

Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102
wbaton@saul.com

Attorneys for Plaintiff
Supernus Pharmaceuticals, Inc.

OF COUNSEL:

Edgar H. Haug
Nicholas F. Giove
Jason A. Kanter
Camille Y. Turner
Anna N. Lukacher
HAUG PARTNERS LLP
745 Fifth Avenue
New York, NY 10151

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SUPERNUS PHARMACEUTICALS, INC.,

Plaintiff,

v.

RICONPHARMA LLC and INGENUS
PHARMACEUTICALS, LLC,

Defendants.

C.A. No. _____

COMPLAINT FOR PATENT
INFRINGEMENT

(Filed Electronically)

Plaintiff Supernus Pharmaceuticals, Inc. (“Supernus” or “Plaintiff”), by its undersigned attorneys, for its Complaint against Defendants RiconPharma LLC (“Ricon”) and Ingenuis Pharmaceuticals, LLC (“Ingenuis”) (collectively, “Defendants”), alleges 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. 11,166,960, attached hereto as Exhibit A (“the ’960 patent” or “the patent in suit”).

THE PARTIES

2. Plaintiff Supernus is a corporation organized and existing under the laws of Delaware, having its principal place of business at 9715 Key West Avenue, Rockville, Maryland 20850.

3. Upon information and belief, RiconPharma LLC (“Ricon”) is a New Jersey limited liability company, having its principal place of business at 100 Ford Road, Suite 9, Denville, New Jersey 07834.

4. Upon information and belief, Ricon is in the business of, *inter alia*, developing, manufacturing, marketing, distributing, and directly and/or indirectly selling generic pharmaceutical products throughout the United States (including in the State of New Jersey), and importing generic pharmaceutical products into the United States (including into the State of New Jersey).

5. Upon information and belief, Ricon either directly or through one or more of its affiliates and/or agents, develops, manufactures, distributes, markets, offers to sell, and sells generic pharmaceutical products, including in the State of New Jersey.

6. Upon information and belief, Defendant Ingenuis Pharmaceuticals, LLC (“Ingenuis”) is a corporation organized and existing under the laws of Delaware, having its principal place of business at 4190 Millenia Road, Orlando, Florida 32839. On information and belief, Ingenuis also has facilities at 140 New Dutch Lane, Fairfield, New Jersey 07004 and, like Ricon, at 100 Ford Road, Suite 9, Denville, New Jersey 07834.

7. Upon information and belief, Ricon and Ingenuis work together for the direct benefit of each other.

8. Upon information and belief, Ingenuis states on its webpage that it entered into a merger agreement with Ricon on August 8, 2014, and that the combined entity has filed multiple

ANDAs. Ingenuis website, <https://www.ingenus.com/riconpharma%C2%ADingenus-merger-7/> (visited Oct. 14, 2022).

9. Upon information and belief, Ingenuis is in the business of, *inter alia*, developing, manufacturing, marketing, distributing, and/or selling generic pharmaceutical products throughout the United States (including in the State of New Jersey), and importing generic pharmaceutical products into the United States (including into the State of New Jersey).

10. Upon information and belief, Ingenuis is registered as a wholesale drug distributor in the State of New Jersey under Registration No. 5004116. Upon information and belief, Ricon, with the assistance of Ingenuis, prepared, and filed Abbreviated New Drug Application (“ANDA”) No. 215796 (“the Ricon ANDA”) with 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 Ricon Product”).

JURISDICTION AND VENUE

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

12. This Court has personal jurisdiction over Defendants under: (i) Fed. R. Civ. P. 4(k)(1); and (ii) N.J. Ct. R. 4:4-4.

13. Upon information and belief, Defendants maintain a regular and established place of business in New Jersey and have purposefully availed themselves of the privilege of doing business in the State of New Jersey by continuously and systematically placing goods in the stream of commerce for distribution and sale throughout the United States, including the State of New Jersey. For example, upon information and belief, Ingenuis states on its website that “Ingenuis’ New Jersey-based Finished Solid Oral Dosage Plant specializes in wet

granulation/drying, dry granulation, dry blending, tableting, coating (aqueous and solvent), encapsulation, full line bottle packaging, and is home to our quality control labs” and that “Ingenus today is poised to file 25 ANDAs a year.” Ingenus website, <https://www.ingenus.com/manufacturing/> (visited Oct. 14, 2022).

14. Upon information and belief, Defendants maintain a broad distributorship network within the State of New Jersey and enjoy substantial income from sales of their generic pharmaceutical products in the State of New Jersey.

15. Upon information and belief, Ingenus is registered as a wholesale drug distributor in the State of New Jersey under the Registration No. 5004116. Ingenus has, therefore, purposefully availed itself of the rights, benefits, and privileges of New Jersey’s laws.

16. Upon information and belief, Ricon and Ingenus have been, and continue to be, joint and primary actors in the drafting, submission, approval, and maintenance of the Ricon ANDA.

17. In addition, this Court has personal jurisdiction over Defendants at least because, upon information and belief, Defendants regularly engage in patent litigation in this Judicial District and previously did not contest personal jurisdiction and venue in *Supernus Pharmaceuticals, Inc. v. RiconPharma LLC, et al.*, Civil Action No. 2:21-cv-12133 (KM)(MAH) (D.N.J.).

18. This Court has personal jurisdiction over Defendants because, *inter alia*:

- (i) Ricon, together with Ingenus, has committed, induced, or contributed to acts of patent infringement in New Jersey, including, but not limited to, the preparation of materials related to the Ricon ANDA submission; (ii) Defendants are doing business in New Jersey and maintain continuous and systematic contacts with this Judicial District, including by having a regular and

established place of business in New Jersey; (iii) Defendants directly or indirectly through agents regularly do or solicit business in New Jersey and/or derive substantial revenue from services or things used or consumed in New Jersey; (iv) Defendants transact business, perform work, and contract to supply services or products in New Jersey; and (v) Ingenuis is registered as a wholesale drug distributor in the State of New Jersey under Registration No. 5004116. For example, FDA requires ANDA filers to prepare test batches of the proposed generic product. *See, e.g.*, FDA website, <https://www.fda.gov/media/107325/download> (visited Oct. 14, 2022). Upon information and belief, the only Ingenuis manufacturing facility identified on Ingenuis' website for non-oncology products and treatments—such as those claimed in the patent in suit—is located in New Jersey. Ingenuis website, <https://www.ingenus.com/manufacturing/> (visited Oct. 14, 2022).

19. Ricon's tortious acts of (i) preparing and filing ANDA No. 215796 with a paragraph IV certification to the patent in suit 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 Ricon Product before the expiration of the patent in suit; and (ii) directing notice of its ANDA submission to Plaintiff Supernus, are acts with real and injurious consequences giving rise to this infringement action, including the present and/or anticipated commercial manufacture, use, and/or sale of the Ricon Product before the expiration of the patent in suit throughout the United States, including in this Judicial District. On information and belief, Ingenuis participated with Ricon in the above-mentioned tortious acts. Because defending against an infringement lawsuit such as this one is an inherent and expected part of a generic ANDA filer's business, Ricon and Ingenuis should reasonably anticipate being sued in New Jersey.

20. Upon information and belief, if ANDA No. 215796 is approved, the Ricon Product will be marketed and distributed by Defendants in the State of New Jersey, prescribed by physicians practicing in the State of New Jersey, dispensed by pharmacies located within the State of New Jersey, and used by patients in the State of New Jersey.

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

22. Venue is proper for Ricon under 28 U.S.C. §§ 1391 and/or 1400(b), because, *inter alia*, Ricon is incorporated in New Jersey, maintains a regular and established place of business in New Jersey, is subject to personal jurisdiction in this Judicial District, has committed acts of infringement and will commit further acts of infringement in this Judicial District, and/or continuously transacts business in this Judicial District. In addition, Ricon does business in this Judicial District through a permanent and continuous presence in the State of New Jersey. Upon information and belief, Ricon employs a salesforce that includes personnel who regularly and continuously work in this Judicial District and, if Ricon succeeds in obtaining FDA approval, Ricon will use its salesforce to sell the Ricon Product in the State of New Jersey.

23. Venue is proper for Ingenuis under 28 U.S.C. §§ 1391 and/or 1400(b), because, *inter alia*, Ingenuis maintains a regular and established place of business in New Jersey, is subject to personal jurisdiction in this Judicial District, and, based on information and belief, has committed an act of infringement and will commit further acts of infringement in this Judicial District, as set forth above, and/or continuously transacts business in this Judicial District, as set forth above. Upon information and belief, Ingenuis employs a salesforce that includes personnel who regularly and continuously work in this Judicial District. In addition, Ingenuis is registered to do business in New Jersey, designating an in-state agent to receive service of process in New

Jersey and, in fact, does business in this Judicial District through a permanent and continuous presence in the State of New Jersey. For example, Ingenuis is registered with the State of New Jersey's Department of Health as a drug wholesaler under Registration No. 5004116 and continuously sells its products in this Judicial District.

FACTS AS TO ALL COUNTS

24. Supernus owns New Drug Application ("NDA") No. 202810, which was approved by 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®.

25. Oxtellar XR® is an antiepileptic drug indicated for: (i) monotherapy and adjunctive therapy in the treatment of partial seizures in adults; and (ii) monotherapy and adjunctive therapy in the treatment of partial seizures in children 6 to 17 years of age.

26. The '960 patent, entitled, "Modified Release Preparations Containing Oxcarbazepine and Derivatives Thereof" was duly and legally issued by the United States Patent and Trademark Office on November 9, 2021, to Supernus upon assignment from inventors Padmanabh P. Bhatt, Argaw Kidane, and Kevin Edwards. Supernus owns all rights, title, and interest in the '960 patent.

27. FDA's publication titled, "Approved Drug Products with Therapeutic Equivalence Evaluations" (commonly known as the "Orange Book") lists ten (10) patents in connection with Supernus's Oxtellar XR®, including the patent in suit. Pursuant to 21 U.S.C. §§ 355(b)(1) and 355(c)(2), these ten (10) patents were submitted to FDA with or after the approval of NDA No. 202810.

28. Upon information and belief, Defendants worked in concert to prepare, submit, and file the Ricon ANDA with 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 Ricon Product and included a “paragraph IV” certification seeking approval before the expiration of the ’960 patent.

29. 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)(7) 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)(7)(i)-(ii).

30. On or about April 20, 2021, Ricon sent a letter purportedly pursuant to § 505(j)(2)(B)(iv) of the FDCA and 21 C.F.R. §§ 314.94, 314.95 regarding the Ricon Product and U.S. Patent Nos. 7,722,898 (the “’898 patent”); 7,910,131 (the “’131 patent”); 8,617,600 (the “’600 patent”); 8,821,930 (the “’930 patent”); 9,119,791 (the “’791 patent”); 9,351,975 (the “’975 patent”); 9,370,525 (the “’525 patent”); 9,855,278 (the “’278 patent”); and 10,220,042 (the “’042 patent”) (the “April 20 Notice Letter”). The ’898 patent, the ’131 patent, the ’600 patent, the ’930 patent, the ’791 patent, the ’975 patent, the ’525 patent, the ’278 patent, and the ’042 patent are nine (9) of the ten (10) patents listed in FDA’s Orange Book as covering Oxtellar XR®. Supernus filed a complaint against Ricon and Ingenuis in this Court on June 3, 2021. *Supernus Pharmas. Inc. v. RiconPharma LLC, et al.*, Civil Action No. 2:21-cv-12133 (KM)(MAH), ECF No. 1.

31. On or about October 7, 2022, Ricon sent a letter purportedly pursuant to § 505(j)(2)(B) of the FDCA and 21 C.F.R. § 314.95 regarding ANDA No. 215796 (the “October 7 Notice Letter”). In this letter, Ricon states that the Ricon ANDA has been submitted under § 505(j) of the FDCA, with a paragraph IV certification to obtain approval to engage in the commercial manufacture, use, or sale of the Ricon Product, before the expiration of the ’960 patent.

32. The October 7 Notice Letter contends that the Ricon Product does not infringe independent claim 1 of the ’960 patent. The October 7 Notice Letter does not include any non-infringement contentions unique to claims 2-6 of the ’960 patent.

33. The October 7 Notice Letter does not include any detailed statement of the factual and legal basis for Defendants’ opinion that the ’960 patent is unenforceable.

34. The October 7 Notice Letter does not include any description of the composition, formulation, ingredients, development, manufacture, or testing of the Ricon Product beyond the vague and unsupported assertions that the Ricon Product “do[es] not include a ‘homogeneous matrix’ formulation,” that “Ricon’s ANDA Products cannot constitute a homogenous matrix because its ingredients are localized in a discrete portion of its tablet rather than uniformly dispersed throughout the entire tablet,” and that “[Ricon’s] ANDA Products do not include a release promoting agent that comprises an enteric polymer.” Although the parties did not reach agreement on mutually acceptable terms for an Offer of Confidential Access pursuant to 21 U.S.C. § 355(j)(5)(C) and 21 C.F.R. § 314.95(c)(8), the parties agreed that the Discovery Confidentiality Order entered in *Supernus Pharms. Inc. v. RiconPharma LLC, et al.*, Civil Action No. 2:21-cv-12133 (KM)(MAH), ECF No. 52, would control Supernus’s “access [to] Ricon’s ANDA previously produced in Case No. 21-12133 on a confidential basis for the sole and

limited purpose of evaluating whether to assert the '960 patent against [Defendants].'" 10/26/22

Email from S. Feldman to N. Giove.

FIRST COUNT
(Defendants' Infringement of the '960 Patent)

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

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

37. Upon information and belief, Defendants included a paragraph IV certification to the '960 patent to obtain approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation of the Ricon Product before expiration of the '960 patent.

38. Upon information and belief, Defendants will commercially manufacture, use, sell, offer for sale, and/or import the Ricon Product upon, or in anticipation of, FDA approval.

39. The submission and filing of ANDA No. 215796 with a paragraph IV certification to the '960 patent for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, offer for sale, and/or importation in the United States of the Ricon Product before the expiration of the '960 patent is an act of infringement by Defendants of one or more claims of the '960 patent under 35 U.S.C. § 271 *et seq.*, including under 35 U.S.C. § 271(e)(2)(A).

40. Defendants' commercial manufacture, use, sale, offer for sale, and/or importation into the United States of the Ricon Product that is the subject of ANDA No. 215796 will infringe, directly and/or indirectly, one or more claims of the '960 patent under 35 U.S.C. § 271(c).

41. Upon information and belief, Defendants' offering for sale and/or sale of the Ricon Product will induce and/or contribute to third-party infringement of one or more claims of the '960 patent under 35 U.S.C. §271.

42. Defendants' infringement of the '960 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 '960 patent.

43. As of the date of the October 7 Notice Letter, Defendants were aware of the existence of the '960 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 '960 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 '960 patent is valid and enforceable;
- ii. A Judgment declaring that, pursuant to 35 U.S.C. § 271(e)(2)(A), the submission to FDA and filing of ANDA No. 215796 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 the Ricon Product was an act of infringement of the '960 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 the Ricon Product prior to the

expiration of the '960 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 the Ricon Product shall be no earlier than the date on which the '960 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 subject of ANDA No. 215796 until the expiration of the '960 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. 215796 that infringes the '960 patent;
- vii. A Judgment declaring that infringement of the '960 patent is willful if Defendants commercially manufacture, use, sell, offer to sell, and/or import any product that is the subject of ANDA No. 215796 that infringes the '960 patent;
- viii. A Judgment declaring that, pursuant to 35 U.S.C. § 285, this is an exceptional case and awarding Supernus its attorneys' fees and costs; and
- ix. Such other and further relief as this Court may deem just and proper.

Dated: October 28, 2022

Respectfully submitted,

By: s/ William C. Baton
Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102
wbaton@saul.com

OF COUNSEL:

Edgar H. Haug
Nicholas F. Giove
Jason A. Kanter
Camille Y. Turner
Anna N. Lukacher
HAUG PARTNERS LLP
745 Fifth Avenue
New York, New York 10151
(212) 588-0888
ehaug@haugpartners.com
ngiove@haugpartners.com
jkanter@haugpartners.com
cturner@haugpartners.com
alukacher@haugpartners.com

*Attorneys for Plaintiff
Supernus Pharmaceuticals, Inc.*

CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

I hereby certify that the matter captioned *Supernus Pharmaceuticals, Inc. v.*

RiconPharma LLC, et al., Civil Action No. 2:21-cv-12133 (KM)(MAH) is related to the matter in controversy because the matter in controversy involves the same Plaintiff, the same defendants, the same ANDA, and because Defendants are seeking FDA approval to market a generic version of the same pharmaceutical product.

I further certify that the matter captioned *Supernus Pharmaceuticals, Inc. v. Apotex Inc., et al.*, Civil Action No. 20-7870 (FLW)(TJB) (consolidated) is related to the matter in controversy because the matter in controversy involves one of the same patents in suit, the same Plaintiff, and because Defendants seeking approval to market a generic version of the same pharmaceutical product.

I hereby certify that, to the best of my knowledge, 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: October 28, 2022

OF COUNSEL:

Edgar H. Haug
Nicholas F. Giove
Jason A. Kanter
Camille Y. Turner
Anna N. Lukacher
HAUG PARTNERS LLP
745 Fifth Avenue
New York, New York 10151

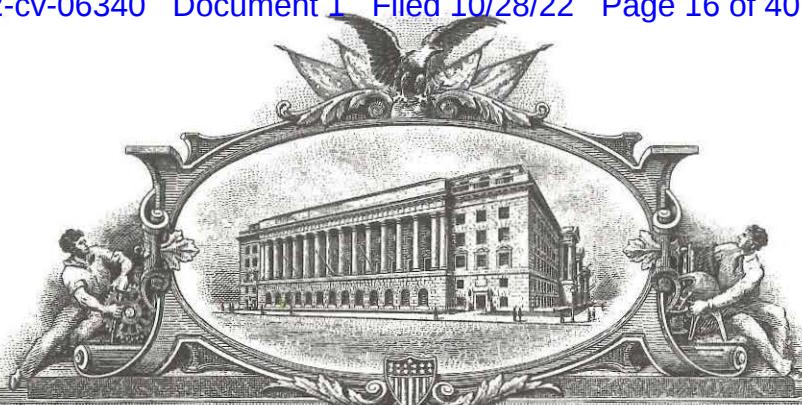
Respectfully submitted,

By: s/ William C. Baton
Charles M. Lizza
William C. Baton
Sarah A. Sullivan
SAUL EWING ARNSTEIN & LEHR LLP
One Riverfront Plaza
1037 Raymond Blvd., Suite 1520
Newark, NJ 07102
wbaton@saul.com

*Attorneys for Plaintiff
Supernus Pharmaceuticals, Inc.*

Exhibit A

8196237



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 13, 2022

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM
THE RECORDS OF THIS OFFICE OF:

PATENT NUMBER: 11,166,960

ISSUE DATE: November 9, 2021

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

Wanda Montgomery
Certifying Officer





US011166960B2

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

(10) **Patent No.: US 11,166,960 B2**
(45) **Date of Patent: *Nov. 9, 2021**

(54) **MODIFIED RELEASE PREPARATIONS
CONTAINING OXCARBAZEPINE AND
DERIVATIVES THEREOF**

(71) **Applicant:** **Supernus Pharmaceuticals, Inc.,**
Rockville, MD (US)

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

This patent is subject to a terminal dis-
claimer.

(21) **Appl. No.: 17/238,796**

(22) **Filed:** **Apr. 23, 2021**

(65) **Prior Publication Data**

US 2021/0236510 A1 Aug. 5, 2021

Related U.S. Application Data

(60) Continuation of application No. 17/081,383, filed on
Oct. 27, 2020, which is a continuation of application
(Continued)

(51) **Int. Cl.**

A61K 9/00	(2006.01)
A61K 31/55	(2006.01)
A61K 9/20	(2006.01)

(52) **U.S. Cl.**
CPC **A61K 31/55** (2013.01); **A61K 9/0073**
(2013.01); **A61K 9/205** (2013.01); **A61K
9/2013** (2013.01);

(Continued)

(58) **Field of Classification Search**

CPC A61K 31/55
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,642,775 A	2/1972	Schindler
3,716,640 A	2/1973	Schindler

(Continued)

FOREIGN PATENT DOCUMENTS

CN	1625390 A	6/2005
EP	0 280 571 B1	8/1993

(Continued)

OTHER PUBLICATIONS

<https://www2.chemistry.msu.edu/faculty/reusch/virttxtjml/basicity.htm>, accessed Jul. 28, 2021 (Year: 2021).*

(Continued)

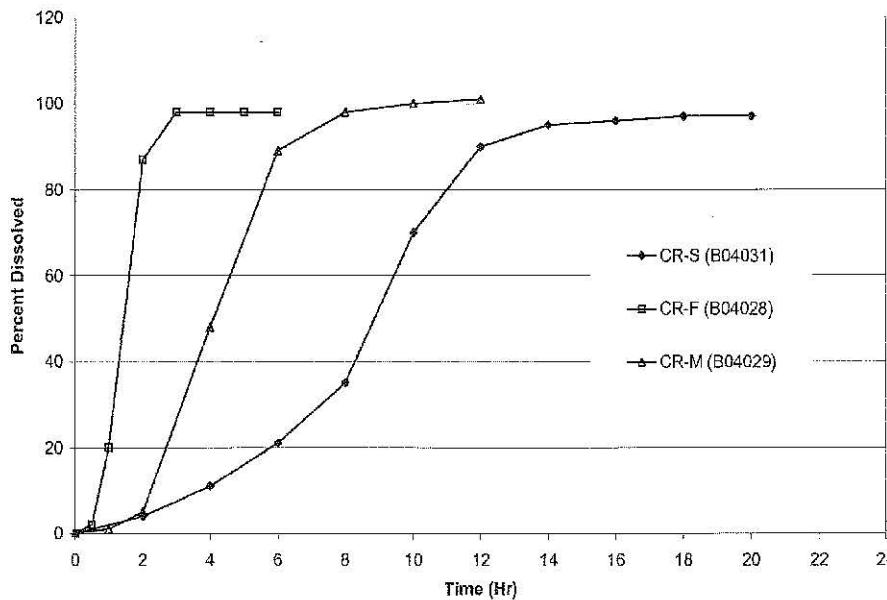
Primary Examiner — Paul W Dickinson

(74) **Attorney, Agent, or Firm:** Foley & Lardner LLP

(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.

6 Claims, 14 Drawing Sheets



US 11,166,960 B2

Page 2

Related U.S. Application Data

No. 16/252,106, filed on Jan. 18, 2019, which is a continuation of application No. 15/834,401, filed on Dec. 7, 2017, now Pat. No. 10,220,042, which is a continuation of application No. 15/166,816, filed on May 27, 2016, now Pat. No. 9,855,278, which is a continuation of application No. 14/836,179, filed on Aug. 26, 2015, now Pat. No. 9,351,975, which is a continuation of application No. 14/445,233, filed on Jul. 29, 2014, now Pat. No. 9,119,791, which is a continuation of application No. 14/103,103, filed on Dec. 11, 2013, now Pat. No. 8,821,930, which is a continuation of application No. 13/476,337, filed on May 21, 2012, now Pat. No. 8,617,600, which is a continuation of application No. 13/137,382, filed on Aug. 10, 2011, now Pat. No. 8,211,464, which is a division of application No. 12/230,275, filed on Aug. 27, 2008, now Pat. No. 8,017,149, which is a 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.
- (52) U.S. Cl.
CPC A61K 9/2027 (2013.01); A61K 9/2031 (2013.01); A61K 9/2054 (2013.01); A61K 2800/56 (2013.01)

(56) References Cited

U.S. PATENT DOCUMENTS

4,221,887 A *	9/1980	Brenner	C08F 8/40 524/186
4,792,452 A	12/1988	Howard et al.	
4,968,508 A	11/1990	Oren et al.	
5,147,655 A	9/1992	Ibsen	
5,326,570 A	7/1994	Rudnic et al.	
5,472,714 A	12/1995	Bourquin	
5,700,832 A	12/1997	Baik et al.	
5,906,832 A	5/1999	Jao et al.	
5,912,013 A	6/1999	Rudnic et al.	
5,980,942 A	11/1999	Katzhendler et al.	
6,287,599 B1	9/2001	Burnside et al.	
6,296,873 B1	10/2001	Katzhendler et al.	
6,572,889 B1	6/2003	Guo	
7,183,272 B2	2/2007	Aronhime et al.	
7,858,122 B2	12/2010	Kshirsagar et al.	
9,119,792 B2	9/2015	Bhatt et al.	
2001/0001658 A1	5/2001	Chen et al.	
2002/0022056 A1	2/2002	Schlutermann	
2002/0155067 A1	10/2002	MacGregor	
2002/0169145 A1	11/2002	Shah et al.	
2003/0175341 A1	9/2003	Rampal et al.	
2003/0180352 A1	9/2003	Patel et al.	
2003/0180362 A1	9/2003	Park et al.	
2003/0190361 A1	10/2003	Schlutermann	
2004/0142033 A1	7/2004	Franke et al.	
2004/0185095 A1	9/2004	Franke et al.	
2004/0197402 A1	10/2004	Sehgal et al.	
2005/0148594 A1	7/2005	Cink et al.	
2005/0202088 A1	9/2005	Hanshermann et al.	
2005/0255156 A1	11/2005	MacGregor	
2005/0271716 A1	12/2005	Murai	
2006/0057203 A1	3/2006	Wolf et al.	
2006/0079502 A1	4/2006	Lang	
2006/0111343 A1	5/2006	Krishnan et al.	
2006/0134196 A1	6/2006	Rosenberg et al.	
2007/0059354 A1	3/2007	Ramakrishnan et al.	
2007/0092559 A1	4/2007	Yuan et al.	
2007/0104778 A1	5/2007	Zeng et al.	
2007/0254033 A1	11/2007	Bhatt et al.	

2009/0004263 A1	1/2009	Bhatt et al.
2009/0005360 A1	1/2009	Bhatt et al.
2009/0137804 A1 *	5/2009	Ding C07D 251/48 544/329
2015/0359748 A1	12/2015	Bhatt et al.

FOREIGN PATENT DOCUMENTS

EP	0 646 374 A1	4/1995
JP	H06-199657 A	7/1994
WO	WO 97/18814 A1	5/1997
WO	WO 02/009675 A1	2/2002
WO	WO 02/094774 A2	11/2002
WO	WO 03/084513 A1	10/2003
WO	WO 03/101430 A1	12/2003
WO	WO 2004/002427 A2	1/2004
WO	WO 2004/026314 A1	4/2004
WO	WO 2006/075925 A2	7/2006

OTHER PUBLICATIONS

Mut, Toxicological screening of human plasma by on-line SPE-HPLC-DAD: identification and quantification of basic drugs and metabolites, *Biomed. Chromatogr.*, 2015, 29, 935-952 (Year: 2015).^{*}
 Ahmed et al., "Preparation and evaluation of sustained release carbamazepine matrix tablets using Eudragit RS 100 and Tragacanth," *Bull. Pharm. Sci.*, Assiut University, 2001, 24(1):73-82.
 Collins et al., "Extended Release Formulations of Anticonvulsant Medications," *CNS Drugs*, Sep. 2000, 14(3):203-212.
 Degussa, *Pharma Polymers News*, 2003, 10:1-4.
 Flesch et al., "Oxcarbazepine final market image tablet formulation bioequivalence study after single administration and at steady state in healthy subjects," *International Journal of Clinical Pharmacology and Therapeutics*, 2002, 40(11):524-532.
<http://www.merriam-webster.com/dictionary/matrix> (accessed Dec. 8, 2008), 3 pages.
 Kibbe, Arthur H., Ph.D., Ed., "Polymethacrylates," *Handbook of Pharmaceutical Excipients*, Third Edition, 2000, 401-406.
 Merriam-Webster online dictionary, "matrix", <http://www.merriam-webster.com/dictionary/matrix>, Dec. 8, 2008, 3 pages.
 Nokhodchi et al., "The effect of various surfactants on the release rate of propranolol hydrochloride from hydroxypropylmethylcellulose (HPMC)-Eudragit matrices," *European Journal of Pharmaceutics and Biopharmaceutics*, 2002, 54:349-356.
 Rowe, Raymond C., Ed., "Polymethacrylates," *Handbook of Pharmaceutical Excipients*, Fourth Edition, 2003, 462-468.
 Sheskey et al., "Roll Compaction Granulation of a Controlled-Release Matrix Tablet Formulation Containing HPMC, Effect of Process Scale-Up on Robustness of Tablets, Tablet Stability, and Predicted In Vivo Performance," *Pharmaceutical Technology*, Nov. 2000, 30-50.
 Walker et al., "Clinical Pharmacokinetics of New Antiepileptic Drugs," *Pharmac. Ther.*, 1995, 67(3):351-384.
 Wellington et al., "Oxcarbazepine: An Update of Its Efficacy in the Management of Epilepsy," *CNS Drugs*, 2001, 15(2):137-163.
 Collins, Extended Release Formulations of Anticonvulsant Medications, *CNS Drugs* 2000, 14(3), 203-212.
 Cairns Donald, "Physicochemical properties of drugs," Chapter 3 from *Essentials of Pharmaceutical Chemistry*, 4th Ed., 2012, 57-79.
 Chemical Book, Oxcarbazepine, CAS 28721-07-5, 2017, 7 pages.
 Li et al., "Investigating the solubilization effect of oxcarbazepine by forming cocrystals," *CrystEngComm*, 2019, 21, 4718-4729, with supporting information, 9 pages.
 May et al., "Clinical Pharmacokinetics of Oxcarbazepine," *Clin. Pharmacokinet.*, 2003, 42(12):1023-1042.
 Ramsay et al., "Metabolism of tricyclic anticonvulsant drugs," *Epilepsy & Behavior*, 2002, 3:S2-S6.
 Shachter, S.C., "Oxcarbazepine," Chapter 11 of *Antiepileptic Drugs Pharmacology and Therapeutics*, Eadie et al., Eds., 1999, 319-330.
 Shorvon, Simon, "Guest Editorial—Oxcarbazepine: a review," *Seizure*, 2000, 9:75-79.
 Vogelpoel et al., "Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms Based on Biopharmaceutics Classification

US 11,166,960 B2

Page 3

(56)

References Cited

OTHER PUBLICATIONS

- System (BCS) Literature Data: Verapamil Hydrochloride, Propranolol Hydrochloride, and Atenolol," Journal of Pharmaceutical Sciences, Aug. 2004, 93(8):1945-1956.
- Beynon et al., Buffer Solutions the Basics, 1996, pp. 20-30.
- Escuder-Gilabert et al., "Potential of biopartitioning micellar chromatography as an in vitro technique for predicting drug penetration across the blood-brain barrier," Journal of Chromatography B, 2004, 807:193-201.
- FDA Approval Package for Trileptal, Application No. 21-014/S-003, 2003, 26 pages.
- Izzo et al., "Separation of olanzapine, carbamazepine and their main metabolites by capillary electrophoresis with pseudo-stationary phases," Journal of Chromatography B, 2001, 752:47-53.
- Masunov et al., "ACD/I-Lab 4.5: An Internet Service Review," J. Chem. Inf. Comput. Sci., 2001, 41(4):1093-1095.
- Mut et al., "Toxicological screening of human plasma by on-line SPE-HPLC-DAD: identification and quantification of acidic and neutral drugs," Biomedical Chromatography, 2016 (online Aug. 10, 2015), 30:343-362.
- Walker, Matthew J., "Training ACD/LogP with Experimental Data," QSAR Comb. Sci., 2004, 23:515-520.

* cited by examiner

FIGURE 1

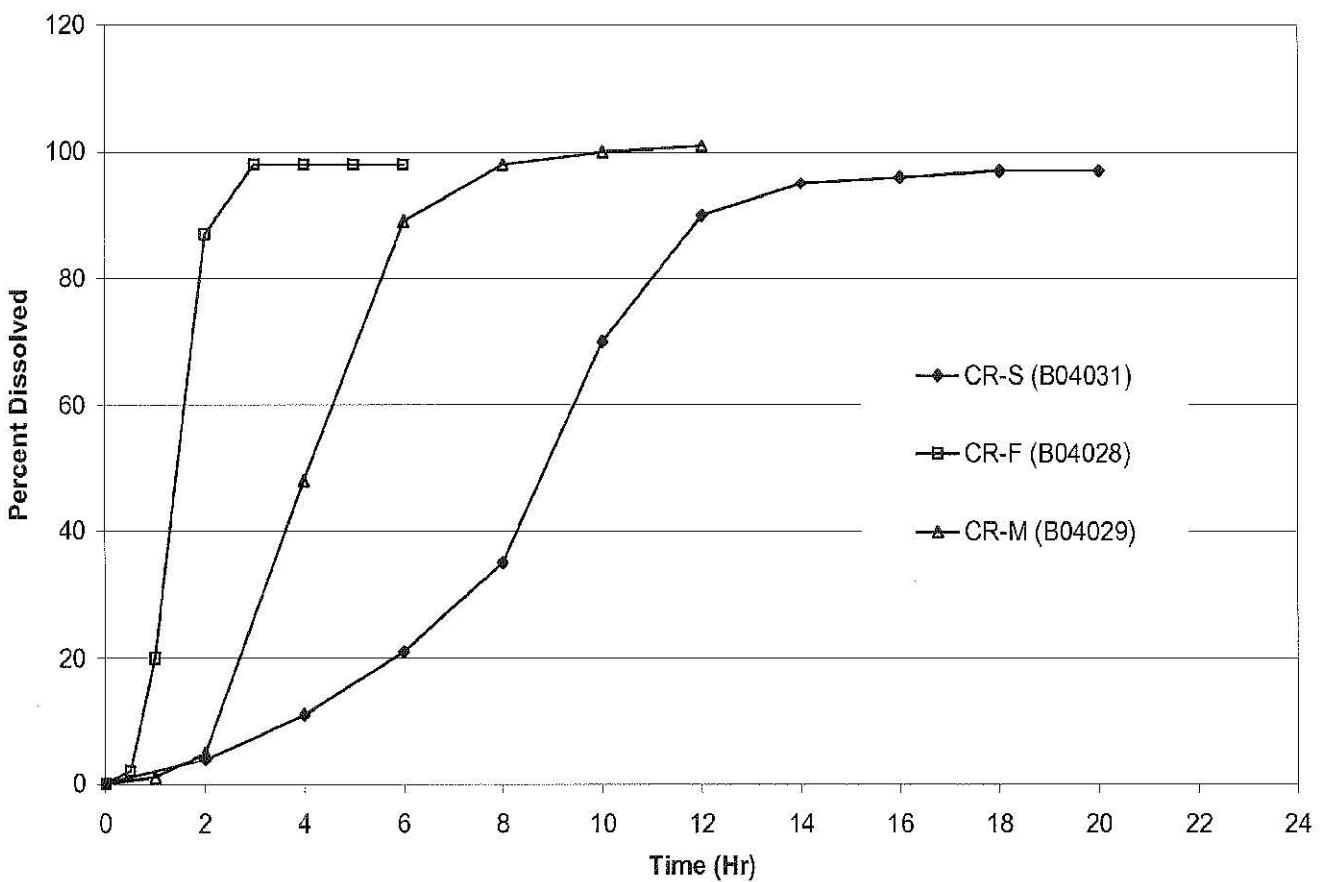


FIGURE 2

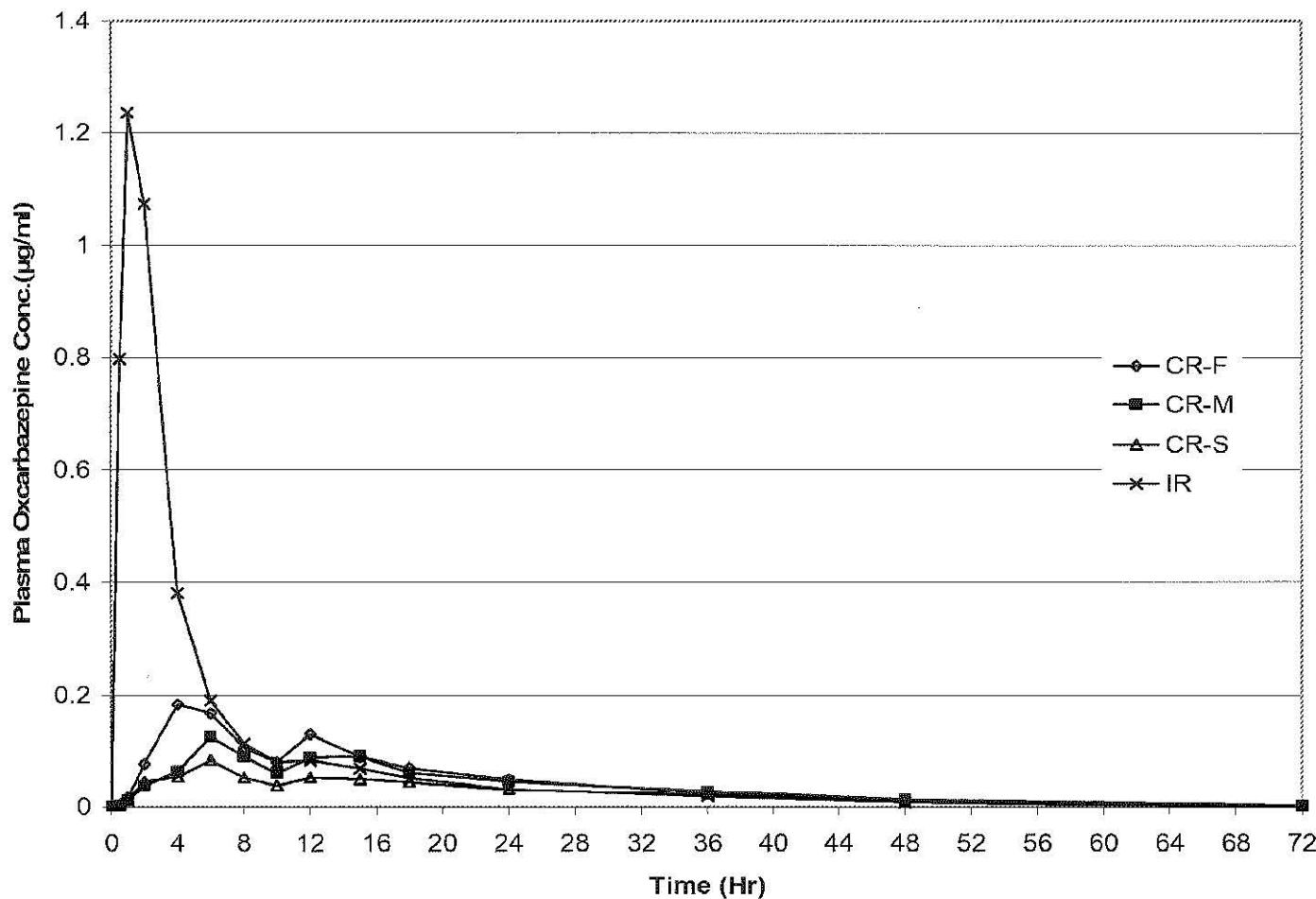
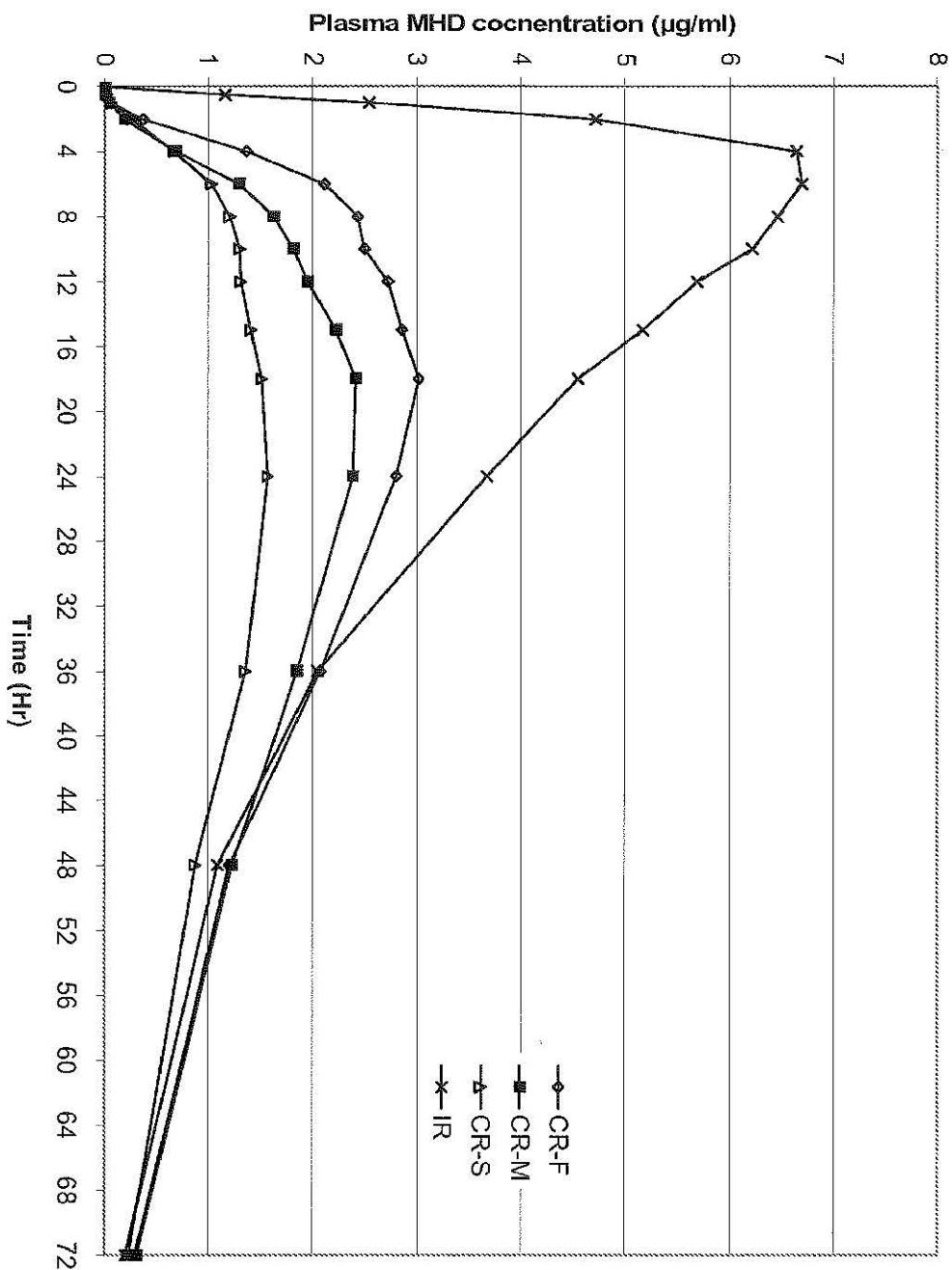


FIGURE 3



U.S. Patent

Nov. 9, 2021

Sheet 4 of 14

US 11,166,960 B2

FIGURE 4

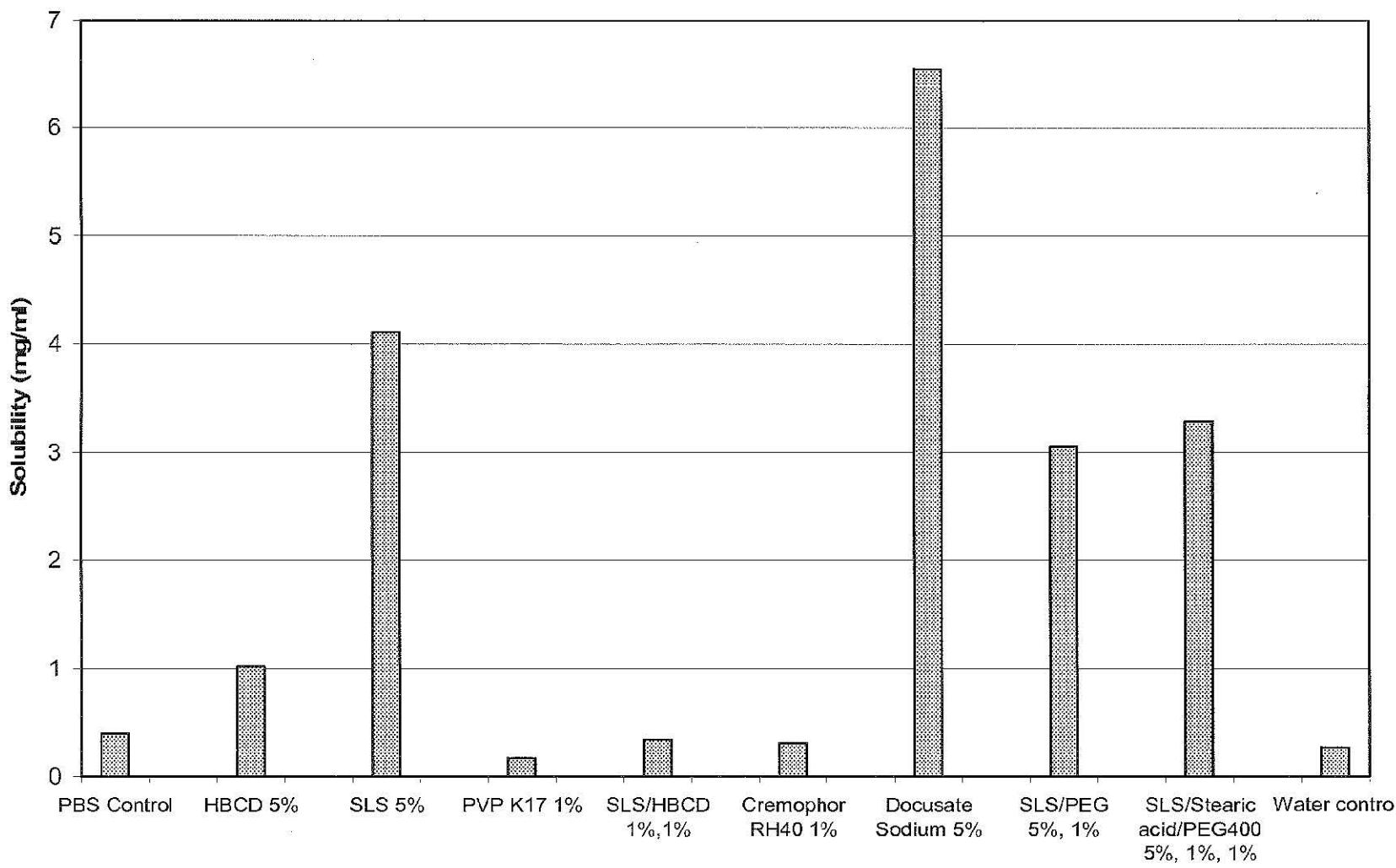


FIGURE 5

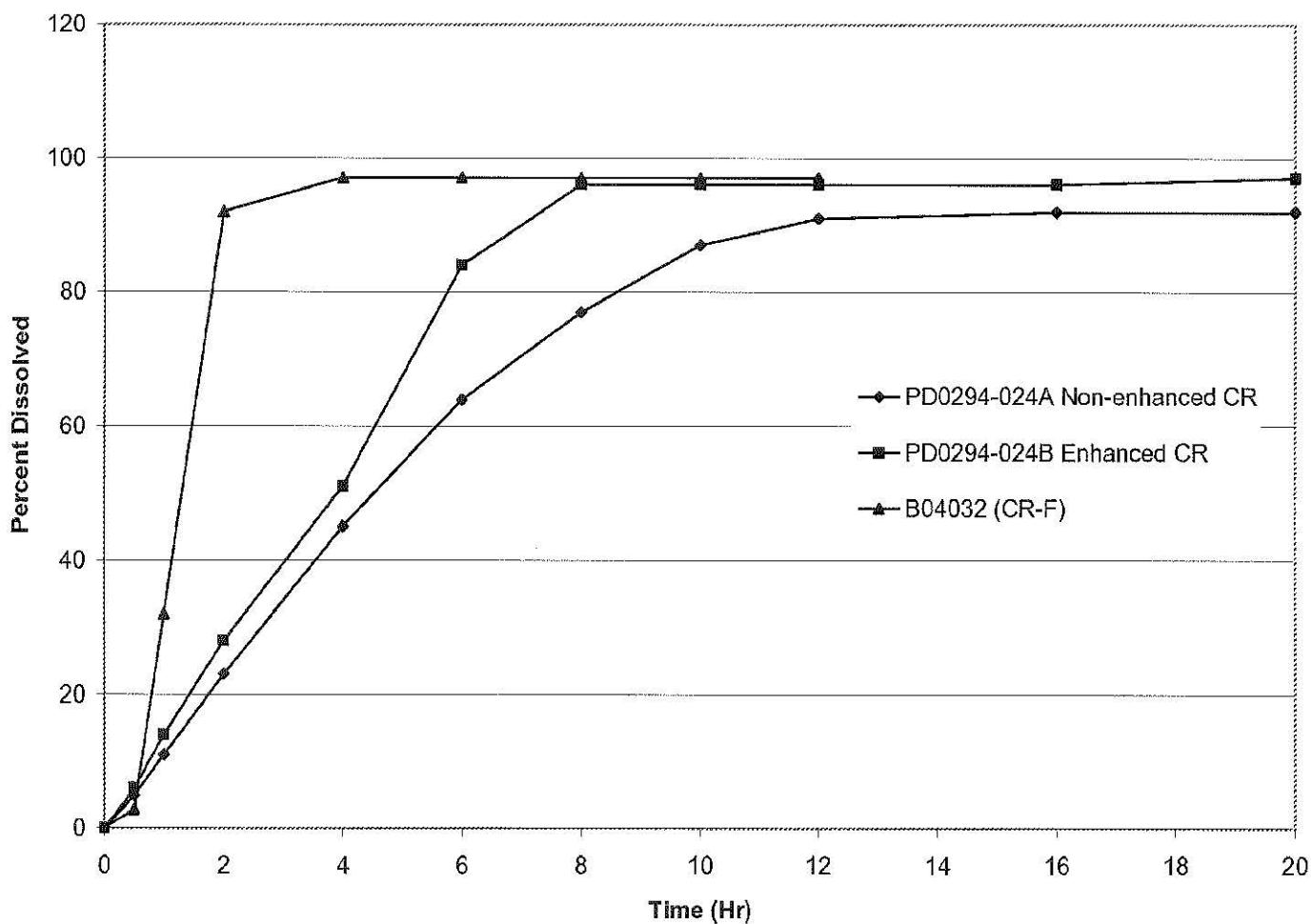


FIGURE 6

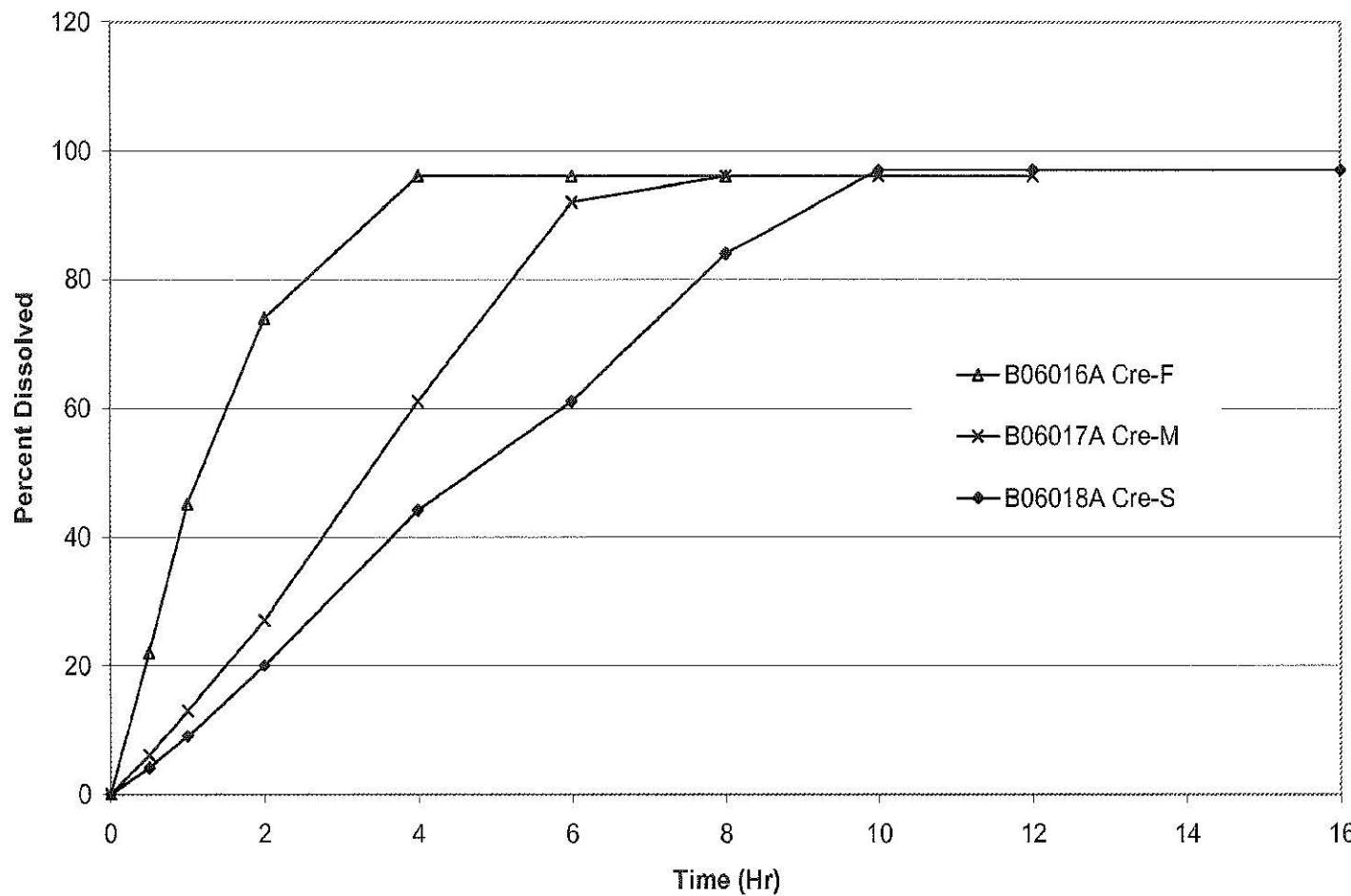


FIGURE 7

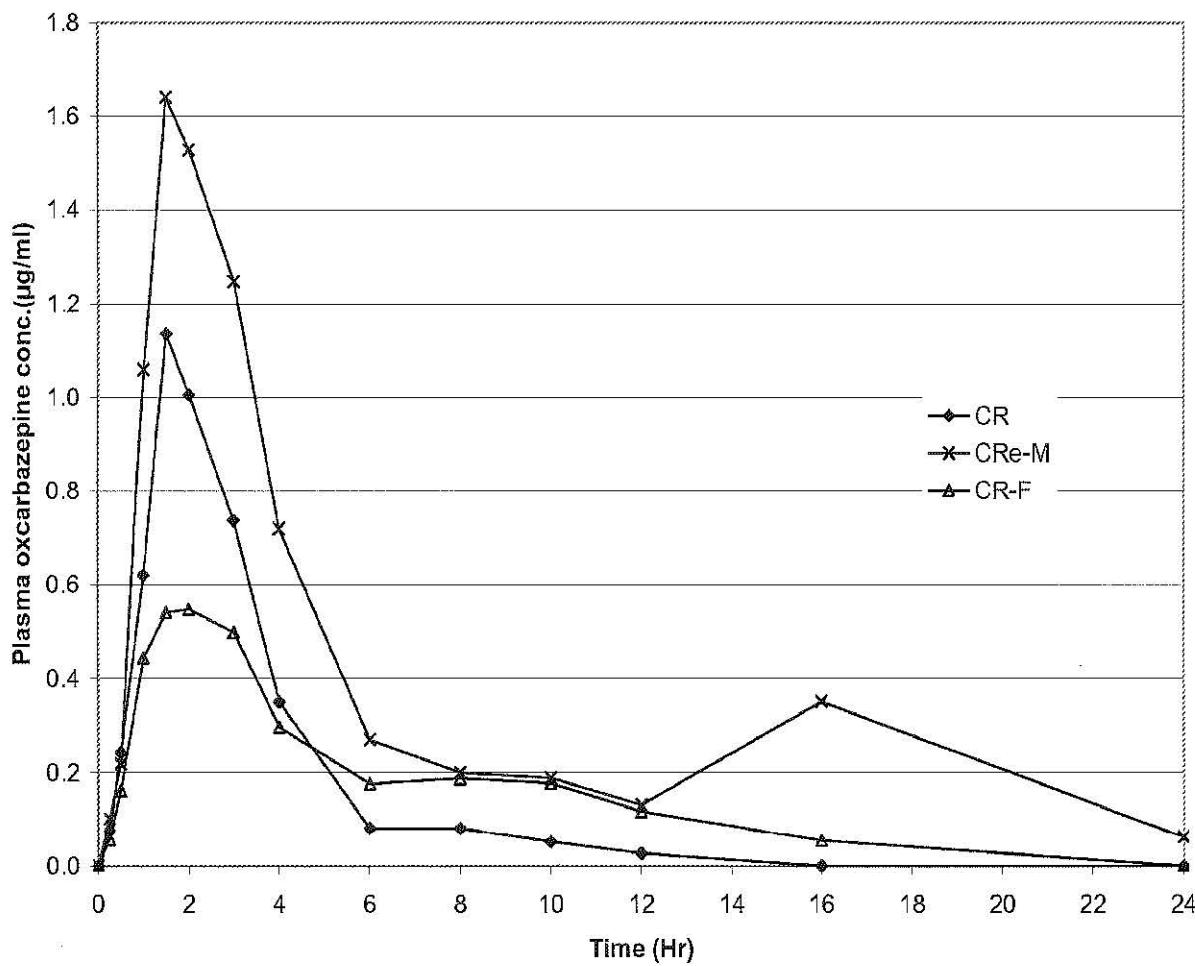


FIGURE 8

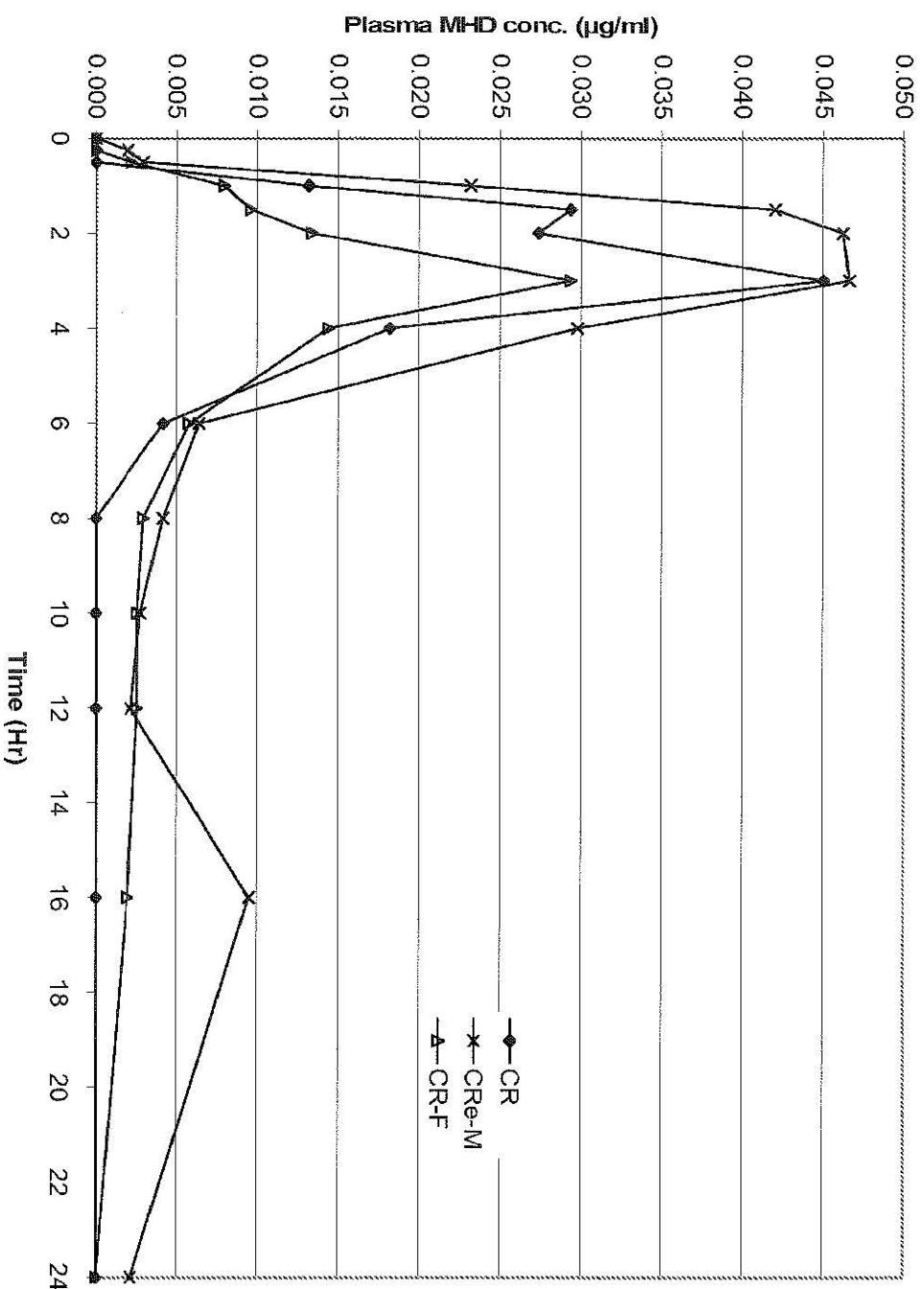


FIGURE 9

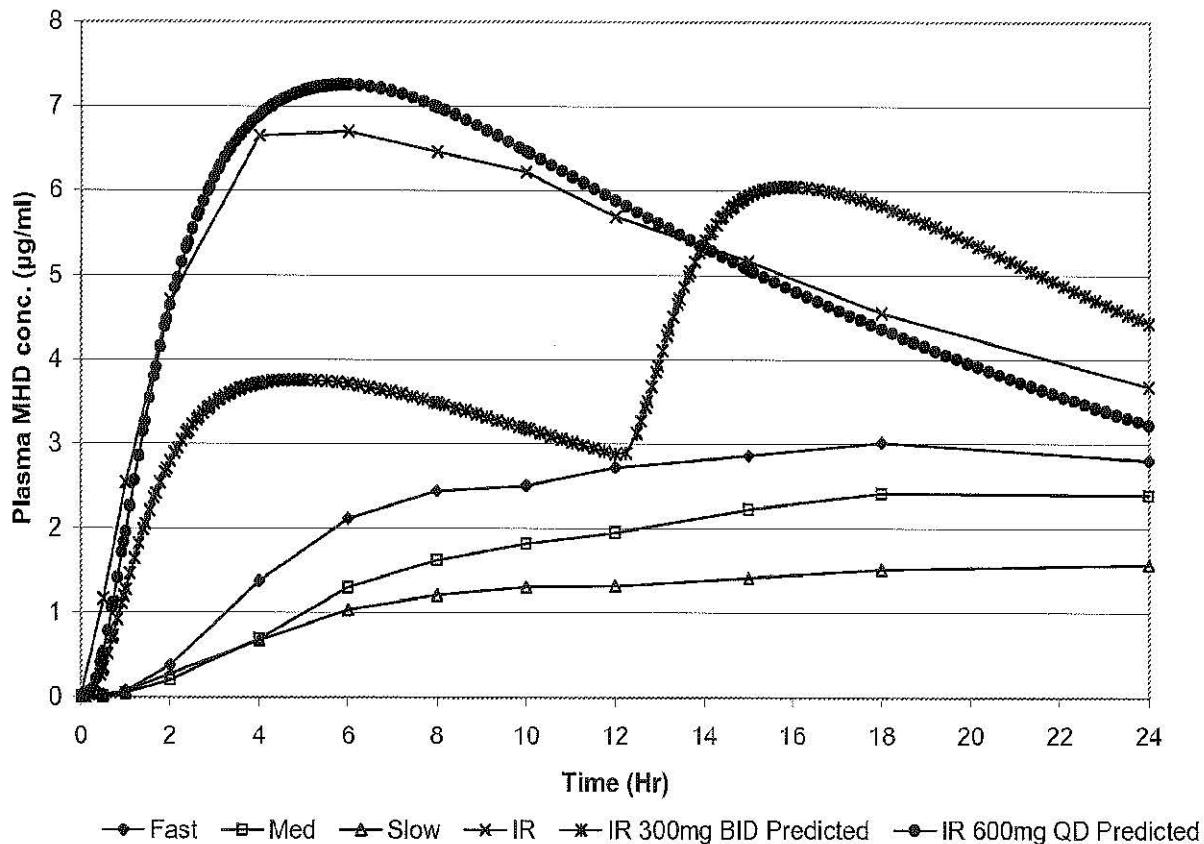


FIGURE 10

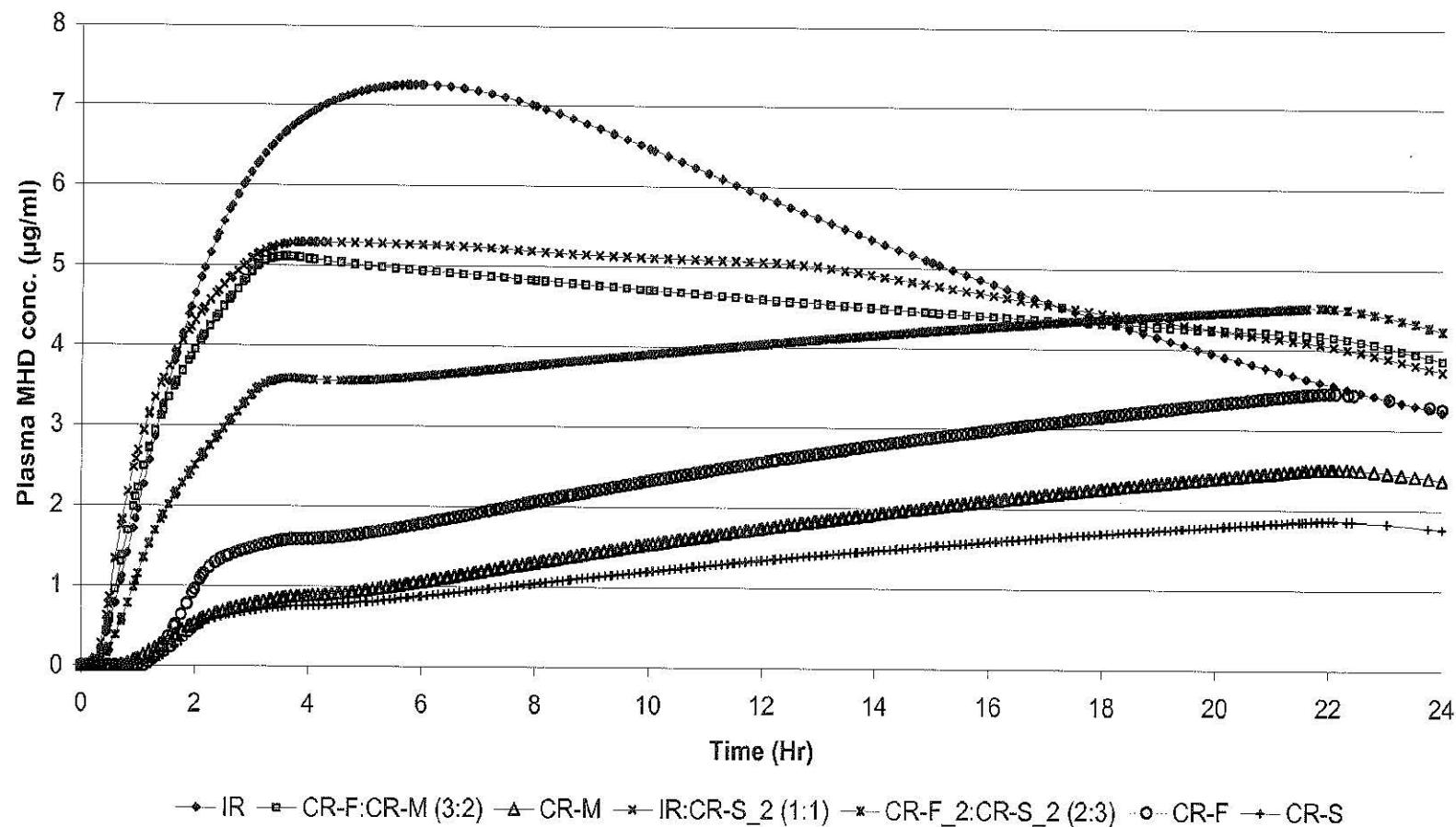


FIGURE 11

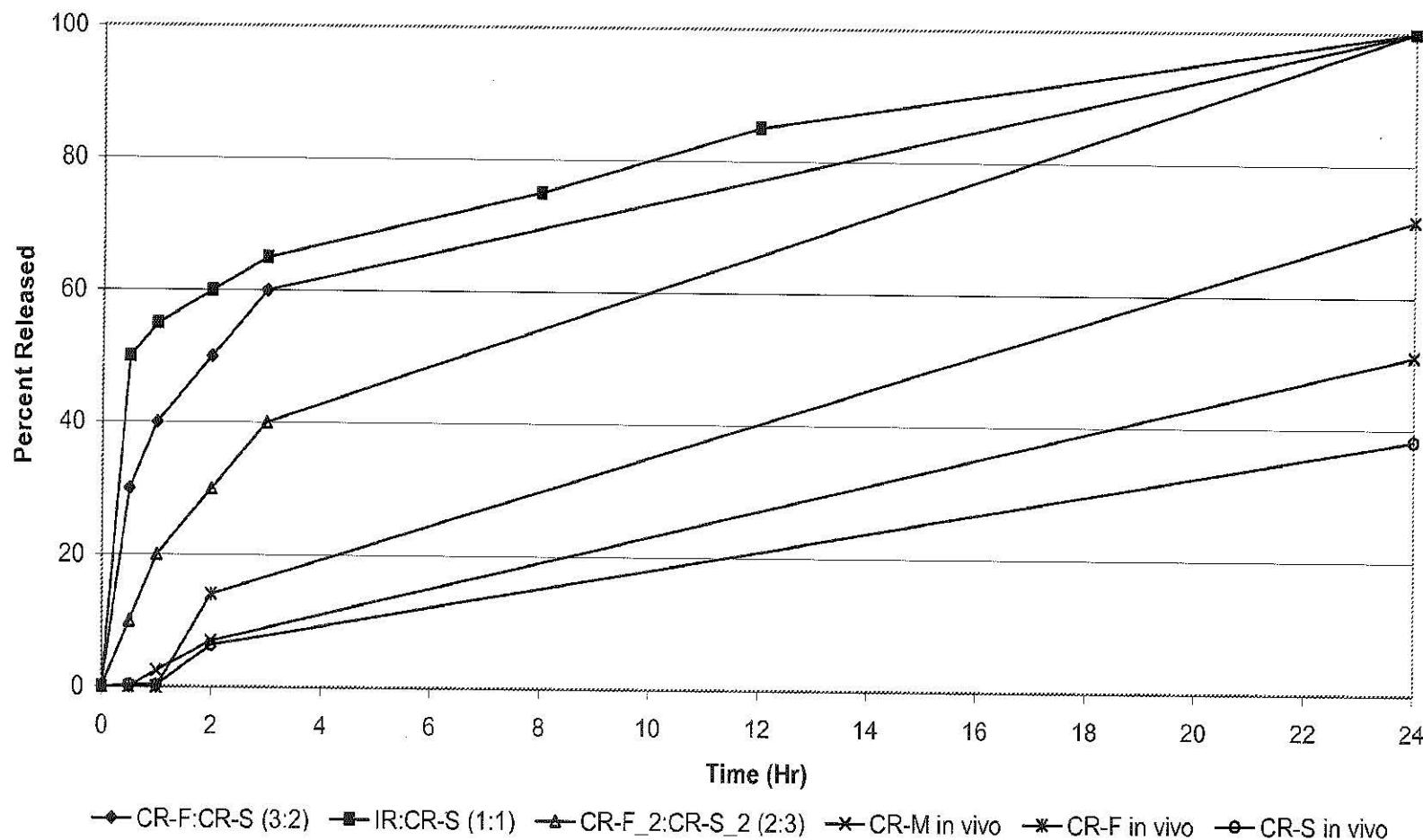


FIGURE 12

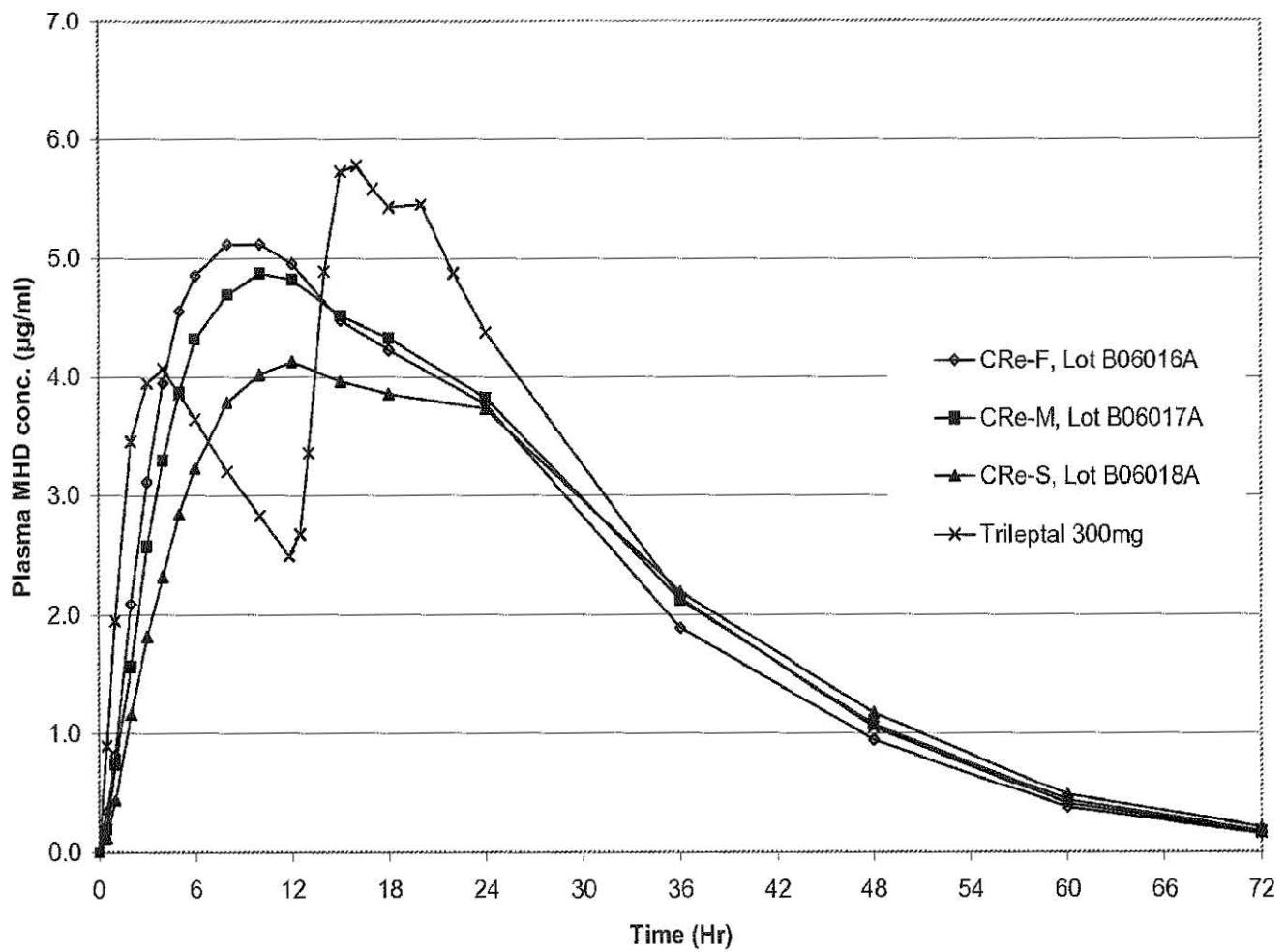


FIGURE 13

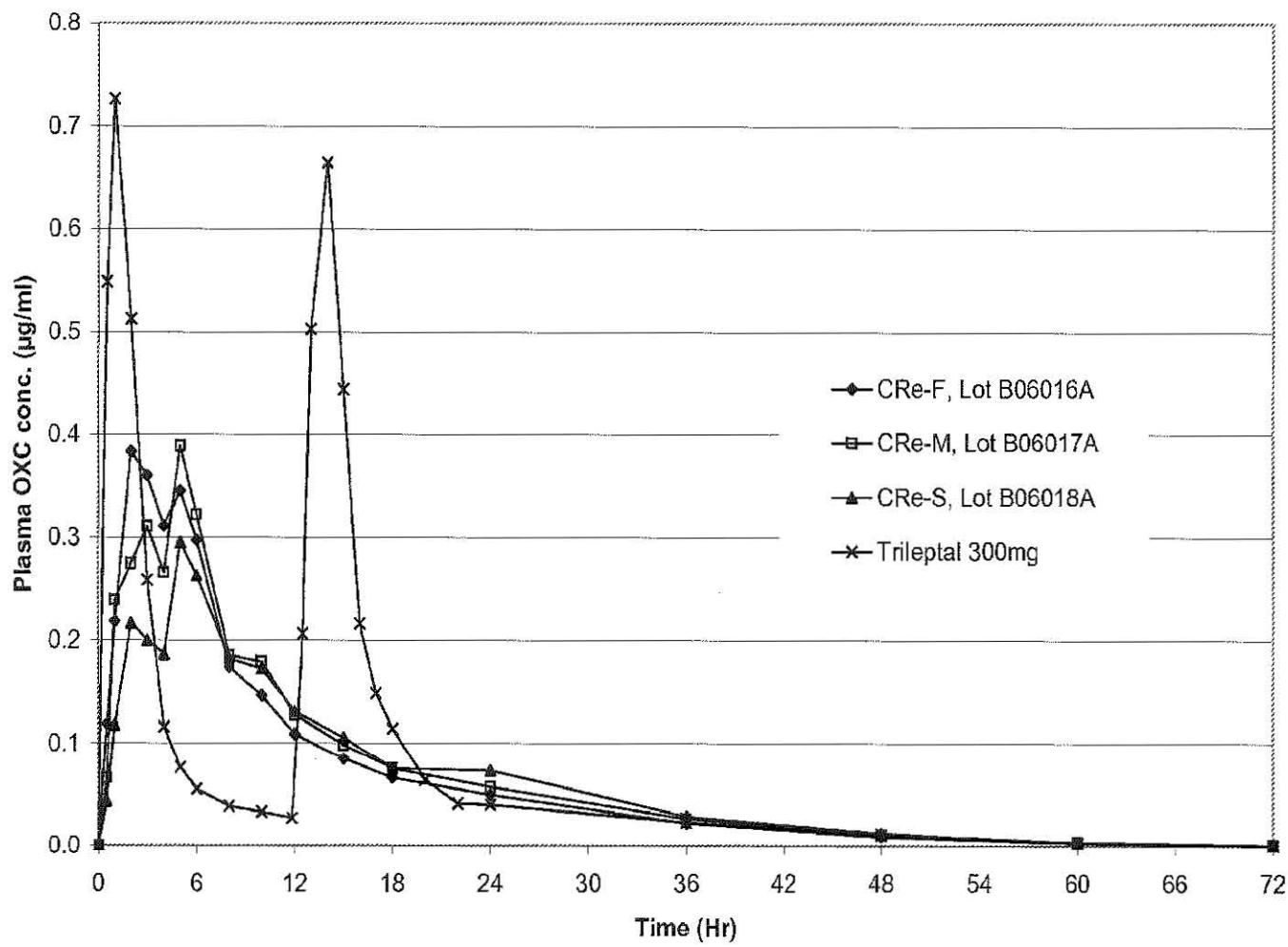
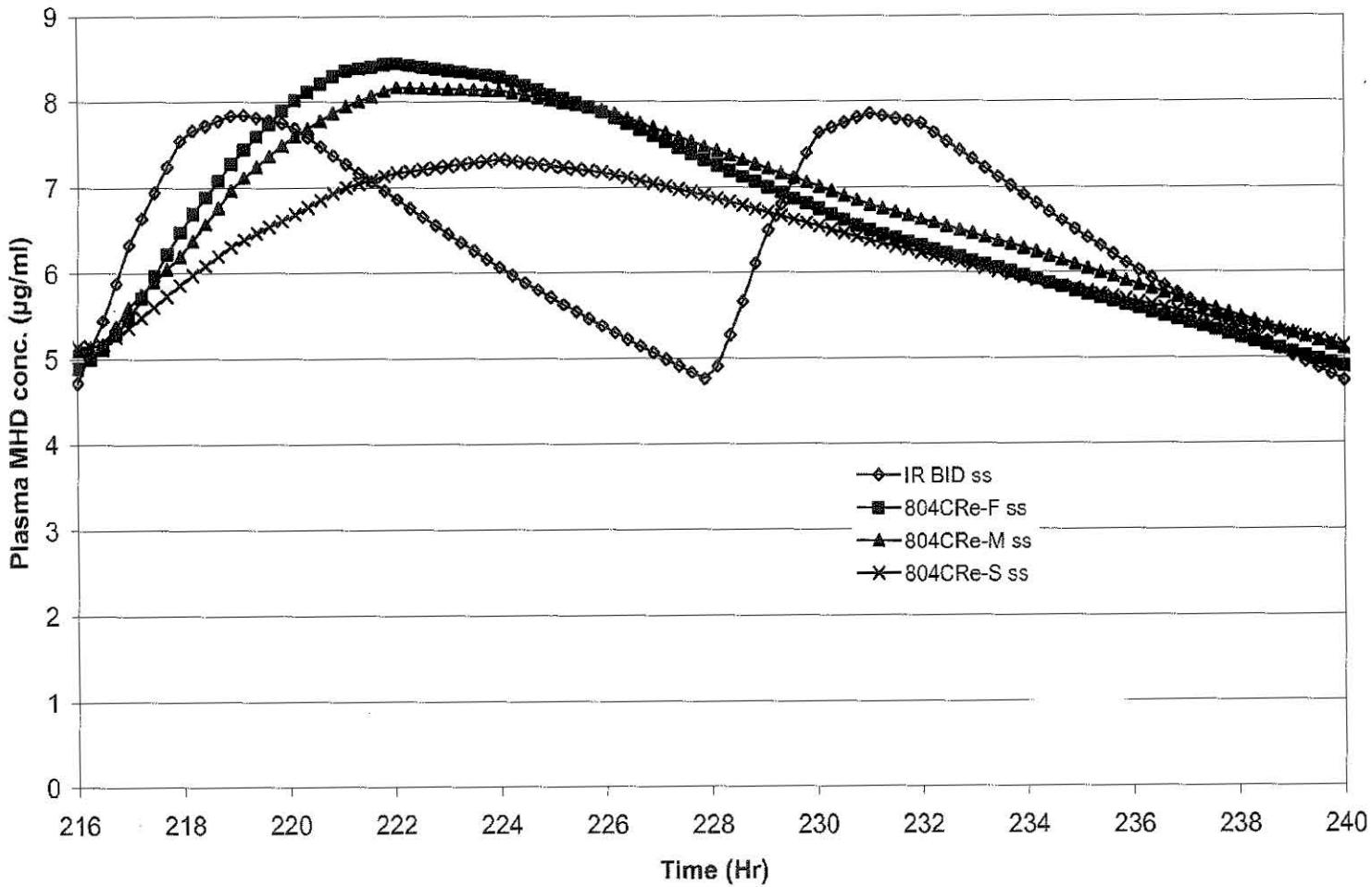


FIGURE 14



US 11,166,960 B2

1

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

**CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a Continuation of U.S. application Ser. No. 17/081,383, filed Oct. 27, 2020, which is a Continuation of U.S. application Ser. No. 16/252,106, filed Jan. 18, 2019, which is a Continuation of U.S. application Ser. No. 15/834,401, filed Dec. 7, 2017, now U.S. Pat. No. 10,221,042, which is a Continuation of U.S. application Ser. No. 15/166,816, filed May 27, 2016, now U.S. Pat. No. 9,855,278, which is a Continuation of U.S. application Ser. No. 14/836,179, filed Aug. 26, 2015, now U.S. Pat. No. 9,351,975, which is a Continuation of U.S. application Ser. No. 14/445,233, filed Jul. 29, 2014, now U.S. Pat. No. 9,119,791, which is a Continuation of U.S. application Ser. No. 14/103,103, filed Dec. 11, 2013, now U.S. Pat. No. 8,821,930, which is a Continuation of U.S. application Ser. No. 13/476,337, filed May 21, 2012, now U.S. Pat. No. 8,617,600, which is a Continuation of U.S. application Ser. No. 13/137,382, filed Aug. 10, 2011, now U.S. Pat. No. 8,211,464, which is a Divisional of U.S. application Ser. No. 12/230,275, filed Aug. 27, 2008, now U.S. Pat. No. 8,017,149, which is a Continuation of U.S. application Ser. No. 11/734,874, filed Apr. 13, 2007, now U.S. Pat. No. 7,722,898, which claims priority to U.S. Provisional Application No. 60/794,837, filed Apr. 26, 2006.

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

2

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 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

US 11,166,960 B2

3

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_{80s} (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.

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_{80s} 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

4

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

10 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) 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.

55 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, methylcellu-

US 11,166,960 B2

5

lose 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 EudragitTM such as the Eudragit L series e.g. Eudragit L 12.5TM, Eudragit L 12.5PTM, Eudragit L100TM, Eudragit L 100-55TM, Eudragit L-30DTM, Eudragit L-30 D-55TM, the Eudragit STM series e.g. Eudragit S 12.5TM, Eudragit S 12.5PTM, Eudragit S100TM. 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.

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 docosate, sodium lauryl sulfate, sodium stearly 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

6

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 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 CarbopolTM) 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

US 11,166,960 B2

7

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), glyceryl-monoleate, 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 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 monoleate; 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 monoleate, 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 stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl 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 stearoyl lactylate; ethoxylated mono- and di-glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and propylene glycol; lactyl 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 stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; cetearyl octanoate; C₁₀-C₃₀

8

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 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.

US 11,166,960 B2

9

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 into VG-65/10M 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-65/10M 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

Ingredients	Formula composition of Oxcarbazepine CR formulations with changing slope		
	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.	—	—	10
LV	—	—	5
Methocel K4M	—	—	5
Premium CR	—	—	—
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.

10

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.

15

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 _{max} (Hr)	6.5	8.4	9.1	1.4
C _{max} (ug/mL)	0.248	0.146	0.103	1.412
AUC _{last} (Hr*ug/mL)	3.0	2.5	1.7	5.7
Rel BA	53%	44%	30%	100%

20

25

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.

40

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
Cremophor 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

45

50

55

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

60

US 11,166,960 B2

11

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

Formulation	Percent Composition of Enhanced (CRe-M) and non-Enhanced (CR) Prototypes	
	% PD0294-005 Enhanced	% PD0294-008 Non-Enhanced
Oxcarbazepine	60	60
Prosolv SMCC50	10	25
PVP K25	5	5
HPMC K4M premium	10	10
SLS	5	0
Eudragit L100-55	10	0
Magnesium Stearate	0.5	0.5

TABLE 5

Formulation	Percent Composition for the three exemplary enhanced formulations: CRe-F, CRe-M, and CRe-S.		
	% PD0294-046 CRe-F	% PD0294-051 CRe-M	% PD0294-054 CRe-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 CR 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 CRe	PD0294-024B	600
3	Oxcarbazepine CR-F	B04032	600

12

TABLE 7

Prototypes	Canine pharmacokinetic profiles for enhanced, non-enhanced and control formulations of oxcarbazepine		
	Non-Enhanced CR (CR) PD0294-024A	Enhanced CR (CRe-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
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

PK Parameters	Pharmacokinetic parameters of the three exemplary solubility enhanced formulations in Example 4 and Trileptal™			
	CRe-F Fast	CRe-M Med	CRe-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 controlled-release 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, and (c) at least one agent that enhances the solubility of oxcarbazepine, and (d) at least one release promoting agent comprising an enteric polymer.

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

3. The formulation of claim 1, wherein the amount of oxcarbazepine in the controlled release formulation is 600 mg.

4. The formulation of claim 1, wherein the enteric polymer comprises a polymer having pH-dependent solubility.

5. The formulation of claim 1, which can be administered once a day.

US 11,166,960 B2

13

6. The formulation of claim 1, wherein the at least one agent that enhances the solubility of oxcarbazepine is selected from the group consisting of surface active agents, complexing agents, cyclodextrins, pH modifying agents, and hydration promoting agents.

5

14

* * * * *