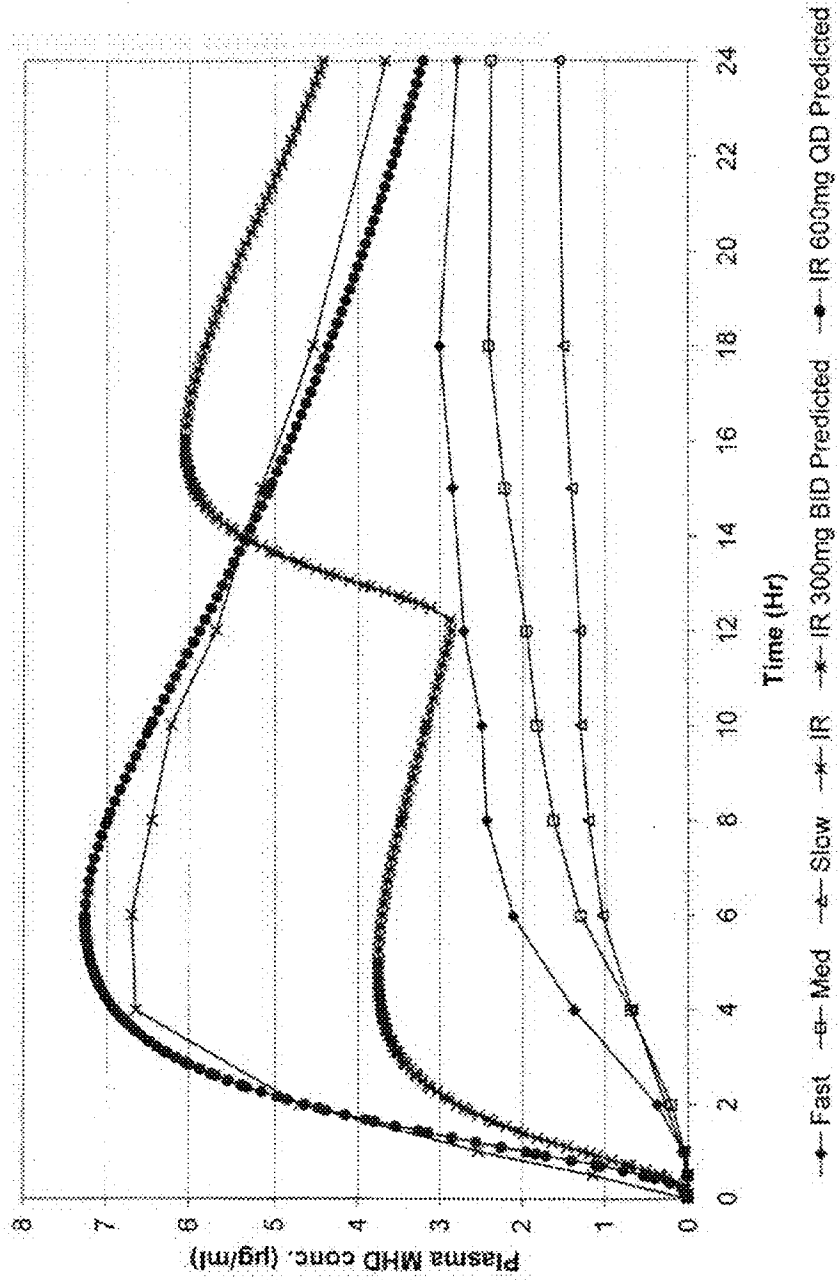


FIGURE 10

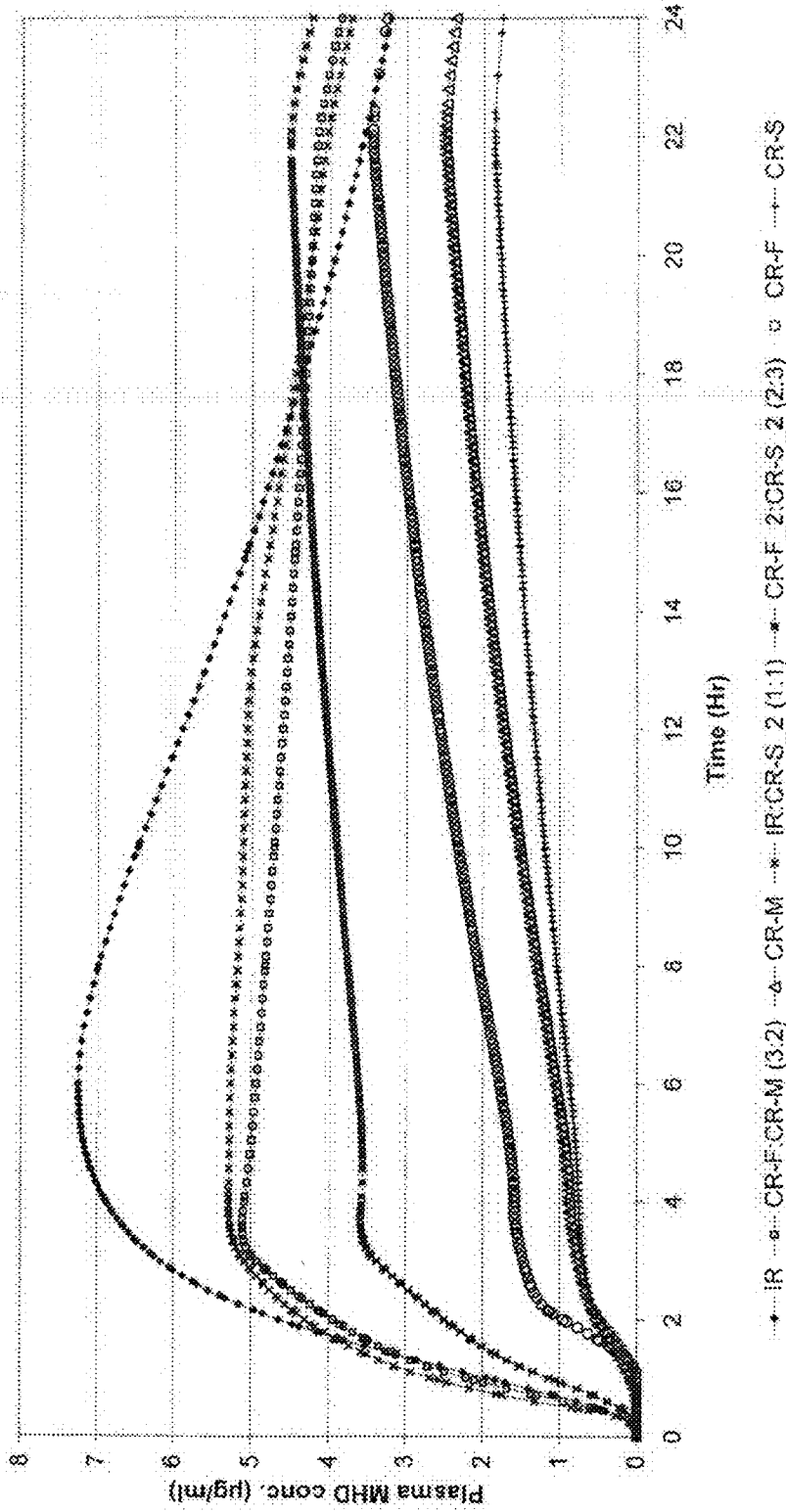


FIGURE 11

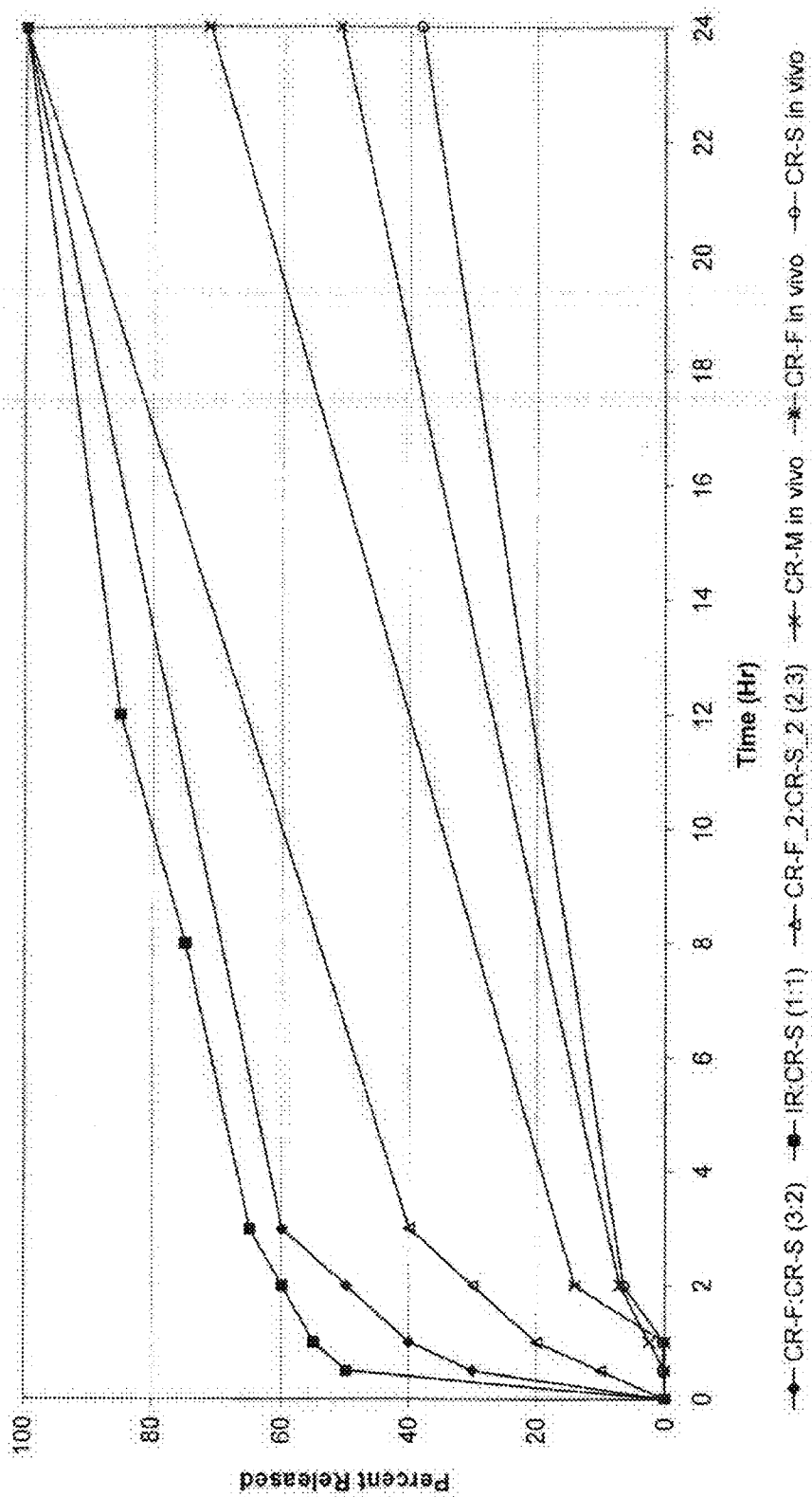


FIGURE 12

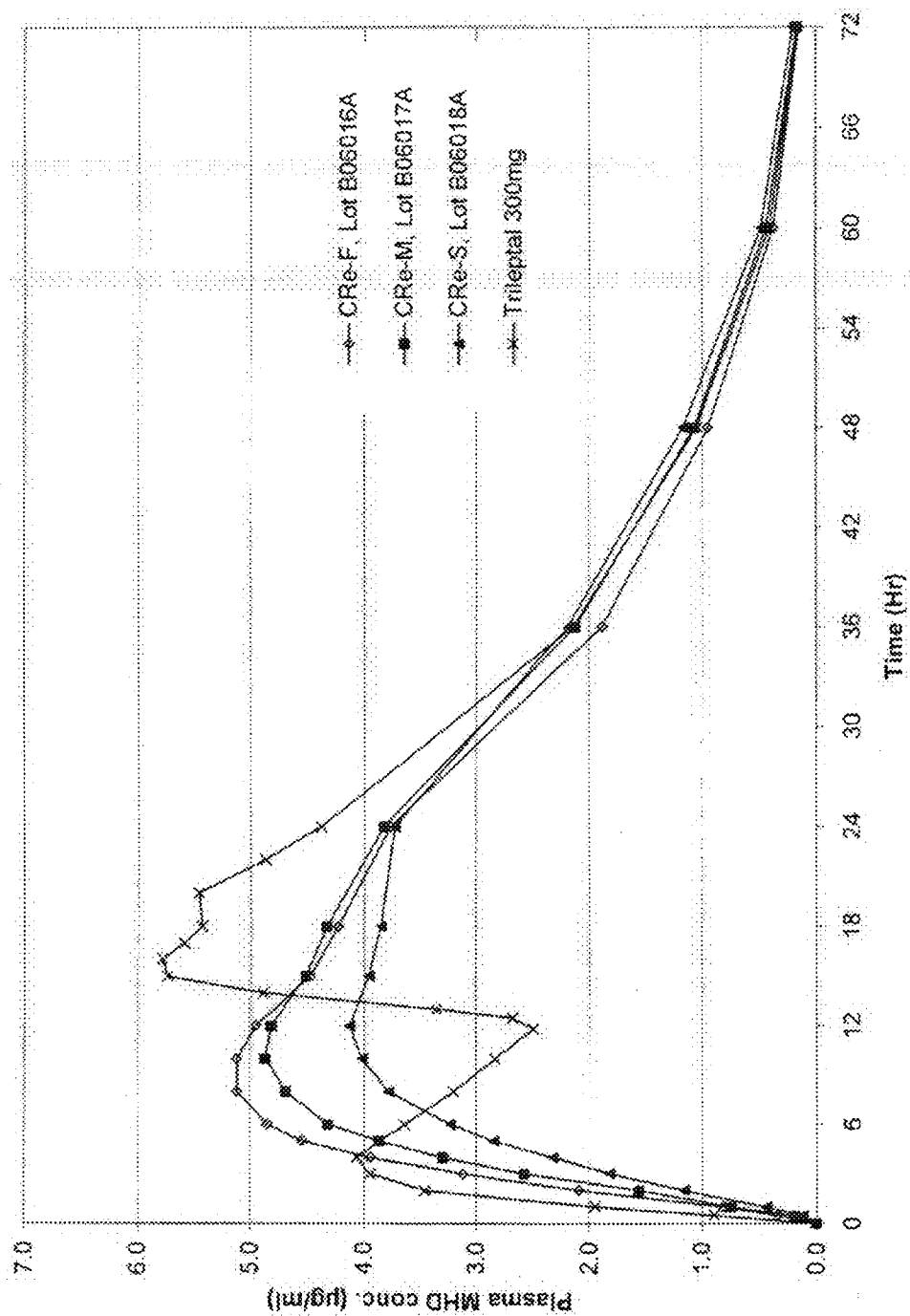


FIGURE 13

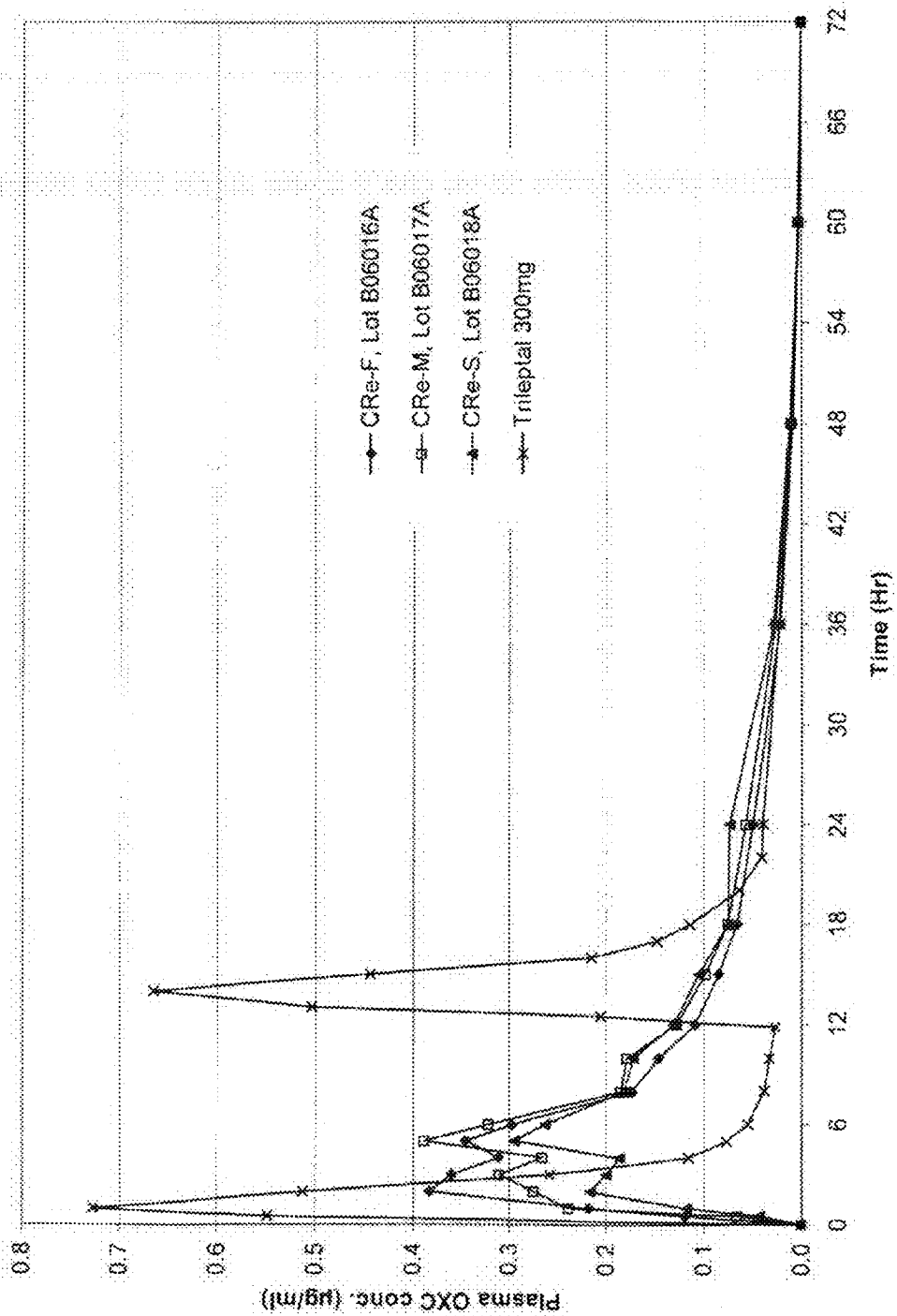
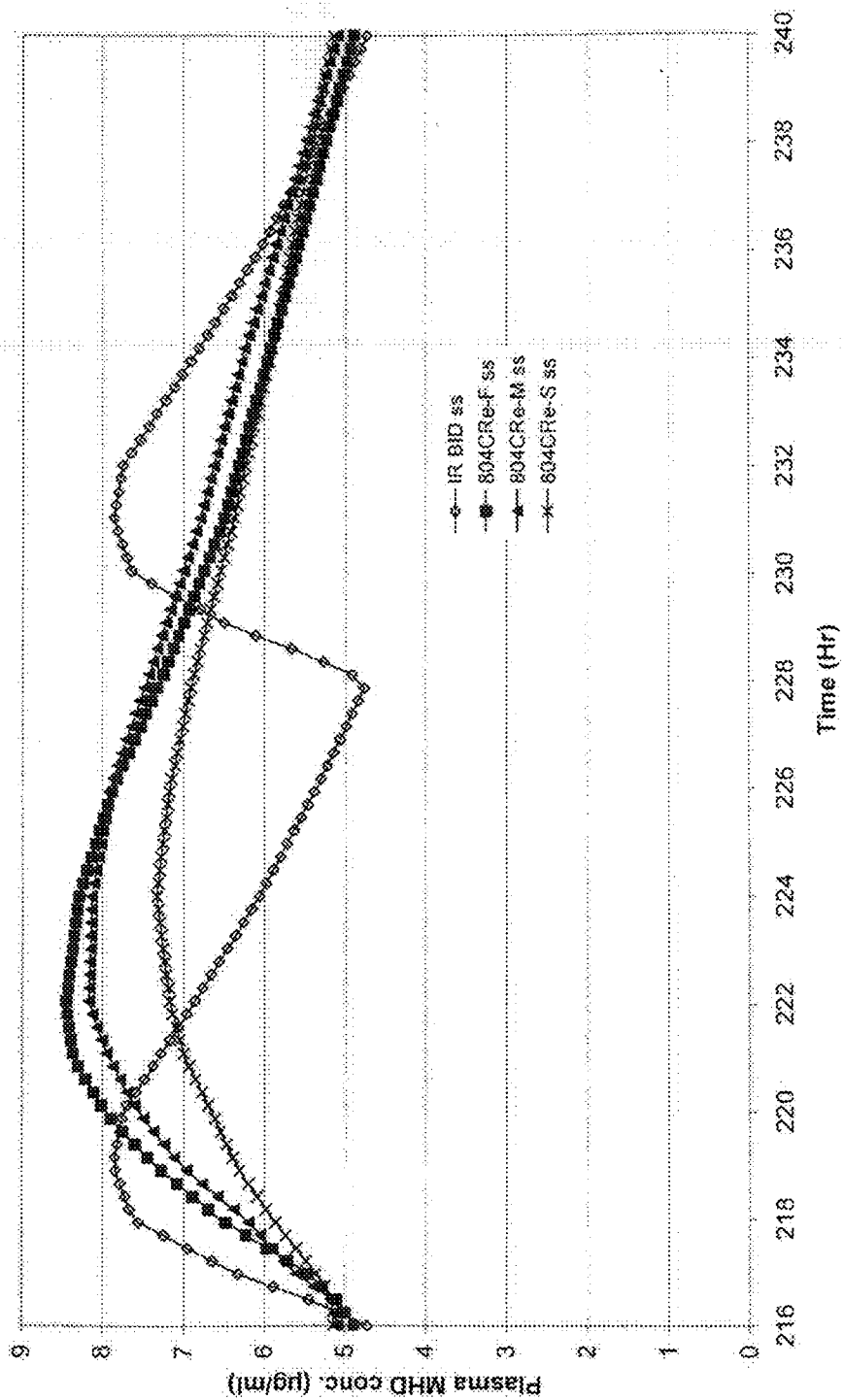


FIGURE 14





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## METHOD OF TREATING SEIZURES USING MODIFIED RELEASE FORMULATIONS OF OXCARBAZEPINE

### CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of U.S. application Ser. No. 11/734,874, filed Apr. 13, 2007, which claims priority to U.S. Provisional Application No. 60/794,837, filed Apr. 26, 2006, the disclosure of which is incorporated herein by reference in its entirety.

### FIELD OF THE INVENTION

The present invention is directed to controlled-release preparations of oxcarbazepine and derivatives thereof for once-a-day administration.

### BACKGROUND OF THE INVENTION

Oxcarbazepine belongs to the benzodiazepine class of drugs and is registered worldwide as an antiepileptic drug. Oxcarbazepine is approved as an adjunct or monotherapy for the treatment of partial seizures and generalized tonic-clonic seizures in adults and children. An immediate-release (IR) formulation of oxcarbazepine is currently on the market under the trade name Trileptal® and is administered twice a day to control epileptic seizures. Such immediate release compositions provide the drug to the patient in a manner that result in a rapid rise of the plasma drug concentration followed by a rapid decline. This sharp rise in drug concentration can result in side effects, and make multiple daily administration of the drug necessary in order to maintain a therapeutic level of the drug in the body. The need for a controlled-release dosage form for drugs taken chronically such as oxcarbazepine and derivatives is self-evident. Patient compliance is greatly improved with controlled-release (CR) dosage forms that are taken, for example, once-a-day. Also, there are significant clinical advantages such as better therapeutic efficacy as well as reduced side effects with controlled-release dosage forms.

Oxcarbazepine and its derivatives contemplated in this invention are poorly soluble in water. Due to their poor solubility, their release from a sustained release dosage form is rather incomplete. Whereas the in vitro release of oxcarbazepine is dependent on the dissolution method, including the dissolution media used, it has been found through in silico modeling that the release of oxcarbazepine in vivo from a traditional sustained-release dosage form is relatively low. This results in reduced bioavailability of the drug making the dosage form ineffective in providing a therapeutically effective concentration in the body. This poses a serious challenge to the successful development of sustained-release dosage forms for oxcarbazepine and its derivatives.

The rate of drug release from a dosage form has a significant impact on the therapeutic usefulness of the drug and its side effects. Hence, drug release profiles must be customized to meet the therapeutic needs of the patient. An example of a customized release profile is one that exhibits a sigmoidal release pattern, characterized by an initial slow release followed by fast release which is then followed by slow release until all of the drug has been released from the dosage form.

Sustained-release dosage forms for oxcarbazepine and derivatives have been described in the art. For example, Katzhendler et al. (U.S. Pat. No. 6,296,873) describes sustained-release delivery systems for carbamazepine and its

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derivatives. Katzhendler et al. teaches that a zero-order release profile is achieved for carbamazepine and derivatives through the use of hydrophilic and hydrophobic polymers. Zero-order (constant) release was achieved using high molecular weight hydroxypropyl methyl cellulose (HPMC) along with some optional hydrophobic excipients. A similar approach is taught by Shah et al. (US Patent Application 20020169145). Franke et al. (US Patent Application 20040142033) discloses sustained-release formulations of oxcarbazepine that are characterized by the release of 55%-85% of the drug in 15 minutes, and up to 95% in 30 minutes. According to the authors, such release profiles provide adequate sustained-release to achieve once-a-day administration of oxcarbazepine. However, the solubility and bioavailability of the drug from these enhanced preparations suitable for once-a-day administration. The prior art does not teach how to make preparations of oxcarbazepine and derivatives characterized by sigmoidal release profiles.

### SUMMARY OF THE INVENTION

It is an object of this invention to provide controlled-release formulations of oxcarbazepine for once-a-day administration. The composition of this invention is administered once-a-day and yet meets the therapeutic need of the patient. It is another object of this invention to improve the bioavailability of oxcarbazepine and derivatives thereof. It is yet another object of this invention to meet the therapeutic need of the patient without causing "spikes" in blood drug concentration that may lead to toxicity. It is yet another object of this invention to keep the blood concentration of the drug within the therapeutic window. It is yet another object of this invention to minimize the fluctuation between the  $C_{max}$  and  $C_{min}$  that is typical of many immediate-release and sustained-release preparations.

Many, if not all, of these objectives may be achieved in this invention through formulations that comprise both solubility-enhancing agents and release-promoting agents, and are characterized by release profiles that meet the requirement for once-a-day administration. The objectives may also be achieved through the combination of a multiplicity of units with different release profiles in one dosage unit. Minipellets/granules/tablets, which can be mixed in a certain ratio, provide a dosage form that meets the above stated therapeutic objectives.

This invention also pertains to multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the drug at a rate that is different from the rate of release from another layer. In multi-layer tablets, each layer may or may not be coated.

All of the advantages that stem from once-daily administration of a drug apply to the compositions of this invention. Some of the specific advantages of this invention may be: reduced fluctuation between  $C_{max}$  and  $C_{min}$  during the course of treatment and hence better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no solubility/release enhancer. The profiles show a non-zero order release with a lag. The  $T_{80\%}$  (time for 80% of the dose to be released in vitro) for the CR-F, CR-M, and CR-S formulations were 2 Hrs, 5 Hrs and 11 Hrs, respec-

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tively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. 2 shows the human pharmacokinetic (PK) profiles with respect to oxcarbazepine for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. 3 shows the PK profiles with respect to the metabolite of oxcarbazepine (MHD) for the three exemplary controlled-release formulations of example 1 versus an immediate-release reference product (Trileptal® 600 mg). The strength of each formulation is 600 mg oxcarbazepine per tablet.

FIG. 4 shows the solubility results of oxcarbazepine with selected excipients.

FIG. 5 shows the dissolution profiles of oxcarbazepine CR formulations with solubility enhancer (CRE), without solubility enhancer (CR) and a "fast formulation" (CR-F) developed in Example 1. The time to dissolve 80% of the drug ( $T_{80}$ ) for CRE, CR, and CR-F are 5-6 Hrs, 8 Hrs, and 1.5 Hrs, respectively.

FIG. 6 shows the dissolution profiles for the fast (CRE-F), medium (CRE-M), and slow (CRE-S) oxcarbazepine formulations containing solubility/release enhancers. The  $T_{80}$ s for the CRE-F, CRE-M, and CRE-S are 1.5 Hrs, 5 Hrs, and 8 Hrs, respectively. USP Apparatus II at 60 RPM was used. Dissolution medium was 1% SLS in water.

FIG. 7 shows the canine pharmacokinetic profiles with respect to oxcarbazepine, comparing the enhanced formulation (CRE) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. 8 shows the canine pharmacokinetic profiles with respect to MHD, comparing the enhanced formulation (CRE) with non-enhanced formulations containing oxcarbazepine (CR and CR-F).

FIG. 9 shows the PK profiles shown in FIG. 8 with in silico predicted PK profile for a twice-a-day 300 mg IR.

FIG. 10 shows in silico predicted PK profiles for various in vitro release profiles.

FIG. 11 shows the in silico predicted in vivo release profiles for the systems in FIG. 10.

FIG. 12 shows human plasma concentration vs. time profiles with respect to MHD of the three Oxcarbazepine CR formulations in Example 4 (CRE-F, CRE-M, CRE-S) and Trileptal® as an IR control, dosed BID.

FIG. 13 shows human plasma concentration vs. time profiles with respect to the oxcarbazepine of the three Oxcarbazepine CR formulations in Example 4 (CRE-F, CRE-M, CRE-S) and Trileptal® as an IR control, dosed BID.

FIG. 14 shows the in silico predicted steady-state plasma profiles for the three exemplary formulations (CRE-F, CRE-M, and CRE-S) described in Example 4.

#### DETAILED DESCRIPTION OF THE INVENTION

It is the object of this invention to provide controlled-release oxcarbazepine formulations suitable for once-a-day administration. It is an additional object of the invention to incorporate a combination of solubility-enhancing excipients and/or release-promoting agents into the formulations to enhance the bioavailability of oxcarbazepine and its derivatives. Such compositions are referred to as enhanced formulations.

Oxcarbazepine was formulated to provide release profiles characterized by slow release initially, followed by rapid release and then followed by another period of slow release. Such a release profile is known to those skilled in the art as

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sigmoidal. Oxcarbazepine formulations with sigmoidal release profiles were tested in human pharmacokinetic (PK) studies. Based on the human data, improvements were made to the formulations by incorporating solubility enhancers and/or release-promoting excipients (such formulation are referred to as enhanced formulations). The enhanced formulations were tested in canine models and were surprisingly found to provide significant increase in bioavailability of oxcarbazepine compared to formulations containing no solubility/release enhancing excipients.

The incorporation of solubility enhancing agents in formulations containing poorly soluble drugs such as oxcarbazepine has a profound effect on the in vivo solubility and hence bioavailability of the drugs. Enhancing the solubility of oxcarbazepine results in an increase in its bioavailability and hence in better therapeutic performance of the drug. A combination of solubility and release promoters is contemplated in this invention. Preferable release promoting agents are pH dependent polymers, also known as enteric polymers. These materials are well known to those skilled in the art and exhibit pH dependent solubility such that they dissolve at pH values higher than about 4.0, while remaining insoluble at pH values lower than 4.0. Solubilizers function by increasing the aqueous solubility of a poorly soluble drug. When a formulation containing both the enteric polymer and solubilizer is exposed to an aqueous media of pH higher than 4.0, the enteric polymer dissolves rapidly leaving a porous structure, resulting in increased contact surface between the aqueous medium and the poorly soluble drug. This increased surface area enhances the efficiency of the solubilizer(s), and hence, the overall solubility and release rate of the drug is enhanced to a point where it impacts the availability of the drug for systemic absorption in patients.

Excipients that function as solubility enhancers can be ionic and non-ionic surfactants, complexing agents, hydrophilic polymers, pH modifiers, such as acidifying agents and alkalinizing agents, as well as molecules that increase the solubility of poorly soluble drug through molecular entrapment. Several solubility enhancers can be utilized simultaneously. All enteric polymers that remain intact at pH value lower than about 4.0 and dissolve at pH values higher than 4.0, preferably higher than 5.0, most preferably about 6.0, are considered useful as release-promoting agents for this invention.

Suitable pH-sensitive enteric polymers include cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic monoester copolymer, methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc. These may be used either alone or in combination, or together with the polymers other than those mentioned above. Preferred enteric polymers are the pharmaceutically acceptable methacrylic acid copolymers. These copolymers are anionic polymers based on methacrylic acid and methyl methacrylate and, preferably, have a mean molecular weight of about 135000. A ratio of free carboxyl groups to methyl-esterified carboxyl groups in these copolymers may range, for example, from 1:1 to 1:3, e.g. around 1:1 or 1:2. Such polymers are sold under the trade name Eudragit™ such as the Eudragit L series e.g. Eudragit L 12.5™, Eudragit L 12.5P™, Eudragit L100™, Eudragit L 100-55™, Eudragit L-30D™, Eudragit L-30D-55™, the Eudragit S™ series e.g. Eudragit S 12.5™, Eudragit S 12.5PT™, Eudragit S100™. The release promoters are not limited to pH dependent polymers. Other hydrophilic

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molecules that dissolve rapidly and leach out of the dosage form quickly leaving a porous structure can be also be used for the same purpose.

The release-promoting agent can be incorporated in an amount from 10% to 90%, preferably from 20% to 80% and most preferably from 30% to 70% by weight of the dosage unit. The agent can be incorporated into the formulation either prior to or after granulation. The release-promoting agent can be added into the formulation either as a dry material, or it can be dispersed or dissolved in an appropriate solvent, and dispersed during granulation.

Solubilizers preferred in this invention include surface active agents such as sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, Tweens® and Spans (PEO modified sorbitan monoesters and fatty acid sorbitan esters), poly(ethylene oxide)-polypropylene oxide-poly(ethylene oxide) block copolymers (aka Pluronics™); complexing agents such as low molecular weight polyvinyl pyrrolidone and low molecular weight hydroxypropyl methyl cellulose; molecules that aid solubility by molecular entrapment such as cyclodextrins, and pH modifying agents, including acidifying agents such as citric acid, fumaric acid, tartaric acid, and hydrochloric acid; and alkalizing agents such as meglumine and sodium hydroxide.

Solubilizing agents typically constitute from 1% to 80% by weight, preferably from 1% to 60%, more preferably from 1% to 50%, of the dosage form and can be incorporated in a variety of ways. They can be incorporated in the formulation prior to granulation in dry or wet form. They can also be added to the formulation after the rest of the materials are granulated or otherwise processed. During granulation, solubilizers can be sprayed as solutions with or without a binder.

This invention also contemplates controlled-release formulations comprising oxcarbazepine that release the drug at variable rates in the GI tract. It is also an object of this invention to design a drug delivery system to deliver drug at a very low rate early, followed by a relatively increased rate. It is another object of this invention to provide a drug release profile that is characterized by an immediate-release followed by a modified-release, such as extended-release (XR) or delayed-release (DR). These types of release profiles ensure that the  $C_{max}$  (maximum concentration of the drug in blood/plasma) is kept within the therapeutic window while extending the maintenance of an effective drug level in the body. The goal of this invention is to develop a controlled-release pharmaceutical composition of oxcarbazepine that provides steady-state blood levels of MHD, an active metabolite of oxcarbazepine, at a concentration of about 2 µg/ml to about 10 µg/ml. In the preferred embodiment, steady-state blood  $C_{max}$  levels of MHD fall in the range of about 6 µg/ml to about 10 µg/ml, and  $C_{min}$  levels of MHD fall in the range of about 2 µg/ml to about 5 µg/ml. Reduced fluctuation between  $C_{max}$  and  $C_{min}$  during the course of treatment results in a better therapeutic profile, reduced side-effects, improved patient compliance, and improved bioavailability of the drug.

The desired drug release pattern contemplated by this invention is achieved by using "matrix" polymers that hydrate and swell in aqueous media, such as biological fluids. As these polymers swell, they form a homogenous matrix structure that maintains its shape during drug release and serves as a carrier for the drug, solubility enhancers and/or release promoters. The initial matrix polymer hydration phase results in slow-release of the drug (lag phase). Once the polymer is fully hydrated and swollen, the porosity of the matrix increases due to the leaching out of the pH-dependent release promoters, and drug is released at a faster rate. The rate of the

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drug release then becomes constant, and is a function of drug diffusion through the hydrated polymer gel.

Thus, the release vs. time curve is characterized by at least two slopes: one slope for the lag phase where drug release rate is low and a second slope where drug release is faster. The slope of the rising part of the release vs. time curve can be customized as to match the rate at which the drug is eliminated from the body. A desired release profile can be achieved by using swellable polymers alone or in combination with binders, such as gelling and/or network forming polymers.

The water-swallowable, matrix forming polymers useful in the present invention are selected from a group comprising cellulosic polymers, such as hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose such as microcrystalline cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose; alginates, gums such as guar and xanthan gums; cross-linked polyacrylic acid derivatives such as Carbomers (aka Carbopol™) available in various molecular weight grades from Noveon Inc. (Cincinnati, Ohio); carageenan; polyvinyl pyrrolidone and its derivatives such as crospovidone; polyethylene oxides; and polyvinyl alcohol. Preferred swellable polymers are the cellulosic compounds, HPMC being the most preferred.

The swellable polymer can be incorporated in the formulation in proportion from 1% to 50% by weight, preferably from 5% to 40% by weight, most preferably from 5% to 20% by weight. The swellable polymers and binders may be incorporated in the formulation either prior to or after granulation. The polymers can also be dispersed in organic solvents or hydro-alcohols and sprayed during granulation.

It is yet another aspect of this invention to prepare formulations of oxcarbazepine that combine multiple modified-release "units," each "unit" prepared according to any one or more of the above-disclosed dosage forms, to provide for a customized release profile.

The modified-release units comprise minipellets/granules/tablets etc., each with unique release profiles, that can be mixed in a certain ratio to provide a dosage form that meets the above-stated therapeutic objectives. Alternatively, multiple modified release units may be formed into of multi-layer tablets. Multi-layer tablets can be prepared with each layer releasing the active compound at a rate that is different from the rate of release of the active ingredient from another layer. In multi-layer tablets, each layer may optionally be coated with controlled-release polymer(s). The combination dosage forms can exhibit release profiles that comprise any/all possible combinations of immediate release (IR), delayed release (DR), and extended release (XR) formulations. Pellets/granules/tablets or each layer of a single tablet may optionally be coated.

Various hydrophobic excipients can be used to modify the hydration rate of the dosage unit when exposed to water or aqueous media. These excipients retard the wetting of the dosage unit and hence modify the release of the active agent. Hydrophobic excipients suitable for this invention are represented by, but not limited to, glyceryl monostearate, mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex, Eastman Fine Chemical Company), glycerylmonooleate, a mixture of mono, di and tri-glycerides (ATMUL 84S), glycerylmonolaurate, glyceryl behenate, paraffin, white wax, long chain carboxylic acids, long chain carboxylic acid esters and long chain carboxylic acid alcohols.

Examples of saturated straight chain acids, useful with the invention, are n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid, capric acid,

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lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid and melissic acid. Also useful are unsaturated monoolefinic straight chain monocarboxylic acids. Examples of these are oleic acid, gadoleic acid and erucic acid. Also useful are unsaturated (polyolefinic) straight chain monocarboxylic acids such as linoleic acid, linolenic acid, arachidonic acid and behenolic acid. Useful branched acids include, for example, diacetyl tartaric acid.

Examples of long chain carboxylic acid esters include, but are not limited to: glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate and glyceryl monolinoleate (Myverol 18-92, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinoleate and glyceryl monogadoleate (Myverol 18-99, Eastman Fine Chemical Company); acetylated glycerides such as distilled acetylated monoglycerides (Myvacet 5-07, 7-07 and 9-45, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); d-alpha tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures of mono- and diglyceride esters such as Atmul (Humko Chemical Division of Witco Chemical); calcium stearyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactic esters of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglycerol citrate; stearyl heptanoate; cetyl esters of waxes; cetearyl octanoate; C<sub>10</sub>-C<sub>30</sub> cholesterol/lavosterol esters; and sucrose long chain carboxylic acid esters. In addition, waxes can be useful alone or preferably in combination with the materials listed above. Examples of these are white wax, paraffin and carnauba wax.

Drug, polymers, and other excipients are typically combined and wet granulated using a granulating fluid. However, other methods of forming granules such as slugging, and roller compaction can also be used to manufacture matrix granules. Matrix tablets can also be made by direct compression. In wet granulation, typical granulating fluids are: water, a mixture of water and alcohol, anhydrous alcohol. Wet granules can be made in any granulating device such as mixers, high shear granulators, and fluid bed granulators. Granules can be dried in appropriate drying equipment such as fluid bed dryers, ovens, microwave dryers etc. Granules can also be air-dried. Dried granules can be milled using appropriate milling device to achieve a particular particle size distribution. Granules can be filled in to capsules, or blended with other excipients and tableted on a tablet press. Granules can also be packaged into sachets for sprinkle application. Other excipients used to aid tableting are well known to those skilled in the art and include magnesium stearate, talc, cabosil etc. Granules and tablets can, optionally, be coated to further modify release rates. Furthermore, formulations can also optionally contain dyes.

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Optionally, but preferably, the tablet composition can contain one or more lubricants, which may be added to assure proper tableting. Non-limiting examples of lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and other waxes, including but not limited to, beeswax, carnauba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol. The lubricant, when present, is typically included in an amount of from about 0.1 wt. % to about 20 wt. % of the composition, preferably from about 1 to about 10 wt. %, and more preferably about 0.3 to about 3.0 wt. %.

The oxcarbazepine dosage can be formulated into tablets, granules, and pellets. The steps involved in the manufacturing of these dosage forms are well known to those skilled in the art. Briefly, tablets can be compressed from directly compressible blend containing the active or pre-formed granules. The tablets can be coated or not coated. The coating may optionally impart modification of release. Granules can be made by high shear granulation or fluid bed processing. The granules may or may not be coated. Pellets can be manufactured by drug layering on inert carriers such as sugar spheres. Pellets can also be manufactured by extrusion/spheronization process. The pellets may or may not be coated. Coated pellets and granules can be filled into capsules.

Formulations of this invention can also be made in pelletized forms, which can be filled into capsules or dispensed in sachets for sprinkle application. Each pellet is composed of the drug, swellable polymer(s) and other excipients that aid the processing. Pellets can be prepared in one of the many ways that are known by those skilled in the art. These include, for example, extrusion/spheronization and roller compaction (slugging). In the extrusion/spheronization technique, drug is mixed with swellable polymer(s), such as cellulosic polymers and other excipients. The blend is then granulated in a high shear granulator. The wet mass is then passed through an extruder and spheronized using a spheronizer. The pellets are then dried in an oven or fluid bed processor. The dried pellets are either processed further or encapsulated without further processing.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The invention now will be described in particularity with the following illustrative examples; however, the scope of the present invention is not intended to be, and shall not be, limited to the exemplified embodiments below.

## EXAMPLES

### Example 1

#### Oxcarbazepine Formulations with Sigmoidal Release Profiles

Table 1 provides the formula composition of oxcarbazepine controlled-release preparations with sigmoidal release profiles. Granules were prepared by high shear granulation using anhydrous ethanol as the granulating liquid. All ingredients, except for magnesium stearate, were charged in to VG-65/10M high shear granulator. The dry powders are

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blended by running the blade for 3 minutes, after which time the anhydrous ethanol was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10M was started and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules were screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The blend was then tableted on a rotary tablet press.

TABLE 1

Formula composition of Oxcarbazepine CR formulations with changing slope			
Ingredients	SLI 530 CR-F (Fast)	SLI530 CR-M (Medium)	SLI530 CR-S (Slow)
Oxcarbazepine	60	60	60
Compritol 888ATO	9.5	7	—
Prosolv HD90	9.8	20.3	15
Kollidon 25	10	—	—
Kollidon 90	—	3	—
Methocel E5 Prem. LV	—	—	10
Methocel K4M Premium CR	—	—	5
Carbopol 971P	10	9	9
Mg Stearate	0.5	0.5	0.5
FD&C Red #40	—	—	0.5
FD&C Blue #1	0.2	—	—
FD&C Yellow #6	—	0.2	—
Anhydrous Ethanol	*	*	*
Total	100	100	100

\* Removed during processing

FIG. 1 shows the dissolution profiles of three exemplary oxcarbazepine CR formulations (CR-F, CR-M, and CR-S). The profiles exhibited non-zero order release.

## Example 2

Human Pharmacokinetic Evaluation of Oxcarbazepine  
CR Formulations from Example 1

The three formulations from the Example 1 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 600 mg) was used as a control reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 2 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. 2 and 3.

TABLE 2

Pharmacokinetic parameters of the three exemplary formulations in example 1 and immediate release reference product.				
PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal™ IR
T <sub>max</sub> (Hr)	6.5	8.4	9.1	1.4
C <sub>max</sub> (ug/mL)	0.248	0.146	0.103	1.412
AUC <sub>last</sub> (Hr*ug/mL)	3.0	2.5	1.7	5.7
Rel BA	53%	44%	30%	100%

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## Example 3

## Solubility Enhancers Screening

The solubility of oxcarbazepine in the presence of excipients was evaluated as follows:

Excipients were dissolved in phosphate buffer to make solutions with concentrations shown in Table 3. One gram of oxcarbazepine was then mixed with 19 gm of the excipient solution. The mixture was rocked overnight at room temperature and then filtered using 0.22 µm filter. The filtrates were analyzed by HPLC. The solubility results are given in Table 3 and FIG. 4.

TABLE 3

Solubility of Oxcarbazepine in the presence of excipients		
Excipients	Excipient conc. (% w/w)	Solubility (mg/mL)
Phosphate Buffer Control	NA	0.4009
Hydroxypropyl betacyclodextrin (HBCD)	5	1.0218
Sodium Lauryl Sulfate (SLS)	5	4.1113
Kollidon 17	1	0.1717
SLS/HBCD	1, 1	0.3489
Cremonophor RH40	1	0.3140
Docusate Sodium	5	6.5524
SLS/Polyethylene Glycol 400 (PEG400)	5, 1	3.0516
SLS/Stearic Acid/PEG400	5, 1, 1	3.2821
De-ionized Water	NA	0.2733

## Example 4

## Formulation of Enhanced Dosage Forms

Tables 4 and 5 provide the composition of the formulation containing solubility- and release-enhancing agents. Granules were manufactured by high shear granulation using water as the granulating liquid. All ingredients, except for magnesium stearate, were charged into a VG-65/10M high shear granulator. The dry powders were blended by running the blade for 3 minutes, upon which time water was sprayed onto the mixing blend at a spray rate of approximately 40-60 gm/min. After about a minute of spray, the chopper on the VG-65/10M was started and run throughout the spray. Once the granulation was completed, the granulation was discharged from the VG high shear granulator, spread on an appropriate tray and placed in an oven to dry at 40° C. for 24 Hrs. Alternatively, granules can be dried using a fluid bed processor. Dry granules are screened through an 18-mesh screen. Screened granules were blended with magnesium stearate in a proportion of 99.5% granules and 0.5% magnesium stearate. The resulting blend was then tableted on a rotary tablet press. Dissolution profiles for these formulations are shown in FIGS. 5 and 6.

TABLE 4

Percent Composition of Enhanced (CR-M) and non-Enhanced (CR) Prototypes		
Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
Oxcarbazepine	60	60
Prosolv SMCC50	10	25
PVP K25	5	5

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TABLE 4-continued

Percent Composition of Enhanced (CR-M) and non-Enhanced (CR) Prototypes		
Formulation	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
HPMC K4M premium	10	10
SLS	5	0
Eudragit L100-55	10	0
Magnesium Stearate	0.5	0.5

TABLE 5

Percent Composition for the three exemplary enhanced formulations: CR-F, CR-M, and CR-S.			
Formulation	% PD0294-046 CR-F	% PD0294-051 CR-M	% PD0294-054 CR-S
Oxcarbazepine	60	60	60
Prosolv SMCC50	15	10	5
PVP K25	5	5	5
HPMC K4M premium	5	10	15
SLS	5	5	5
Eudragit L100-55	10	10	10
Magnesium Stearate	0.5	0.5	0.5

Example 5

Canine PK Studies on Formulations from Example 4, Table 4 and Example 1. (SLI530CR-F)

Six male beagle dogs were dosed orally with the formulations in the order given in Table 6. Blood was drawn over a 24 Hr period and blood samples were analyzed by HPLC. A noncompartmental analysis of the data was used to generate  $T_{max}$ ,  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$ . Relative Bioavailability was calculated in Excel using the  $AUC_{last}$  and  $AUC_{inf}$  for the CRf formulation as the control. The PK profiles for oxcarbazepine and 10-hydroxycarbazepine are given in FIGS. 7 and 8.

TABLE 6

Prototypes tested in dogs			
Phase	Test Article	SLI Lot #	Dose (mg)
1	Oxcarbazepine CR	PD0294-024A	600
2	Oxcarbazepine CR-M	PD0294-024B	600
3	Oxcarbazepine CR-F	B04032	600

TABLE 7

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine			
Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CR-M) PD0294-024B	Fast CR (CR-F) B04032
$T_{max}$	1.5	1.8	1.7
$C_{max}$	1.20	1.72	0.7
$AUC_{last}$	3.44	7.98	3.41

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TABLE 7-continued

Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine			
Prototypes	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CR-M) PD0294-024B	Fast CR (CR-F) B04032
$AUC_{inf}$	3.74	11.09	4.01
Rel $BA_{last}$	101%	234%	100%
Rel $BA_{inf}$	93%	276%	100%

Example 6

In Silico Modeling of Various Release Profiles of Oxcarbazepine XR

In silico modeling was carried out for various hypothetical systems. Results are shown in FIGS. 9-11.

Example 7

Human Pharmacokinetic Evaluation of Solubility Enhanced Oxcarbazepine CR Formulations from Example 4

The three solubility enhanced prototypes from the Example 4 were evaluated in humans to obtain pharmacokinetic information. An immediate release tablet (Trileptal® 300 mg) given BID was used as a reference. The formulations were examined in a randomized, single dose, crossover study in healthy human volunteers. Blood samples were analyzed for both the parent molecule oxcarbazepine and its metabolite (the monohydroxy derivative, MHD).

Table 8 provides the mean PK parameters for MHD. The PK profiles are shown in FIGS. 12 and 13.

TABLE 8

Pharmacokinetic parameters of the three exemplary solubility enhanced formulations in Example 4 and Trileptal™				
PK Parameters	CR-F Fast	CR-M Med	CR-S Slow	Trileptal™ BID
$T_{max}$ (Hr)	9	11	14	16
$C_{max}$ (ug/mL)	5.32	5.14	4.40	6.23
$AUC_{last}$ (Hr*ug/mL)	160.3	161.3	148.9	167.1
Rel BA	96%	97%	89%	100%

What is claimed is:

1. A method of treating seizures comprising administering to a subject in need thereof a pharmaceutical formulation comprising a homogeneous matrix comprising:

- (a) oxcarbazepine;
- (b) a matrix-forming polymer selected from the group consisting of cellulosic polymers, alginates, gums, cross-linked polyacrylic acid, carageenan, polyvinyl pyrrolidone, polyethylene oxides, and polyvinyl alcohol;
- (c) at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents; and
- (d) at least one release promoting agent comprising a polymer having pH-dependent solubility selected from the group consisting of cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate,

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polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)), and methyl acrylate-methacrylic acid copolymers.

2. The method of claim 1, wherein the surface active agents comprise sodium docusate, sodium lauryl sulfate, sodium stearyl fumarate, polyethylene oxide (PEO) modified sorbitan monoesters, fatty acid sorbitan esters, polyethylene oxide-polypropylene oxide-(poly(ethylene oxide)) block copolymers, or combinations thereof.

3. The method of claim 1, wherein the cellulosic polymers are selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), methylcellulose (MC), powdered cellulose, cellulose acetate, sodium carboxymethylcellulose, calcium salt of carboxymethylcellulose, and ethylcellulose.

4. The method of claim 1, wherein the release promoting agent is incorporated in an amount from 10% to 90% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

5. The method of claim 4, wherein the release promoting agent is incorporated in an amount from 30% to 70% by weight of the formulation, and the agent that enhances the solubility of oxcarbazepine is incorporated in an amount from 1% to 80% by weight of the formulation.

6. The method of claim 1, wherein the amount of oxcarbazepine is effective to produce a steady state blood level of monohydroxy derivative of oxcarbazepine in the range of about 2  $\mu\text{g/ml}$  to about 10  $\mu\text{g/ml}$ .

7. The method of claim 1, wherein the formulation is effective in minimizing fluctuations between  $C_{min}$  and  $C_{max}$  of monohydroxy derivative of oxcarbazepine.

8. The method of claim 7, which provides  $C_{max}$  levels of monohydroxy derivative of oxcarbazepine in the range of about 6  $\mu\text{g/ml}$  to about 10  $\mu\text{g/ml}$  and  $C_{min}$  levels of monohydroxy derivative of oxcarbazepine in the range of about 2  $\mu\text{g/ml}$  to about 5  $\mu\text{g/ml}$ .

9. The method of claim 1, wherein the amount of oxcarbazepine in the formulation is 600 mg.

10. The method of claim 1, wherein the formulation is in the form of pellets, tablets, granules or capsules.

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11. The method of claim 10, wherein the formulation is in the form of tablets.

12. The method of claim 11, wherein each tablet comprises 600 mg of oxcarbazepine.

13. The method of claim 1, wherein the matrix-forming polymer is present in the amount of 1% to 50% by weight of the formulation.

14. The method of claim 1, wherein the formulation further comprises a lubricant selected from the group consisting of magnesium stearate, calcium stearate, zinc stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, sodium stearyl fumarate, hydrogenated vegetable oils, and waxes.

15. The method of claim 14, wherein the wax is selected from the group consisting of beeswax, carnuba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, and stearyl alcohol.

16. The method of claim 14, wherein the lubricant is incorporated in the formulation in an amount of from 0.1% to 20% by weight of the formulation.

17. The method of claim 1, wherein the polymer having pH-dependent solubility remains intact at pH values of below 4 and dissolves at pH values of more than 4.

18. The method of claim 1, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 5.

19. The method of claim 1, wherein the polymer having pH-dependent solubility dissolves at pH values of more than 6.

20. The method of claim 1, wherein the formulation comprises HPMC and polyvinyl pyrrolidone as matrix-forming polymers; sodium lauryl sulfate as the agent that enhances the solubility of oxcarbazepine, and Eudragit L100-55 (Methacrylic Acid-Ethyl Acrylate Copolymer (1:1)) as the release promoting agent.

21. The method of claim 1, wherein the formulation is administered once a day.

22. The method of claim 1, wherein the seizure is an epileptic seizure.

23. The method of claim 22, wherein the epileptic seizure is a partial seizure or a generalized tonic-clonic seizure.

24. The method of claim 1, wherein the patient is an adult or child.

\* \* \* \* \*