William C. Baton
Jamie L. Lucia
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, New Jersey 07102-5426
(973) 286-6700
wbaton@saul.com
jlucia@saul.com

Attorneys for Plaintiff
Rhodes Pharmaceuticals L.P.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

RHODES PHARMACEUTICALS L.P., **Plaintiff,** **v.** **ACTAVIS, INC., ACTAVIS ELIZABETH LLC, ACTAVIS LLC, and ALLERGAN PLC,** **Defendants.**	**Civil Action No. 16-2667 (WHW) (CLW)** **FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff Rhodes Pharmaceuticals L.P. ("Rhodes" or "Plaintiff") for its First Amended Complaint against Defendants Actavis, Inc., Actavis Elizabeth LLC ("Actavis Elizabeth"), Actavis LLC and Allergan plc (collectively, "Actavis" or "Defendants") hereby 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, 35 U.S.C. §§ 271 and 281. This action relates to Abbreviated New Drug Application ("ANDA") No. 208861 filed by or for the benefit of Defendants with the United States Food and Drug Administration ("FDA") for approval to

market generic versions of Plaintiff's Aptensio XR® pharmaceutical products that are sold in the United States.

THE PARTIES

2. Plaintiff Rhodes Pharmaceuticals L.P. ("Rhodes") is a limited partnership organized and existing under the laws of the State of Delaware, having a principal place of business at 498 Washington Street, Coventry, RI 02816. Rhodes is the registered holder of approved New Drug Application No. 205831, which covers Aptensio XR®.

3. Upon information and belief, Defendant Actavis Elizabeth is a limited liability company organized and existing under the laws of the State of Delaware, having its principal place of business at 200 Elmora Avenue, Elizabeth, New Jersey 07207. Actavis Elizabeth is registered to do business in New Jersey under Business I.D. No. 0600272818. Upon information and belief, Actavis Elizabeth is in the business of, *inter alia*, developing, manufacturing, and obtaining regulatory approval of generic copies of branded pharmaceutical products throughout the United States, including within this Judicial District.

4. Upon information and belief, Actavis, Inc. is a Nevada corporation, having its principal place of business at 400 Interpace Parkway, Parsippany, New Jersey 07054. Actavis, Inc. is registered to do business in New Jersey under Business I.D. No. 0101005391. Upon information and belief, Actavis, Inc. is in the business of, *inter alia*, developing, manufacturing, and obtaining regulatory approval of generic copies of branded pharmaceutical products throughout the United States, including within this Judicial District.

5. Upon information and belief, Defendant Actavis LLC is a limited liability company organized and existing under the laws of Delaware, having its principal place of

business at 400 Interpace Parkway, Parsippany, New Jersey 07054. On information and belief, Actavis LLC was formerly known as Actavis Inc.

6. Upon information and belief, Defendant Allergan plc, f/k/a Actavis plc, is a publicly-traded company organized and existing under the laws of Ireland, having its corporate headquarters at Clonshaugh Business and Technology Park, Coolock, Dublin, D17 E400, Ireland, and U.S. administrative headquarters at 400 Interpace Parkway, Parsippany, New Jersey 07054.

7. Upon information and belief, Actavis Elizabeth is a wholly owned subsidiary of Actavis, Inc. On information and belief, Actavis, Inc. is a wholly owned subsidiary of Allergan plc. On information and belief, Actavis Inc., and Actavis Elizabeth have at least one officer and/or director in common. On information and belief, Allergan plc is the global parent of, *inter alia*, Actavis LLC, Actavis Elizabeth, and Actavis, Inc.

JURISDICTION AND VENUE

8. This Court has subject matter jurisdiction under 28 U.S.C. §§ 1331 and 1338(a).

9. This Court has personal jurisdiction over Actavis, Inc., by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. Upon information and belief, Actavis, Inc. maintains its principal place of business in New Jersey, is registered to do business in New Jersey, and either directly or through one or more of its wholly owned subsidiaries and/or agents, develops, manufactures, distributes, markets, offers to sell, and sells generic drug products for sale and use throughout the United States, including within this Judicial District.

10. This Court has personal jurisdiction over Actavis Elizabeth by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. Upon information and belief, Actavis Elizabeth maintains its principal place of business in New Jersey, is registered to

do business in New Jersey, and directly or indirectly develops, manufactures, distributes, markets, offers to sell, and sells generic drug products for sale and use throughout the United States, including within this Judicial District.

11. This Court has personal jurisdiction over Actavis LLC by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. Upon information and belief, Actavis LLC maintains its principal place of business in New Jersey and directly or indirectly develops, manufactures, distributes, markets, offers to sell, and sells generic drug products for sale and use throughout the United States, including within this Judicial District.

12. This Court has personal jurisdiction over Allergan plc by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. Upon information and belief, Allergan plc maintains its U.S. administrative headquarters in New Jersey and directly or indirectly develops, manufactures, distributes, markets, offers to sell, and sells generic drug products, including generic drug products manufactured by Actavis LLC, for sale and use throughout the United States, including within this Judicial District. According to Allergan plc's Form 10-Q, filed November 6, 2015, "Allergan plc is a global specialty pharmaceutical company engaged in the development, manufacturing, marketing, and distribution of brand name [], medical aesthetics, generic, branded generic, biosimilar and over-the-counter [] pharmaceutical products." Upon information and belief, Allergan plc purposefully has conducted and continues to conduct business in this Judicial District. Upon information and belief, Allergan plc conducts research and development activities and manufactures finished products in the State of New Jersey, and owns property, including facilities used for research and development and manufacturing, in the State of New Jersey.

13. Because Defendants are headquartered and/or registered to do business in New Jersey, they are subject to general personal jurisdiction in this Judicial District.

14. Upon information and belief, Actavis, Inc. sells products manufactured by Actavis Elizabeth in New Jersey and throughout the United States.

15. Upon information and belief, Actavis LLC, Actavis, Inc., Actavis Elizabeth, and Allergan plc operate as a single integrated business. Upon information and belief, Allergan plc's Form 10-Q, filed November 6, 2015, and Form 10-K, filed February 26, 2016, indicate that it files a single financial report to the SEC for itself and its subsidiaries. Upon information and belief, Allergan plc, Actavis Elizabeth, and Actavis, Inc. share at least one corporate officer.

16. Upon information and belief, Actavis LLC, Actavis Elizabeth, and Actavis, Inc. have previously submitted to the jurisdiction of this Court. Upon information and belief, Actavis LLC and Actavis Elizabeth have availed themselves of the legal protections of the State of New Jersey, having asserted counterclaims in this jurisdiction.

17. Upon information and belief, Defendants acted in concert to develop the generic Methylphenidate Hydrochloride Extended-Release Capsules described in ANDA No. 208861 and to seek approval from the FDA to sell such products throughout the United States, including within this Judicial District.

18. Upon information and belief, upon approval of ANDA No. 208861, the Defendants and/or their subsidiaries, affiliates or agents will market, sell and/or distribute the generic pharmaceutical products that are the subject of that ANDA throughout the United States, including in this Judicial District, and will derive substantial revenue therefrom.

19. Upon information and belief, venue is proper in this Judicial District under 28 U.S.C. §§ 1391(c) and (d), and § 1400(b).

THE PATENTS-IN-SUIT

20. United States Patent No. 6,419,960 ("the '960 Patent"), entitled "Controlled Release Formulations Having Rapid Onset and Rapid Decline of Effective Plasma Drug Concentrations" was duly and legally issued by the United States Patent and Trademark Office ("the USPTO") on July 16, 2002. Plaintiff Rhodes is the owner of the entire right, title, and interest in the '960 Patent by assignment, and possesses the right to sue for and obtain equitable relief and damages for infringement of the '960 Patent. A true and correct copy of the '960 Patent is attached as Exhibit A.

21. United States Patent No. 7,083,808 ("the '808 Patent"), entitled "Controlled/Modified Release Oral Methylphenidate Formulations" was duly and legally issued by the USPTO on August 1, 2006. Plaintiff Rhodes is the owner of the entire right, title, and interest in the '808 Patent by assignment, and possesses the right to sue for and obtain equitable relief and damages for infringement of the '808 Patent. A true and correct copy of the '808 Patent is attached as Exhibit B.

22. United States Patent No. 7,247,318 ("the '318 Patent"), entitled "Controlled Release Formulations Having Rapid Onset and Rapid Decline of Effective Plasma Drug Concentrations" was duly and legally issued by the USPTO on July 24, 2007. Plaintiff Rhodes is the owner of the entire right, title, and interest in the '318 Patent by assignment, and possesses the right to sue for and obtain equitable relief and damages for infringement of the '318 Patent. A true and correct copy of the '318 Patent is attached as Exhibit C.

23. United States Patent No. 8,580,310 ("the '310 Patent"), entitled "Controlled Release Formulations Having Rapid Onset and Rapid Decline of Effective Plasma Drug Concentrations" was duly and legally issued by the USPTO on November 12, 2013. Plaintiff

Rhodes is the owner of the entire right, title, and interest in the '310 Patent by assignment, and possesses the right to sue for and obtain equitable relief and damages for infringement of the '310 Patent. A true and correct copy of the '310 Patent is attached as Exhibit D.

24. United States Patent No. 9,066,869 ("the '869 Patent"), entitled "Controlled Release Formulations Having Rapid Onset and Rapid Decline of Effective Plasma Drug Concentrations" was duly and legally issued by the USPTO on June 30, 2015. Plaintiff Rhodes is the owner of the entire right, title, and interest in the '869 Patent by assignment, and possesses the right to sue for and obtain equitable relief and damages for infringement of the '869 Patent. A true and correct copy of the '869 Patent is attached as Exhibit E.

APTENSIO XR®

25. Rhodes is the holder of New Drug Application ("NDA") No. 205831 for Aptensio XR® Methylphenidate Hydrochloride Extended-Release Capsules. Aptensio XR® was approved by the FDA on April 17, 2015 as 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg dosages. In conjunction with NDA No. 205831, the '960 Patent, '808 Patent, '318 Patent, '310 Patent, and '869 Patent are listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations ("the Orange Book") for Aptensio XR®.

ACTAVIS'S INFRINGING ANDA SUBMISSION

26. Upon information and belief, Actavis Elizabeth filed or caused to be filed with the FDA ANDA No. 208861, under Section 505(j) of the Federal Food Drug and Cosmetic Act and 21 U.S.C. § 355(j) to obtain FDA approval for the commercial manufacture, use, sale, offer for sale, and/or importation in the United States of Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 15 mg, 20 mg, 40 mg, 50 mg and 60 mg dosages. On information and belief, Actavis Elizabeth also filed an amendment to ANDA No. 208861 to obtain FDA approval

for the commercial manufacture, use, sale, offer for sale, and/or importation in the United States of Methylphenidate Hydrochloride Extended-Release Capsules, 30 mg dosage ("Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules"), which are a generic version of Plaintiff's 30 mg Aptensio XR® Methylphenidate Hydrochloride Extended-Release Capsules.

27. By letter dated March 28, 2016 (the "ANDA Notice Letter"), Actavis Elizabeth notified Plaintiff that Actavis Elizabeth had amended ANDA No. 208861 seeking approval to market Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules prior to the expiration of the '960 Patent, '808 Patent, '318 Patent, '310 Patent, and '869 Patent, and that Actavis Elizabeth was providing information to Plaintiff pursuant to 21 U.S.C. § 355(j)(2)(B) and 21 C.F.R. § 314.95.

28. The present case was initiated before the expiration of forty-five days from the date Plaintiff received the March 28, 2016 ANDA Notice Letter.

COUNT ONE: INFRINGEMENT OF THE '960 PATENT

29. Plaintiff incorporates by reference paragraphs 1-28 of this First Amended Complaint as if fully set forth herein.

30. On information and belief, Defendants submitted ANDA No. 208861 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules in the United States before the expiration of the '960 Patent.

31. By their ANDA Notice Letter, Defendants informed Plaintiff that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '960 Patent is invalid, unenforceable, or will not be infringed by the commercial

manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules.

32. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208861 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules before the expiration of the '960 Patent constitutes infringement of one or more claims of the '960 Patent, either literally or under the doctrine of equivalents.

33. Upon FDA approval of Actavis's ANDA No. 208861, Actavis will further infringe the '960 Patent under 35 U.S.C. § 271(a), (b) and/or (c), by making, using, offering to sell, and selling its Methylphenidate Hydrochloride Extended-Release Capsules in the United States and/or importing such products into the United States.

34. On information and belief, Defendants were aware of the '960 Patent at the time Actavis's ANDA application was submitted to the FDA.

35. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

COUNT TWO: INFRINGEMENT OF THE '808 PATENT

36. Plaintiff incorporates by reference paragraphs 1-35 of this First Amended Complaint as if fully set forth herein.

37. On information and belief, Defendants submitted ANDA No. 208861 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules in the United States before the expiration of the '808 Patent.

38. By their ANDA Notice Letter, Defendants informed Plaintiff that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '808 Patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules.

39. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208861 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules before the expiration of the '808 Patent constitutes infringement of one or more claims of the '808 Patent, either literally or under the doctrine of equivalents.

40. Upon FDA approval of Actavis's ANDA No. 208861, Actavis will further infringe the '808 Patent under 35 U.S.C. § 271(a), (b) and/or (c), by making, using, offering to sell, and selling its Methylphenidate Hydrochloride Extended-Release Capsules in the United States and/or importing such products into the United States.

41. On information and belief, Defendants were aware of the '808 Patent at the time Actavis's ANDA application was submitted to the FDA.

42. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

COUNT THREE: INFRINGEMENT OF THE '318 PATENT

43. Plaintiff incorporates by reference paragraphs 1-42 of this First Amended Complaint as if fully set forth herein.

44. On information and belief, Defendants submitted ANDA No. 208861 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules in the United States before the expiration of the '318 Patent.

45. By their ANDA Notice Letter, Defendants informed Plaintiff that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '318 Patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules.

46. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208861 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules before the expiration of the '318 Patent constitutes infringement of one or more claims of the '318 Patent, either literally or under the doctrine of equivalents.

47. Upon FDA approval of Actavis's ANDA No. 208861, Actavis will further infringe the '318 Patent under 35 U.S.C. § 271(a), (b) and/or (c), by making, using, offering to sell, and selling its Methylphenidate Hydrochloride Extended-Release Capsules in the United States and/or importing such products into the United States.

48. On information and belief, Defendants were aware of the '318 Patent at the time Actavis's ANDA application was submitted to the FDA.

49. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

COUNT FOUR: INFRINGEMENT OF THE '310 PATENT

50. Plaintiff incorporates by reference paragraphs 1-49 of this First Amended Complaint as if fully set forth herein.

51. On information and belief, Defendants submitted ANDA No. 208861 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules in the United States before the expiration of the '310 Patent.

52. By their ANDA Notice Letter, Defendants informed Plaintiff that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '310 Patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules.

53. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208861 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules before the expiration of the '310 Patent constitutes infringement of one or more claims of the '310 Patent, either literally or under the doctrine of equivalents.

54. Upon FDA approval of Actavis's ANDA No. 208861, Actavis will further infringe the '310 Patent under 35 U.S.C. § 271(a), (b) and/or (c), by making, using, offering to sell, and selling its Methylphenidate Hydrochloride Extended-Release Capsules in the United States and/or importing such products into the United States.

55. On information and belief, Defendants were aware of the '310 Patent at the time Actavis's ANDA application was submitted to the FDA.

56. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

COUNT FIVE: INFRINGEMENT OF THE '869 PATENT

57. Plaintiff incorporates by reference paragraphs 1-56 of this First Amended Complaint as if fully set forth herein.

58. On information and belief, Defendants submitted ANDA No. 208861 to the FDA under 21 U.S.C. § 355(j) in order to obtain approval to market Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules in the United States before the expiration of the '869 Patent.

59. By their ANDA Notice Letter, Defendants informed Plaintiff that they had submitted to the FDA, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), a certification alleging that the '869 Patent is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules.

60. Under 35 U.S.C. § 271(e)(2)(A), the submission by Defendants to the FDA of ANDA No. 208861 to obtain approval for the commercial manufacture, use, sale, offer for sale, or importation into the United States of Actavis's 30 mg Methylphenidate Hydrochloride Extended-Release Capsules before the expiration of the '869 Patent constitutes infringement of one or more claims of the '869 Patent, either literally or under the doctrine of equivalents.

61. Upon FDA approval of Actavis's ANDA No. 208861, Actavis will further infringe the '869 Patent under 35 U.S.C. § 271(a), (b) and/or (c), by making, using, offering to

sell, and selling its Methylphenidate Hydrochloride Extended-Release Capsules in the United States and/or importing such products into the United States.

62. On information and belief, Defendants were aware of the '869 Patent at the time Actavis's ANDA application was submitted to the FDA.

63. Plaintiff will be substantially and irreparably harmed by the infringing activities described above unless those activities are enjoined by this Court. Plaintiff has no adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully requests the following relief:

A. A Judgment that the claims of the '960, '808, '318, '310, and '869 Patents (the "Patents-in-Suit") are valid and enforceable;

B. A Judgment that the submission of ANDA No. 208861 by Defendants infringes one or more claims of each of the Patents-in-Suit under 35 U.S.C. § 271(e)(2);

C. A Judgment providing that, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any FDA approval of Defendants' ANDA No. 208861 shall be no earlier than the latest expiration date of the Patents-in-Suit and any additional periods of exclusivity that Plaintiff is or may become entitled to;

D. A Judgment pursuant to 35 U.S.C. § 271(e)(4)(B) permanently enjoining Defendants, their officers, agents, attorneys, and employees, and all persons acting in privity or concert with any of them, from making, using, selling, offering to sell, or importing the methylphenidate hydrochloride products described in Defendants' ANDA No. 208861 prior to the latest expiration of the Patents-in-Suit and any additional periods of exclusivity to which Plaintiff is or may become entitled to;

E. Attorneys' fees in this action pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court may deem just and proper.

Dated: June 21, 2016

Respectfully submitted,

By: s/ Jamie L. Lucia

William C. Baton
Jamie L. Lucia
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, New Jersey 07102-5426
(973) 286-6700
wbaton@saul.com
jlucia@saul.com

Attorneys for Plaintiff
Rhodes Pharmaceuticals L.P.

Of Counsel:
John L. Abramic
Katherine Johnson
STEPTOE & JOHNSON LLP
115 South LaSalle Street, Suite 3100
Chicago, IL 60603
(312) 577 1264
jabramic@steptoe.com
kjohnson@steptoe.com

Cassandra A. Adams
STEPTOE & JOHNSON LLP
1114 Avenue of the Americas
New York, NY 10036
(212) 378-7615
cadams@steptoe.com

Li Guo
STEPTOE & JOHNSON LLP
1330 Connecticut Avenue, N.W.
Washington, D.C. 20036
(202) 429-1322
lguo@steptoe.com

EXHIBIT A

US006419960B1

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

(10) **Patent No.: US 6,419,960 B1**
(45) **Date of Patent: Jul. 16, 2002**

(54) **CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS**

(75) Inventors: **Thinnayam N. Krishnamurthy**, Scarborough; **Andrew Darke**, Newmarket, both of (CA)

(73) Assignee: **Euro-Celtique S.A.**, Luxembourg (LU)

(*) 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.: **09/465,159**

(22) Filed: **Dec. 16, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/112,617, filed on Dec. 17, 1998.

(51) **Int. Cl.**[7] **A61K 9/16**; A61K 9/14; A61K 9/20; A61K 9/22; A61K 9/26

(52) **U.S. Cl.** **424/490**; 424/461; 424/464; 424/489; 424/490; 424/494; 424/468; 424/469

(58) **Field of Search** 424/461, 464, 424/484, 489, 490, 494, 468, 469

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WO	WO9703673	2/1997	..... A61K/31/445
WO	WO9814168	4/1998	..... A61K/9/00

OTHER PUBLICATIONS

US Published Patent Application 2001/0012847 A1, Aug. 9, 2001,Lam, et al.

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Primary Examiner—Thurman K. Page
Assistant Examiner—S. Tran
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

The invention is directed to oral modified/controlled release drug formulations which provide a rapid initial onset of effect and a prolonged duration of effect. Preferably, the peak concentration is lower than that provided by the reference standard for immediate release formulations of the drug, and the duration of effect falls rapidly at the end of the dosing interval.

18 Claims, 8 Drawing Sheets

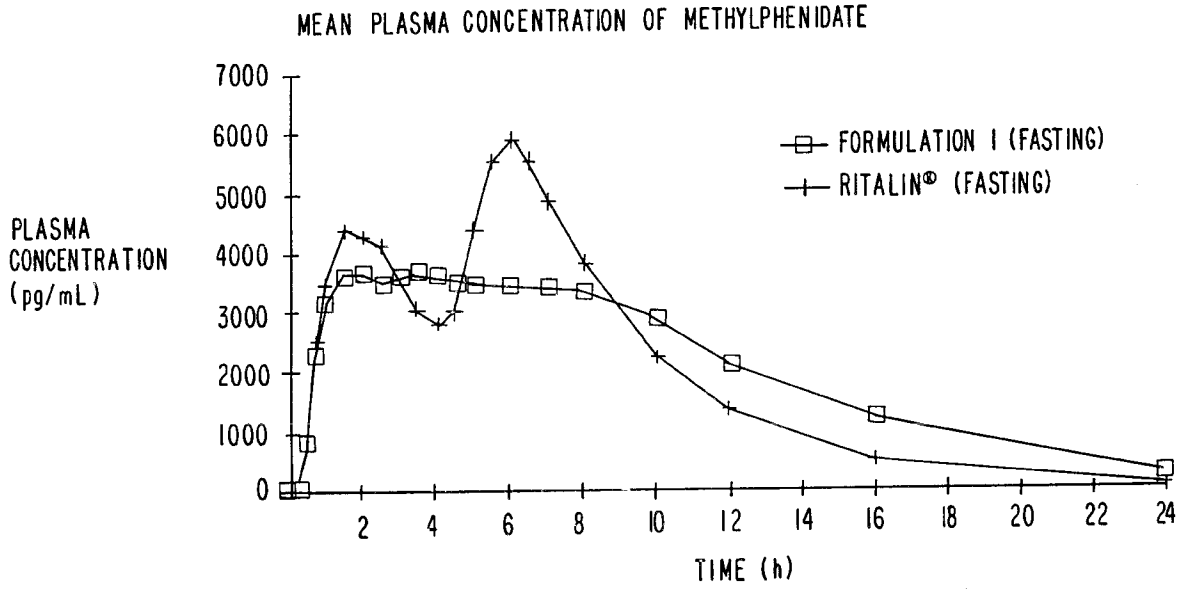


FIG.1

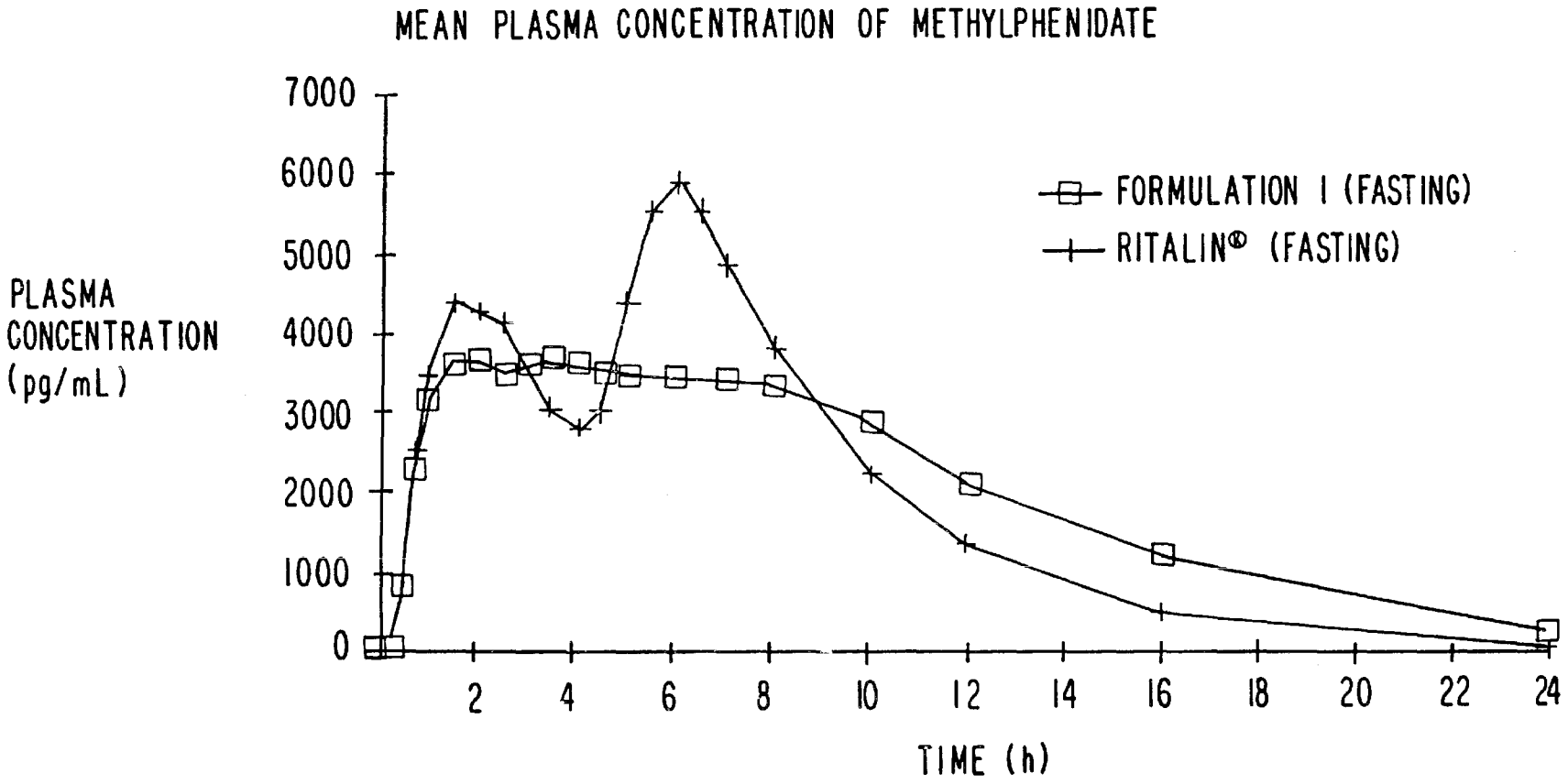

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (FASTING)
RITALIN® (FASTING)

FIG. 2

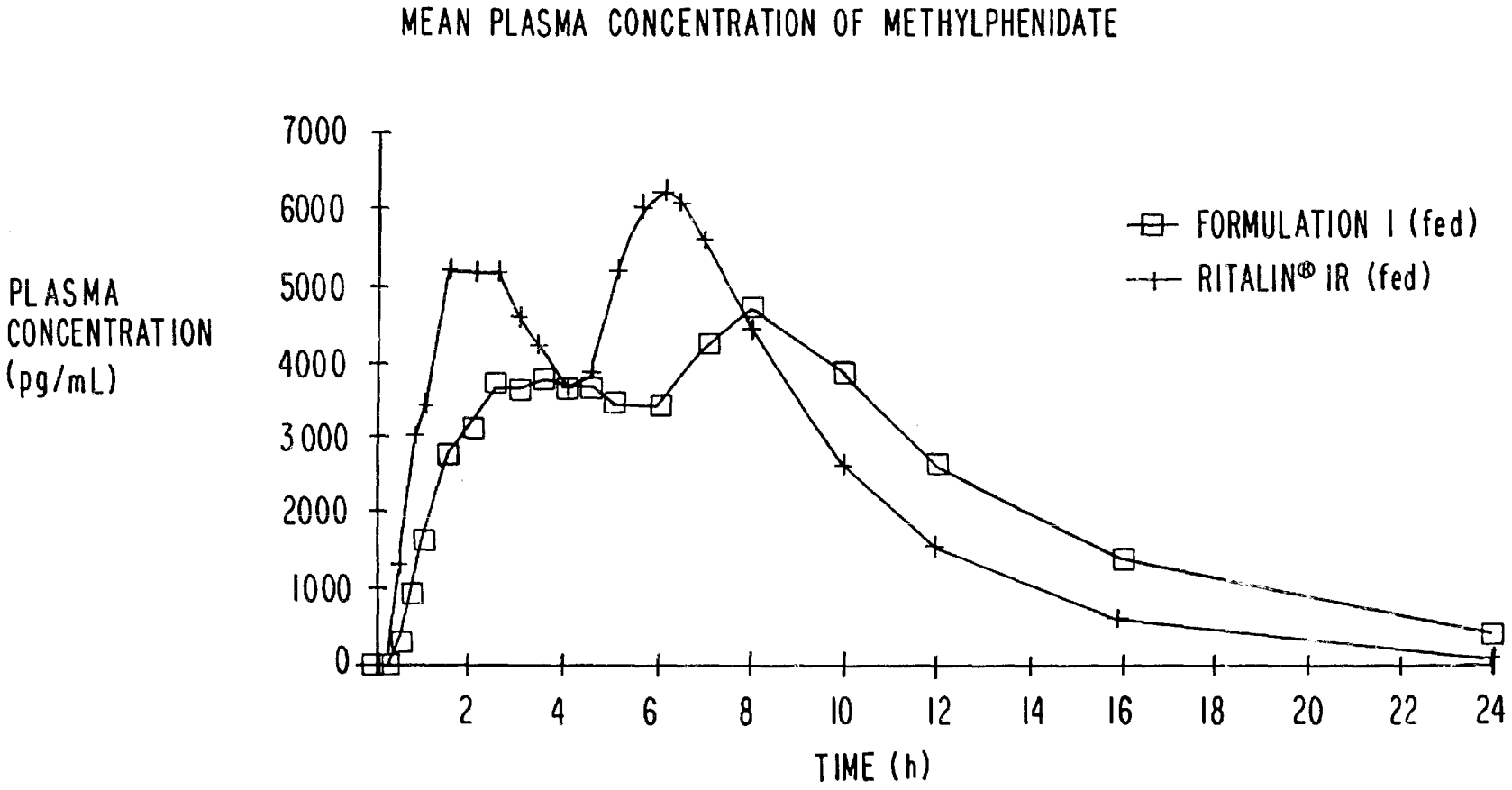

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (fed)
RITALIN® IR (fed)

FIG.3

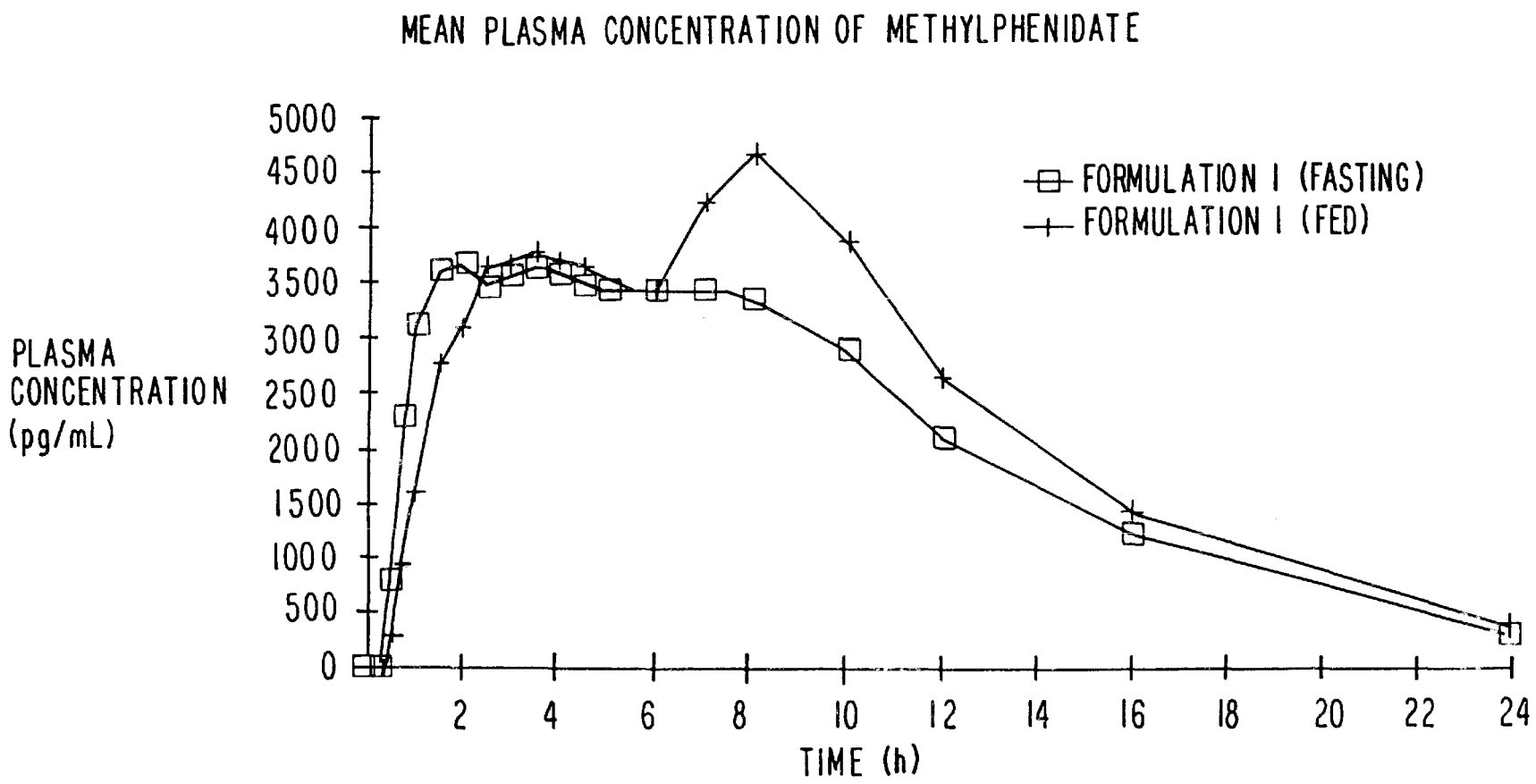

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (FASTING)
FORMULATION I (FED)

FIG. 4

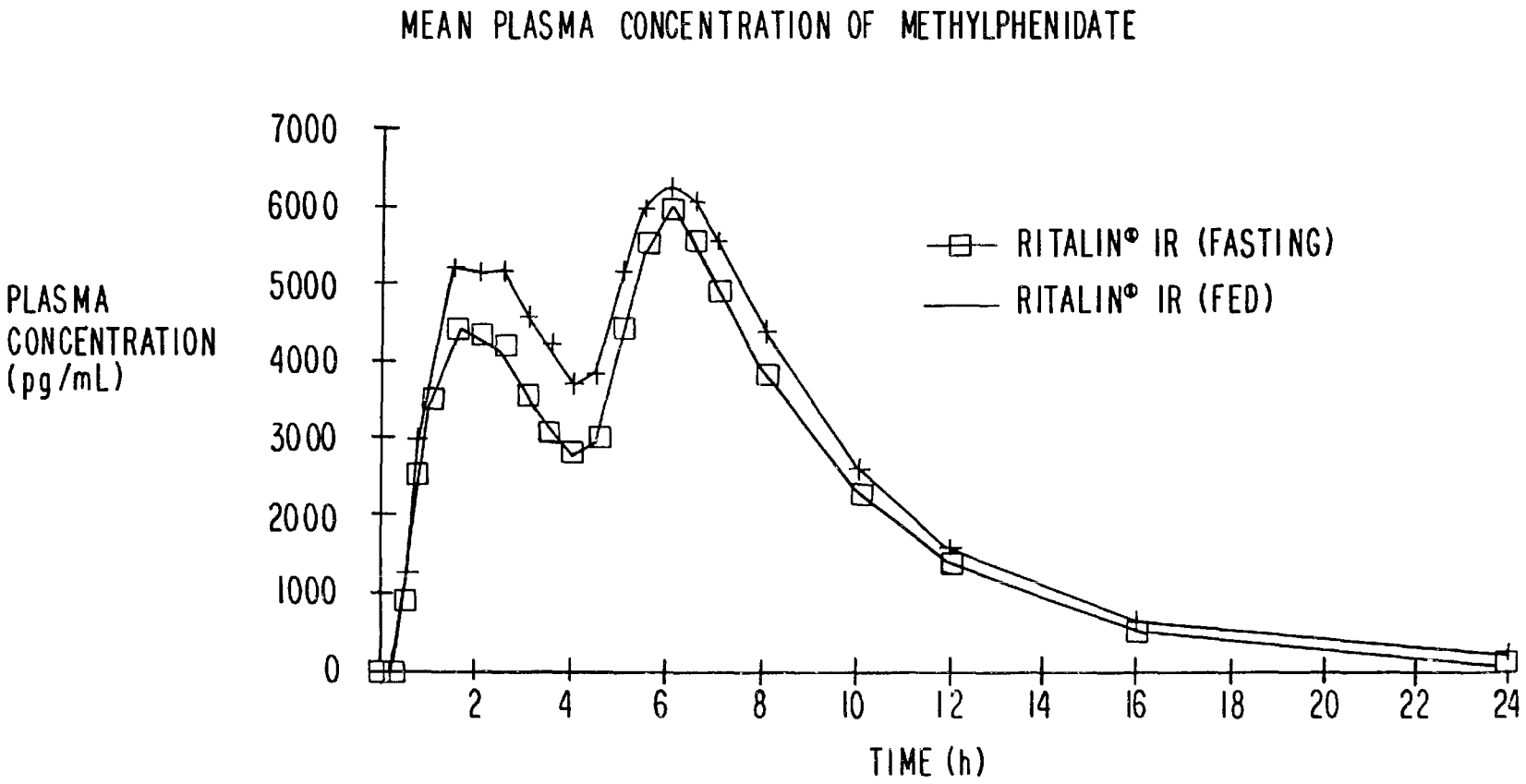

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
RITALIN® IR (FASTING)
RITALIN® IR (FED)

FIG.5

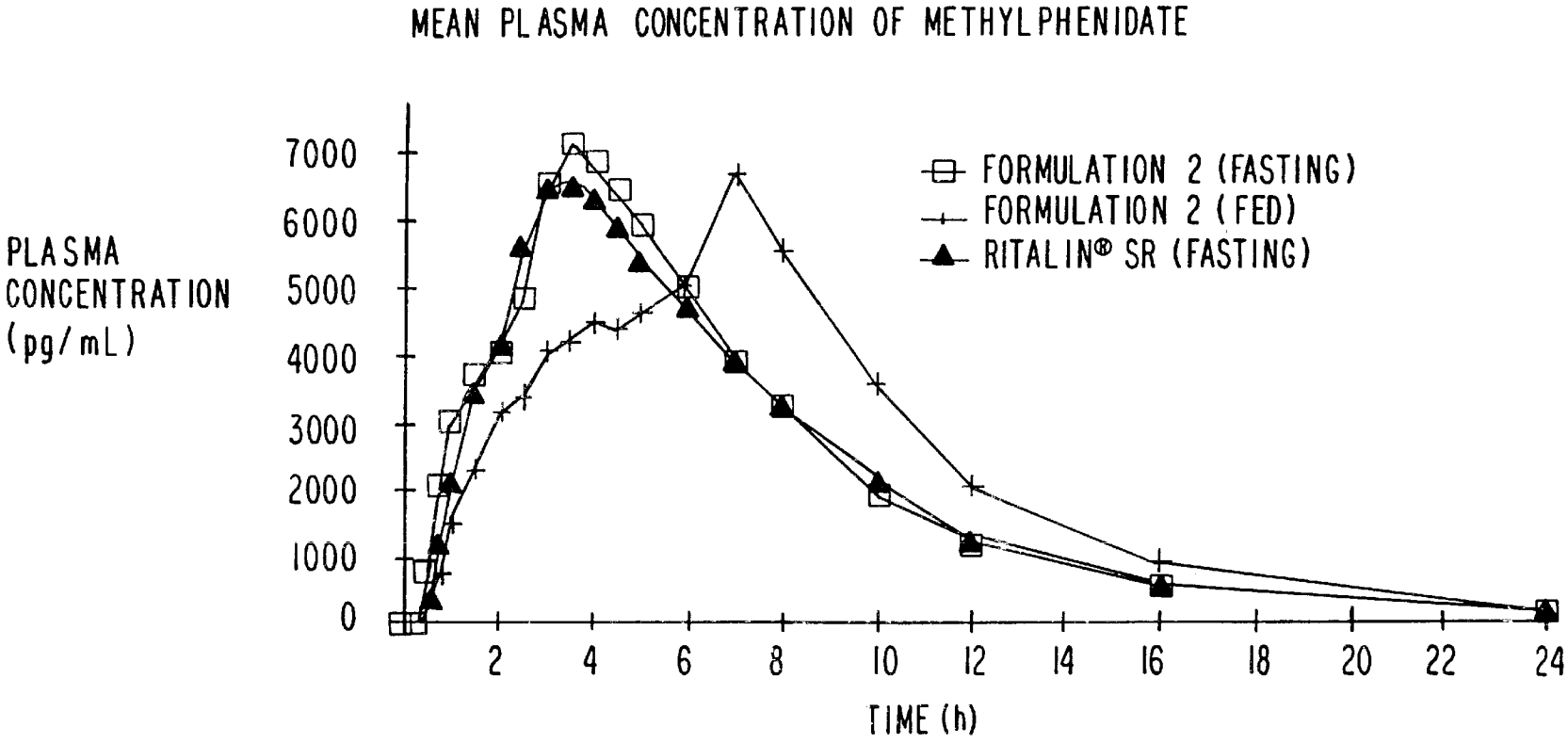

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FASTING)
FORMULATION 2 (FED)
RITALIN® SR (FASTING)

FIG.6

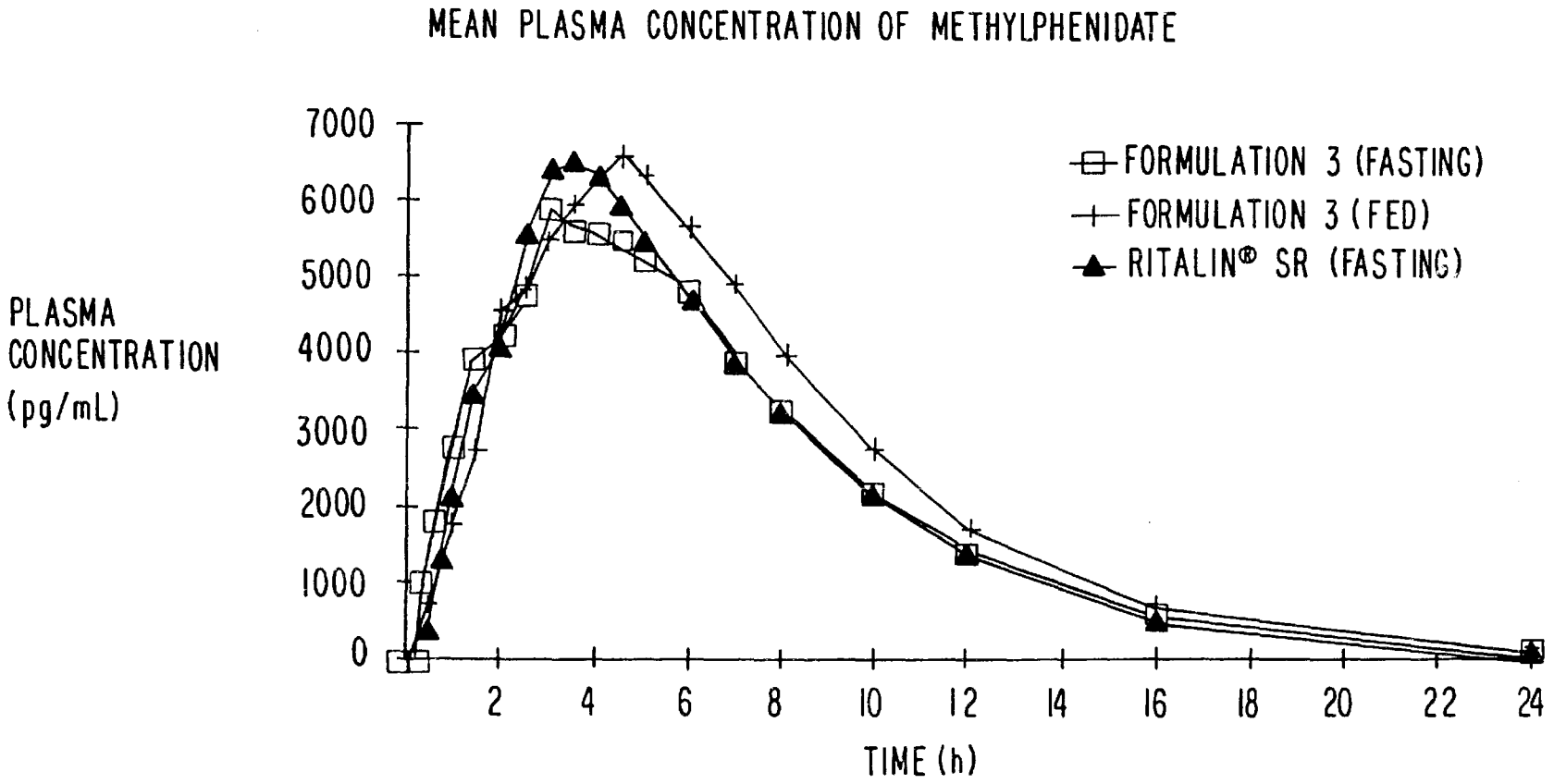

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 3 (FASTING)
FORMULATION 3 (FED)
RITALIN® SR (FASTING)

FIG. 7

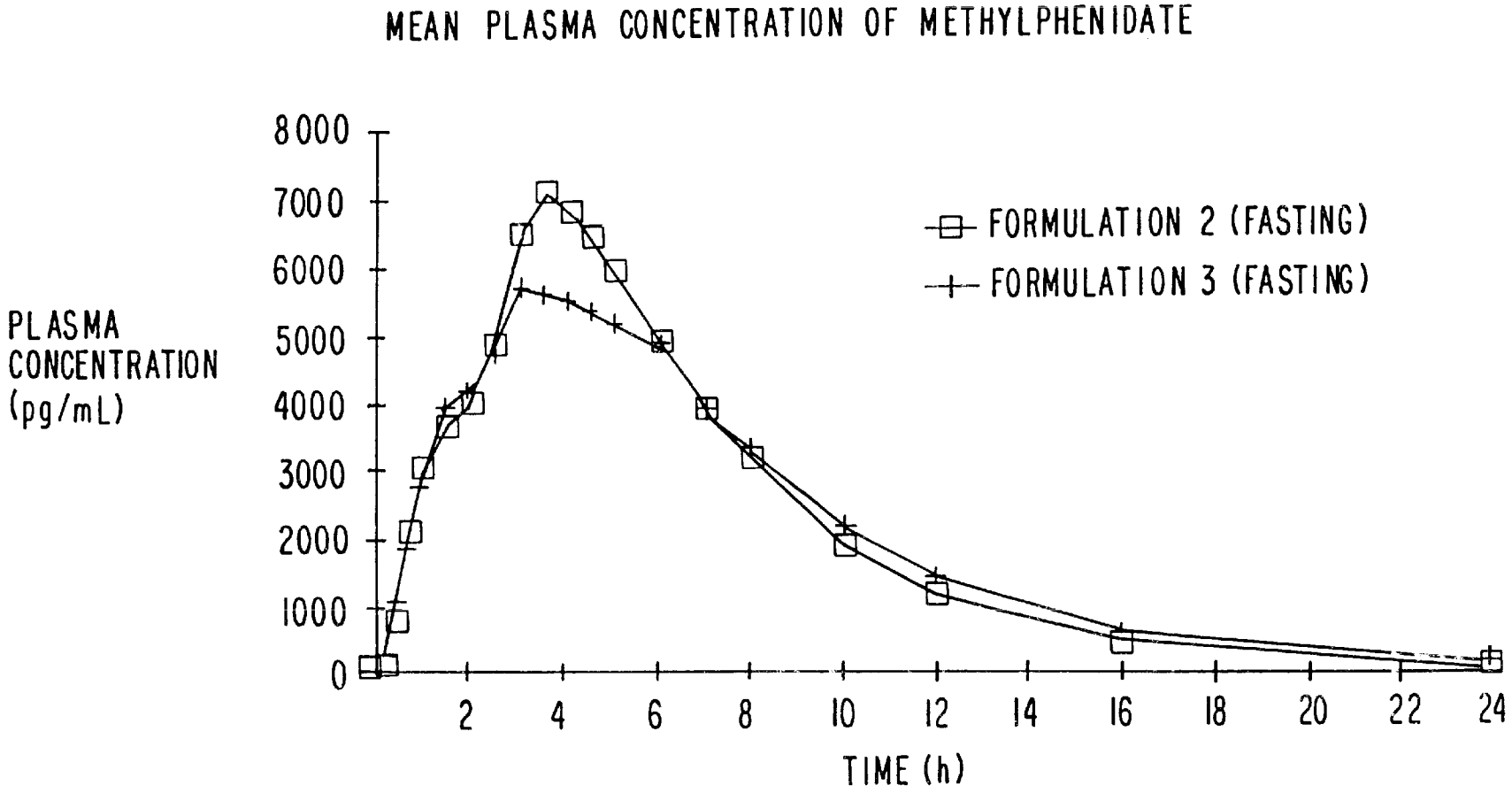
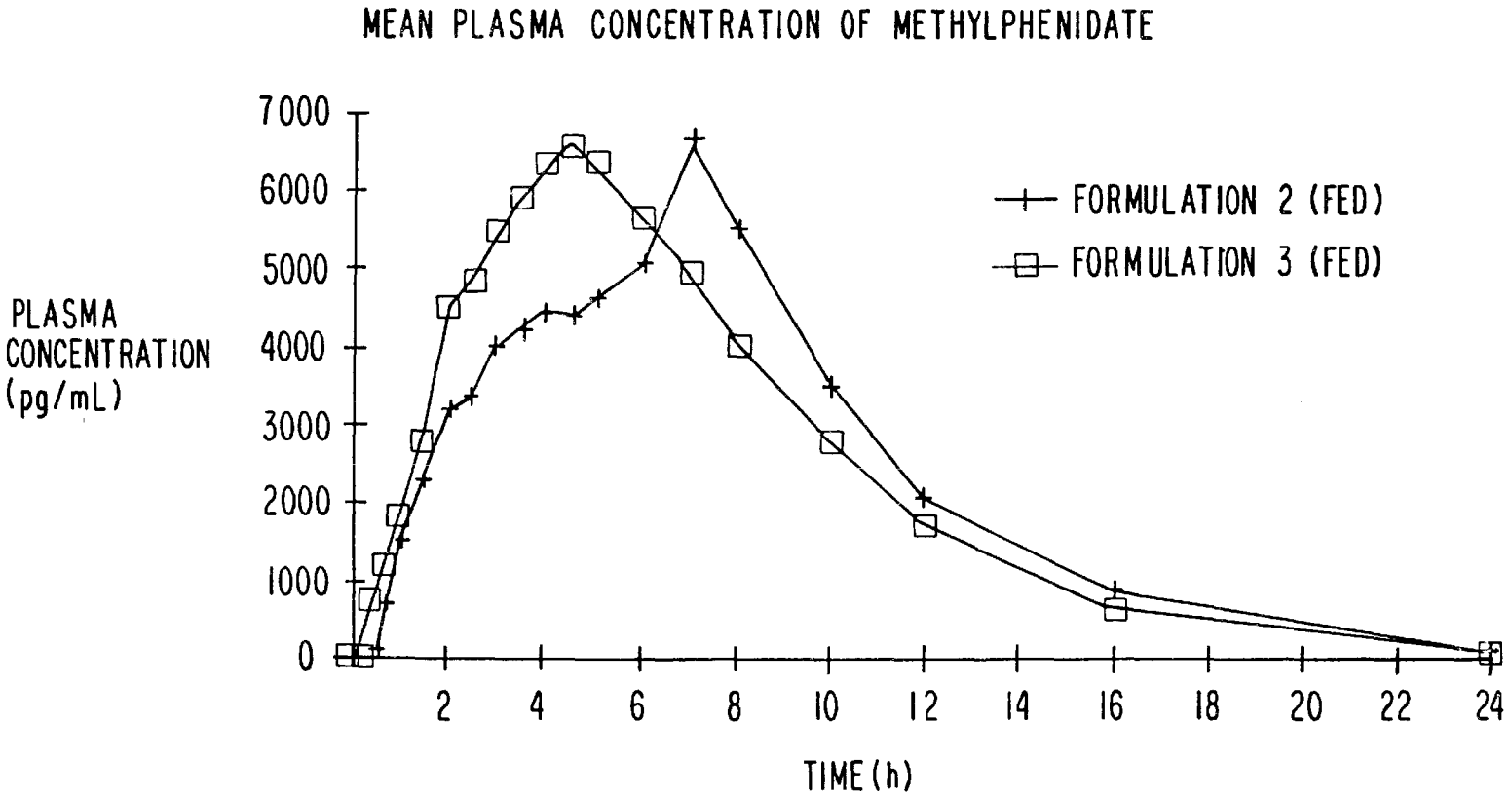

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
8000
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FASTING)
FORMULATION 3 (FASTING)

FIG. 8


MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FED)
FORMULATION 3 (FED)

CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS

This application claims priority from U.S. Provisional Application No. 60/112,617, filed Dec. 17, 1998, the disclosure of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. It is the intent of all sustained release formulations to provide a longer period of pharmacologic action after administration than is ordinarily obtained after administration of immediate-release dosage forms. Sustained release compositions may be used to delay absorption of a medicament until it has reached certain portions of the alimentary tract, and maintain a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered. Such longer periods of response provide for many therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. Thus, therapy may be continued without interrupting the sleep of the patient, which is of special importance, for example, when treating a patient for moderate to severe pain (e.g., a post-surgery patient, a cancer patient, etc.), or for those patients who experience migraine headaches on awakening, as well as for the debilitated patient for whom sleep is essential. A further general advantage of longer acting drug preparations is improved patient compliance resulting from the avoidance of missed doses through patient forgetfulness.

Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occurs because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance therapy of the patient. In view of this, it is considered a goal of many skilled in the art that a controlled release dosage form will ideally provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ratio. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

It is known in the pharmaceutical art to prepare compositions which provide for sustained release of pharmacologically active substances contained in the compositions after oral admimistration to humans and animals. Sustained release formulations known in the art include specially coated pellets, coated tablets and capsules, and ion exchange resins, wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ration. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

Controlled release formulations known in the art include specially coated beads or pellets, coated tablets and ion exchange resins, wherein the slow release of the active drug is brought about through selective breakdown of the coating of the preparation or through formulation with a special matrix to affect the release of the drug. Some controlled release formulations provide for sequential release of a single dosage of an active medicament at predetermined periods after administration.

While controlled and/or sustained release compositions have constituted a definite advance in the art, improvements in these compositions have been sought, particularly for preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD), diabetes etc.

Attention Deficit Disorders are the most common psychiatric disorders in children (Campbell et al. 1992) with reported rates ranging from 4% to 9% (Aman et al. 1983). Attention Deficit Disorder (ADD) is characterized by inattention and impulsivity and may be present with hyperactivity (ADHD) (Shaywitz et al. 1984). Other characteristics may include aggressiveness, stealing, lying, truancy, setting fires, running away, explosiveness, cognitive and learning problems as well as poor social skills (Campbell et al. 1992). It is four to five times more frequent in boys than girls (Campbell et al. 1992).

Stimulant medication, such as amphetamines, have been shown to be the most effective agents in the treatment of children with disorders of activity modulation and attention regulation and result in significant improvement in 70 to 80 per cent of affected children (Shaywitz et al. 1984). Positive effects of stimulants have been documented in a variety of areas including behavioral, social, perceptual performance, motor activity, impulse control, attention regulation and cognitive performance (Barkley 1977, Kavale 1983, Offenbacher et al. 1983, Rosenthalet al 1978).

Methylphenidate {dl-threo-methyl-2-phenyl-2-(2-piperidyl)acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The efficacy of methylphenidate ("MPH") in improving attention and behavioral symptoms has been supported by many studies.

Immediate release methylphenidate preparations, because of their short half-life, require frequent administration at short intervals to ensure adequate treatment throughout a child's school day. The rapid onset and offset of immediate release methylphenidate preparations means that a medicated child with attention deficit disorder will be maximally affected only for relatively brief periods during the day. Due to its short half-life, MPH is usually given twice per day, usually once after breakfast and once during the school day, an event that some children and some school personnel apparently avoid, resulting in poor compliance with prescribed regimens (Brown et al., 1985; Firestone 1982). Compliance is a major problem for children who require a midday or midafternoon dose as many schools prohibit children from taking medications during the school day and others often insist that all medications be given by a nurse. Poor compliance in taking medication may explain, in part,

the variable and conflicting results reported in many studies of the effect of medication on improving the behavior of hyperactive children. These limitations of immediate release methylphenidate led to interest in products with longer effective periods of action. These limitations of immediate release methylphenidate preparations led to interest in products with longer effective periods of action.

A sustained release form of methylphenidate (Ritalin® SR) is commercially available. As a result of many clinical trials, various opinion leaders in treatment of attention deficit hyperactivity disorder have made the following comments regarding Ritalin® SR (sustained release methylphenidate) produced by Ciba-Geigy: (i) Ritalin® SR does not have a sufficiently early onset of effect to allow for behavioral management in the early morning; (ii) Ritalin® SR does not have the beneficial late effects that would be produced by a lunch time dose of immediate release methylphenidate, thus defeating the purpose of using an SR formulation; (iii) The effects of Ritalin® SR are inconsistent or erratic over the course of the day.

There is a need in the art to develop drug formulations which provide a rapid onset, a prolonged action, followed by rapid offset of effect in order to overcome the deficiencies of the current state of the art.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which results in improved patient compliance.

It is an object of the present invention to provide new oral dosage formulations which represent improvements over currently available preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD).

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which ensure adequate treatment throughout a child's school day.

It is an object of the present invention to provide new oral dosage formulations which allow a child with attention deficit disorder to be maximally treated throughout the daytime, while being administered only once, i.e., in the morning.

It is a further object of the present invention to provide new controlled/modified release oral dosage formulations which provide a rapid onset and rapid offset with an extended release of active medicaments incorporated therein.

It is yet another object of the present invention to provide new controlled/modified release oral dosage formulations which are useful in all types of pharmaceutically active ingredients and which can extend the time of release of all such ingredients.

It is yet another object of the present invention to provide an oral controlled release formulation which combines both a rapid onset and sustained plasma concentrations throughout the day, followed by a rapid drop-off of plasma concentrations of drug to below minimum effective concentrations.

It is yet another object of the present invention to provide a "multi-layer release" (MLR) technology which is useful for all types of pharmaceutically active ingredients and which can extend the duration of action for a desired length of time.

To address the above-mentioned deficiencies as well as other goals, the present invention is directed in part to a controlled release product which is intended to combined both a rapid onset and sustained plasma concentrations throughout the day. Significantly, the formulations of the present invention provide a rapid onset, a prolonged action, followed by rapid offset of effect, i.e., a "square wave" profile.

The invention is directed in part to controlled/modified release formulations based on a multi-layered release ("MLR") technology. The drug product can be in a tablet or a multiparticulate formulation contained within an oral gelatin capsule.

In the case of beads, encapsulated in a capsule, each bead contains a series of layers with different characteristics—an outer immediate release layer, a release delaying layer (enteric coat), a controlled release layer over an immediate release layer. The MLR formulation is designed such that upon oral administration, the formulation provides a rapid dissolution and absorption of the outer layer of the formulation which contains a portion of the drug in immediate release form, thereby resulting in a rapid rise of the drug to therapeutic plasma levels. This is followed by a period of no absorption (due to an enteric coating), followed thereafter by a controlled release of the drug from the formulation to maintain plasma levels. After absorption of the drug from an immediate release core, plasma levels then rapidly decrease. By virtue of the release of the drug from the MLR formulation, the plasma level of the drug, when plotted on a time/concentration curve, takes the appearance of a "square wave".

In certain further preferred embodiments, the formulation provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and provides effective blood levels for at least about 6 hours after administration.

In certain further preferred embodiments, the formulation exhibits a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit a "plateau" which lasts from about 6 hours to about 12 hours. The "plateau" is characterized by a stabilized plasma concentration, wherein the plasma level at the end of the measured interval does not differ by more than 20%, preferably by no more than 10% of the plasma concentration at the beginning of the measured interval.

In certain further preferred embodiments, the formulation exhibits a bimodal release of active agent from the dosage form. Bimodal release of the active agent is characterized by the active agent being release from the dosage form by more than one distinct release rate. In some embodiments, the release rates can be separated by a no-release or a substantially no-release interval, although this is not always necessary.

In certain further preferred embodiments, the formulation exhibits a biphasic absorption of the active agent. Biphasic absorption of the active agent is characterized by the active agent being absorbed through a natural barrier (e.g. the mucosal lining of the gastrointestinal tract) by more than one distinct absorption rate. In some embodiments, the absorption rates can be separated by a no-absorption or a substantially no-absorption interval, although this is not always necessary. A formulation can exhibit both biphasic absorption and bimodal release of the active agent, with the biphasic absorption being a function of the bimodal release rate. However, biphasic absorption is not always attributed to release rate and can occur in a formulation not exhibiting bimodal release.

In other preferred embodiments the formulation exhibits bimodal release and/or biphasic absorption to provide a

"plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit bimodal release and/or biphasic absorption to provide a "plateau" which lasts from about 6 hours to about 12 hours. Other embodiments maintain effective plasma levels of the active agent for about 16 to about 18 hours after administration of the dosage form.

In certain preferred embodiments, an acrylic resin is utilized to provide the controlled slow release of therapeutically active ingredients over a predetermined or a specified period of time, the acrylic resin thereby comprising a significant part of the "base composition". Base compositions prepared from such acrylic resins provide sustained release of therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration, generally oral administration, in humans or animals.

In other embodiments of the invention, the formulations of the invention are composed of:

(i) a mixture of immediate release particles (e.g., beads) and enteric coated immediate release particles (e.g., beads); (ii) a mixture of immediate release particles (e.g., beads) and enteric coated controlled release particles (e.g., beads) or (iii) a mixture of immediate release particles (e.g., beads) and controlled release particles (e.g., beads). In each such instance, the mixture of particles possessing different release properties are blended together and filled into hard gelatin capsules.

In certain preferred embodiments, the controlled/modified release drug formulations of the invention consist of a plurality of beads, each containing an immediate-release component in combination with an enteric coated controlled-release component to produce a delay in the absorption process. The drug product is an oral capsule containing beads. Each bead contains a series of layers with different release characteristics—an outer immediate release layer; a release delaying layer; a controlled release layer; and an immediate release core. The final product is a capsule containing multi-layer release (MLR) beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption of the drug. In certain embodiments, the immediate release component represents 40% of the total dose per bead and the controlled release component represents 60%. This formulation is designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug. The results of a bioavailability study of this formulation indicate a biphasic release profile that is consistent with the pharmaceutical rationale discussed herein.

In other embodiments of the invention, the bead size of the formulations can be adjusted in order to obtain a desired pharmacokinetic profile based on the correlation between gastric emptying and bead size. A smaller bead size exhibits faster gastric emptying as compared to a larger bead size.

Other objects and advantages of the present invention will be apparent from the further reading of the specification and of the appended claims.

The term "pH-dependent" for purposes of the present invention is defined as having characteristics (e.g. dissolution) which vary according to environmental pH (e.g., due to changes in the in-vitro dissolution media, or due to passage of the dosage form through the gastrointestinal tract.

The term "pH-independent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH, in that a difference, at any given time, between an amount of methylphenidate released at one pH and an amount released at any other pH, when measured in-vitro using the USP Paddle Method of U.S. Pharmacopeia XXII (1990) at 100 rpm in 900 ml aqueous buffer, is no greater than 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. **1** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fasting conditions.

FIG. **2** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fed conditions.

FIG. **3** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 as a function of time when given under fasting and fed conditions.

FIG. **4** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Ritalin® as a function of time when given under fasting and fed conditions.

FIG. **5** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 2 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **6** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 3 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **7** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fasting conditions as a function of time.

FIG. **8** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fed conditions as a function of time.

DETAILED DESCRIPTION

The drug used in the formulations of the invention may be selected from a wide variety of pharmaceutically active drugs such as diabetes drugs, attention deficit hyperactivity controlled drugs, analgesics, anti-obesity preparations, anti-inflammatories, antihistamines, antitussives, decongestants, antinausea agents, narcotics, bronchodilators, cardiovasculars, central nervous system (CNS) drugs, nicotine replacement therapy, nitrates, sleeping aids/sedatives, vitamins, etc.

The controlled/modified release preparations of the present invention may be used in conjunction with any

multiparticulate system, such as granules, spheroids, beads, pellets, ion-exchange resin beads, and other multiparticulate systems in order to obtain a desired sustained-release of the therapeutically active agent. Beads, granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable unit dosage form. An amount of the multiparticulates effective to provide the desired dose of drug over time may be placed in a capsule, may be contained in a packet and sprinkled onto food, or may be incorporated in any other suitable oral solid form, such as a tablet. On the other hand, the present invention can be in the form of a matrix tablet. With respect to all such optional formulations, it is desired that the formulation be prepared such that an initial immediate release of drug provides an early onset of effect, which onset is analogous to an immediate release formulation, and that the formulation further provide a sustained release component which maintains therapeutically effective levels of the drug in the plasma for the desired amount of time, followed by a relatively rapid drop-off in blood plasma levels relative to typical sustained release formulations. Viewed as an in vivo time/concentration plot, the plasma level of the drug from the formulations of the present invention have the appearance of a "square wave". The immediate release component preferably represents from about 30% to about 40% of the total dose and the controlled release component preferably represents from about 60% to about 70% of the total dose of methylphenidate contained in the formulations of the present invention. In certain preferred embodiments, including the MLR embodiments of the invention, the immediate release component represents about 40% of the total dose and the controlled release component represents about 60% of the total dose of methylphenidate contained in the formulation.

In the case of methylphenidate, it is desired that the onset of action occurs from about 0.5 to about 4 hours, and preferably from about 0.5 to about 2 hours after the oral dosage form is administered, and it is further desired that the dosage form no longer provides effective plasma levels of methylphenidate from about 8 to about 12, more preferably from about 8 to about 10 hours, after oral administration of the dose. In this manner, the dose of methylphenidate can be administered to a child in the morning before school begins, provides the desired effect at the start of the school day, with the pharmacologic action of the drug not waning until after the school day ends, and preferably before dinner so that the drug does not have the side effect of acting as an appetite suppressant.

The formulations of the present invention are designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug.

It is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability. Bioavailability, in a more meaningful sense, is the degree, or amount, to which a drug substance is absorbed into the systemic circulation in order to be available to a target tissue site. To be absorbed, an active drug substance must be in a solution. The time required for a given proportion of an active drug substance contained in a dosage unit to enter into solution in appropriate physiological fluids is known as the dissolution time. The dissolution time for an active substance from a dosage unit is determined as the proportion of the amount of active drug substance released from the dosage unit over a specified time by a test method conducted under standardized conditions. The physiological fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.

Although there are many diverse factors which influence the dissolution of a drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from a specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in this steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiological conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium, providing for a steady state absorption.

The transport across a tissue absorption site in the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane, since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e. the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the gastrointestinal tract into the blood stream.

Notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, in many cases and important correlation can be established between the in vitro dissolution time determined for a dosage form and the in vivo bioavailability. This correlation is so firmly established in the art that dissolution time has become generally descriptive of bioavailability potential for many classes of active components contained in a particular dosage form. In view of this relationship, the dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating whether a controlled release formulation should be tested in vivo.

With the above in mind, the in-vitro dissolution of the drug at various time points for formulation in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%

In certain preferred embodiments of the present invention, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0–45%
1	10–50%
4	30–80%
8	NLT 65%
12	NLT 80%

Sustained Release Coatings

In certain preferred embodiments, the drug is incorporated into or onto a substrate and a sustained release coating is applied thereto. For example, the drug may be contained within or on a substrate as follows: (i) incorporated into matrix spheroids (e.g., together with a pharmaceutically acceptable spheronizing agent such as microcrystalline cellulose), (ii) coated onto inert pharmaceutically acceptable beads (e.g., nonpareil beads); (iii) incorporated into a normal release tablet core; or (iv) incorporated into a tablet core which comprises a matrix including a sustained release carrier material. Thereafter, a sustained release coating is applied onto substrates such as those mentioned in (i)–(iv) above. The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the drug in desired areas of the gastrointestinal (GI) tract, e.g., the stomach or small intestine. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) comprising the drug is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Such formulations are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference. The particles are preferably film coated with a material that permits release of the drug so as to achieve, in combination with the other stated properties, a desired in-vitro release rate and in-vivo plasma levels. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Acrylic Polymers

The hydrophobic material comprising the controlled release coating may comprise a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there

are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from R öhm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dis-solution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material such as an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When the aqueous dispersion of hydrophobic material is used to coat a substrate including the drug, for example, inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. Alternatively, the substrate may be a tablet core coated with the sustained release coating, and optionally a further film-forming agent or colorant, such as Opadry®.

In formulations where an aqueous dispersion of an hydrophobic polymer such as an alkylcellulose is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60° C and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

In formulations where an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45° C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

The sustained release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the drug to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

The plasticized aqueous dispersion of hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined sustained release of the therapeutically active agent (i.e., drug) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the drug from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The substrate of the present invention may be prepared by a spheronizing agent together with the active agent ingredient that can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredients and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer or ethyl cellulose. In such embodiments, the sustained-release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

In a particular preferred embodiment of the invention, the controlled/modified release methylphenidate formulation is prepared as a multilayered release (MLR) formulation comprising coated inert beads. A summary of one method of manufacturing such a formulation is outlined as follows. First, immediate release (IR) drug-coated beads are prepared by spraying a solution of methylphenidate in water over sugar beads in a fluid bed dryer with a drug load of about 8%. The spray process is carried out in a fluid bed dryer, equipped with a Wurster column. A clear overcoat of HPMC is applied using an Opadry® material (e.g., Opadry® Clear (Formula No: YS-1-7006)), to a weight gain of about 1%. Next, a controlled release coating is applied to the IR beads,

which converts the same into controlled release (CR) beads. This is accomplished by spraying a solution of Eudragit® RS 30 D, triethyl citrate (plasticizer) and talc (glidant), onto the IR beads. Next, the coated beads are cured in order to obtain a stabilized release rate of the therapeutically active agent. In preferred embodiments of the present invention where the CR coating utilizes an acrylic resin to control the release of the drug, the CR beads at this stage are subjected to oven curing at a temperature above the Tg of the plasticized acrylic polymer of the required time period, the optimum values of the temperature and time for the particular formulation being determined experimentally. In certain embodiments of the present invention, the stabilized products is obtained via oven curing conducted at a temperature of about 40–50° C. for a time period of about 12 to about 24 hours or longer. An enteric coating is then applied onto the CR beads to convert the same into enteric coated CR (ECCR) beads. This is accomplished by spraying a solution of Eudragit® L 30 D-55 dispersion, triethyl citrate (plasticizer) and talc (glidant) onto the CR beads. Finally, an immediate release coating is applied onto the ECCR beads (referred to as, e.g., an IR Topcoat). This is accomplished by spraying a solution of methylphenidate in water over EC CR beads.

Results of initial studies show that this formulation is stable under room temperature (25° C., 60% RH) and accelerated conditions (40° C., 75% RH).

In certain preferred embodiments of the present invention, an effective amount of the drug in immediate release form is included in the drug formulation. The immediate release form of the drug is included in an amount which is effective to shorten the time to maximum concentration of the drug in the blood (e.g., plasma), such that time to T_{max} is shortened to a time of, e.g., from about 0.5 to about 2 hours. By including an amount of immediate release drug in the formulation, the time to onset of action is significantly reduced, and is the same or earlier than that of the reference standard immediate release treatment (e.g., Ritalin IR). In such embodiments, an effective amount of the drug in immediate release form may be coated onto the substrates (e.g., multiparticulates or tablets) of the present invention. For example, where the extended release of the drug from the formulation is due to a controlled release coating, the immediate release layer can be overcoated on top of the controlled release coating. On the other hand, the immediate release layer may be coated onto the surface of substrates wherein the drug is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising an effective unit dose of the drug (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the drug dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release drug as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the drug. One skilled in the art would recognize still other alternative manners of incorporating the immediate release drug portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Methylphenidate HCl Immediate Release Beads

TABLE 1

Ingredients	%
Methylphenidate hydrochloride	15.0
Sugar bead 14/18	80.0
Opadry ® clear YS-1-7006	5.0
Water	q.s.
Total	100.0

1. Charge Nitro-Aeromatic Strea 1 Fluid Bed Wurster Coater with 14/18 mesh Nupareil® PG (sugar spheres NF).
2. Coat the beads at 60° C. by spraying a solution of methylphenidate hydrochloride (12% w/w) and Opadry clear (4% w/w) in water.
3. Once the coating is completed, allow the beads to dry at 60° C. for 2 or 3 minutes.
4. Cool the beads in a shallow pan at room temperature.
5. Break agglomerates, if any.
6. Sift the beads through Tyler 10 mesh sieve (1.77 mm opening) and then through Tyler 20 mesh sieve (850 micrometer opening) to remove fines.
7. Apply top coat to beads by spraying a solution of coloured Opadry clear solution (4% w/w) to a theoretical weight gain of 1% w/w.

After the completion of the overcoat, the beads are then filled into hard gelatin capsules at a strength of 20 mg.

Dissoultion testing was conducted on the bead filled IR capsules using USP Apparatus 1 (basket method) in 500 of simulated gastric juice without enzyme, 100 rpm at 37° C. The results are as follows.

TABLE 2

Time (minutes)	% Methylphenidate HCl dissolved
10	92.7
20	95.7
30	97.7
45	98.5

The dissolution results as set forth in the above table indicate that 98.5% of the methylphenidate hydrochloride was dissolved in 45 minutes.

EXAMPLE 2

Methylphenidate HCl Controlled-Release (CR) Beads with Acrylic Polymer Coating

TABLE 3

Ingredients	%
Methylphenidate IR beads	86.20
Eudragit ® RS 30 D	8.63
Triethyl citrate	1.72
Talc	3.45
Water	q.s.
Total	100.0

The controlled-release coating is manufactured as follows:

1. The Eudragit® RS 30 D is plasticized with triethyl citrate and talc approximately 30 minutes.

2. A load of the IR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~8%.
3. Upon completion of the coating, the beads are cured for 24 hours at 40–45° C.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR capsules using the following USP Apparatus (basket method). The capsules were placed into 500 mL of simulated gastric juice without enzyme, for first 2 hours at 100 rpm and 37° C. and then placed into 500 mL simulated intestinal fluid without enzyme for the remainder of the testing period. The results are as follows:

TABLE 4

Time (hours)	Methylphenidate HCl dissolved
1	6.9
2	16.2
3	26.1
4	35.7
6	59.8
8	74.7
12	75.4
18	82.5
24	92.8

The dissolution results as set forth in the above table indicate that 92.8% of methylphenidate hydrochloride dissolved in 24 hours.

EXAMPLES 3 & 4

Dependence of Release Rate of Methylphenidate HCl from Controlled-Release (CR) Beads on Amount of Acrylic Polymer Coating

By adjusting the amount of Eudragit® RS 30 D applied, the release rate can be adjusted. This effect is illustrated in 3 and 4 below:

TABLE 5

	%	
Ingredients	Example 3	Example 4
Methylphenidate HCl IR Bead	91.2	94.0
Eudragit ® RS 30 D	5.8	3.9
Triethyl citrate	1.0	0.7
Talc	2.0	1.4
Water	—	—
Total	100.0	100.0

The method of manufacturing the controlled-release beads in Examples 3 and 4 is similar to the method described under Example 2, by varying the proportion of beads and Eudragit® RS 30D.

The cured beads were filled into hard gelatin capsules at a strength of 20 mg.

The dissolution results, conducted under conditions identical to those found under Example 2, are shown below:

TABLE 6

Time	% Methylphenidate HCl dissolved	
(hours)	Example 3	Example 4
1	18.7	49.5
2	35.1	73.3
3	49.0	81.5
4	60.6	85.2
6	75.7	90.4
8	77.3	90.7
12	82.1	92.8

The dissolution set forth in the above table, indicate that 82.1% and 92.8% respectively of methyphenidate hydrochloride is dissolved in 12 hours. However, the release of drug from Example 4 was significantly faster at time points 1, 2, 3, 4, 6 and 8 hours.

EXAMPLE 5

Enteric Coated (EC) Coated Release (CR) Beads—EC·CR Beads

TABLE 7

Ingredients	%
Methylphenidate CR beads	83.2
Eudragit ® L 30 D55	9.9
Triethyl citrate	2.0
Talc	4.9
Water	q.s.
Total	100.0

The enteric coating procedure is described below:

1. The Eudragit® L 30 D 55 is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the methylphenidate CR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~9%.
3. Upon completion of the coating, the beads are cured for 18 hours at 40° C.
4. The cured beads are then sieved through Tyler 10 mesh (1.7 mm opening) and Tyler 20 mesh (850 micrometer opening) sieves to remove any fines.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR filled capsules using USP Apparatus 1 (basket method) 500 mL at 100 rpm and 37° C. using SGF without enzyme for the first 2 hour and SIF without enzyme for the rest of the testing period. Results are shown below:

TABLE 8

Time	% Methylphenidate HCl dissolved		
(hours)	Lot 1	Lot 2	Lot 3
1	0.4	1.0	2.0
2	2.2	5.4	7.4
3	18.8	27.8	61.3
4	36.7	48.3	87.0
6	59.5	75.5	98.8
8	76.9	90.1	100.0
12	82.3	99.6	—

The dissolution results as set forth in the above table indicate that very little drug is dissolved in gastric juice after

enteric coating and that the dissolution profile of the CR beads has been modified.

EXAMPLE 6

Formulations for Clinical Trials

Examples 6A, 6B and 6C below set forth the formulations developed and tested in clinical studies.

EXAMPLE 6A: (IR·EC·CR Beads)

Immediate Release (IR) Coating of Enteric Coated Controlled-Release (EC·CR) Methylphenidate Beads

The (IR·EC·CR Beads) formulation, hereinafter referred to as Formulation 1, is a capsule containing multi-layer release beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption equal to or greater than Ritalin® IR immediate release tablets. The immediate release component represent 40% of the total dose per bead and the controlled release component represents 60%.

TABLE 9

Ingredients	%
Enteric coated Controlled Release Methylphenidate HCl beads	91.4
Methylphenidate hydrochloride USP	6.5
Opadry ® clear YS-1-7006	2.1
Water	q.s.
Total	100.0

The application of an immediate release coat on the top of Enteric Coated CR beads is described below:

1. Dissolve methylphenidate HCl USP and Opadry in water with stirring.
2. Load EC–CR beads into a Wurster insert of an Aeromatic Fluid Bed Dryer.
3. Spray the beads with the coating solution using a 1 mm spray nozzle at a temperature of not more than 50° C.
4. Once the coating is completed, cool the beads at room temperature and pass through Tyler sieves 10 and 20 mesh to remove fines.

The beads were then filled into a hard gelatin capsule to a 20 mg strength.

Dissolution testing was conducted on the bead filled capsules of Formulation 1 using USP Apparatus 1 (basket method) 100 rpm, 500 mL at 37° C.—simulated gastric juice without enzyme 1st and 2nd hours; 3rd hour onwards simulated intestinal fluid without enzyme.

The results are as follows:

TABLE 10

Time (hours)	% Methylphenidate HCl dissolved
5 minutes	37.0
10 minutes	38.0
15 minutes	39.0
30 minutes	40.0
60 minutes	40.0
2	40.1
3	51.4
4	61.0
6	75.6
8	87.0
12	87.5

The dissolution results as set forth in the above table indicate a rapid onset on dissolution, followed by prolonged action.

EXAMPLE 6B: (IR+EC·CR Blend)

Combination of Immediate Release Methylphenidate Beads (IR) and Enteric Coated Controlled-Release (EC·CR) Methylphenidate Beads

The enteric-coated controlled release beads (EC·CR) beads described in Example 5 may be mixed with the immediate release (IR) beads described in Example 1 in varying proportions and placed in capsules to obtain the final blended dosage form, (IR+EC·CR Blend), hereinafter referred to as Formulation 2. Formulation 2 was designed to provide a faster rate of absorption of the controlled release portion than Formulation 1. The immediate release component represents 35% of the total dose per capsule and the controlled release component represents 65%.

Dissolution testing was performed and the comparative results are shown in Table 11 below.

EXAMPLE 6C: (IR·CR Beads)

Immediate Release (IR) Coating of Controlled-Release (CR) Methylphenidate Beads

The IR·CR Beads formulation, hereinafter referred to as Formulation 3, is a capsule containing single beads made up of an immediate release topcoat and a controlled release core, and is designed to provide an intermediate rate of absorption of the controlled release portion between that of the controlled release formulations of Formulations 1 and 2. The immediate release component represents 30% of the total dose per bead and the controlled release component represents 70%.

The immediate release topcoat is applied to CR beads as described in Example 6A for Formulation 1.

The dissolution profiles of Formulations 1–3 and Ritalin® SR, used as a comparator, are shown in Table 11 below. Hours 1 and 2 are in 500 ml of simulated gastric fluid. Simulated intestinal fluid (500 ml) is used from the third hour onwards. The results of the dissolution testing confirmed the anticipated in vitro dissolution profile.

TABLE 11

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
10 min	21.4	38.0	32.0	28.6
30 min	31.4	40.0	36.7	34.0
1	45.7	40.0	38.2	40.5

TABLE 11-continued

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
2	62.3	40.1	40.4	57.6
3	75.8	51.4	68.1	70.6
4	79.5	61.0	86.4	79.5
6	88.0	75.6	95.4	89.6
8	90.7	87.0	96.2	92.7
12	91.3	87.5	97.0	93.1

EXAMPLE 7

Four Way Comparison of Single Dose Formulation 1 (Fed and Fasted with Two Doses of Ritulin IR (Fed and Fasted)

The bioavailability of Methylphenidate MLR capsules was investigated in a four-way blind study which compared the Formulation 1 20 mg single dosage formulation under fed and fasted conditions with two doses (4 hours apart) of Ritalin® IR.

Healthy male volunteers were given a single dose of 20 mg Formulation 1 or two doses of immediate release methylphenidate 10 mg administered four hours apart under both fed and fasting conditions (n=12). "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 4 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, under fasting conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, administered 5 minutes after a high fat breakfast.

Treatment 4: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, administered 5 minutes after a high fat breakfast.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Formulation 1 and at pre-dose, 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Ritulin® IR. Plasma was harvested from each blood sample and stored in a −20° C. freezer until assayed for plasma methylphenidate concentration. Assay of plasma methylphenidate concentrations was performed using gas chromatography/mass spectrometry (GC/MS).

The mean plasma concentrations, standard deviations and coefficients of variation are shown as a function of time in Tables 12 and 13, for fasting and fed conditions, respectively.

This data is presented graphically in FIGS. **1**–**4**. FIG. **1** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fasting conditions. FIG. **2** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fed conditions. FIG. **3** presents the mean plasma concentration versus time for Formulation 1 under fed and fasting conditions. FIG. **4** presents the mean plasma concentration versus time for Ritalin® under fed and fasting conditions.

TABLE 12

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fasting)

Sample Time	Formulation 1			Ritalin		
(h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	—
0.250	0.00	0.00	—	0.00	0.00	—
0.500	817.53	801.84	98.08	883.96	686.65	77.68
0.750	2268.79	1128.12	49.72	2485.74	828.38	33.33
1.00	3108.79	756.66	24.34	3468.74	1172.28	33.80
1.50	3597.88	740.36	20.58	4388.04	998.86	22.76
2.00	3675.60	1315.29	35.78	4289.39	1144.40	26.68
2.50	3469.81	882.62	25.44	4121.37	1014.57	24.62
3.00	3573.56	1031.61	28.87	3528.56	863.25	24.46
3.50	3637.01	1008.73	27.74	3020.93	716.36	23.71
4.00	3604.03	1071.59	29.73	2747.91	698.95	25.44
4.50	3494.44	1069.13	30.60	2958.49	799.89	27.04
5.00	3446.41	1069.50	31.03	4394.22	1603.40	36.49
5.50	—	—	—	5525.84	1766.58	31.97
6.00	3421.13	1166.25	34.09	5927.06	1955.99	33.00
6.50	—	—	—	5528.41	1758.49	31.81
7.00	3422.32	958.42	28.00	4560.45	1482.24	30.50
8.00	3338.59	724.49	21.70	3795.34	1500.79	39.54
10.0	2858.42	612.21	21.42	2223.48	926.11	41.65
12.0	2073.97	536.08	25.85	1334.71	523.37	39.21
16.0	1180.67	502.11	42.53	455.86	287.79	63.13
24.0	275.87	201.51	73.04	55.10	99.99	181.46

TABLE 13

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fed)

Sample Time	Formulation 1			Ritalin		
(h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	—
0.250	0.00	0.00	—	53.12	133.84	251.95
0.500	291.66	271.58	93.11	1256.61	1602.66	127.54
0.750	910.22	653.80	71.83	2984.60	3406.53	114.14
1.00	1580.66	983.13	62.20	3400.39	2301.87	67.69
1.50	2760.68	797.24	28.88	5205.16	1882.17	36.16
2.00	3098.73	874.49	28.22	5146.55	1617.43	31.43
2.50	3655.68	982.31	26.87	5157.11	1227.99	23.81
3.00	3625.88	797.55	22.00	4546.61	932.94	20.52
3.50	3717.71	951.58	25.60	4184.34	1080.71	25.83
4.00	3650.63	875.97	23.99	3652.57	1023.22	28.01
4.50	3627.41	835.40	23.03	3811.27	1103.83	28.96
5.00	3430.14	783.72	22.85	5158.45	1714.53	33.24
5.50	—	—	—	5982.98	1618.65	27.05
6.00	3418.03	937.07	27.42	6228.81	1591.64	25.55
6.50	—	—	—	6054.32	1919.95	31.71
7.00	4218.94	775.86	18.39	5538.57	1741.02	31.43
8.00	4679.67	1126.52	24.07	4350.90	1611.95	37.05
10.0	3858.58	1045.56	27.10	2577.66	896.59	34.78
12.0	2610.98	902.53	34.57	1521.52	611.54	40.19
16.0	1372.86	737.71	53.74	577.90	334.26	57.84
24.0	334.79	306.63	91.59	94.23	144.99	153.86

EXPERIMENTAL RESULTS

Pharmacokinetic parameters were calculated based on the data from the four-way study. AUC_{0-t}(pg·h/mL), AUC_{0-inf} (pg·h/mL), $AUC_{t/inf}$(%), C_{max}(pg/mL), T_{max}(hours), $T_{1/2}$ el(hours), K_{el}(hour^{-1}), TLIN(hours) and LQCT(hours) were calculated as described below.

For purposes of the present invention, the following terms are meant to have the following meanings:

Analysis of Pharmacokinetic Data and Statistical Analysis

calculations. Sampling times are present in concentration tables and graphs of statistical report.

The mean, standard deviation (SD), and coefficient of variation (CV) were calculated for plasma concentrations of methylphenidate for each sampling time and treatment. As well, the mean, SD, and CV were calculated for the AUC_{0-t}(pg·h/mL), AUC_{0-inf}(pg·h/mL), C_{max}(pg/mL), T_{max}(hours), $T_{1/2}$ el(hours), K_{el}(hour^{-1}), TLIN(hours) and LQCT(hours). The calculation of these pharmacokinetic parameters is explained below.

AUC_{0-t}	Area under the concentration-time curve from time zero to the time of the last non-zero concentration (this corresponds to the area under the concentration-time curve, over the dosing interval of the test formulation for both controlled-release and immediate-release formulations)
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity
C.I.	Confidence interval
CV	Coefficient of variation
C_{max}	Maximum observed concentration
K_{el}	Elimination rate constant
LQCT	The last quantifable concentration time
SD	Standard deviation
TLIN	The time point where log-linear elimination begins
$T_{1/2\ el}$	Time for observed C_{max}
Sampling Time	Time post dose of plasma collection based on parameters to be studied
Scheduled Time	The predetermined (clock) time at which the samples are to be taken
Actual time	The exact (clock) time at which the sample was taken

Time deviations during sampling for drugs with a $T_{max} \geqq 4$ hours were treated as follows: between 0 and 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of blood collection was <10%. Above 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of plasma collection was <15%. When sampling times were used when previously described acceptance criteria, the corrected sampling items were used when performing pharmacokinetic parameters

Areas under the Concentration-Time Curves

AUC_{0-t} was calculated using the linear trapezoidal rule.

The AUC_{0-t} was derived where t is the time (t) of the last measurable (non-zero) concentration (C_t) for each treatment.

The AUC_{0-inf} was calculated as:

$$AUC_{0-1} + \frac{C_t}{K_{el}}$$

Where C_t=the last non-zero concentration for that treatment, AUC_{0-t}=the AUC from time zero to the time of the last non-zero concentration for that treatment and K_{el}=the elimination rate constant.

Maximum Observed Concentration and Time of Observed Peak Concentration The maximum observed concentration, C_{max}, and the observed time to reach peak concentration, T_{max}, was determined for each subject and for each treatment.

Half-Life and Elimination Rate Constant

To calculate the elimination rate constant (K_{el}), linear regression analyses were performed on the natural log (Ln) of plasma concentration values (y) versus time (x). Calculations were made between a time point where log-linear elimination phase begins (LQCT) occurred. The K_{el} was taken as the slope multiplied by (−1) and the apparent half-life ($T_{1/2}$ el) as $0.693/K_{el}$.

TLIN and LQCT

TLIN, the time point where log-linear elimination begins, and LQCT, the last quantifiable concentration time were determined for each subject and for each treatment.

Percent Drug Absorbed

Percent drug absorbed was calculated at each sampling time (t) by Modified Wagner-Nelson's method, as implemented in Kinetica software, version 2.0.1 according to the following formula:

$$\frac{C_t + (K_{el} \times AUC_{0-t})}{(K_{el} \times AUC_{0-inf})} \times 100$$

All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.050. Based on the pairwise comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} data, the relative ratios of the geometric means, calculated according to the formulation "$e^{(X-Y)} \times 100$", as well as the 90% geometric confidence intervals were determined.

The plasma concentration of unchanged methylphenidate following administration of the controlled release formulation Formulation 1 reached the maximum concentration (C_{max}) at a mean of 3.27 hours under fasting conditions and 7.29 hours under fed conditions reflecting a biphasic absorption profile. The plasma concentration of unchanged methylphenidate following maximum concentration (C_{max}) at 5.96 hours under fasting conditions and 3.54 hours under fed conditions. When the determination of C_{max} was restricted to the first dose of immediate release methylphenidate, the T_{max} was 1.71 hours under fasting conditions and 1.63 hours under fed conditions.

The complete pharnacokinetic parameters of controlled release methylphenidate 20 mg Formulation 1 and immediate release methylphenidate 10 mg (Ritalin® IR) under fed and fasted conditions are summarized in Tables 14 and 15 below.

TABLE 14

Pharmacokinetic Parameters for Formulation 1

Parameters	Formulation 1 (fasting) Mean ± SD	CV (%)	Formulation 1 (fed) Mean ± SD	CV (%)
AUC_{0-t}(pg.h/mL)	48493.80 ± 13430.27	27.69	54686.38 ± 15118.66	27.65
AUC_{0-inf}(pg.h/mL)	51213.86 ± 3260.14	26.59	57931.47 ± 16762.54	28.94
C_{max}(pg/mL)	4410.25 ± 1188.68	26.95	4879.37 ± 1027.85	21.07
T_{max}(h)	3.27 ± 2.54	77.64	7.29 ± 1.29	17.65
$K_{el}(h^{-1})$	0.1672 ± 0.0339	20.25	0.1812 ± 0.0392	21.65
$T_{1/2\ el}$(h)	4.32 ± 0.96	22.18	4.06 ± 1.25	30.91

TABLE 15

Pharmacokinetic Parameters for Ritalin ® IR

Parameters	RITALIN ® (fasting) Mean ± SD	CV (%)	RITALIN ® (fed) Mean ± SD	CV (%)
AUC_{0-t}(pg.h/mL)	44644.22 ± 13806.82	30.93	52781.49 ± 15194.94	28.79
AUC_{0-inf}(pg.h/mL)	46466.23 ± 14012.73	30.16	54783.17 ± 15311.08	27.95
C_{max}(pg/mL)	6536.04 ± 1669.29	25.54	7571.74 ± 1534.58	20.27
T_{max}(h)	5.96 ± 0.54	9.09	3.54 ± 2.42	68.43
$K_{el}(h^{-1})$	0.2481 ± 0.0550	22.17	0.2449 ± 0.0719	29.37
$T_{1/2el}$(h)	2.93 ± 0.71	24.10	3.08 ± 0.96	31.26

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatment 1 was significantly different from the AUC_{0-t} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized in Table 16 below:

TABLE 16

AUC_{0-t} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	109.90%	104.08%	88.65%
90% Geometric C.I.	102.59% to 117.74%	97.15% to 111.50%	82.75% to 94.97%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for

this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatment 1 was significantly different from the AUC_{0-inf} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized below in Table 17:

TABLE 17

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	111.65%	105.86%	88.85%
90% Geometric C.I.	104.09% to 119.95%	98.70% to 113.55%	82.84% to 95.30%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 1 was not significantly different from the C_{max} of treatment 3. However, Duncan's Multiple Range Test detected statistically significant differences for C_{max} when comparing treatments 1 and 2 and treatments 3 and 4. The statistical analyses performed on the data are summarized below in Table 18:

TABLE 18

C_{max}(pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	67.48%	64.38%	89.37%
90% Geometric C.I.	60.28% to 75.54%	57.51% to 72.07%	79.83% to 100.04%

The ANOVA and Duncan's Multiple Range Test performed on the T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 3 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the $T_{1/2}$ eldata detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 3 for $T_{1/2}$ el. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 and treatments 3 and 4 for this parameter.

The results of the ANOVA and Duncan's Multiple Range Test performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were detected by Duncan's Multiple Range Test between treatments 1 and 2 and treatments 3 and 4, but not for treatments 1 and 3.

SUMMARY AND ANALYSIS

The AUC and C_{max} ratios of controlled release methylphenidate 20 mg Formulation 1 under fed and fasted conditions are summarized in Table 19 below. A comparison of the AUC and C_{max} ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fasting conditions are summarized in Table 20 below. Table 21 shows the comparative ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fed conditions.

Treatment 1 (Formulation 1, fasting) versus Treatment 3 (Formulation 1, fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2}$ el. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 3 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed K_{el} and $T_{1/2}$ el. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test product (Formulation 1, fasting) to reference product (Formulation 1, fed) were found to be within 80 to 125%. This is summarized in Table 19 below:

TABLE 19

	Formulation 1 (Fed) vs. Formulation 1 (Fast)		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.80%	112.54%	111.90%
90% Geometric C.I.[2]	105.29%–120.84%	104.93%–120.71%	99.96%–125.27%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1(fed)-Formulation 1 (fasting)}]} \times 100$

[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 1, fasting) versus Treatment 2 (Ritalin®, fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2}$ el, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for all parameters. With the exception of C_{max}, all formulation ratios as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of test product (Formulation 1) to reference product (Ritalin) were found to be within the 80 to 125%. This is summarized in Table 20 below:

TABLE 20

	Formulation 1 (Fast) vs Ritalin ® (Fast)		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.90%	111.65%	67.48%
90% Geometric C.I.[2]	102.59%–117.74%	104.09%–119.75%	60.28%–75.54%

[1]Calculated using geometric means according to the formula:
$e^{[\text{Formulation 1 (fast) - Ritalin IR (fast)}]} \times 100$

[2]90% Geometric Confidence Interval using log-transformed data

Treatment 3 (Formulation 1, fed) versus Treatment 4 (Ritalin®, fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, T_{el}, $T_{1/2}$ el. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for all parameters with the exception of ln-transformed AUC_{0-t} and AUC_{0-inf}. With the exception of C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80% to 125%. This is summarized in Table 21 below:

TABLE 21

	Formulation 1 (Fed) vs. Ritalin ® IR (Fed)		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.08%	105.86%	64.38%
90% Geometric C.I.[2]	97.15%–111.50%	98.70%–113.55%	57.51%–72.07%

[1]Calculated using geometric means according to the formula:
$e^{[\text{Formulation 1 (fed)-Ritalin IR (fed)}]} \times 100$

[2]90% Geometric Confidence Interval using log-transformed data

CONCLUSIONS

Review of individual plasma MPH time curves indicates the following:

Plasma MPH concentrations at 12 hours were higher on Formulation 1 than on Ritalin IR in all subjects, under both fed and fasted conditions.

A biphasic profile was apparent under fasted conditions in 7–10/12 subjects and in 8–10/12 under fed conditions. The mean curve showing a stable plateau under fasted conditions is therefore not fully representative of the individual profiles. The enteric coat therefore gave rise to a biphasic profile in some subjects even under fasted conditions.

Under fasted conditions the apparent rate of rise of plasma MPH was equivalent to, or faster than, that of Ritalin IR in 8/12 subjects under fasted conditions and 4–5/12 subjects under fed conditions. The mean curves which demonstrate an equivalent rate of rise under fasted conditions and a slower rise under fed conditions were therefore largely reflective of the individual profiles.

The bioavailability of Formulation 1 relative to Ritalin IR was acceptable under both fed and fasted conditions (Relative AUC_{inf} 106% and 112%). There was an increase in AUC of both Formulation 1 and Ritalin when given with food (13.1% and 17.9% respectively).

Formulation 1 had a more prolonged mean plasma MPH concentration time profile than two doses of Ritalin IR. An across study comparison indicates that Formulation 1 also has a more prolonged profile than Ritalin SR.

Under fasted conditions Formulation 1 had a mean initial rate of rise of plasma MPH that is similar to Ritalin IR and a relatively flat plateau until 8 hours post-dose.

Under fed conditions, the initial rise in plasma MPH from Formulation 1 was slower than under fasted conditions and the plateau showed a biphasic profile. This was consistent with predictions that the enteric coat would delay release of the controlled release component and that this delay would be longer under fed conditions (allowing the initial plasma concentration peak, due to the IR component, to fall prior to the start of release from the controlled release component).

Formulation 1 results in both a fast initial rate of rise of plasma methylphenidate concentration, and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Formulation 1 therefore has the potential to meet the dual objectives of rapid onset and prolonged duration that are considered desirable characteristics of a controlled release methylphenidate formulation for the treatment of ADD/ADHD.

An initial pilot bioavailability study completed in adult healthy volunteers has confirmed that a single 20 mg dose of this formulation has an equivalent extent of absorption to two doses of immediate release methylphenidate (10 mg) given 4 hours apart. Maximal plasma concentrations with the controlled release formulation are similar to those attained with the first dose of immediate release methylphenidate and from approximately 10 hours post-dose, are higher than those following the second dose of immediate release methylphenidate.

The results indicate the potential for a single morning dose of this formulation to produce clinical effects that are at least equivalent to those of two doses of immediate-release methylphenidate given at breakfast and lunchtime, with a duration of action that may reduce the need for a third dose of immediate release methylphenidate later in the day.

EXAMPLE 8

Five-Way Comparison of Single Dose Formulation 2 (Fed and Fasted), Single Dose Formulation 3 (Fed and Fasted) and Single Dose Ritulin SR (Fasted)

A five-way blind study was conducted which compared a single dose of Formulation 2, 20 mg, both fed and fasted, a

single dose of Formulation 3, 20 mg, both fed and fasted, and Ritalin SR 20 mg single dose fasted. According to the published literature and anecdotal comments from physicians, Ritalin SR is used in less than 20% of methylphenidate treated patients.

Twelve healthy male volunteers were given a single dose of either 20 mg Formulation 2 or Formulation 3 administered four hours apart under both fed and fasting conditions (n=12), or slow-release 20 mg methylphenidate (Ritalin SR) under fasting conditions. "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 5 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning, under fed conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fasting conditions.

Treatment 4: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg, capsule, under fed conditions.

Treatment 5: Reference Product: methylphenidate slow-release 20 mg tablet Ritalin SR (Novartis) under fasting conditions.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose. Plasma was harvested from each blood sample and stored in a −20C freezer until assayed for plasma methylphenidate concentration.

The data is presented graphically in FIGS. **5–8**. FIG. **5** presents the mean plasma concentration versus time for Formulation 2 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **6** presents the mean plasma concentration versus time for Formulation 3 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **7** presents the mean plasma concentration versus time for Formulations 2 and 3 under fasting conditions. FIG. **8** presents the mean plasma concentration versus time for Formulations 2 and 3 under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg (Formulation 2 and 3) under fed and fasting conditions, and for slow release methylphenidate 20 mg (Ritalin® SR) under fasting conditions are summarized in Tables 22–24 below.

TABLE 22

Pharmacokinetic Parameters for Formulation 2

Parameters		Treatment 1, Fasting Means ± SD	CV(%)	Treatment 2, Fed Mean ± SD	CV(%)
AUC_{0-t}	(pg.h/mL)	48190.73 ± 11668.71	24.21	53452.63 ± 12820.39	23.98
AUC_{0-inf}	(pg.h/mL)	49787.07 ± 12053.23	24.21	55690.49 ± 12691.52	22.79
C_{max}	(pg.h/mL)	7498.57 ± 1968.38	26.25	6879.09 ± 1486.53	21.61
T_{max}	(h)	3.63 ± 0.57	15.70	6.42 ± 1.08	16.89
K_{el}	(h^{-1})	0.2391 ± 0.0428	17.91	0.2321 ± 0.0342	14.75
$T_{1/2}$	(h)	3.00 ± 0.64	21.32	3.05 ± 0.48	15.74

TABLE 23

Pharmacokinetic Parameters for Formulation 3

Parameters		Treatment 3, Fasting Means ± SD	CV(%)	Treatment 4, Fed Mean ± SD	CV(%)
AUC_{0-t}	(pg.h/mL)	48057.06 ± 14743.87	30.68	54128.75 ± 14787.94	27.32
AUC_{0-inf}	(pg.h/mL)	49984.68 ± 14873.03	29.76	56315.66 ± 14779.59	26.24
C_{max}	(pg.h/mL)	6080.97 ± 2048.60	33.69	6959.07 ± 559.34	22.41
T_{max}	(h)	3.46 ± 0.89	25.76	4.42 ± 0.56	12.62
K_{el}	(h^{-1})	0.2009 ± 0.0468	23.32	0.2057 ± 0.0390	18.97
$T_{1/2}$	(h)	3.65 ± 0.97	26.52	3.49 ± 0.70	20.01

TABLE 24

Pharmacokinetic Parameters for Ritalin SR ®

Parameters	Mean ± SD	CV (%)
AUC_{0-t}(pg.h/mL)	47404.51 ± 12754.66	26.91
AUC_{0-inf}(pg.h/mL)	49252.17 ± 12841.52	26.07
C_{max}(pg/mL)	6783.09 ± 1496.65	22.06
T_{max}(h)	3.50 ± 0.43	12.18
K_{el}(h^{-1})	0.2282 ± 0.0320	14.01
$T_{1/2\ el}$(h)	3.10 ± 0.47	15.14

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 3 was significantly different from the C_{max} of treatments 4 and 5. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for C_{max} when comparing treatment 1 vs. treatment 2 or treatment 1 vs treatment 5. The statistical analyses performed on the data are summarized in Table 25 below:

TABLE 25

C_{max}(pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	103.73%	84.78%	109.25%	87.40%
90% Geometric C.I.	98.94% to 115.14%	78.59% to 91.45%	101.28% to 117.85%	81.05% to 94.26%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, and treatments 3 and 4 for this parameter. Duncan's Multiple Range Test did not detect statistically significant differences between treatments for Tm,a when comparing treatments 1 vs. 3 or treatments 3 vs. 5.

The ANOVA performed on the $T_{1/2}$ eldata detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 5 for $T_{1/2}$ el. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were not detected by Duncan's Multiple Range Test, between treatments for K_{el} when comparing treatments 1 and 2, treatments 3 and 4, or treatments 1 and 5. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatments 1 and 3 was significantly different from the AUC_{0-t} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-t} when comparing treatment 1 vs treatment 5, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 26:

TABLE 26

AUC_{0-t} (pg · h/mL)	Treatment 1 vs. Treatment 2	Treatment 3 vs. Treatment 4	Treatment 1 vs. Treatment 5	Treatment 3 vs. Treatment 5
Ratio	89.21%	88.23%	101.82%	100.63%
90% Geometric C.I.	84.03% to 94.71%	83.10% to 93.67%	95.91% to 108.10%	94.81% to 106.81%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatments 1 and 3 was significantly different from the AUC_{0-inf} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-inf} when comparing treatment 1 vs treatment 3, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 27:

TABLE 27

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	88.33%	88.14%	101.14%	100.82%
90%	83.50% to	83.32% to	95.61% to	95.33% to

TABLE 27-continued

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Geometric C.I.	93.44%	93.24%	106.99%	106.63%

Treatment 1 (Formulation 2, Fasting) vs. Treatment 2 (Formulation 2, Fed)

The ANOVAs detected statistically significant differences between fed and fasting conditions, treatments 1 and 2, for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2}$ eland K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed $T_{1/2}$ eland K_{el}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 28 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 2. However, this food effect was less than 20% on average.

TABLE 28

Formulation 2, Fed versus Fasting

	AUC_{0-1}	AUC_{0-inf}	C_{max}
Ratio[1]	112.09%	113.21%	93.69%
90% Geometric C.I.[2]	105.58% to 119.00%	107.03% to 119.76%	86.85% to 101.07%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 2(Fed)-Formulation 2 (Fasting)})} \times 100$

[2]90% Geometric Confidence Interval using In-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 4 (Formulation 3, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2}$ eland K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for untransformed $T_{1/2}$ eland K_{el}. With the exception of lower 90% geometric confidence interval for C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 29 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 3. However, this food effect was less than 20% on average.

TABLE 29

Formulation 3, Fed versus Fasting

	AUC_{0-1}	AUC_{0-inf}	C_{max}
Ratio[1]	113.35%	113.45%	117.96%
90% Geometric C.I.[2]	106.76% to 120.33%	107.25% to 120.01%	109.35% to 127.25%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 3 (fed)-Formulation 3 (Fasting)})} \times 100$

[2]90% Geometric Confidence Interval using In-transformed data

Treatment 1 (Formulation 2, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2}$ eland K_{el}. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 5 for all parameters. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 30 below. Thus, Formulation 2

is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 30

Formulation 2 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.82%	101.14%	106.99%
90% Geometric C.I.[2]	95.91% to 108.10%	95.61% to 106.99%	101.28 to 117.85%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 2 (fast)-Ritalin SR (Fast)})} \times 100$

[2]90% Geometric Confidence Interval using In-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2}$ eland K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for ln-transformed C_{max} and untransformed $T_{1/2}$ eland K_{el}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 31 below. Thus, Formulation 3 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 31

Formulation 3 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.63%	100.82%	87.40%
90% Geometric C.I.[2]	94.81% to 106.81%	95.33% to 106.63%	81.05 to 94.26%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation (fast)-Ritalin SR (Fast)})} \times 100$

[2]90% Geometric Confidence Interval using In-transformed data

CONCLUSIONS

The bioavailability of Formulation 2 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 101%—Fed conditions not tested). The bioavailability of Ritalin SR® under fasted conditions is similar to that of Ritalin® IR, as discussed in Example 7 (AUC_{inf} 29.2 vs. 46.5 ng.h/mL, respectively). Literature data which indicates that Ritalin® IR and SR are absorbed at equivalent rates suggests that comparisons between the studies presented in Examples 7 and 8 are reasonable.

Bioavailability of Formulations 1 and 2 are similar under fasted and fed conditions (fasted: 49.8 vs. 51.2 ng.h/mL; fed: 55.7 vs. 57.9 ng.h/mL).

From the mean curves of Formulation 2 and Ritalin SR®, the initial rate of rise of plasma MPH concentration is slightly faster for Formulation 2 compared to Ritalin SR®. Under fed conditions, the rate of rise of plasma MPH with Formulation 2 decreased and T_{max} was delayed in comparison to both Formulation 2 fasted and Ritalin SR® fasted.

Bioavailability of Formulation 3 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 100.8%—fed conditions not tested).

Bioavailability of Formulations 1 and 3 are similar under fasted and fed conditions (fasted: 50.0 versus 51.2 ng/hmL; fed: 56.3 versus 57.9 ng·h/mL). Note also that Formulations 2 and 3 have almost identical AUC values.

From the mean curves for Formulation 3 and Ritalin SR®, the initial rate of rise of plasma MPH concentrations is slightly faster for Formulation 3 compared to Ritalin SR®.

In contrast to Formulation 2, the effect of food on the initial rate of concentration rise is minimal. Since Formulation 3 does not contain an enteric coat, this suggests that food slows the initial release from the IR component of formulations that contain an enteric coat, both when the enteric coat is part of the same bead (underneath the IR coat in the case of Formulation 1) and when it is in a separate bead (as for Formulation 2).

Also in contrast to Formulation 2, the T_{max} of the mean curve of Formulation 3 occurs at a similar time to that of Ritalin SR® under fed and fasted conditions. For Formulation 2 (and Formulation 1) the T_{max} of the second absorption phase under fed conditions is substantially delayed relative to Ritalin SR®.

CONCLUSIONS—EXAMPLES 7 and 8

1. Formulation 1 has both a fast initial rate of rise, at least under fasted conditions and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Since these conditions represent the extremes of "food stress", one might predict that administration in association with normal meals and times would provide an intermediate profile. It is also possible that gastric emptying in children on a normal meal schedule will be faster than in adults fed a high fat meal—this will tend to make the second absorption phase occur earlier and produce lower concentrations from 12 hours onwards. Formulation 1 therefore meets the dual objectives of rapid onset and prolonged duration.
2. Formulation 2 is also very similar to Ritalin SR® under fasted conditions but shows a delayed peak under fed conditions such that plasma MPH concentrations are higher than Ritalin SR®(fasted) from 6 hours post dose onwards. The controlled release component in Formulation 2 is faster releasing than the one in Formulation 1 and plasma MPH concentrations are lower for Formulation 2 from about 10 hours post dose.
3. Overall, Formulation 3 (non-enteric coated) has a profile very similar to Ritalin SR® under both fed and fasted

conditions. The IR component of Formulation 3 provides some increase in initial absorption rate relative to Ritalin SR® under fasted conditions. Since concentrations later in the day are similar for the two formulations, this confirms the concept that a fast initial rise and higher concentrations later in the day are not possible at the same dose, unless a delay is introduced into the release of a component of the total dose.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. An oral controlled release formulation which provides a rapid onset of therapeutic effect and a rapid drop in plasma concentration after a prolonged period of therapeutic effect, comprising

a plurality of substrates comprising a portion of the effective dose of a drug in immediate release form,

a hydrophobic material coated onto the surface of said substrates in an amount sufficient to retard the release of said drug,

an enteric coating applied over said hydrophobic coating in an amount sufficient to substantially delay the release of said drug from said substrate until after said formulation passes through the stomach,

the formulation further comprising the remaining portion of said drug in immediate release form;

wherein the oral dosage form provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and wherein the duration of effect provided by the drug contained in the formulation falls below effective plasma concentrations at about 8 to about 12 hours after oral administration.

2. The formulation of claim **1**, wherein said remaining portion of said drug is applied to said substrates over said enteric coating.

3. The formulation of claim **1**, wherein a unit dose of said plurality of substrates are contained within a gelatin capsule, and said remaining portion of said drug is also contained within said gelatin capsule in a form selected from the group consisting of an immediate release powder, an immediate release granulate, immediate release matrix spheroids, immediate release beads, and as a coating applied onto the surface of said enteric coated substrates.

4. The formulation of claim **1**, wherein said hydrophobic material comprises a plasticized aqueous dispersion of an acrylic polymer which is sprayed onto the surface of said substrates.

5. The formulation of claim **4**, wherein said substrates are subjected to oven curing at a temperature above the glass transition temperature of the plasticized acrylic polymer at a temperature from about 40 to about 50° C. for a time period of at least about 12 hours prior to the application of said enteric coating.

6. The formulation of claim **1**, which provides a peak plasma concentration of the drug which is from about 1.0 to about 2.0 times the plasma concentration of the drug provided by the formulation at about 9 hours after oral administration.

7. The formulation of claim **1**, wherein the oral dosage form provides a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration.

8. The formulation of claim **6**, wherein the peak plasma concentration is from about 1.0 to about 1.7 times the plasma concentration of drug provided by the formulation at about 9 hours after oral administration.

9. The formulation of claim **6**, wherein the duration of effect provided by the drug contained in the oral dosage form falls below effective plasma concentrations at about 8 to about 10 hours after oral administration.

10. The formulation of claim **9**, which provides a "square wave" plasma profile.

11. The formulation of claim **9**, which provides an in-vitro dissolution as follows:

Time (hours)	% Drug Dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%

12. A method for preparing an oral controlled release formulation which provides a rapid onset of therapeutic effect and a rapid drop in plasma concentration after a prolonged period of therapeutic effect, comprising

preparing a plurality of substrates comprising a portion of the effective dose of a drug in immediate release form by spraying a solution of the drug onto said substrates;

applying a hydrophobic material to said substrates in an amount to retard the release of said drug;

applying an enteric coating over said hydrophobic coating in an amount sufficient to substantially delay the release of said drug from said substrate until after said formulation passes through the stomach;

applying an immediate release overcoat of said drug onto said enteric coated substrates;

wherein the oral dosage form provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and wherein the duration of effect provided by the drug contained in the formulation falls below effective plasma concentrations at about 8 to about 12 hours after oral administration.

13. The method of claim **12**, wherein the hydrophobic material is derived from an aqueous dispersion of plasticized acrylic polymer, said hydrophobic material being subjected to oven curing at a temperature above the glass transition temperature of the plasticized acrylic polymer at a temperature from about 40 to about 50° C. for a time period of about 12 to about 24 hours, prior to the application of said enteric coating.

14. The method claim **12**, wherein said enteric coating is derived from a solution of acrylic/methacrylic copolymers dispersion, triethyl citrate and talc.

15. The method of claim **12**, wherein formulation provides an in-vitro dissolution as follows:

Time (hours)	% Drug Dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%

16. The method of claim **15**, wherein said formulation provides a time to maximum plasma concentration of the drug at about 0.5 to about 4 hours after oral administration and a peak plasma concentration of the drug which is from about 1.0 to about 2.0 times the plasma concentration of the drug provided by the formulation at about 9 hours after oral administration.

17. The method of claim **15**, wherein the plasma concentration of the drug when administered to a human patient falls below effective plasma concentrations at about 8 to about 12 hours after oral administration.

18. The method of claim **17**, wherein the formulation provides a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration.

* * * * *

EXHIBIT B

US007083808B2

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

(10) **Patent No.: US 7,083,808 B2**
(45) **Date of Patent: Aug. 1, 2006**

(54) **CONTROLLED/MODIFIED RELEASE ORAL METHYLPHENIDATE FORMULATIONS**

(75) Inventors: **Paul D. Goldenheim**, Wilton, CT (US); **Richard S. Sackler**, Greenwich, CT (US); **Thinnayam N. Krishnamurthy**, Ontario (CA); **Andrew Darke**, Ontario (CA); **Benjamin Oshlaci**, New York, NY (US)

(73) Assignee: **Euro-Celtique S.A.**, Luxembourg (LU)

(*) 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.: **10/741,081**

(22) Filed: **Dec. 19, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/465,158, filed on Dec. 16, 1999, now Pat. No. 6,673,367.

(60) Provisional application No. 60/112,667, filed on Dec. 17, 1998.

(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61K 9/16	(2006.01)
A61K 9/22	(2006.01)
A61K 9/48	(2006.01)
A61K 9/52	(2006.01)

(52) **U.S. Cl.** **424/490**; 424/451; 424/452; 424/457; 424/458; 424/464; 424/465; 424/468; 424/469; 424/489

(58) **Field of Classification Search** 424/451, 424/452, 457, 458, 464, 465, 468, 469, 470, 424/489, 490

See application file for complete search history.

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Primary Examiner—Susan T. Tran
(74) *Attorney, Agent, or Firm*—Davidson Davidson and Kappel, LLC

(57) **ABSTRACT**

The invention is directed to oral modified/controlled release methylphenidate formulations which provide a rapid initial onset of effect and a prolonged duration of effect. Preferably, the peak concentration is lower than that provided by the reference standard for immediate release methylphenidate formulations, and the duration of effect falls rapidly at the end of the dosing interval so as not to affect the appetite of the patient at dinner nor the patient's sleep thereafter.

10 Claims, 11 Drawing Sheets

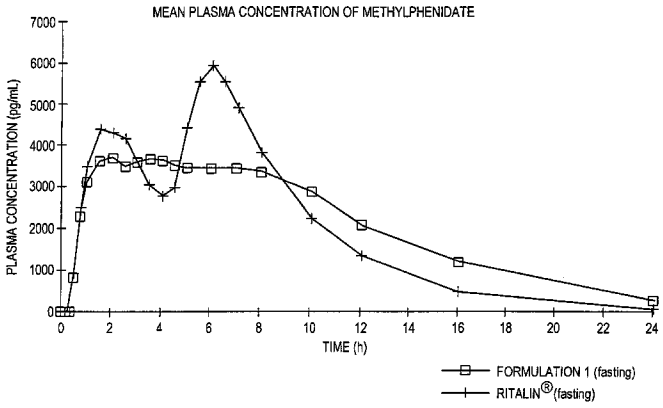

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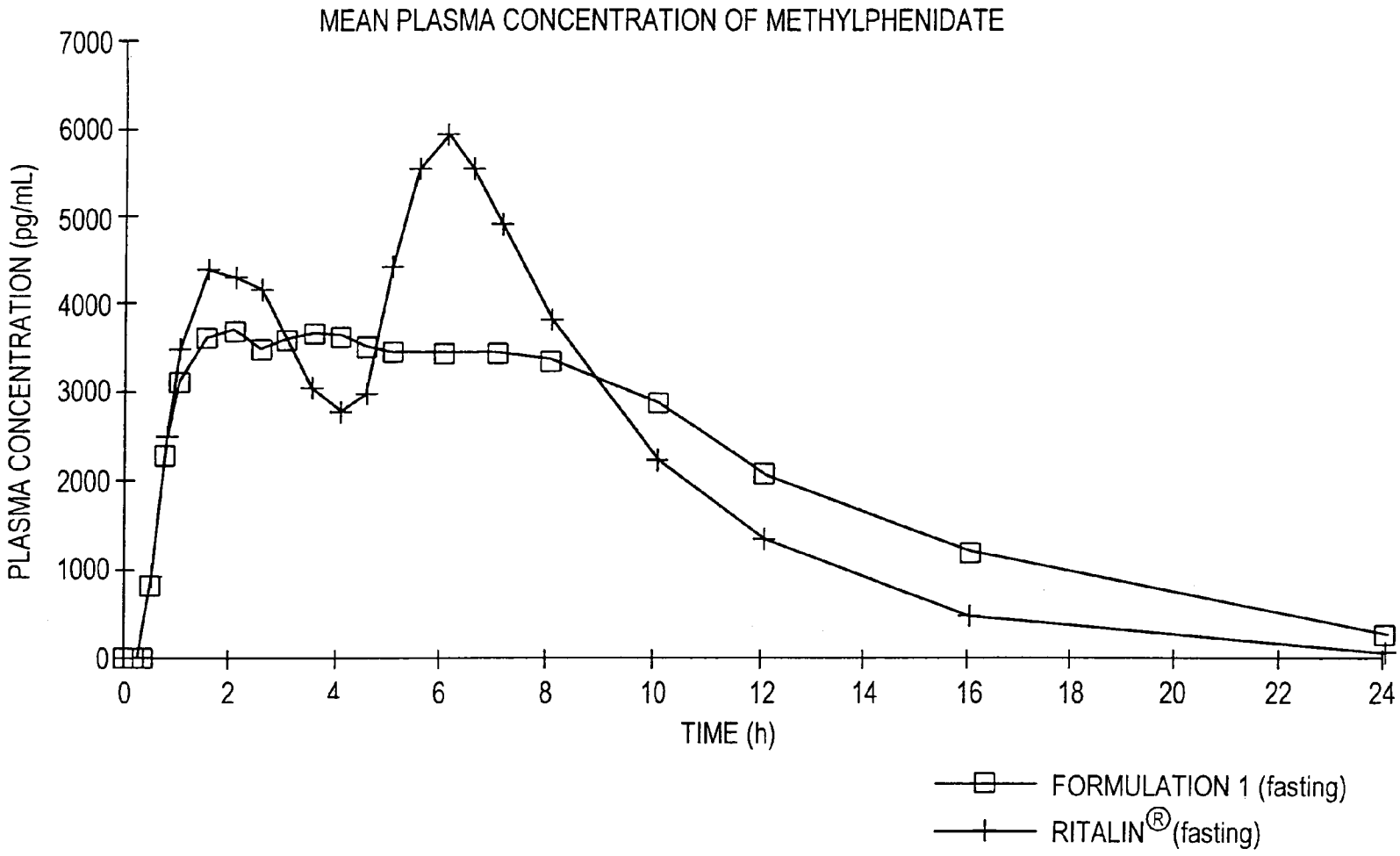
FIG. 1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PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 1 (fasting)
RITALIN® (fasting)

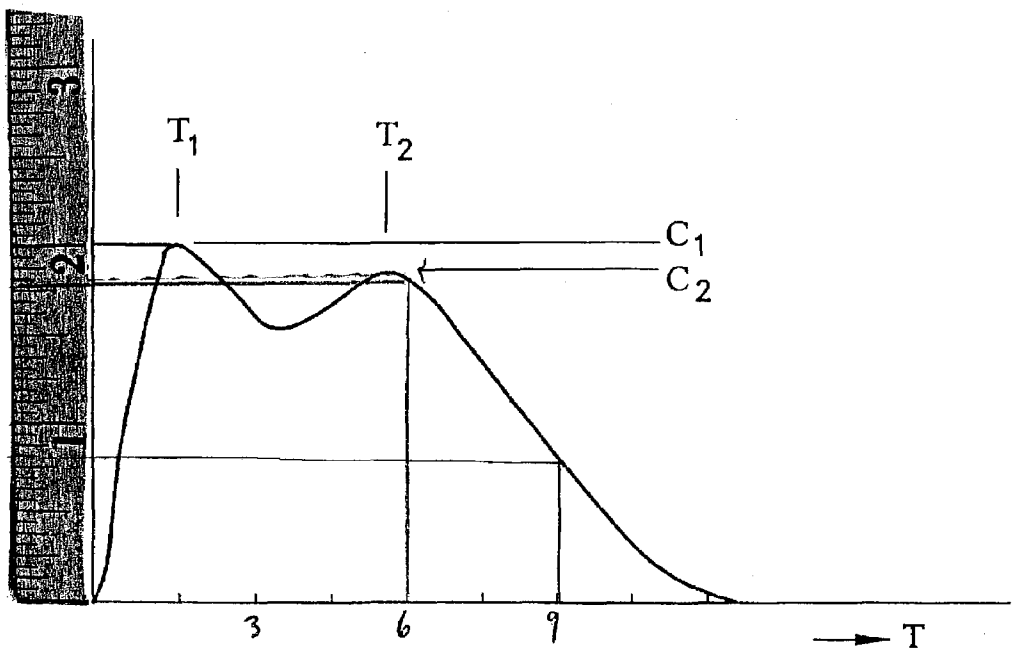


FIG. 2

FIG. 3

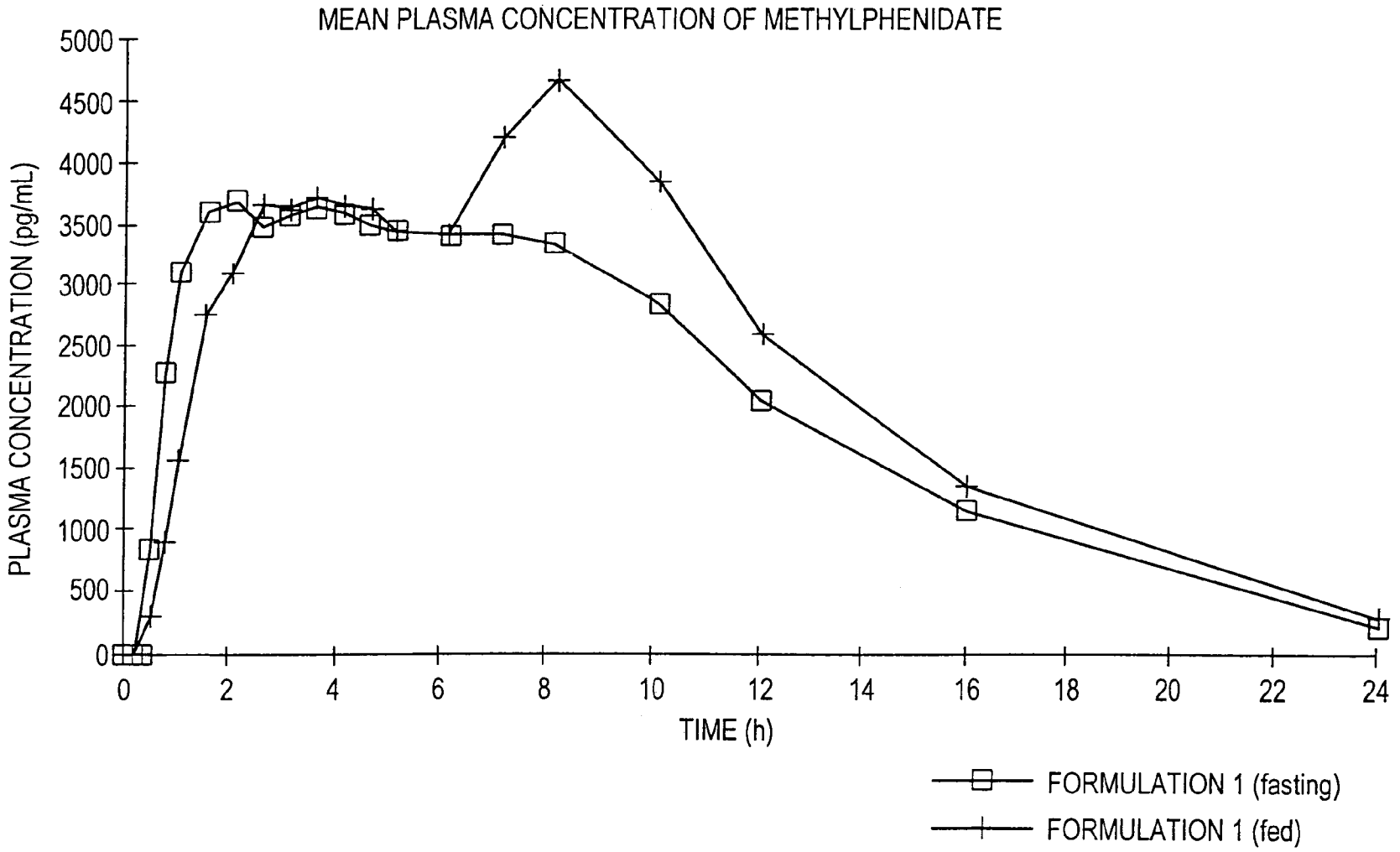

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 1 (fasting)
FORMULATION 1 (fed)

FIG. 4

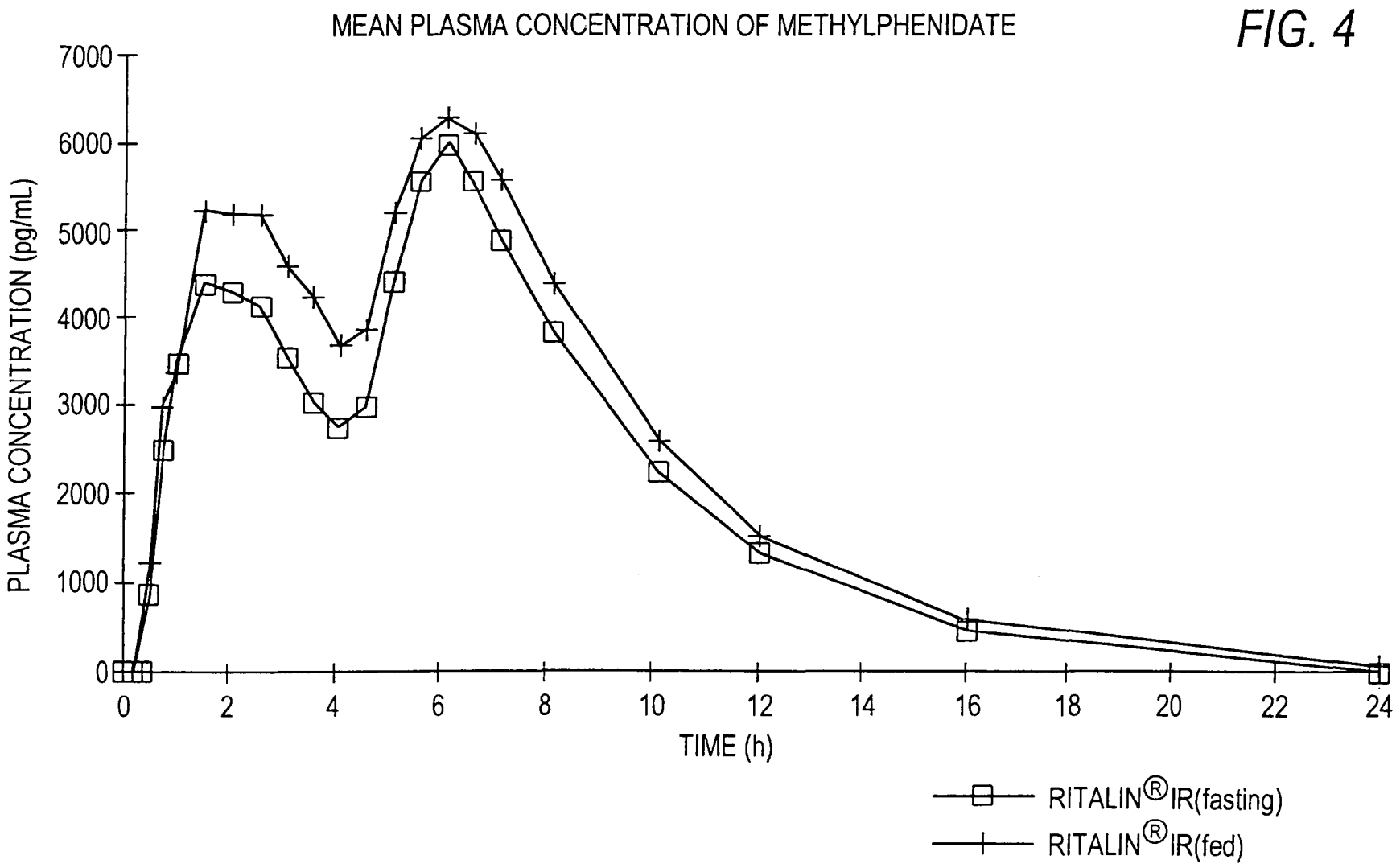

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
RITALIN® IR(fasting)
RITALIN® IR(fed)

FIG. 5

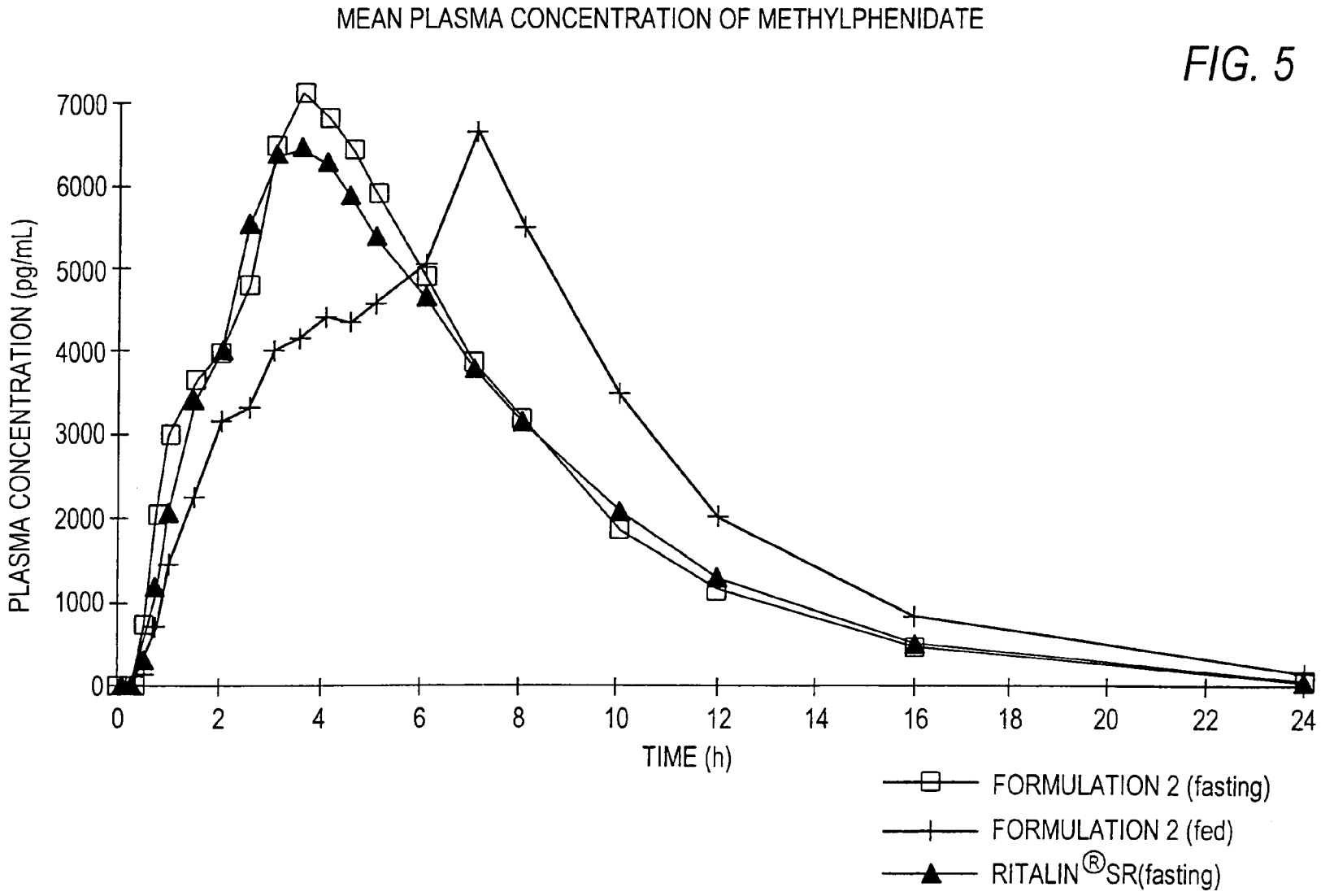

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (fasting)
FORMULATION 2 (fed)
RITALIN®SR(fasting)

FIG. 6

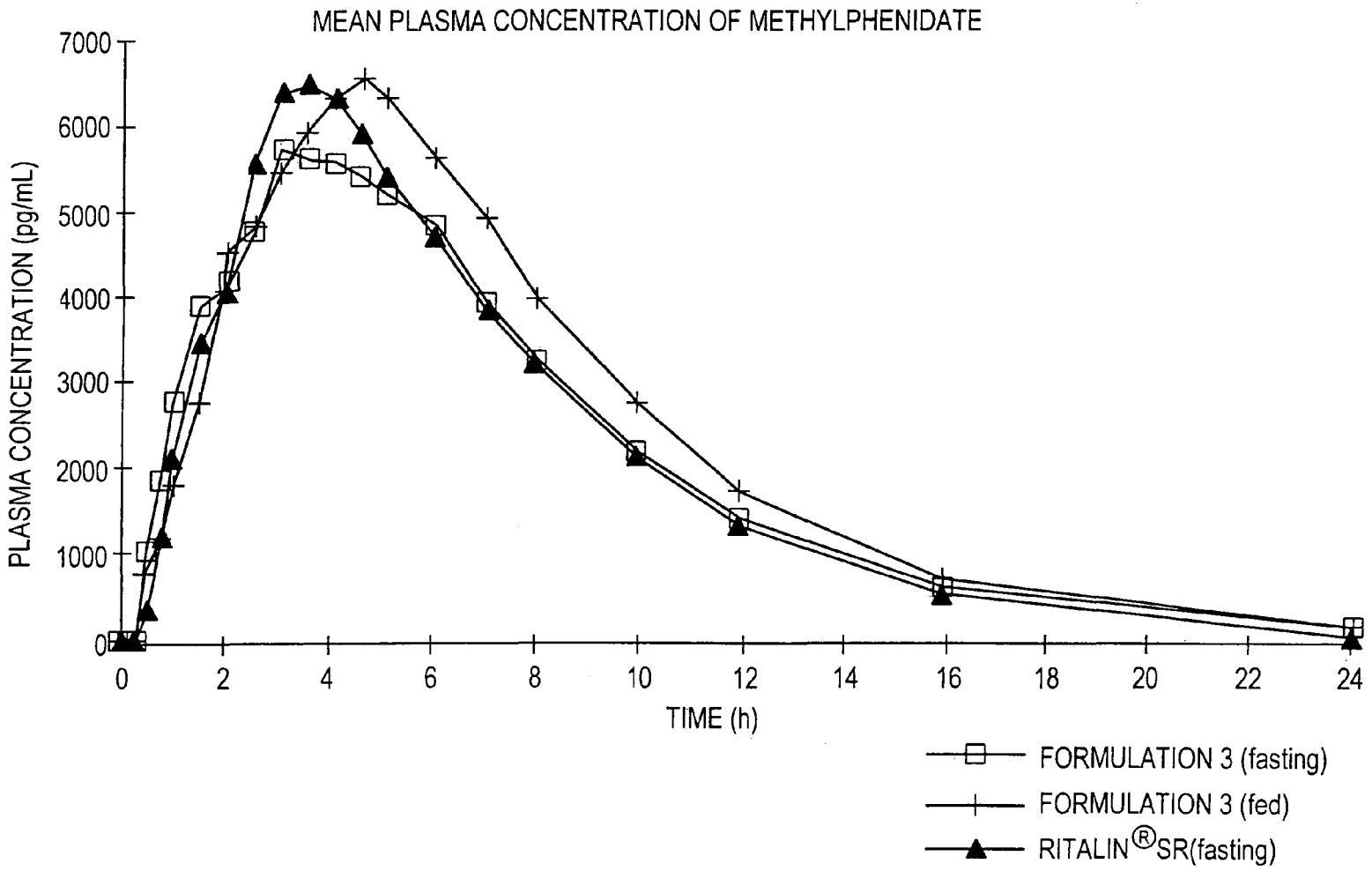

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 3 (fasting)
FORMULATION 3 (fed)
RITALIN®SR(fasting)

FIG. 7

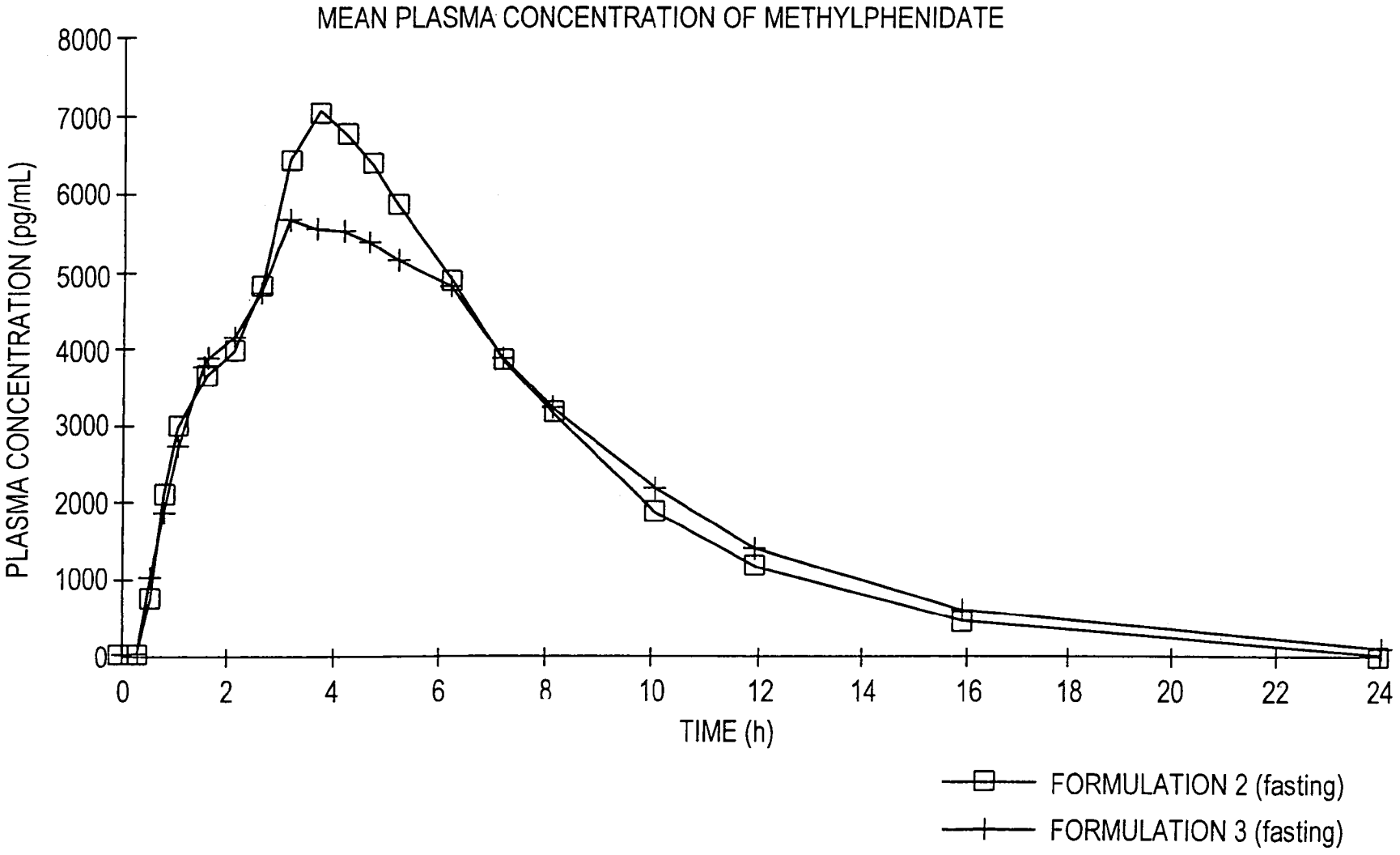

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
8000
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (fasting)
FORMULATION 3 (fasting)

FIG. 8

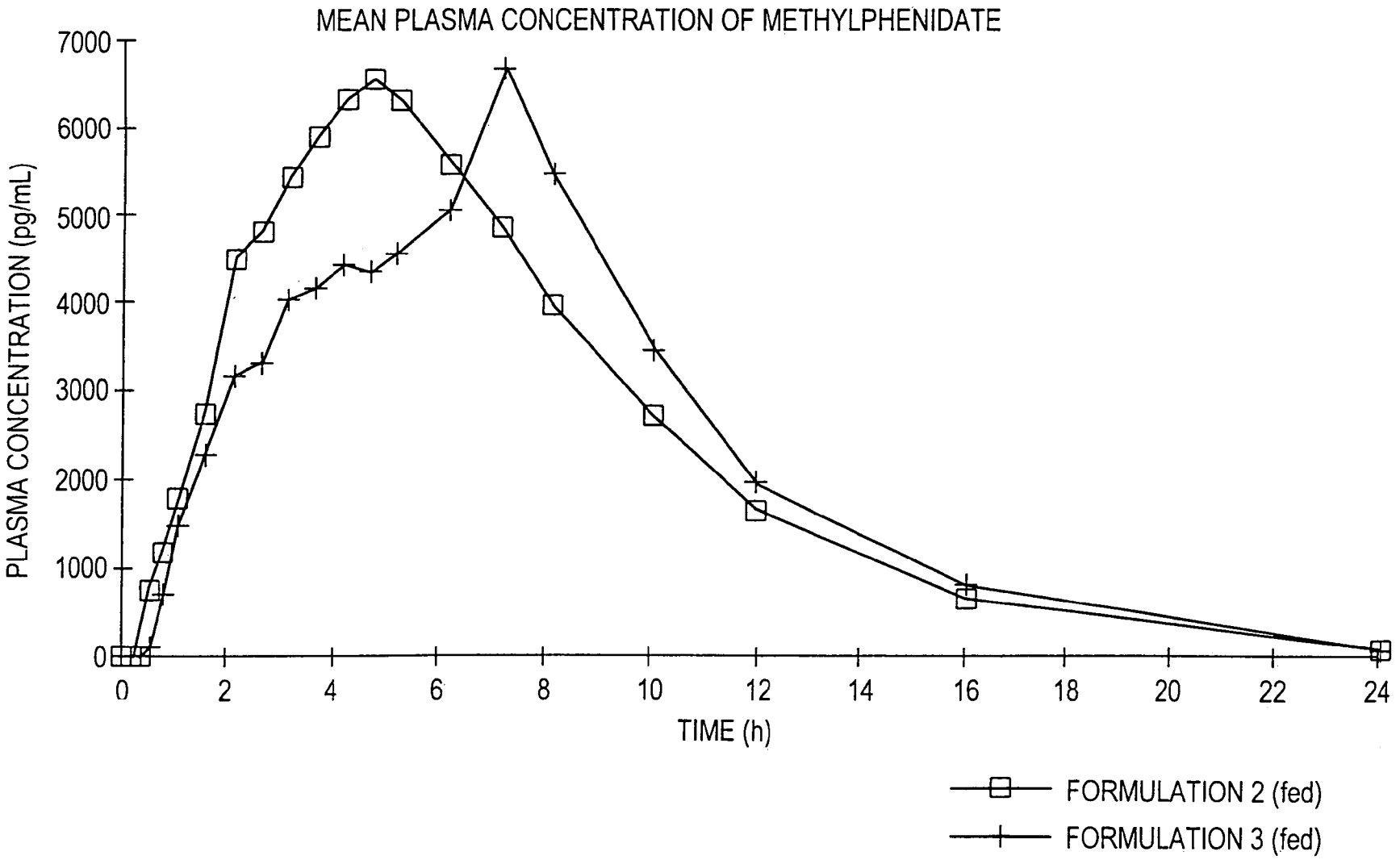

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (fed)
FORMULATION 3 (fed)

FIG. 9

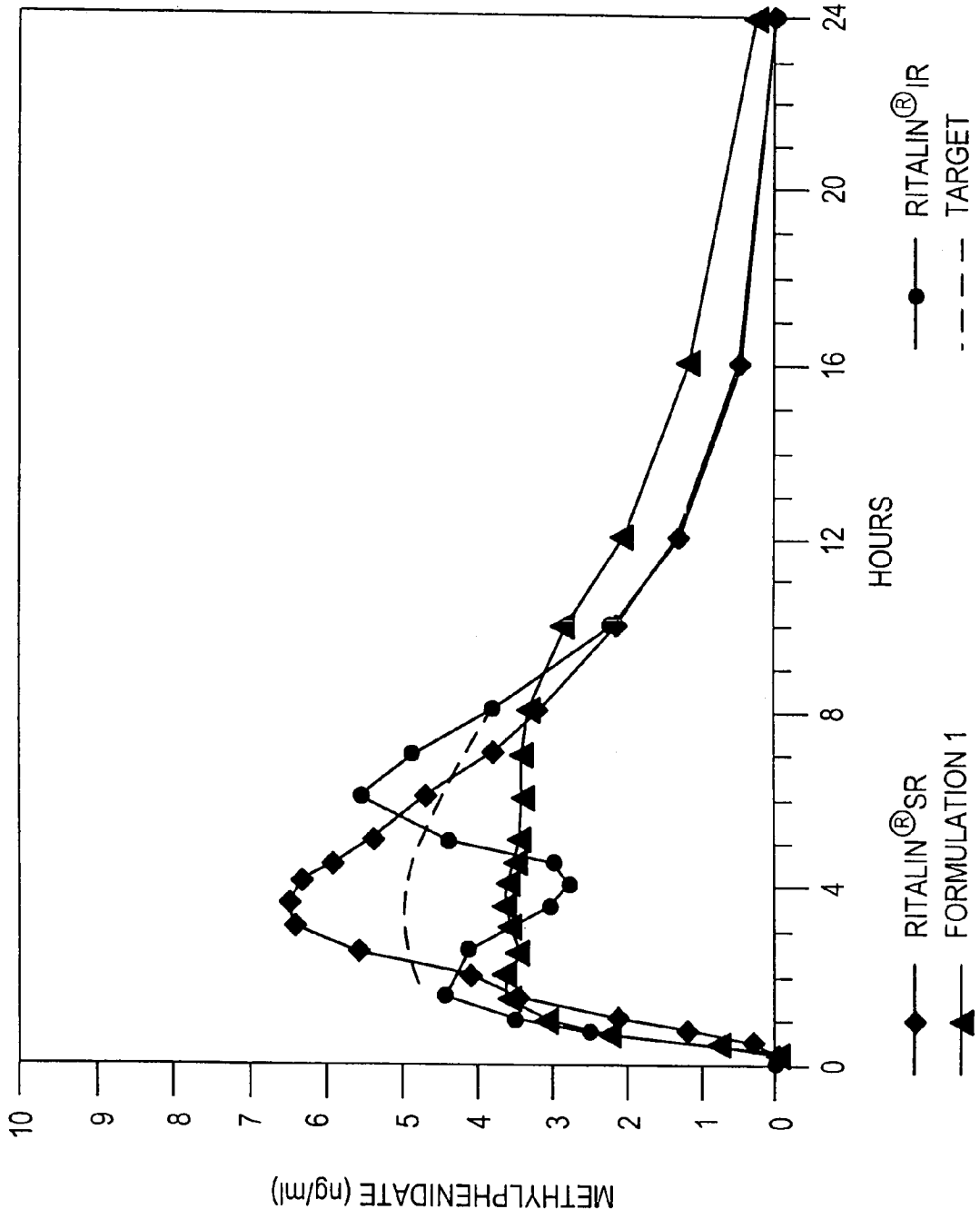

METHYLPHENIDATE (ng/ml)
0
1
2
3
4
5
6
7
8
9
10
HOURS
0
4
8
12
16
20
24
RITALIN®SR
FORMULATION 1
RITALIN®IR
TARGET

FIG. 10

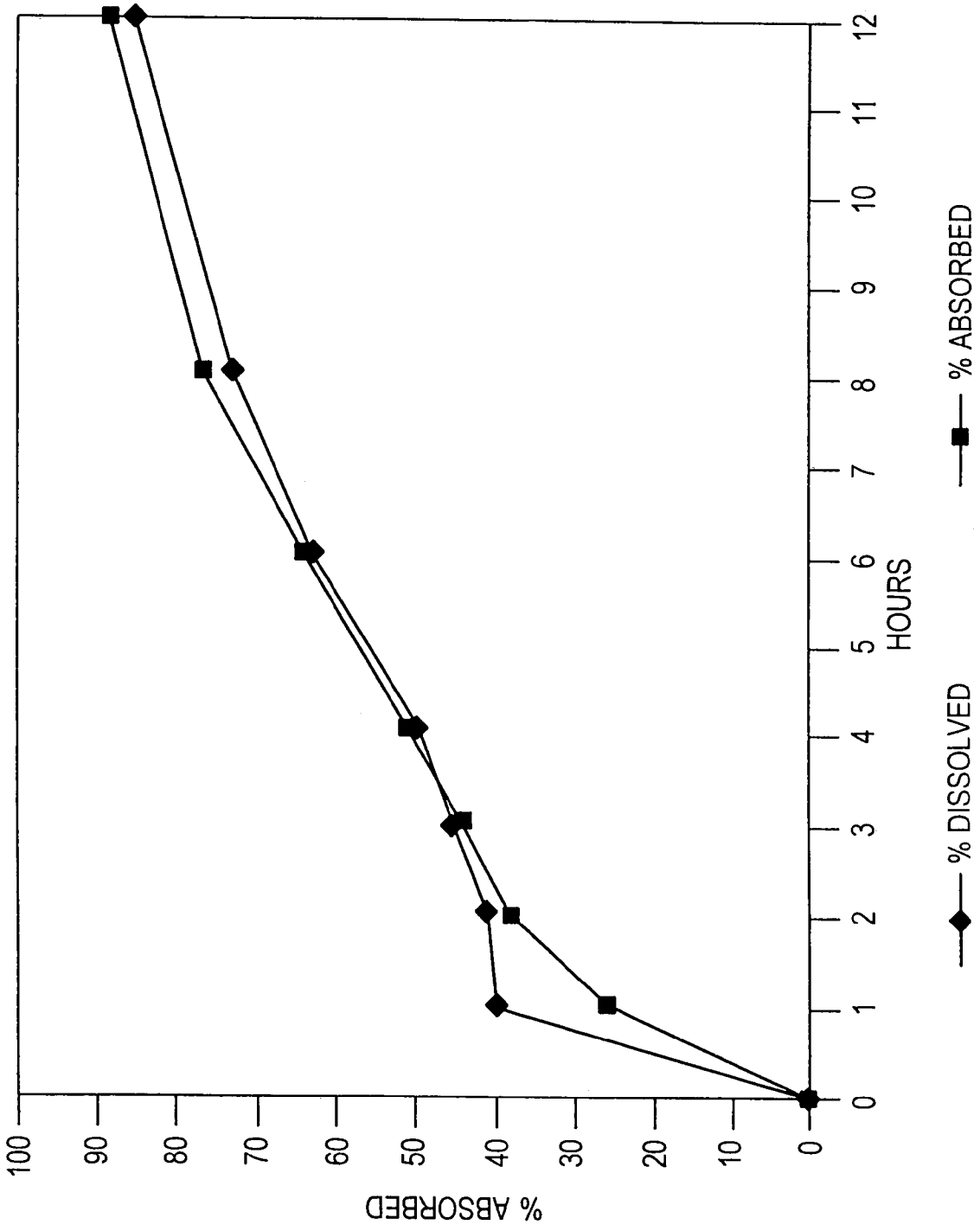
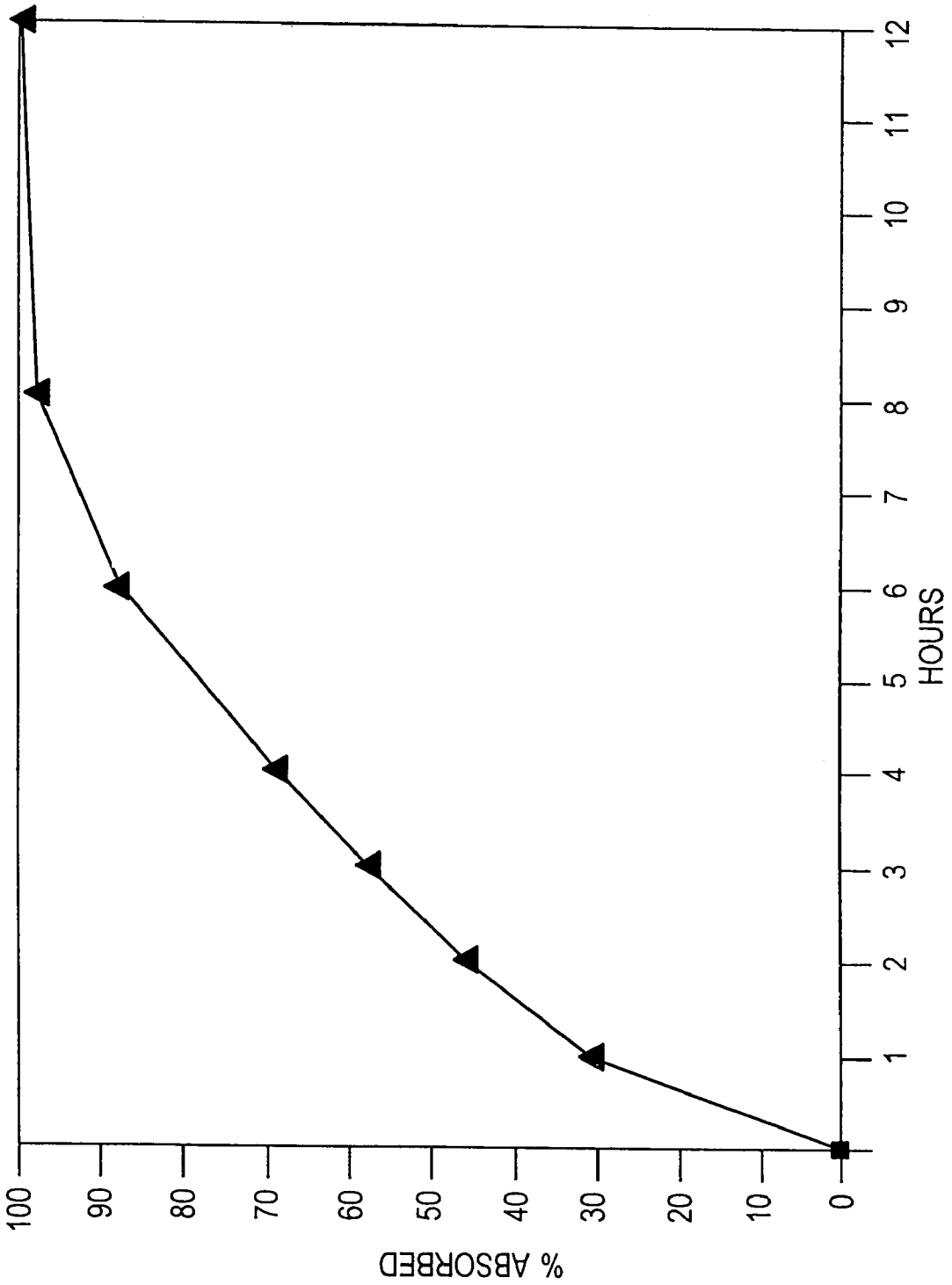

% ABSORBED
100
90
80
70
60
50
40
30
20
10
0
0
1
2
3
4
5
6
7
8
9
10
11
12
HOURS
% DISSOLVED
% ABSORBED

FIG. 11


% ABSORBED
100
90
80
70
60
50
40
30
20
10
0
HOURS
1
2
3
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CONTROLLED/MODIFIED RELEASE ORAL METHYLPHENIDATE FORMULATIONS

This application is a continuation of U.S. patent application Ser. No. 09/465,158, filed Dec. 16, 1999, now U.S. Pat. No. 6,673,367 which claims the benefit of U.S. Provisional Application No. 60/112,667, filed Dec. 17, 1998, the disclosure of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. It is the intent of all sustained release formulations to provide a longer period of pharmacologic action after administration than is ordinarily obtained after administration of immediate-release dosage forms. Sustained release compositions may be used to delay absorption of a medicament until it has reached certain portions of the alimentary tract, and maintain a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered. Such longer periods of response provide for many therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. Thus, therapy may be continued without interrupting the sleep of the patient, which is of special importance, for example, when treating a patient for moderate to severe pain (e.g., a post-surgery patient, a cancer patient, etc.), or for those patients who experience migraine headaches on awakening, as well as for the debilitated patient for whom sleep is essential. A further general advantage of longer acting drug preparations is improved patient compliance resulting from the avoidance of missed doses through patient forgetfulness.

Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occurs because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance therapy of the patient. In view of this, it is considered a goal of many skilled in the art that a controlled release dosage form will ideally provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ratio. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

It is known in the pharmaceutical art to prepare compositions which provide for sustained release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Sustained release formulations known in the art include specially coated pellets, coated tablets and capsules, and ion exchange resins, wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

While controlled and/or sustained release compositions have constituted a definite advance in the art, improvements in these compositions have been sought, particularly for

preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD), diabetes etc.

Attention Deficit Disorders are the most common psychiatric disorders in children (Campbell et al. 1992) with reported rates ranging from 4% to 9% (Aman et al. 1983). Attention Deficit Disorder (ADD) is characterized by inattention and impulsivity and may be present with hyperactivity (ADHD) (Shaywitz et al. 1984). Other characteristics may include aggressiveness, stealing, lying, truancy, setting fires, running away, explosiveness, cognitive and learning problems as well as poor social skills (Campbell et al. 1992). It is four to five times more frequent in boys than girls (Campbell et al. 1992).

Stimulant medication, such as amphetamines, have been shown to be the most effective agents in the treatment of children with disorders of activity modulation and attention regulation and result in significant improvement in 70 to 80 percent of affected children (Shaywitz et al. 1984). Positive effects of stimulants have been documented in a variety of areas including behavioral, social, perceptual performance, motor activity, impulse control, attention regulation and cognitive performance (Barkley 1977, Kavale 1983, Offenbacher et al. 1983, Rosenthal et al 1978).

Methylphenidate {dl-threo-methyl-2-phenyl-2-(2-piperidyl)acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The efficacy of methylphenidate ("MPH") in improving attention and behavioral symptoms has been supported by many studies.

Immediate release methylphenidate preparations, because of their short half-life, require frequent administration at short intervals to ensure adequate treatment throughout a child's school day. The rapid onset and offset of immediate release methylphenidate preparations means that a medicated child with attention deficit disorder will be maximally affected only for relatively brief periods during the day. Due to its short half-life, MPH is usually given twice per day, usually once after breakfast and once during the school day, an event that some children and some school personnel apparently avoid, resulting in poor compliance with prescribed regimens (Brown et al., 1985; Firestone 1982). Compliance is a major problem for children who require a midday or midafternoon dose as many schools prohibit children from taking medications during the school day and others often insist that all medications be given by a nurse. Poor compliance in taking medication may explain, in part, the variable and conflicting results reported in many studies of the effect of medication on improving the behavior of hyperactive children. These limitations of immediate release methylphenidate led to interest in products with longer effective periods of action. These limitations of immediate release methylphenidate preparations led to interest in products with longer effective periods of action.

A sustained release form of methylphenidate (Ritalin® SR) is commercially available. As a result of many clinical trials, various opinion leaders in treatment of attention deficit hyperactivity disorder have made the following comments regarding Ritalin® SR (sustained release methylphenidate) produced by Ciba-Geigy: (i) Ritalin® SR does not have a sufficiently early onset of effect to allow for behavioral management in the early morning; (ii) Ritalin® SR does not have the beneficial late effects that would be produced by a lunch time dose of immediate release methylphenidate, thus defeating the purpose of using an SR

formulation; (iii) The effects of Ritalin® SR are inconsistent or erratic over the course of the day.

There is a need in the art to develop drug formulations which provide a rapid onset, a prolonged action, followed by rapid offset of effect in order to overcome the deficiencies of the current state of the art.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which results in improved patient compliance.

It is an object of the present invention to provide new oral dosage formulations which represent improvements over currently available preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD).

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which ensure adequate treatment throughout a child's school day.

It is an object of the present invention to provide new oral dosage formulations which allow a child with attention deficit disorder to be maximally treated throughout the daytime, while being administered only once, i.e., in the morning.

It is a further object of the present invention to provide new controlled/modified release oral dosage formulations which provide a rapid onset and rapid offset with an extended release of active medicaments incorporated therein.

It is yet another object of the present invention to provide new controlled/modified release oral dosage formulations which are useful in all types of pharmaceutically active ingredients and which can extend the time of release of all such ingredients.

It is yet another object of the present invention to provide an oral controlled release formulation which combines both a rapid onset and sustained plasma concentrations throughout the day.

It is yet another object of the present invention to provide a "multi-layer release" (MLR) technology which is useful for all types of pharmaceutically active ingredients and which can extend the duration of action for a desired length of time.

To address the above-mentioned deficiencies as well as other goals, the present invention is directed in part to a controlled release product which is intended to combined both a rapid onset and sustained plasma concentrations throughout the day. Significantly, the formulations of the present invention provide a rapid onset, a prolonged action, followed by rapid offset of effect, i.e., a "square wave" profile.

In accordance with the above objects and others, the present invention is directed in part to an oral dosage form comprising an effective amount of methylphenidate or a pharmaceutically acceptable salt thereof and at least one release modifying material which causes the formulation to provide a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration, a peak plasma concentration from about 3 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form, wherein the peak plasma concentration is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration, and wherein the duration of effect provided by the methylphenidate contained in the formulation falls below effective plasma concentrations at about 8 to about 12 hours after oral administration. In certain preferred embodiments, the oral dosage form provides a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration. In certain further preferred embodiments, the peak plasma concentration is from about 1.0 to about 1.7 times the plasma concentration of methylphenidate provided by the oral dosage form at about 9 hours after oral administration. In certain further preferred embodiments, the duration of effect provided by the methylphenidate contained in the oral dosage form falls below effective plasma concentrations at about 8 to about 10 hours after oral administration.

In certain further preferred embodiments, the formulation provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and provides effective blood levels for at least about 6 hours after administration.

In certain further preferred embodiments, the formulation exhibits a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit a "plateau" which lasts from about 6 hours to about 12 hours. The "plateau" is characterized by a stabilized plasma concentration, wherein the plasma level at the end of the measured interval does not differ by more than 20%, preferably by no more than 10% of the plasma concentration at the beginning of the measured interval.

In certain further preferred embodiments, the formulation exhibits a bimodal release of active agent from the dosage form. Bimodal release of the active agent is characterized by the active agent being release from the dosage form by more than one distinct release rate. In some embodiments, the release rates can be separated by a no-release or a substantially no-release interval, although this is not always necessary.

In certain further preferred embodiments, the formulation exhibits a biphasic absorption of the active agent. Biphasic absorption of the active agent is characterized by the active agent being absorbed through a natural barrier (e.g. the mucosal lining of the gastro-intestinal tract) by more than one distinct absorption rate. In some embodiments, the absorption rates can be separated by a no-absorption or a substantially no-absorption interval, although this is not always necessary. A formulation can exhibit both biphasic absorption and bimodal release of the active agent, with the biphasic absorption being a function of the bimodal release rate. However, biphasic absorption is not always attributed to release rate and can occur in a formulation not exhibiting bimodal release.

In preferred embodiments the formulation exhibits bimodal release and/or biphasic absorption to provide a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit bimodal release and/or biphasic absorption to provide a "plateau" which lasts from about 6 hours to about 12 hours. Other embodiments, maintain effective plasma levels of the active agent for about 16 to about 18 hours after administration of the dosage form.

The present invention is further directed to an oral dosage form comprising an effective amount of methylphenidate or a pharmaceutically acceptable salt thereof and at least one release modifying material which causes the formulation to provide a in-vitro dissolution of the drug of from about 0 to about 45% released after 0.25 hour; from about 10 to about 50% released after about 1 hour; from about 30 to about 80% drug released after about 4 hours; not less than about 65% drug released after 8 hours; and not less than about 80% of the drug released after about 12 hours; the oral dosage form

when orally administered to a human patient further providing a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration, and a duration of effect which lasts from about 8 to about 10 hours after oral administration, wherein the plasma concentration of the drug rapidly falls at about 8 to about 10 hours after oral administration to a level which is below the minimum effective plasma concentration. In certain preferred embodiments, the oral dosage form, when orally administered to a human patient, provides a peak plasma concentration from about 4 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form. In certain preferred embodiments, the oral dosage form, when orally administered, provides a peak plasma concentration from about 5 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form. In certain further preferred embodiments, the oral dosage form provides peak plasma concentration from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration, and more preferably from about 1.0 to about 1.7 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration.

With respect to the drug methylphenidate and ADHD, the benefits of the new formulations described herein include: a) the ability to obviate the need for a lunch-time dose at school and b) an onset of drug effect which is equivalent to that of an immediate release methylphenidate formulation; and c) the duration of action extending beyond the school day, i.e., a duration of effective blood levels of 10–12 hours.

In certain embodiments of the invention, the controlled/modified release formulation is based on a multi-layered release ("MLR") technology, and the drug product can be in an oral capsule containing beads. In the case of beads, encapsulated in a capsule, each bead contains a series of layers with different characteristics—an outer immediate release layer, a release delaying layer (enteric coat), a controlled release layer over an immediate release layer. The MLR formulation is designed such that upon oral administration, the formulation provides a rapid dissolution and absorption of the outer layer of the formulation which contains a portion of the drug in immediate release form, thereby resulting in a rapid rise of the drug to therapeutic plasma levels. This is followed by a period of no absorption (due to an enteric coating), followed thereafter by a controlled release of the drug from the formulation to maintain plasma levels. After absorption of the drug from an immediate release core, plasma levels then rapidly decrease. By virtue of the release of the drug from the MLR formulation, the plasma level of the drug, when plotted on a time/concentration curve, takes the appearance of a "square wave".

In certain preferred embodiments, an acrylic resin is utilized to provide the controlled slow release of therapeutically active ingredients over a predetermined or a specified period of time, the acrylic resin thereby comprising a significant part of the "base composition". Base compositions prepared from such acrylic resins provide sustained release of therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration, generally oral administration, in humans or animals.

In other embodiments of the invention, the formulations of the invention are composed of:

(i) a mixture of immediate release particles (e.g., beads) and enteric coated immediate release particles (e.g., beads); (ii) a mixture of immediate release particles (e.g., beads) and enteric coated controlled release particles (e.g., beads) or (iii) a mixture of immediate release particles (e.g., beads) and controlled release particles (e.g., beads). In each such instance, the mixture of particles possessing different release properties are blended together and filled into hard gelatin capsules.

In certain preferred embodiments, the controlled/modified release methylphenidate formulations of the invention consist of a plurality of single beads, each containing an immediate-release component in combination with an enteric coated controlled-release component to produce a delay in the absorption process. The drug product is an oral capsule containing methylphenidate beads. Each bead contains a series of layers with different release characteristics—an outer immediate release layer; a release delaying layer; a controlled release layer; and an immediate release core. The final product is a capsule containing multi-layer release (MLR) beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption equal to or greater than Ritalin immediate release tablets. The immediate release component represents 40% of the total dose per bead and the controlled release component represents 60%. This formulation is designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then rapidly decrease according to the elimination kinetics of methylphenidate. The results of a bioavailability study of this formulation indicate a biphasic release profile that is consistent with the pharmaceutical rationale discussed herein.

In other embodiments of the invention, the bead size of the formulations can be adjusted in order to obtain a desired pharmacokinetic profile based on the correlation between gastric emptying and bead size. A smaller bead size exhibits faster gastric emptying as compared to a larger bead size.

Other objects and advantages of the present invention will be apparent from the further reading of the specification and of the appended claims.

The term "pH-dependent" for purposes of the present invention is defined as having characteristics (e.g. dissolution) which vary according to environmental pH (e.g., due to changes in the in-vitro dissolution media, or due to passage of the dosage form through the gastrointestinal tract.

The term "pH-independent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH, in that a difference, at any given time, between an amount of methylphenidate released at one pH and an amount released at any other pH, when measured in-vitro using the USP Paddle Method of U.S. Pharmacopeia XXII (1990) at 100 rpm in 900 ml aqueous buffer, is no greater than 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. **1** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are

treated with Formulation 1 and Ritalin® as a function of time when given under fasting conditions.

FIG. **2** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fed conditions.

FIG. **3** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 as a function of time when given under fasting and fed conditions.

FIG. **4** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Ritalin® as a function of time when given under fasting and fed conditions.

FIG. **5** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 2 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **6** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 3 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **7** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fasting conditions as a function of time.

FIG. **8** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fed conditions as a function of time.

FIG. **9** a graphical representation of one target plasma drug concentration profile in accordance with the invention.

FIG. **10** is a graphical representation of the correlation of the in-vitro drug dissolution profile with the in-vivo absorption profile of Formulation 1.

FIG. **11** is a graphical representation of a target absorption profile of a formulation in accordance with the invention.

DETAILED DESCRIPTION

Methylphenidate (2-Piperidineacetic acid, α-phenyl-, methyl ester) is a piperidine derivative that is structurally related to amphetamine, and is commercially available in the form of the hydrochloride salt. Methylphenidate is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The controlled/modified release methylphenidate formulations of the invention are thought to act by increasing extracellular dopamine and norepinephrine with the presumed mechanism of action being uptake block at the nerve terminal transporters.

The pharmacological properties of methylphenidate are essentially the same as the amphetamines. However, in contrast to amphetamines, methylphenidate is a mild CNS stimulant with more prominent effects on mental than motor activities. Methylphenidate contains erythro and threo isomers. Locomotor stimulant action is specific to stereostructure, whereas monoamine oxidase inhibition is not. It has been speculated that the mechanism of locomotor stimulant action of methylphenidate may be other than the inhibition of monoamine oxidase. Studies suggest that synaptic inhibition of catecholamine uptake by d-threo methylphenidate may be involved fundamentally in behavioral and pressor effects of the racemic drug. Methylphenidate promotes a dose-dependent behavioral profile that is very comparable to that of amphetamine. Amphetamine increases extracellular norepinephrine and serotonin in addition to its effects on dopamine. Recently work indicates that acute methylphenidate administration increases extracellular dopamine and norepinephrine, consistent with its presumed mechanism of action as a uptake blocker of the nerve terminal transporters.

Peak blood levels following the administration of methylphenidate have been noted at 1 to 3 hours (Faraj et al., 1974; Milberg et al., 1975). The half-life of the drug ranges from 2 to 4 hours (Faraj et al., 1974; Hungund et al., 1979; Soldin et al., 1979) in adults and children. Hungund et al. (1979) reported on the pharmacokinetics of methylphenidate in four hyperkinetic children. The mean half-life was 2.5 hours. Although there was little variability in this parameter, body clearance varied by a factor of three. This suggested that plasma methylphenidate levels are subject to a considerable degree of inter-patient variability.

The primary route of metabolism for methylphenidate is de-esterification to ritalinic acid, which accounts for 75% to 91% of total urinary methylphenidate. Other metabolic products arise from p-hydroxylation or oxidation to the lactam.

The methylphenidate formulations of the present invention may be administered to children 6 years and over, and preferably have a duration of action from about 8 to about 12 hours, preferably from about 8 to about 10 hours. The inventive methylphenidate formulation should be taken at breakfast time and is designed to replace two separate doses of methylphenidate immediate release given at breakfast and lunch time. Patients who require more frequent administration of immediate release methylphenidate than twice daily may be given an additional dose of immediate release methylphenidate at suppertime, when receiving the inventive methylphenidate formulation. The contents of the Methylphenidate MLR capsules may be sprinkled on soft foods before administration.

The controlled/modified release preparations of the present invention may be used in conjunction with any multiparticulate system, such as granules, spheroids, beads, pellets, ion-exchange resin beads, and other multiparticulate systems in order to obtain a desired sustained-release of the therapeutically active agent. Beads, granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable unit dosage form. An amount of the multiparticulates effective to provide the desired dose of drug over time may be placed in a capsule, may be contained in a packet and sprinkled onto food, or may be incorporated in any other suitable oral solid form, such as a tablet. On the other hand, the present invention can be in the form of a matrix tablet. With respect to all such optional formulations, it is desired that the formulation be prepared such that an initial immediate release of drug provides an early onset of effect, which onset is analogous to an immediate release formulation, and that the formulation further provide a sustained release component which maintains therapeutically effective levels of the drug in the plasma for the desired amount of time, followed by a relatively rapid drop-off in blood plasma levels relative to typical sustained release formulations. Viewed as an in vivo time/concentration plot, the plasma level of the drug from the formulations of the present invention have the appearance of a "square wave". The immediate release component preferably represents from about 30% to about 40% of the total dose and the controlled

release component preferably represents from about 60% to about 70% of the total dose of methylphenidate contained in the formulations of the present invention. In certain preferred embodiments, including the MLR embodiments of the invention, the immediate release component represents about 40% of the total dose and the controlled release component represents about 60% of the total dose of methylphenidate contained in the formulation.

In the case of methylphenidate, it is desired that the onset of action occurs from about 0.5 to about 4 hours, and preferably from about 0.5 to about 2 hours after the oral dosage form is administered, and it is further desired that the dosage form no longer provides effective plasma levels of methylphenidate from about 8 to about 12, more preferably from about 8 to about 10 hours, after oral administration of the dose. In this manner, the dose of methylphenidate can be administered to a child in the morning before school begins, provides the desired effect at the start of the school day, with the pharmacologic action of the drug not waning until after the school day ends, and preferably before dinner so that the drug does not have the side effect of acting as an appetite suppressant.

The formulations of the present invention are designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then rapidly decrease according to the elimination kinetics of methylphenidate.

It is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability. Bioavailability, in a more meaningful sense, is the degree, or amount, to which a drug substance is absorbed into the systemic circulation in order to be available to a target tissue site. To be absorbed, an active drug substance must be in a solution. The time required for a given proportion of an active drug substance contained in a dosage unit to enter into solution in appropriate physiological fluids is known as the dissolution time. The dissolution time for an active substance from a dosage unit is determined as the proportion of the amount of active drug substance released from the dosage unit over a specified time by a test method conducted under standardized conditions. The physiological fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.

Although there are many diverse factors which influence the dissolution of a drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from a specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in this steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiological conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium, providing for a steady state absorption.

The transport across a tissue absorption site in the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane, since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e. the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the gastrointestinal tract into the blood stream.

Notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, in many cases an important correlation can be established between the in vitro dissolution time determined for a dosage form and the in vivo bioavailability. This correlation is so firmly established in the art that dissolution time has become generally descriptive of bioavailability potential for many classes of active components contained in a particular dosage form. In view of this relationship, the dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating whether a controlled release formation should be tested in vivo.

With the above in mind, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Methylphenidate HCl dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%

In certain preferred embodiments of the present invention, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Methylphenidate HCl dissolved
0.25	0–45%
1	10–50%
4	30–80%
8	NLT 65%
12	NLT 80%

Sustained Release Coatings

In certain preferred embodiments, the drug is incorporated into or onto a substrate and a sustained release coating is applied thereto. For example, the drug may be contained within or on a substrate as follows: (i) incorporated into matrix spheroids (e.g., together with a pharmaceutically acceptable spheronizing agent such as microcrystalline cellulose), (ii) coated onto inert pharmaceutically acceptable beads (e.g., nonpareil beads); (iii) incorporated into a normal release tablet core; or (iv) incorporated into a tablet core which comprises a matrix including a sustained release

carrier material. Thereafter, a sustained release coating is applied onto substrates such as those mentioned in (i)–(iv) above. The dosage forms of the present invention may optionally coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the drug in desired areas of the gastrointestinal (GI) tract, e.g., the stomach or small intestine. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) comprising the drug, is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Such formulations are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference. The particles are preferably film coated with a material that permits release of the drug so as to achieve, in combination with the other stated properties, a desired in-vitro release rate and in-vivo plasma levels. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Acrylic Polymers

The hydrophobic material comprising the controlled release coating may comprise a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer; poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly (methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D.

The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material such as an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When the aqueous dispersion of hydrophobic material is used to coat a substrate including the drug, for example, inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. Alternatively, the substrate may be a tablet core coated with the sustained release coating, and optionally a further film-forming agent or colorant, such as Opadry®.

In formulations where an aqueous dispersion of an hydrophobic polymer such as an alkylcellulose is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60° C. and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

In formulations where an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45° C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

The sustained release profile of the coated formulations of the invention-can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the drug to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-

formulated aqueous dispersions of ethyl-cellulose, such as Aquacoat® or Surelease®, may be used. If Surelease is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

The plasticized aqueous dispersion of hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined sustained release of the therapeutically active agent (i.e., drug) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the drug from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The substrate of the present invention may be prepared by a spheronizing agent together with the active agent ingredient that can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredients and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer or ethyl cellulose. In such embodiments, the sustained-release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

In a particular preferred embodiment of the invention, the controlled/modified release methylphenidate formulation is prepared as a multilayered release (MLR) formulation comprising coated inert beads. A summary of one method of manufacturing such a formulation is outlined as follows. First, immediate release (IR) methylphenidate beads are prepared by spraying a solution of methylphenidate in water over sugar beads in a fluid bed dryer with a drug load of about 8%. The spray process is carried out in a fluid bed dryer, equipped with a Wurster column. A clear overcoat of HPMC is applied using an Qpadry® material (e.g., Opadry® Clear (Formula No: YS-1-7006)), to a weight gain of about 1%. Next, a controlled release coating is applied to the IR beads, which converts the same into controlled release (CR) beads. This is accomplished by spraying a solution of Eudragit® RS 30 D, triethyl citrate (plasticizer) and talc (glidant), onto the IR beads. Next, the coated beads are cured in order to obtain a stabilized release rate of the therapeutically active agent. In preferred embodiments of the present invention where the CR coating utilizes an acrylic resin to control the release of the drug, the CR beads at this stage are subjected to oven curing at a temperature above the Tg of the plasticized acrylic polymer of the required time period, the optimum values of the temperature and time for the particular formulation being determined experimentally. In certain embodiments of the present invention, the stabilized products is obtained via oven curing conducted at a temperature of about 40–50° C. for a time period of about 12 to about 24 hours or longer. An enteric coating is then applied onto the CR beads to convert the same into enteric coated CR (ECCR) beads. This is accomplished by spraying a solution of Eudragit® L 30 D-55 dispersion, triethyl citrate (plasticizer) and talc (glidant) onto the CR beads. Finally, an immediate release coating is applied onto the ECCR beads (referred to as, e.g., an IR Topcoat). This is accomplished by spraying a solution of methylphenidate in water over EC CR beads.

Results of initial studies show that this formulation is stable under room temperature (25° C., 60% RH) and accelerated conditions (40° C., 75% RH).

Sustained Release Matrices

In certain preferred embodiments of the present invention, the sustained release formulation comprises a matrix including the drug and a sustained release carrier (which may comprise one or more hydrophobic materials, such as an alkylcellulose and/or an acrylic polymer as previously defined herein). The materials suitable for inclusion in a sustained release matrix will depend on the method used to form the matrix.

Suitable materials for inclusion in the sustained release matrices of the invention, in addition to the drug, include:

(A) hydrophilic and/or hydrophobic materials, such as gums; alkylcelluloses; cellulose ethers, including hydroxyalkylcelluloses and carboxyalkylcelluloses; acrylic resins, including all of the acrylic polymers and copolymers discussed above, and protein derived materials. This list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting the desired sustained release profile of the drug is meant to be included herein. The dosage form may comprise, e.g., from about 1% to about 80% by weight of such material.

In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxy-ethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly (methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing. In yet other embodiments, the hydrophobic material is an alkylcellulose.

(B) digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural or synthetic waxes, polyhydric alcohols, including polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of such material. In certain embodiments, a combination of two or more hydrocarbon materials are included in the matrix formulations. If an additional hydrocarbon material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same.

Preferred hydrocarbons are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends, and have a melting point from about 30° C. to about 200° C., preferably from about 45° C. to about 90° C.

For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30° C. to about 100° C. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax.

The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl, cetyl and/or cetostearyl alcohol. The amount of aliphatic alcohol, if included in the present oral dosage form, will be determined, as above, by the precise rate of drug release required. In certain embodiments, the oral dosage form contains between 20% and 50% (by wt) aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the drug from the formulation.

Suitable polyalkylene glycols include, for example, polypropylene glycol or polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1,000 and 15,000 especially between 1,500 and 12,000.

In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and drug or an drug salt; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12}–C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/drug with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the drug.

In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrices

In certain preferred embodiments of the present invention, the sustained release matrices also be prepared via melt-granulation or melt-extrusion techniques. Such formulations are described in U.S. patent application Ser. No. 08/334,209, filed Nov. 4, 1994 and U.S. patent application Ser. No. 08/833,948, filed Apr. 10, 1997, both of which are hereby incorporated by reference in their entireties. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage

form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Pat. No. 4,861,598, assigned to the Assignee of the present invention and hereby incorporated by reference in its entirety.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association (1986), incorporated by reference herein.

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending the drug analgesic (i.e., drug) together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours. The multiparticulates may be divided into unit doses via placement into a gelatin capsule, or may be compressed into a suitable tablet form.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 to about 12 mm in length and have a diameter of from about 0.1 to about 5 mm In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in *Remington's Pharmaceutical Sciences*, (Arthur Osol, editor), 1553–1593 (1980), incorporated by reference herein.

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Pat. No. 4,957,681 (Klimesch, et. al.), described in additional detail above and hereby incorporated by reference.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular drug analgesic compound utilized and the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents disclosed above before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release therapeutically active agent for prompt therapeutic effect. The immediate release therapeutically active agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., controlled release coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of controlled release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and

then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the therapeutically active agent, which is added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

The substrates of the present invention may be also be prepared via a melt pelletization technique. In such circumstances, the active drug in finely divided form is combined with a binder (also in particular form and other optional inert ingredients, and thereafter the mixture is pelletized, e.g. by mechanically working the mixture in a high shear mixer to form the pellets (granules, spheres). Thereafter, the pellets (granules, spheres) may be sieved in order to obtain pellets of the requisite size. The binder material is preferably in particulate form and has a melting point above about 40° C. Suitable binder substances include, for example, hydrogenated castor oil, hydrogenated vegetable oil, other hydrogenated fats, fatty acid esters, fatty acid glycerides, and the like.

Proposed strengths of the methylphenidate formulations of the invention may be, e.g., 10, 15, 20 and 30 mg. In MLR methylphenidate multiparticulate formulations of the invention, proposed capsule sizes and fill weights for such dosage strengths are as follows:

Strength	Fill Weight	Capsule Size
10 mg	100 mg	4
15 mg	150 mg	3
20 mg	200 mg	2
30 mg	300 mg	1

In certain preferred embodiments of the present invention, an effective amount of the drug in immediate release form is included in the drug formulation. The immediate release form of the drug is included in an amount which is effective to shorten the time to maximum concentration of the drug in the blood (e.g., plasma), such that time to T_{max} is shortened to a time of, e.g., from about 0.5 to about 2 hours. By including an amount of immediate release drug in the formulation, the time to onset of action is significantly reduced, and is the same or earlier than that of the reference standard IR treatment (Ritalin IR).

In such embodiments, an effective amount of the drug in immediate release form may be coated onto the substrates (e.g., multiparticulates or tablets) of the present invention. For example, where the extended release of the drug from the formulation is due to a controlled release coating, the immediate release layer can be overcoated on top of the controlled release coating. On the other hand, the immediate release layer may be coated onto the surface of substrates wherein the drug is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising an effective unit dose of the drug (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the drug dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release drug as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the drug. One skilled in the art would recognize still other alternative manners of incorporating the immediate release drug portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Methylphenidate HCl Immediate Release Beads

TABLE 1

Ingredients	%
Methylphenidate hydrochloride	15.0
Sugar bead 14/18	80.0
Opadry ® clear YS-1-7006	5.0
Water	q.s.
Total	100.0

1. Charge Niro-Aeromatic Strea 1 Fluid Bed Wurster Coater with 14/18 mesh Nupareil® PG (sugar spheres NF).
2. Coat the beads at 60° C. by spraying a solution of methylphenidate hydrochloride (12% w/w) and Opadry clear (4% w/w) in water.
3. Once the coating is completed, allow the beads to dry at 60° C. for 2 or 3 minutes.
4. Cool the beads in a shallow pan at room temperature.
5. Break agglomerates, if any.
6. Sift the beads through Tyler 10 mesh sieve (1.77 mm opening) and then through Tyler 20 mesh sieve (850 micrometer opening) to remove fines.
7. Apply top coat to beads by spraying a solution of coloured Opadry clear solution (4% w/w) to a theoretical weight gain of 1% w/w.

After the completion of the overcoat, the beads are then filled into hard gelatin capsules at a strength of 20 mg.

Dissolution testing was conducted on the bead filled IR capsules using USP Apparatus 1 (basket method) in 500 mL of simulated gastric juice without enzyme, 100 rpm at 37° C. The results are as follows:

TABLE 2

Time (minutes)	% Methylphenidate HCl dissolved
10	92.7
20	95.7
30	97.7
45	98.5

The dissolution results as set forth in the above table indicate that 98.5% of the methylphenidate hydrochloride was dissolved in 45 minutes.

EXAMPLE 2

Methylphenidate HCl Controlled-Release (CR) Beads with Acrylic Polymer Coating

TABLE 3

Ingredients	%
Methylphenidate IR beads	86.20
Eudragit ® RS 30 D	8.63
Triethyl citrate	1.72
Talc	3.45
Water	q.s.
Total	100.0

The controlled-release coating is manufactured as follows:

1. The Eudragit® RS 30 D is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the IR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~8%.
3. Upon completion of the coating, the beads are cured for 24 hours at 40–45° C.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR capsules using the following USP Apparatus (basket method). The capsules were placed into 500 mL of simulated gastric juice without enzyme, for first 2 hours at 100 rpm and 37° C. and then placed into 500 mL simulated intestinal fluid without enzyme for the remainder of the testing period. The results are as follows:

TABLE 4

Time (hours)	Methylphenidate HCl dissolved
1	6.9
2	16.2
3	26.1
4	35.7
6	59.8
8	74.7
12	75.4
18	82.5
24	92.8

The dissolution results as set forth in the above table indicate that 92.8% of methylphenidate hydrochloride dissolved in 24 hours.

EXAMPLES 3 & 4

Dependence of Release Rate of Methylphenidate HCl from Controlled-Release (CR) Beads on Amount of Acrylic Polymer Coating

By adjusting the amount of Eudragit® RS 30 D applied, the release rate can be adjusted. This effect is illustrated in Examples 3 and 4 below:

TABLE 5

	%	
Ingredients	Example 3	Example 4
Methylphenidate HCl IR Bead	91.2	94.0
Eudragit ® RS 30 D	5.8	3.9
Triethyl citrate	1.0	0.7
Talc	2.0	1.4
Water	—	—
Total	100.0	100.0

The method of manufacturing the controlled-release beads in Examples 3 and 4 is similar to the method described under Example 2, by varying the proportion of beads and Eudragit® RS 30 D.

The cured beads were filled into hard gelatin capsules at a strength of 20 mg.

The dissolution results, conducted under conditions identical to those found under Example 2, are shown below:

TABLE 6

Time	% Methylphenidate HCl dissolved	
(hours)	Example 3	Example 4
1	18.7	49.5
2	35.1	73.3
3	49.0	81.5
4	60.6	85.2
6	75.7	90.4
8	77.3	90.7
12	82.1	92.8

The dissolution results as set forth in the above table, indicate that 82.1% and 92.8% respectively of methylphenidate hydrochloride is dissolved in 12 hours. However, the release of drug from Example 4 was significantly faster at time points 1, 2, 3, 4, 6 and 8 hours.

EXAMPLE 5

Enteric Coated (EC) Coated Release (CR) Beads—EC•CR Beads

TABLE 7

Ingredients	%
Methylphenidate CR beads	83.2
Eudragit ® L 30 D55	9.9
Triethyl citrate	2.0
Talc	4.9
Water	q.s.
Total	100.0

The enteric coating procedure is described below:

1. The Eudragit® L 30 D 55 is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the methylphenidate CR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 nm spray nozzle and the beads are coated to a weight gain of ~9%.

3. Upon completion of the coating, the beads are cured for 18 hours at 40° C.
4. The cured beads are then sieved through Tyler 10 mesh (1.7 mm opening) and Tyler 20 mesh (850 micrometer opening) sieves to remove any fines.

The beads were then filled onto hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR filled capsules using USP Apparatus 1 (basket method) 500 mL at 100 rpm and 37° C. using SGF without enzyme for the first 2 hours and SIF without enzyme for the rest of the testing period. Results are shown below:

TABLE 8

Time	% Methylphenidate HCl dissolved		
(hours)	Lot 1	Lot 2	Lot 3
1	0.4	1.0	2.0
2	2.2	5.4	7.4
3	18.8	27.8	61.3
4	36.7	48.3	87.0
6	59.5	75.5	98.8
8	76.9	90.1	100.0
12	82.3	99.6	—

The dissolution results as set forth in the above table indicate that very little drug is dissolved in gastric juice after enteric coating and that the dissolution profile of the CR beads has been modified.

EXAMPLE 6

Formulations for Clinical Trials

Examples 6A, 6B and 6C below set forth the formulations developed and tested in clinical studies.

EXAMPLE 6A

IR•EC•CR Beads

Immediate Release (IR) Coating of Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The (IR•EC•CR Beads) formulation, hereinafter referred to as Formulation 1, is a capsule containing multi-layer release beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption equal to or greater than Ritalin® IR immediate release tablets. The immediate release component represent 40% of the total dose per bead and the controlled release component represents 60%.

TABLE 9

Ingredients	%
Enteric coated Controlled Release Methylphenidate HCl beads	91.4
Methylphenidate hydrochloride USP	6.5
Opadry ® clear YS-1-7006	2.1
Water	q.s.
Total	100.0

The application of an immediate release coat on the top of Enteric Coated CR beads is described below:

1. Dissolve methylphenidate HCl USP and Opadry in water with stirring.
2. Load EC•CR beads into a Wurster insert of an Aeromatic Fluid Bed Dryer.
3. Spray the beads with the coating solution using a 1 mm spray nozzle at a temperature of not more than 50° C.
4. Once the coating is completed, cool the beads at room temperature and pass through Tyler sieves 10 and 20 mesh to remove fines.

The beads were then filled into a hard gelatin capsule to a 20 mg strength.

Dissolution testing was conducted on the bead filled capsules of Formulation 1 using USP Apparatus 1 (basket method) 100 rpm, 500 mL at 37° C.—simulated gastric juice without enzyme 1st and 2nd hours; 3rd hour onwards simulated intestinal fluid without enzyme.

The results are as follows:

TABLE 10

Time (hours)	% Methylphenidate HCl dissolved
5 minutes	37.0
10 minutes	38.0
15 minutes	39.0
30 minutes	40.0
60 minutes	40.0
2	40.1
3	51.4
4	61.0
6	75.6
8	87.0
12	87.5

The dissolution results as set forth in the above table indicate a rapid onset on dissolution, followed by prolonged action.

EXAMPLE 6B

IR+EC•CR Blend

Combination of Immediate Release Methylphenidate Beads (IR) and Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The enteric-coated controlled release beads (EC•CR) beads described in Example 5 may be mixed with the immediate release (IR) beads described in Example 1 in varying proportions and placed in capsules to obtain the final blended dosage form, (IR+EC•CR Blend), hereinafter referred to as Formulation 2. Formulation 2 was designed to provide a faster rate of absorption of the controlled release portion than Formulation 1. The immediate release component represents 35% of the total dose per capsule and the controlled release component represents 65%.

Dissolution testing was performed and the comparative results are shown in Table 11 below.

EXAMPLE 6C

IR•CR Beads

Immediate Release (IR) Coating of Controlled-Release (CR) Methylphenidate Beads

The IR•CR Beads formulation, hereinafter referred to as Formulation 3, is a capsule containing single beads made up of an immediate release topcoat and a controlled release core, and is designed to provide an intermediate rate of absorption of the controlled release portion between that of the controlled release formulations of Formulations 1 and 2. The immediate release component represents 30% of the total dose per bead and the controlled release component represents 70%.

The immediate release topcoat is applied to CR beads as described in Example 6A for Formulation 1.

The dissolution profiles of Formulations 1–3 and Ritalin® SR, used as a comparator, are shown in Table 11 below. Hours 1 and 2 are in 500 ml of simulated gastric fluid. Simulated intestinal fluid (500 ml) is used from the third hour onwards. The results of the dissolution testing confirmed the anticipated in vitro dissolution profile.

TABLE 11

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
10 min	21.4	38.0	32.0	28.6
30 min	31.4	40.0	36.7	34.0
1	45.7	40.0	38.2	40.5
2	62.3	40.1	40.4	57.6
3	75.8	51.4	68.1	70.6
4	79.5	61.0	86.4	79.5
6	88.0	75.6	95.4	89.6
8	90.7	87.0	96.2	92.7
12	91.3	87.5	97.0	93.1

EXAMPLE 7

Four Way Comparison of Single Dose Formulation 1 (Fed and Fasted) with Two Doses of Ritalin IR (Fed and Fasted)

The bioavailability of Methylphenidate MLR capsules was investigated in a four-way blind study which compared the Formulation 120 mg single dosage formulation under fed and fasted conditions with two doses (4 hours apart) of Ritalin® IR.

Healthy male volunteers were given a single dose of 20 mg Formulation 1 or two doses of immediate release methylphenidate 10 mg administered four hours apart under both fed and fasting conditions (n=12). "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatment according to Williams design 4 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, the morning under fasting conditions.

Treatment 2: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, under fasting conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, administered 5 minutes after a high fat breakfast.

Treatment 4. Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, administered 5 minutes after a high fat breakfast.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Formulation 1 and at pre-dose, 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Ritalin® IR. Plasma was harvested from each blood sample and stored in a −20° C. freezer until assayed for plasma methylphenidate concentration. Assay of plasma methylphenidate concentrations was performed using gas chromatography/mass spectrometry (GC/MS).

The mean plasma concentrations, standard deviations and coefficients of variation are shown as a function of time in Tables 12 and 13, for fasting and fed conditions, respectively.

This data is presented graphically in FIGS. **1**–**4**. FIG. **1** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fasting conditions. FIG. **2** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fed conditions. FIG. **3** presents the mean plasma concentration versus time for Formulation 1 under fed and fasting conditions. FIG. **4** presents the mean plasma concentration versus time for Ritalin® under fed and fasting conditions.

TABLE 12

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fasting)

	Formulation 1			Ritalin		
Sample Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	—
0.250	0.00	0.00	—	0.00	0.00	—
0.500	817.53	801.84	98.08	883.96	686.65	77.68
0.750	2268.79	1128.12	49.72	2485.74	828.38	33.33
1.00	3108.79	756.66	24.34	3468.74	1172.28	33.80
1.50	3597.88	740.36	20.58	4388.04	998.86	22.76
2.00	3675.60	1315.29	35.78	4289.39	1144.40	26.68
2.50	3469.81	882.62	25.44	4121.37	1014.57	24.52
3.00	3573.56	1031.61	28.87	3528.56	863.25	24.46
3.50	3637.01	1008.73	27.74	3020.93	716.36	23.71
4.00	3604.03	1071.59	29.73	2747.91	698.95	25.44
4.50	3494.44	1069.13	30.60	2958.49	799.89	27.04
5.00	3446.41	1069.50	31.03	4394.22	1603.40	36.49
5.50	—	—	—	5525.84	1766.58	31.97
6.00	3421.13	1166.25	34.09	5927.06	1955.99	33.00
6.50	—	—	—	5528.41	1758.49	31.81
7.00	3422.32	958.42	28.00	4860.45	1482.24	30.50
8.00	3338.59	724.49	21.70	3795.34	1500.79	39.54
10.0	2858.42	612.21	21.42	2223.48	926.11	41.65
12.0	2073.97	536.08	25.85	1334.71	523.37	39.21
16.0	1180.67	502.11	42.53	455.86	287.79	63.13
24.0	275.87	201.51	73.04	55.10	99.99	181.46

TABLE 13

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fed)

	Formulation 1			Ritalin		
Sample Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	—
0.250	0.00	0.00	—	53.12	133.84	251.95
0.500	291.66	271.58	93.11	1256.61	1602.66	127.54
0.750	910.22	653.80	71.83	2984.60	3406.53	114.14
1.00	1580.66	983.13	62.20	3400.39	2301.87	67.69
1.50	2760.68	797.24	28.88	5205.16	1882.17	36.16
2.00	3098.73	874.49	28.22	5146.55	1617.43	31.43
2.50	3655.68	982.31	26.87	5157.11	1227.99	23.81
3.00	3625.88	797.55	22.00	4546.61	932.94	20.52
3.50	3717.71	951.58	25.60	4184.34	1080.71	25.83
4.00	3650.63	875.97	23.99	3652.57	1023.22	28.01
4.50	3627.41	835.40	23.03	3811.27	1103.83	28.96
5.00	3430.14	783.72	22.85	5158.45	1714.53	33.24
5.50	—	—	—	5982.98	1618.65	27.05
6.00	3418.03	937.07	27.42	6228.81	1591.64	25.55
6.50	—	—	—	6054.32	1919.95	31.71
7.00	4218.94	775.86	18.39	5538.57	1741.02	31.43
8.00	4679.67	1126.52	24.07	4350.90	1611.95	37.05
10.0	3858.58	1045.56	27.10	2577.66	896.59	34.78
12.0	2610.98	902.53	34.57	1521.52	611.54	40.19
16.0	1372.86	737.71	53.74	577.90	334.26	57.84
24.0	334.79	306.63	91.59	94.23	144.99	153.86

Experimental Results

Pharmacokinetic parameters were calculated based on the data from the four-way study. AUC_{0-t} (pg·h/mL), AUC_{0-inf} (pg·h/mL), $AUC_{t/inf}$ (%), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours) were calculated as described below.

For purposes of the present invention, the following terms are meant to have the following meanings:

Analysis of Pharmacokinetic Data and Statistical Analysis

AUC_{0-t} Area under the concentration-time curve from time zero to the time of the last non-zero concentration (this corresponds to the area under the concentration-time curve, over the dosing interval of the test formulation for both controlled-release and immediate-release formulations)

AUC_{0-inf} Area under the concentration-time curve from time zero to infinity

C.I. Confidence interval

CV Coefficient of variation

C_{max} Maximum observed concentration

K_{el} Elimination rate constant

LQCT The last quantifiable concentration time

SD Standard deviation

TLIN The time point where log-linear elimination begins

$T_{1/2\ el}$ Time for observed C_{max}

Sampling Time Time post dose of plasma collection based on parameters to be studied

Scheduled Time The predetermined (clock) time at which the samples are to be taken

Actual time The exact (clock) time at which the sample was taken

Time deviations during sampling for drugs with a $T_{max} \leqq 4$ hours were treated as follows: between 0 and 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of blood collection was <10%. Above 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of plasma collection was <15%. When sampling times were used when previously described acceptance criteria, the corrected sampling items were used when performing pharmacokinetic parameters calculations. Sampling times are present in concentration tables and graphs of statistical report.

The mean, standard deviation (SD), and coefficient of variation (CV) were calculated for plasma concentrations of methylphenidate for each sampling time and treatment. As well, the mean, SD, and CV were calculated for the AUC_{0-t} (pg·h/mL), AUC_{0-inf} (pg·h/mL), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours). The calculation of these pharmacokinetic parameters is explained below.

Areas Under the Concentration-Time Curves

AUC_{0-t} was calculated using the linear trapezoidal rule.

The AUC_{0-t} was derived where t is the time (t) of the last measurable (non-zero) concentration (C_t) for each treatment.

The AUC_{0-inf} was calculated as:

$$AUC_{0-t} + \frac{C_t}{K_{el}}$$

Where C_t=the last non-zero concentration for that treatment, AUC_{0-t}=the AUC from time zero to the time of the last non-zero concentration for that treatment and K_{el}=the elimination rate constant.

Maximum Observed Concentration and Time of Observed Peak Concentration

The maximum observed concentration, C_{max}, and the observed time to reach peak concentration, T_{max}, was determined for each subject and for each treatment.

Half-Life and Elimination Rate Constant

To calculate the elimination rate constant (K_{el}), linear regression analyses were performed on the natural log (Ln) of plasma concentration values (y) versus time (x). Calculations were made between a time point where log-linear elimination phase begins (LQCT) occurred. The K_{el} was taken as the slope multiplied by (−1) and the apparent half-life ($T_{1/2\ el}$) as $0.693/K_{el}$.

TLIN and LQCT

TLIN, the time point where log-linear elimination begins, and LQCT, the last quantifiable concentration time were determined for each subject and for each treatment.

Percent Drug Absorbed

Percent drug absorbed was calculated at each sampling time (t) by Modified Wagner-Nelson's method, as implemented in Kinetica software, version 2.0.1 according to the following formula:

$$\frac{C_t + (K_{el} \times AUC_{0-t})}{(K_{el} \times AUC_{0-inf})} \times 100$$

All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.050. Based on the

pairwise comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} data, the relative ratios of the geometric means, calculated according to the formulation "$e^{(X-Y)}\times 100$", as well as the 90% geometric confidence intervals were determined.

Results

The plasma concentration of unchanged methylphenidate following administration of the controlled release formulation Formulation 1 reached the maximum concentration (C_{max}) at a mean of 3.27 hours under fasting conditions and 7.29 hours under fed conditions reflecting a biphasic absorption profile. The plasma concentration of unchanged methylphenidate following administration of two doses of the immediate release formulation (Ritalin® IR) reached the maximum concentration (C_{max}) at 5.96 hours under fasting conditions and 3.54 hours under fed conditions. When the determination of C_{max} was restricted to the first dose of immediate release methylphenidate, the T_{max} was 1.71 hours under fasting conditions and 1.63 hours under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg Formulation 1 and immediate release methylphenidate 10 mg (Ritalin® IR) under fed and fasted conditions are summarized in Tables 14 and 15 below.

TABLE 14

Pharmacokinetic Parameters for Formulation 1

Parameters	Formulation 1 (fasting) Mean ± SD	CV (%)	Formulation 1 (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	48493.80 ± 13430.27	27.69	54686.38 ± 15118.66	27.65
AUC_{0-inf} (pg · h/mL)	51213.86 ± 13260.14	26.59	57931.47 ± 16762.54	28.94
C_{max} (pg/mL)	4410.25 ± 1188.68	26.95	4879.37 ± 1027.85	21.07
T_{max} (h)	3.27 ± 2.54	77.64	7.29 ± 1.29	17.65
K_{el} (h^{-1})	0.1672 ± 0.0339	20.25	0.1812 ± 0.0392	21.65
$T_{1/2el}$(h)	4.32 ± 0.96	22.18	4.06 ± 1.25	30.91

TABLE 15

Pharmacokinetic Parameters for Ritalin ® IR

Parameters	RITALIN ® (fasting) Mean ± SD	CV (%)	RITALIN ® (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	44644.22 ± 13806.82	30.93	52781.49 ± 15194.94	28.79
AUC_{0-inf} (pg · h/mL)	46466.23 ± 14012.73	30.16	54783.17 ± 15311.08	27.95
C_{max} (pg/mL)	6536.04 ± 1669.29	25.54	7571.74 ± 1534.58	20.27
T_{max} (h)	5.96 ± 0.54	9.09	3.54 ± 2.42	68.43
K_{el} (h^{-1})	0.2481 ± 0.0550	22.17	0.2449 ± 0.0719	29.37
$T_{1/2el}$(h)	2.93 ± 0.71	24.10	3.08 ± 0.96	31.26

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Dunican's Multiple Range Test, the AUC_{0-t} of treatment 1 was significantly different from the AUC_{0-t} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized in Table 16 below:

TABLE 16

	AUC_{0-t} (pg · h/mL)		
	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	109.90%	104.08%	88.65%
90% Geometric C.I.	102.59% to 117.74%	97.15% to 111.50%	82.75% to 94.97%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatment 1 was significantly different from the AUC_{0-inf} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized below in Table 17:

TABLE 17

	AUC_{0-inf} (pg · h/mL)		
	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	111.65%	105.86%	88.85%
90% Geometric C.I.	104.09% to 119.95%	98.70% to 113.55%	82.84% to 95.30%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 1 was not significantly different from the C_{max} of treatment 3. However, Duncan's Multiple Range Test detected statistically significant differences for C_{max} when comparing treatments 1 and 2 and treatments 3 and 4. The statistical analyses performed on the data are summarized below in Table 18:

TABLE 18

	C_{max} (pg/mL)		
	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	67.48%	64.38%	89.37%
90% Geometric C.I.	60.28% to 75.54%	57.51% to 72.07%	79.83% to 100.04%

The ANOVA and Duncan's Multiple Range Test performed on the T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 3 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 3 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 and treatments 3 and 4 for this parameter.

The results of the ANOVA and Duncan's Multiple Range Test performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were detected by Duncan's Multiple Range Test between treatments 1 and 2 and treatments 3 and 4, but not for treatments 1 and 0.3.

Summary and Analysis

The AUC and C_{max} ratios of controlled release methylphenidate 20 mg Formulation 1 under fed and fasted conditions are summarized in Table 19 below. A comparison of the AUC and C_{max} ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fasting conditions are summarized in Table 20 below. Table 21 shows the comparative ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fed conditions.

Treatment 1 (Formulation 1, Fasting) Versus Treatment 3 (Formulation 1, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 3 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed K_{el} and $T_{1/2\ el}$. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test product (Formulation 1, fasting) to reference product (Formulation 1, fed) were found to be within 80 to 125%. This is summarized in Table 19 below:

TABLE 19

Formulation 1 (Fed) vs. Formulation 1 (Fast)			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.80%	112.54%	111.90%
90% Geometric C.I.[2]	105.29%–120.84%	104.93%–120.71%	99.96%–125.27%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1 (fed)}-\text{Formulation 1 (fasting)}]} \times 100$

[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 1, Fasting) Versus Treatment 2 (Ritalin®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for all parameters. With the exception of C_{max}, all formulation ratios as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80 to 125%. This is summarized in Table 20 below:

TABLE 20

Formulation 1 (Fast) vs Ritalin ® (Fast)			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.90%	111.65%	67.48%
90% Geometric C.I.[2]	102.59%–117.74%	104.09%–119.75%	60.28%–75.54%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1 (fast)}-\text{Ritalin IR (fast)}]} \times 100$

[2]90% Geometric Confidence Interval using log-transformed data

Treatment 3 (Formulation 1, Fed) Versus Treatment 4 (Ritalin®, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for all parameters with the exception of ln-transformed AUC_{0-t} and AUC_{0-inf}. With the exception of C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80% to 125%. This is summarized in Table 21 below:

TABLE 21

Formulation 1 (Fed) vs. Ritalin ® IR (Fed)			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.08%	105.86%	64.38%
90% Geometric C.I.[2]	97.15%–111.50%	98.70%–113.55%	57.51%–72.07%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1 (fed)}-\text{Ritalin IR (fed)}]} \times 100$

[2]90% Geometric Confidence Interval using log-transformed data

Conclusions

Review of individual plasma MPH time curves indicates the following:

Plasma MPH concentrations at 12 hours were higher on Formulation 1 than on Ritalin IR in all subjects, under both fed and fasted conditions.

A biphasic profile was apparent under fasted conditions in 7–10/12 subjects and in 8–10/12 under fed conditions. The mean curve showing a stable plateau under fasted conditions is therefore not fully representative of the individual profiles. The enteric coat therefore gave rise to a biphasic profile in some subjects even under fasted conditions.

Under fasted conditions the apparent rate of rise of plasma MPH was equivalent to, or faster than, that of Ritalin IR in 8/12subjects under fasted conditions and 4–5/12 subjects under fed conditions. The mean curves which demonstrate an equivalent rate of rise under fasted conditions and a slower rise under fed conditions were therefore largely reflective of the individual profiles.

The bioavailability of Formulation 1 relative to Ritalin IR was acceptable under both fed and fasted conditions (Relative AUC_{inf} 106% and 112%). There was an increase in AUC of both Formulation 1 and Ritalin when given with food (13.1% and 17.9% respectively).

Formulation 1 had a more prolonged mean plasma MPH concentration time profile than two doses of Ritalin IR. An across study comparison indicates that Formulation 1 also has a more prolonged profile than Ritalin SR.

Under fasted conditions Formulation 1 had a mean initial rate of rise of plasma MPH that is similar to Ritalin IR and a relatively flat plateau until 8 hours post-dose.

Under fed conditions, the initial rise in plasma NTH from Formulation 1 was slower than under fasted conditions and the plateau showed a biphasic profile. This was consistent with predictions that the enteric coat would delay release of the controlled release component and that this delay would be longer under fed conditions (allowing the initial plasma concentration peak, due to the IR component, to fall prior to the start of release from the controlled release component).

Formulation 1 results in both a fast initial rate of rise of plasma methylphenidate concentration, and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Formulation 1 therefore has the potential to meet the dual objectives of rapid onset and prolonged duration that are considered desirable characteristics of a controlled release methylphenidate formulation for the treatment of ADD/ADHD.

An initial pilot bioavailability study completed in adult healthy volunteers has confirmed that a single 20 mg dose of this formulation has an equivalent extent of absorption to two doses of immediate release methylphenidate (10 mg) given 4 hours apart. Maximal plasma concentrations with the controlled release formulation are similar to those attained with the first dose of immediate release methylphenidate and from approximately 10 hours post-dose, are higher than those following the second dose of immediate release methylphenidate.

The results indicate the potential for a single morning dose of this formulation to produce clinical effects that are at least equivalent to those of two doses of immediate-release methylphenidate given at breakfast and lunchtime, with a duration of action that may reduce the need for a third dose of immediate release methylphenidate later in the day.

EXAMPLE 8

Five-Way Comparison of Single Dose Formulation 2 (Fed and Fasted), Single Dose Formulation 3 (Fed and Fasted) and Single Dose Ritalin SR (Fasted)

A five-way blind study was conducted which compared a single dose of Formulation 2, 20 mg, both fed and fasted, a single dose of Formulation 3, 20 mg, both fed and fasted, and Ritalin SR 20 mg single dose fasted. According to the published literature and anecdotal comments from physicians, Ritalin SR is used in less than 20% of methylphenidate treated patients.

Twelve healthy male volunteers were given a single dose of either 20 mg Formulation 2 or Formulation 3 administered four hours apart under both fed and fasting conditions (n=12), or slow-release 20 mg methylphenidate (Ritalin SR) under fasting conditions. "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 5 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning, under fed conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fasting conditions.

Treatment 4: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fed conditions.

Treatment 5: Reference Product: methylphenidate slow-release 20 mg tablet Ritalin SR (Novartis) under fasting conditions.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose. Plasma was harvested from each blood sample and stored in a −20 C freezer until assayed for plasma methylphenidate concentration.

The data is presented graphically in FIGS. **5**–**8**. FIG. **5** presents the mean plasma concentration versus time for Formulation 2 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **6** presents the mean plasma concentration versus time for Formulation 3 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **7** presents the mean plasma concentration versus time for Formulations 2 and 3 under fasting conditions. FIG. **8** presents the mean plasma concentration versus time for Formulations 2 and 3 under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg (Formulation 2 and 3) under fed and fasting conditions, and for slow release methylphenidate 20 mg (Ritalin® SR) under fasting conditions are summarized in Tables 22–24 below.

TABLE 22

Pharmacokinetic Parameters for Formulation 2

	Treatment 1, Fasting		Treatment 2, Fed	
Parameters	Means ± SD	CV (%)	Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	48190.73 ± 11668.71	24.21	53452.63 ± 12820.39	23.98
AUC_{0-inf} (pg · h/mL)	49787.07 ± 12053.23	24.21	55690.49 ± 12691.52	22.79
C_{max} (pg · h/mL)	7498.57 ± 1968.38	26.25	6879.09 ± 1486.53	21.61
T_{max} (h)	3.63 ± 0.57	15.70	6.42 ± 1.08	16.89
K_{el} (h^{-1})	0.2391 ± 0.0428	17.91	0.2321 ± 0.0342	14.75
$T_{1/2}$ (h)	3.00 ± 0.64	21.32	3.05 ± 0.48	15.74

TABLE 23

Pharmacokinetic Parameters for Formulation 3

	Treatment 3, Fasting		Treatment 4, Fed	
Parameters	Means ± SD	CV (%)	Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	48057.06 ± 14743.87	30.68	54128.75 ± 14787.94	27.32
AUC_{0-inf} (pg · h/mL)	49984.68 ± 14873.03	29.76	56315.66 ± 14779.59	26.24
C_{max} (pg · h/mL)	6080.97 ± 2048.60	33.69	6959.07 ± 1559.34	22.41
T_{max} (h)	3.46 ± 0.89	25.76	4.42 ± 0.56	12.62
K_{el} (h^{-1})	0.2009 ± 0.0468	23.32	0.2057 ± 0.0390	18.97
$T_{1/2}$ (h)	3.65 ± 0.97	26.52	3.49 ± 0.70	20.01

TABLE 24

Pharmacokinetic Parameters for Ritalin SR ®

Parameters	Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	47404.51 ± 12754.66	26.91
AUC_{0-inf} (pg · h/mL)	49252.17 ± 12841.52	26.07
C_{max} (pg/mL)	6783.09 ± 1496.65	22.06
T_{max} (h)	3.50 ± 0.43	12.18
K_{el} (h^{-1})	0.2282 ± 0.0320	14.01
$T_{1/2el}$ (h)	3.10 ± 0.47	15.14

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 3 was significantly different from the C_{max} of treatments 4 and 5. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for C_{max} when comparing treatment 1 vs. treatment 2 or treatment 1 vs treatment 5. The statistical analyses performed on the data are summarized in Table 25 below:

TABLE 25

	C_{max} (pg/mL)			
	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	103.73%	84.78%	109.25%	87.40%
90% Geometric C.I.	98.94% to 115.14%	78.59% to 91.45%	101.28% to 117.85%	81.05% to 94.26%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, and treatments 3 and 4 for this parameter. Duncan's Multiple Range Test did not detect statistically significant differences between treatments for T_{max} a when comparing treatments 1 vs. 3 or treatments 3 vs. 5.

The ANOVA performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 5 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were not detected by Duncan's Multiple Range Test, between treatments for K_{el} when comparing treatments 1 and 2, treatments 3 and 4, or treatments 1 and 5. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatments 1 and 3 was significantly different from the AUC_{0-t} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-t} when comparing treatment 1 vs treatment 5, or treatment 3 vs

treatment 5. The statistical analyses performed on the data are summarized below in Table 26:

TABLE 26

	AUC_{0-t} (pg · h/mL)			
	Treatment 1 vs. Treatment 2	Treatment 3 vs. Treatment 4	Treatment 1 vs. Treatment 5	Treatment 3 vs. Treatment 5
Ratio	89.21%	88.23%	101.82%	100.63%
90% Geometric C.I.	84.03% to 94.71%	83.10% to 93.67%	95.91% to 108.10%	94.81% to 106.81%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatments 1 and 3 was significantly different from the AUC_{0-inf} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-inf} when comparing treatment 1 vs treatment 3, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 27:

TABLE 27

	AUC_{0-int} (pg · h/mL)			
	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	88.33%	88.14%	101.14%	100.82%
90% Geometric C.I.	83.50% to 93.44%	83.32% to 93.24%	95.61% to 106.99%	95.33% to 106.63%

Treatment 1 (Formulation 2, Fasting) vs. Treatment 2 (Formulation 2, Fed)

The ANOVAs detected statistically significant differences between fed and fasting conditions, treatments 1 and 2, for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed $T_{1/2el}$ and K_{el}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 28 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 2. However, this food effect was less than 20% on average.

TABLE 28

	Formulation 2, Fed versus Fasting		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1] 90%	112.09% 105.58% to	113.21% 107.03% to	93.69% 86.85% to 101.07%
Geometric C.I.[2]	119.00%	119.76%	

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 2 (Fed)}-\text{Formulation 2 (Fasting)})} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 4 (Formulation 3, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for untransformed $T_{1/2el}$ and K_{el}. With the exception of lower 90% geometric confidence interval for C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 29 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 3. However, this food effect was less than 20% on average.

TABLE 29

	Formulation 3, Fed versus Fasting		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	113.35%	113.45%	117.96%
90% Geometric C.I.[2]	106.76% to 120.33%	107.25% to 120.01%	109.35% to 127.25%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 3 (fed)}-\text{Formulation 3 (Fasting)})} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 2, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 5 for all parameters. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 30 below. Thus, Formulation 2 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 30

	Formulation 2 (Fasting) versus Ritalin SR (Fasting)		
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.82%	101.14%	106.99%
90% Geometric C.I.[2]	95.91% to 108.10%	95.61% to 106.99%	101.28 to 117.85%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 2 (fast)}-\text{Ritalin SR (Fast)})} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for ln-transformed C_{max} and untransformed $T_{1/2el}$ and K_{el}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 31 below. Thus, Formulation 3 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 31

Formulation 3 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.63%	100.82%	87.40%
90% Geometric C.I.[2]	94.81% to 106.81%	95.33% to 106.63%	81.05 to 94.26%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation (fast)}-\text{Ritalin SR (Fast)}) \times 100}$

[2]90% Geometric Confidence Interval using ln-transformed data

Conclusions

The bioavailability of Formulation 2 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 101%—Fed conditions not tested).

The bioavailability of Ritalin SR® under fasted conditions is similar to that of Ritalin® IR, as discussed in Example 7 (AUC_{inf} 29.2 vs. 46.5 ng.h/mL, respectively). Literature data which indicates that Ritalin® IR and SR are absorbed at equivalent rates suggests that comparisons between the studies presented in Examples 7 and 8 are reasonable.

Bioavailability of Formulations 1 and 2 are similar under fasted and fed conditions (fasted: 49.8 vs. 51.2 ng.h/mL; fed: 55.7 vs. 57.9 ng.h/mL).

From the mean curves of Formulation 2 and Ritalin SR®, the initial rate of rise of plasma MPH concentration is slightly faster for Formulation 2 compared to Ritalin SR®. Under fed conditions, the rate of rise of plasma MPH with Formulation 2 decreased and T_{max} was delayed in comparison to both Formulation 2 fasted and Ritalin SR® fasted.

Bioavailability of Formulation 3 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 100.8%—fed conditions not tested).

Bioavailability of Formulations 1 and 3 are similar under fasted and fed conditions (fasted: 50.0 versus 51.2 ng/hmL; fed: 56.3 versus 57.9 ng·h/mL). Note also that Formulations 2 and 3 have almost identical AUC values.

From the mean curves for Formulation 3 and Ritalin SR®, the initial rate of rise of plasma MPH concentrations is slightly faster for Formulation 3 compared to Ritalin SR®.

In contrast to Formulation 2, the effect of food on the initial rate of concentration rise is minimal. Since Formulation 3 does not contain an enteric coat, this suggests that food slows the initial release from the IR component of formulations that contain an enteric coat, both when the enteric coat is part of the same bead (underneath the IR coat in the case of Formulation 1) and when it is in a separate bead (as for Formulation 2).

Also in contrast to Formulation 2, the T_{max} of the mean curve of Formulation 3 occurs at a similar time to that of Ritalin SR® under fed and fasted conditions. For Formulation 2 (and Formulation 1) the T_{max} of the second absorption phase under fed conditions is substantially delayed relative to Ritalin SR®.

Conclusions

EXAMPLES 7 AND 8

1. Formulation 1 has both a fast initial rate of rise, at least under fasted conditions and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Since these conditions represent the extremes of "food stress", one might predict that administration in association with normal meals and times would provide an intermediate profile. It is also possible that gastric emptying in children on a normal meal schedule will be faster than in adults fed a high fat meal—this will tend to make the second absorption phase occur earlier and produce lower concentrations from 12 hours onwards. Formulation 1 therefore meets the dual objectives of rapid onset and prolonged duration.
2. Formulation 2 is also very similar to Ritalin SR® under fasted conditions but shows a delayed peak under fed conditions such that plasma MPH concentrations are higher than Ritalin SR® (fasted) from 6 hours post dose onwards. The controlled release component in Formulation 2 is faster releasing than the one in Formulation 1 and plasma MPH concentrations are lower for Formulation 2 from about 10 hours post dose.
3. Overall, Formulation 3 (non-enteric coated) has a profile very similar to Ritalin SR® under both fed and fasted conditions. The IR component of Formulation 3 provides some increase in initial absorption rate relative to Ritalin SR® under fasted conditions. Since concentrations later in the day are similar for the two formulations, this confirms the concept that a fast initial rise and higher concentrations later in the day are not possible at the same dose, unless a delay is introduced into the release of a component of the total dose.

EXAMPLE 9

Example 9 is directed to another embodiment of the invention wherein a formulation is prepared which provides both rapid initial onset of effect and prolonged duration, and which provides a peak concentration which is not lower than Ritalin IR, while providing a prolonged duration which is not too long and which does not cause insomnia at night. An ideal target plasma drug concentration profile is shown in FIG. **9**, which is a plot of Ritalin IR versus Ritalin SR versus Formulation 1 (described above in Example 7) versus the "target" formulation of Example 9.

Assuming first order elimination of methylphenidate in human, the first order elimination rate constant was estimated from the linear terminal slope of plasma methylphenidate concentration curve (as plotted in log-linear paper) following oral administration of Ritalin IR. The absorption profile of Formulation 1 described above can be obtained following deconvolution calculation of the plasma drug concentration profile of the same using the Wagner-Nelsen Method ("Fundamentals of Clinical Pharmacokinetics" by John G. Wagner, Drug Intelligence Publications, Inc. 1975, page 174). The in-vitro drug dissolution profile correlates

well with the in-vivo absorption profile, as shown in FIG. **10**. This correlation indicates that the in-vitro dissolution method can be used to predict in-vivo drug absorption.

To obtain a target absorption/dissolution profile, assuming first order elimination of methylphenidate in human, the first order elimination rate constant was estimated from the linear terminal slope of the plasma methylphenidate concentration curve (as plotted in log-linear paper) following oral administration of Ritalin IR, via the Wagner-Nelsen Method. The target absorption profile is depicted in FIG. **11**. Based on the established in-vitro/in-vivo correlation as shown in FIG. **10**, assuming a similar drug release mechanism is utilized, this in-vivo absorption curve can be taken as the target dissolution profile.

EXAMPLE 10

In Example 10, a methylphenidate formulation in accordance with the present invention is prepared utilizing a melt extrusion granulation (MEG) technique. The ingredients are set forth in the following Table 32.

TABLE 32

Ingredient	mg/tablet
Methylphenidate HCl	15.0
Eudragit RSPO	25.0
Stearyl Alcohol	25.0
Eudragit L 100-55	5.0
Avicel PH 102	30.0
Talc	2.0
Magnesium Stearate	1.0
	103

Method of Manufacture:

The Methylphenidate HCl, Eudragit RSPO, Stearyl Alcohol, Eudragit L100-55 and Avicel are blended. The powder blend is fed into a turn screw melt extruder. The heating zones are set to 80° C. and screw speed at 30 rpm, and the powder is fed through the extruder at the elevated temperature, and is extruded as warm strands through a die plate with holes of 1 mm. The extruded strands are cooled on the conveyor belt. The cooled strands are then broken into smaller pieces. The broken strands are then milled into a granulation using a Fitzmill. The granulation is then blended with the talc and magnesium stearate and compressed into tablets using a tabletting machine.

The expected dissolution of both these tablets, using USP basket apparatus 1 with a paddle speed of **100** rpm in 500 ml SGF at pH 1.2 for two hours followed by 500 ml phosphate buffer at pH 5.8 is set forth in Table 33:

TABLE 33

	In-Vitro Dissolution	
Hour	% Dissolved	Target % Dissolved
1	31	31
3	61	58
8	89	98

EXAMPLE 11

In Example 11, a methylphenidate formulation in accordance with the present invention is prepared utilizing the melt extrusion granulation (MEG) technique as set forth in Example 10. The ingredients are set forth in Table 34.

TABLE 34

Ingredient	mg/tablet
Methylphenidate HCl	15.0
Eudragit RSPO	25.0
Stearyl Alcohol	15.0
Eudragit L 100-55	5.0
Avicel PH 102	30.0
Polyethylene glycol 8000	10.0
Talc	2.0
Magnesium Stearate	1.0
	103

The expected dissolution of both these tablets, using USP basket apparatus 1 with a paddle speed of 100 rpm in 500 ml SGF at pH 1.2 for two hours followed by 500 ml phosphate buffer at pH 5.8 is set forth in Table 35:

TABLE 35

Hour	% Dissolved	Target % Dissolved
1	30	31
3	59	58
8	90	98

EXAMPLE 12

In Example 12, another method of producing controlled release Methylphenidate HCl tablets in accordance with the present invention is utilized, via a direct compression technique. The ingredients of Example 12 are set forth in Table 36 below:

TABLE 36

Ingredient	mg/tablet
Methylphenidate HCl	15.0
Lactose DT	15.0
Methocel	67.0
Talc	2.0
Magnesium Stearate	1.0
	100

Method of Manufacture:

The ingredients are blended. The blended material is compressed into tablets. When these tablets were tested for dissolution using the same methodology noted above, the results were as set forth in Table 37 below:

TABLE 37

Hour	% Dissolved	Target % Dissolved
1	33	31
3	71	58
8	98	98

EXAMPLE 13

In Example 13, the method of producing controlled release Methylphenidate HCl tablets in accordance with

Example 12 is utilized, via a direct compression technique to produce another formulation. The ingredients of Example 13 are set forth in Table 38 below:

TABLE 38

Ingredient	mg/tablet
Methylphenidate HCl	15.0
Lactose DT	15.0
Eudragit L 100-55	15.0
Methocel	52.0
Talc	2.0
Magnesium Stearate	1.0
	100

When the tablets were tested for dissolution using the same methodology noted above, the results were as set forth in Table 39 below:

TABLE 39

Hour	% Dissolved	Target % Dissolved
1	37	31
3	67	58
8	87	98

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. An oral dosage form comprising an effective amount of methylphenidate or a pharmaceutically acceptable salt thereof, wherein a portion of the methylphenidate or pharmaceutically acceptable salt thereof is in immediate release form and a portion of the methylphenidate or pharmaceutically acceptable salt thereof is in controlled release form, the controlled release form comprising a substrate comprising about 60% to about 70% of the methylphenidate or a pharmaceutically acceptable salt thereof and at least one pH dependent release modifying coating, wherein the pH dependent release modifying coating is applied to obtain a weight gain from about 2 to about 25% of the substrate, the formulation providing a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration, a peak plasma concentration from about 3 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form, wherein the peak concentration is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration, wherein the formulation provides an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate HCl dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%

and wherein the duration of effect provided by the methylphenidate contained in the formulation falls below effective plasma concentrations at about 8 to about 12 hours after oral administration,

wherein about 30% to about 40% of the methylphenidate or pharmaceutically acceptable salt thereof is in immediate release form.

2. The oral dosage form of claim **1**, wherein the oral dosage form provides a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration.

3. The oral dosage form of claim **2**, wherein the peak plasma concentration is from about 1.0 to about 1.7 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration.

4. The oral dosage form of claim **3**, wherein the duration of effect provided by the methylphenidate contained in the oral dosage form falls below effective plasma concentrations at about 8 to about 10 hours after oral administration.

5. The oral dosage form of claim **1**, which provides a "square wave" plasma profile as depicted by Formulation 1.

6. The oral dosage form of claim **1**, which provides an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate HCl dissolved
0.25	0–45%
1	10–50%
4	30–80%
8	NLT 65%
12	NLT 80%

7. The oral dosage form of claim **1**, wherein the pH dependent release modifying coating is selected from the group consisting of shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, a pH dependent methacrylic acid ester copolymer and zein.

8. The oral dosage form of claim **7**, wherein the pH dependent coating is a pH dependent methacrylic acid ester copolymer.

9. The oral dosage form of claim **1**, wherein the substrate comprises methylphenidate or pharmaceutically acceptable salt thereof coated onto inert beads.

10. The oral dosage form of claim **9**, wherein the coated inert beads are overcoated with at least a portion of the pH dependent release modifying coating.

* * * * *

EXHIBIT C

US007247318B2

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

(10) **Patent No.: US 7,247,318 B2**
(45) **Date of Patent: *Jul. 24, 2007**

(54) **CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS**

(75) Inventors: **Thinnayam N. Krishnamurthy**, Ontario (CA); **Andrew Darke**, Ontario (CA)

(73) Assignee: **Purdue Pharma**, Pickering, Ontario (CA)

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

This patent is subject to a terminal disclaimer.

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(22) Filed: **May 28, 2002**

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US 2003/0054033 A1 Mar. 20, 2003

Related U.S. Application Data

(63) Continuation of application No. 09/465,159, filed on Dec. 16, 1999, now Pat. No. 6,419,960.

(60) Provisional application No. 60/112,617, filed on Dec. 17, 1998.

(51) **Int. Cl.**
A61K 9/14 (2006.01)
A61K 9/16 (2006.01)
A61K 9/48 (2006.01)

(52) **U.S. Cl.** **424/490**; 424/451; 424/452; 424/489; 424/491; 424/497

(58) **Field of Classification Search** 424/451, 424/452, 464, 465, 468–472, 489, 490, 494, 424/457, 458, 459, 460, 491–498
See application file for complete search history.

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Primary Examiner—Susan Tran
(74) *Attorney, Agent, or Firm*—Davidson, Davidson & Kappel

(57) **ABSTRACT**

The invention is directed to oral modified/controlled release drug formulations which provide a rapid initial onset of effect and a prolonged duration of effect. Preferably, the peak concentration is lower than that provided by the reference standard for immediate release formulations of the drug, and the duration of effect falls rapidly at the end of the dosing interval.

12 Claims, 8 Drawing Sheets

Figure 1. Mean Plasma Concentration of Methylphenidate

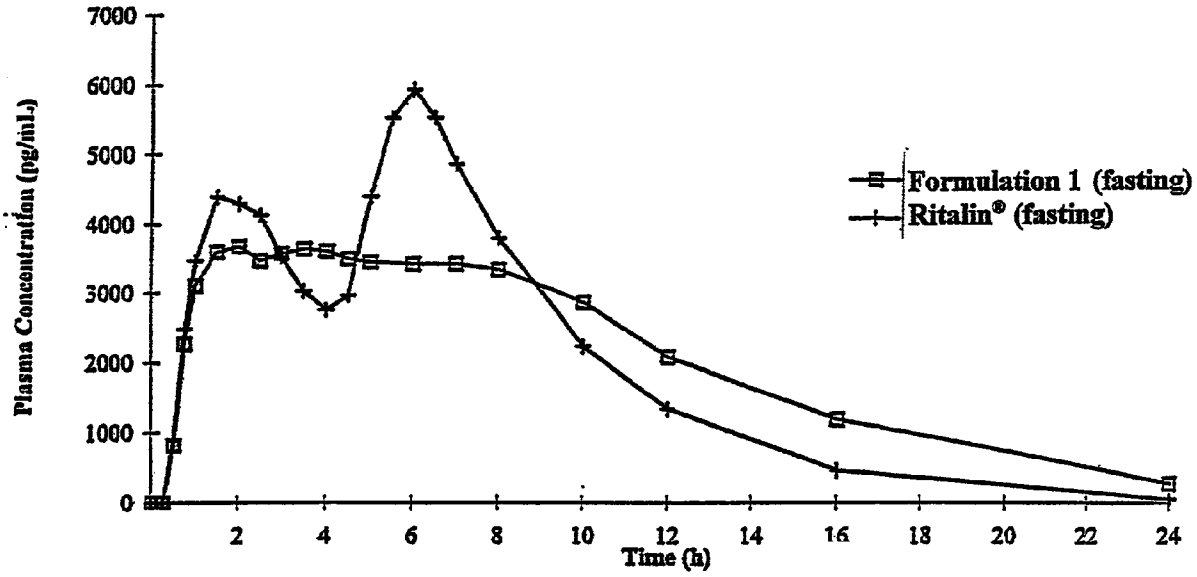


Figure 2 Mean Plasma Concentration of Methylphenidate

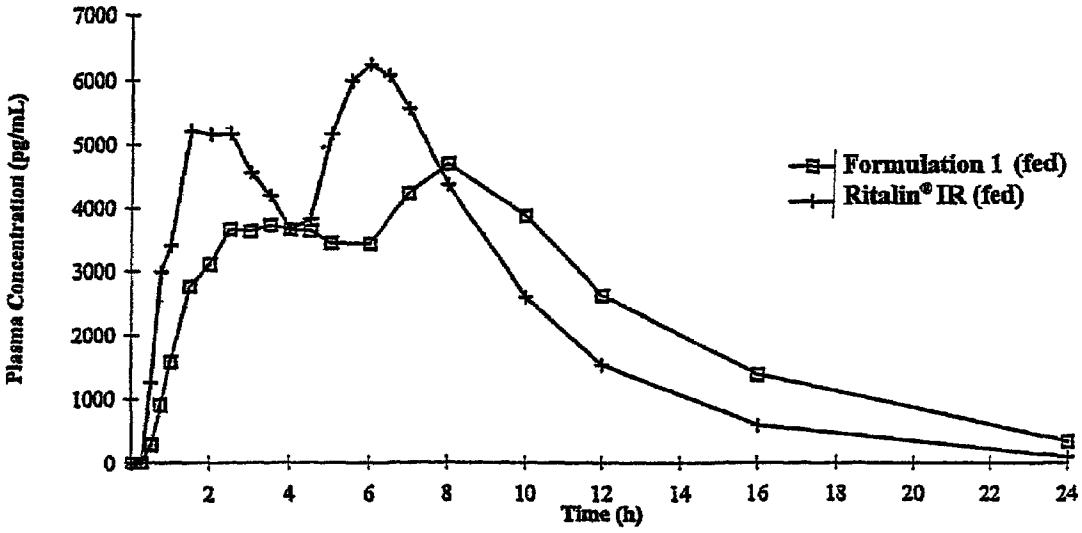


Figure 3 Mean Plasma Concentration of Methylphenidate

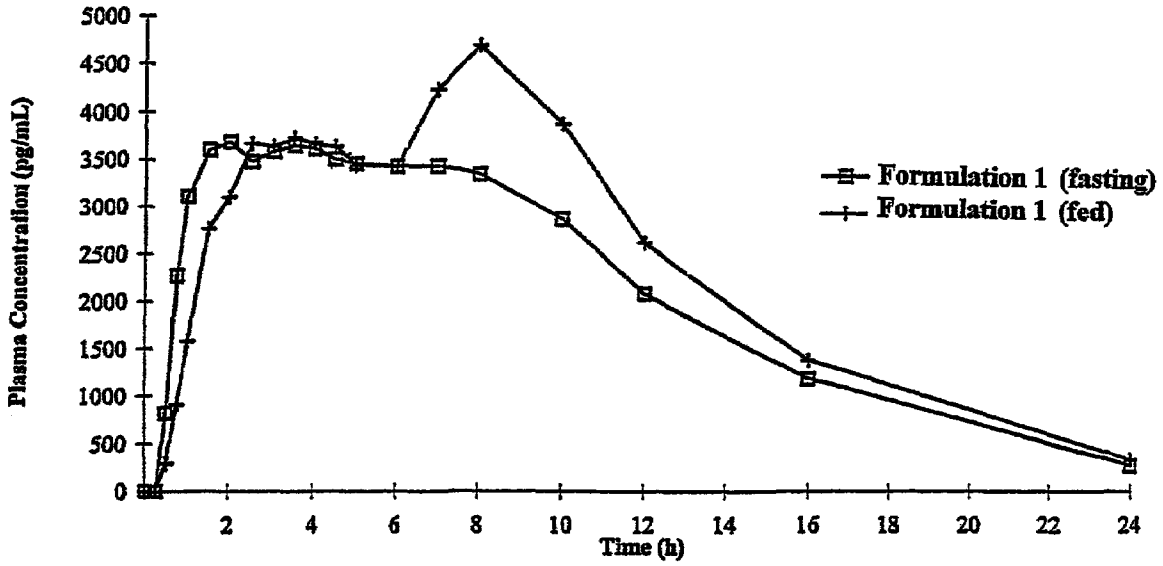


Figure 4 Mean Plasma Concentration of Methylphenidate

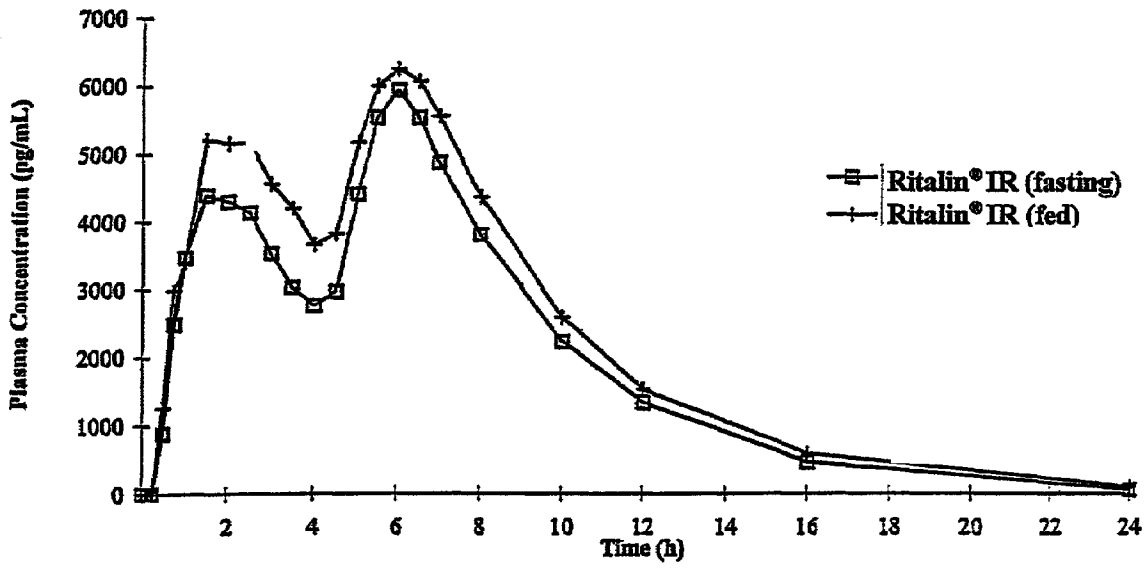


Figure 5 Mean Plasma Concentration of Methylphenidate

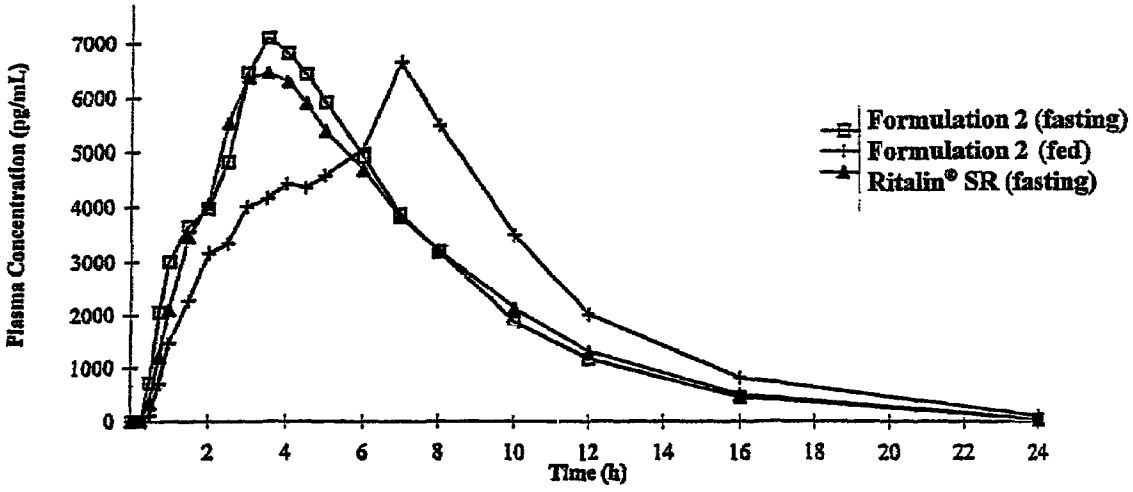


Figure 6 Mean Plasma Concentration of Methylphenidate

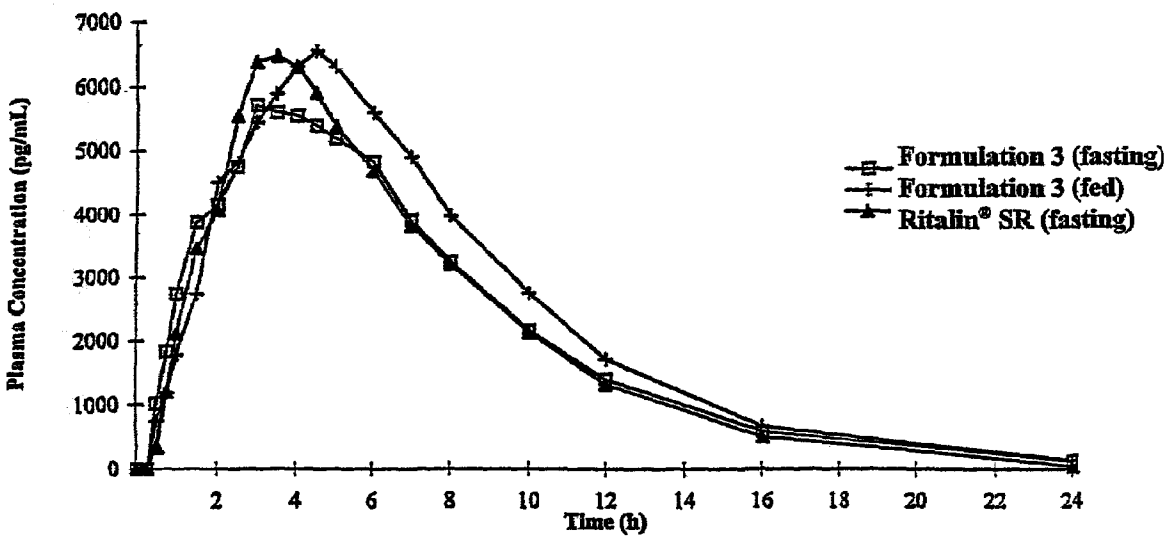


Figure 7 Mean Plasma Concentration of Methylphenidate

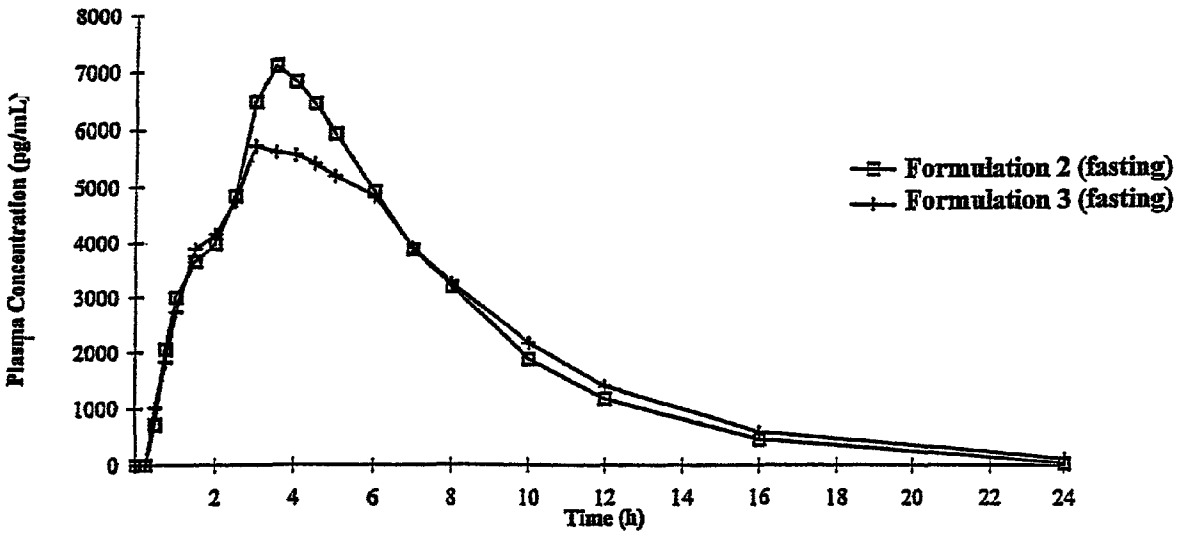
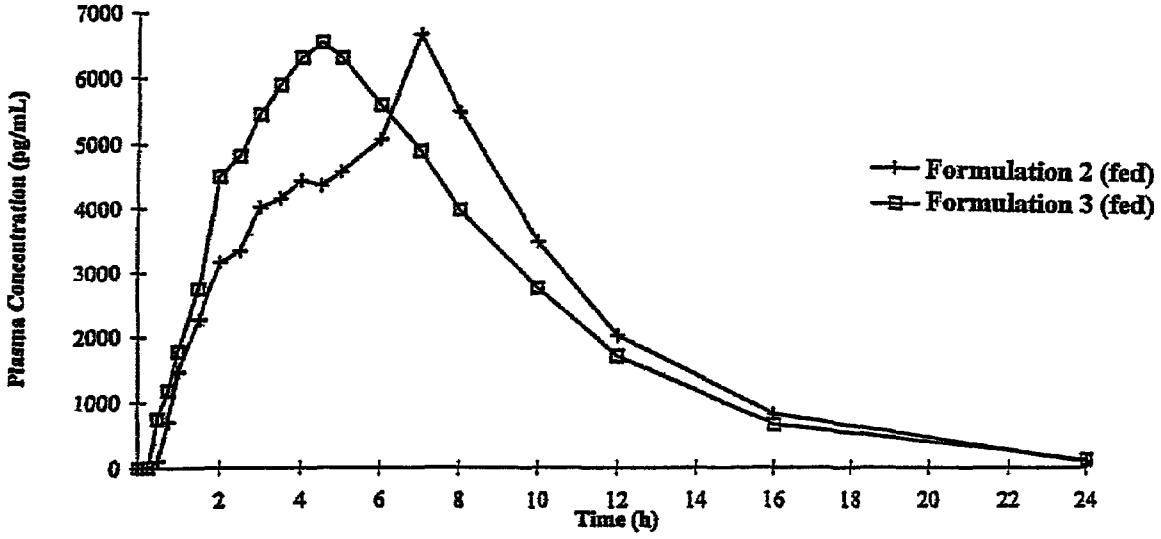


Figure 8 Mean Plasma Concentration of Methylphenidate



CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS

This application is a continuation of U.S. patent application Ser. No. 09/465,159, filed Dec. 16, 1999 now U.S. Pat. No. 6,419,960, which claims priority from U.S. Provisional Application No. 60/112,617, filed Dec. 17, 1998, the disclosures of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. It is the intent of all sustained release formulations to provide a longer period of pharmacologic action after administration than is ordinarily obtained after administration of immediate-release dosage forms. Sustained release compositions may be used to delay absorption of a medicament until it has reached certain portions of the alimentary tract, and maintain a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered. Such longer periods of response provide for many therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. Thus, therapy may be continued without interrupting the sleep of the patient, which is of special importance, for example, when treating a patient for moderate to severe pain (e.g., a post-surgery patient, a cancer patient, etc.), or for those patients who experience migraine headaches on awakening, as well as for the debilitated patient for whom sleep is essential. A further general advantage of longer acting drug preparations is improved patient compliance resulting from the avoidance of missed doses through patient forgetfulness.

Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occurs because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance therapy of the patient. In view of this, it is considered a goal of many skilled in the art that a controlled release dosage form will ideally provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ratio. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

It is known in the pharmaceutical art to prepare compositions which provide for sustained release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Sustained release formulations known in the art include specially coated pellets, coated tablets and capsules, and ion exchange resins, wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ration. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

Controlled release formulations known in the art include specially coated beads or pellets, coated tablets and ion exchange resins, wherein the slow release of the active drug is brought about through selective breakdown of the coating of the preparation or through formulation with a special matrix to affect the release of the drug. Some controlled release formulations provide for sequential release of a single dosage of an active medicament at predetermined periods after administration.

While controlled and/or sustained release compositions have constituted a definite advance in the art, improvements in these compositions have been sought, particularly for preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD), diabetes etc.

Attention Deficit Disorders are the most common psychiatric disorders in children (Campbell et al. 1992) with reported rates ranging from 4% to 9% (Aman et al. 1983). Attention Deficit Disorder (ADD) is characterized by inattention and impulsivity and may be present with hyperactivity (ADHD) (Shaywitz et al. 1984). Other characteristics may include aggressiveness, stealing, lying, truancy, setting fires, running away, explosiveness, cognitive and learning problems as well as poor social skills (Campbell et al. 1992). It is four to five times more frequent in boys than girls (Campbell et al. 1992).

Stimulant medication, such as amphetamines, have been shown to be the most effective agents in the treatment of children with disorders of activity modulation and attention regulation and result in significant improvement in 70 to 80 per cent of affected children (Shaywitz et al. 1984). Positive effects of stimulants have been documented in a variety of areas including behavioral, social, perceptual performance, motor activity, impulse control, attention regulation and cognitive performance (Barkley 1977, Kavale 1983, Offenbacher et al. 1983, Rosenthalet al 1978).

Methylphenidate {d1-threo-methyl-2-phenyl-2-(2-piperidyl)acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The efficacy of methylphenidate ("MPH") in improving attention and behavioral symptoms has been supported by many studies.

Immediate release methylphenidate preparations, because of their short half-life, require frequent administration at short intervals to ensure adequate treatment throughout a child's school day. The rapid onset and offset of immediate release methylphenidate preparations means that a medicated child with attention deficit disorder will be maximally affected only for relatively brief periods during the day. Due to its short half-life, MPH is usually given twice per day, usually once after breakfast and once during the school day, an event that some children and some school personnel apparently avoid, resulting in poor compliance with prescribed regimens (Brown et al., 1985; Firestone 1982). Compliance is a major problem for children who require a midday or midafternoon dose as many schools prohibit children from taking medications during the school day and others often insist that all medications be given by a nurse.

Poor compliance in taking medication may explain, in part, the variable and conflicting results reported in many studies of the effect of medication on improving the behavior of hyperactive children. These limitations of immediate release methylphenidate led to interest in products with longer effective periods of action. These limitations of immediate release methylphenidate preparations led to interest in products with longer effective periods of action.

A sustained release form of methylphenidate (Ritalin® SR) is commercially available. As a result of many clinical trials, various opinion leaders in treatment of attention deficit hyperactivity disorder have made the following comments regarding Ritalin® SR (sustained release methylphenidate) produced by Ciba-Geigy: (i) Ritalin® SR does not have a sufficiently early onset of effect to allow for behavioral management in the early morning; (ii) Ritalin® SR does not have the beneficial late effects that would be produced by a lunch time dose of immediate release methylphenidate, thus defeating the purpose of using an SR formulation; (iii) The effects of Ritalin® SR are inconsistent or erratic over the course of the day.

There is a need in the art to develop drug formulations which provide a rapid onset, a prolonged action, followed by rapid offset of effect in order to overcome the deficiencies of the current state of the art.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which results in improved patient compliance.

It is an object of the present invention to provide new oral dosage formulations which represent improvements over currently available preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD).

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which ensure adequate treatment throughout a child's school day.

It is an object of the present invention to provide new oral dosage formulations which allow a child with attention deficit disorder to be maximally treated throughout the daytime, while being administered only once, i.e., in the morning.

It is a further object of the present invention to provide new controlled/modified release oral dosage formulations which provide a rapid onset and rapid offset with an extended release of active medicaments incorporated therein.

It is yet another object of the present invention to provide new controlled/modified release oral dosage formulations which are useful in all types of pharmaceutically active ingredients and which can extend the time of release of all such ingredients.

It is yet another object of the present invention to provide an oral controlled release formulation which combines both a rapid onset and sustained plasma concentrations throughout the day, followed by a rapid drop-off of plasma concentrations of drug to below minimum effective concentrations.

It is yet another object of the present invention to provide a "multi-layer release" (MLR) technology which is useful for all types of pharmaceutically active ingredients and which can extend the duration of action for a desired length of time.

To address the above-mentioned deficiencies as well as other goals, the present invention is directed in part to a controlled release product which is intended to combined both a rapid onset and sustained plasma concentrations throughout the day. Significantly, the formulations of the present invention provide a rapid onset, a prolonged action, followed by rapid offset of effect, i.e., a "square wave" profile.

The invention is directed in part to controlled/modified release formulations based on a multi-layered release ("MLR") technology. The drug product can be in a tablet or a multiparticulate formulation contained within an oral gelatin capsule.

In the case of beads, encapsulated in a capsule, each bead contains a series of layers with different characteristics—an outer immediate release layer, a release delaying layer (enteric coat), a controlled release layer over an immediate release layer. The MLR formulation is designed such that upon oral administration, the formulation provides a rapid dissolution and absorption of the outer layer of the formulation which contains a portion of the drug in immediate release form, thereby resulting in a rapid rise of the drug to therapeutic plasma levels. This is followed by a period of no absorption (due to an enteric coating), followed thereafter by a controlled release of the drug from the formulation to maintain plasma levels. After absorption of the drug from an immediate release core, plasma levels then rapidly decrease. By virtue of the release of the drug from the MLR formulation, the plasma level of the drug, when plotted on a time/concentration curve, takes the appearance of a "square wave".

In certain further preferred embodiments, the formulation provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and provides effective blood levels for at least about 6 hours after administration.

In certain further preferred embodiments, the formulation exhibits a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit a "plateau" which lasts from about 6 hours to about 12 hours. The "plateau" is characterized by a stabilized plasma concentration, wherein the plasma level at the end of the measured interval does not differ by more than 20%, preferably by no more than 10% of the plasma concentration at the beginning of the measured interval.

In certain further preferred embodiments, the formulation exhibits a bimodal release of active agent from the dosage form. Bimodal release of the active agent is characterized by the active agent being release from the dosage form by more than one distinct release rate. In some embodiments, the release rates can be separated by a no-release or a substantially no-release interval, although this is not always necessary.

In certain further preferred embodiments, the formulation exhibits a biphasic absorption of the active agent. Biphasic absorption of the active agent is characterized by the active agent being absorbed through a natural barrier (e.g. the mucosal lining of the gastro-intestinal tract) by more than one distinct absorption rate. In some embodiments, the absorption rates can be separated by a no-absorption or a substantially no-absorption interval, although this is not always necessary. A formulation can exhibit both biphasic absorption and bimodal release of the active agent, with the biphasic absorption being a function of the bimodal release rate. However, biphasic absorption is not always attributed to release rate and can occur in a formulation not exhibiting bimodal release.

In other preferred embodiments the formulation exhibits bimodal release and/or biphasic absorption to provide a

"plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit bimodal release and/or biphasic absorption to provide a "plateau" which lasts from about 6 hours to about 12 hours. Other embodiments maintain effective plasma levels of the active agent for about 16 to about 18 hours after administration of the dosage form.

In certain preferred embodiments, an acrylic resin is utilized to provide the controlled slow release of therapeutically active ingredients over a predetermined or a specified period of time, the acrylic resin thereby comprising a significant part of the "base composition". Base compositions prepared from such acrylic resins provide sustained release of therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration, generally oral administration, in humans or animals.

In other embodiments of the invention, the formulations of the invention are composed of:

(i) a mixture of immediate release particles (e.g., beads) and enteric coated immediate release particles (e.g., beads); (ii) a mixture of immediate release particles (e.g., beads) and enteric coated controlled release particles (e.g., beads) or (iii) a mixture of immediate release particles (e.g., beads) and controlled release particles (e.g., beads). In each such instance, the mixture of particles possessing different release properties are blended together and filled into hard gelatin capsules.

In certain preferred embodiments, the controlled/modified release drug formulations of the invention consist of a plurality of beads, each containing an immediate-release component in combination with an enteric coated controlled-release component to produce a delay in the absorption process. The drug product is an oral capsule containing beads. Each bead contains a series of layers with different release characteristics—an outer immediate release layer; a release delaying layer; a controlled release layer; and an immediate release core. The final product is a capsule containing multi-layer release (MLR) beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption of the drug. In certain embodiments, the immediate release component represents 40% of the total dose per bead and the controlled release component represents 60%. This formulation is designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug. The results of a bioavailability study of this formulation indicate a biphasic release profile that is consistent with the pharmaceutical rationale discussed herein.

In other embodiments of the invention, the bead size of the formulations can be adjusted in order to obtain a desired pharmacokinetic profile based on the correlation between gastric emptying and bead size. A smaller bead size exhibits faster gastric emptying as compared to a larger bead size.

Other objects and advantages of the present invention will be apparent from the further reading of the specification and of the appended claims.

The term "pH-dependent" for purposes of the present invention is defined as having characteristics (e.g. dissolution) which vary according to environmental pH (e.g., due to changes in the in-vitro dissolution media, or due to passage of the dosage form through the gastrointestinal tract.

The term "pH-independent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH, in that a difference, at any given time, between an amount of methylphenidate released at one pH and an amount released at any other pH, when measured in-vitro using the USP Paddle Method of U.S. Pharmacopeia XXII (1990) at 100 rpm in 900 ml aqueous buffer, is no greater than 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. **1** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fasting conditions.

FIG. **2** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fed conditions.

FIG. **3** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 as a function of time when given under fasting and fed conditions.

FIG. **4** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Ritaline® as a function of time when given under fasting and fed conditions.

FIG. **5** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **6** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 3 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **7** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 2 and 3 under fasting conditions as a function of time.

FIG. **8** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 2 and 3 under fed conditions as a function of time.

DETAILED DESCRIPTION

The drug used in the formulations of the invention may be selected from a wide variety of pharmaceutically active drugs such as diabetes drugs, attention deficit hyperactivity controlled drugs, analgesics, anti-obesity preparations, anti-inflammatories, antihistamines, antitussives, decongestants, antinausea agents, narcotics, bronchodilators, cardiovasculars, central nervous system (CNS) drugs, nicotine replacement therapy, nitrates, sleeping aids/sedatives, vitamins, etc.

The controlled/modified release preparations of the present invention may be used in conjunction with any multiparticulate system, such as granules, spheroids, beads,

pellets, ion-exchange resin beads, and other multiparticulate systems in order to obtain a desired sustained-release of the therapeutically active agent. Beads, granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable unit dosage form. An amount of the multiparticulates effective to provide the desired dose of drug over time may be placed in a capsule, may be contained in a packet and sprinkled onto food, or may be incorporated in any other suitable oral solid form, such as a tablet. On the other hand, the present invention can be in the form of a matrix tablet. With respect to all such optional formulations, it is desired that the formulation be prepared such that an initial immediate release of drug provides an early onset of effect, which onset is analogous to an immediate release formulation, and that the formulation further provide a sustained release component which maintains therapeutically effective levels of the drug in the plasma for the desired amount of time, followed by a relatively rapid drop-off in blood plasma levels relative to typical sustained release formulations. Viewed as an in vivo time/concentration plot, the plasma level of the drug from the formulations of the present invention have the appearance of a "square wave". The immediate release component preferably represents from about 30% to about 40% of the total dose and the controlled release component preferably represents from about 60% to about 70% of the total dose of methylphenidate contained in the formulations of the present invention. In certain preferred embodiments, including the MLR embodiments of the invention, the immediate release component represents about 40% of the total dose and the controlled release component represents about 60% of the total dose of methylphenidate contained in the formulation.

In the case of methylphenidate, it is desired that the onset of action occurs from about 0.5 to about 4 hours, and preferably from about 0.5 to about 2 hours after the oral dosage form is administered, and it is further desired that the dosage form no longer provides effective plasma levels of methylphenidate from about 8 to about 12, more preferably from about 8 to about 10 hours, after oral administration of the dose. In this manner, the dose of methylphenidate can be administered to a child in the morning before school begins, provides the desired effect at the start of the school day, with the pharmacologic action of the drug not waning until after the school day ends, and preferably before dinner so that the drug does not have the side effect of acting as an appetite suppressant.

The formulations of the present invention are designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug.

It is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability. Bioavailability, in a more meaningful sense, is the degree, or amount, to which a drug substance is absorbed into the systemic circulation in order to be available to a target tissue site. To be absorbed, an active drug substance must be in a solution. The time required for a given proportion of an active drug substance contained in a dosage unit to enter into solution in appropriate physiological fluids is known as the dissolution time. The dissolution time for an active substance from a dosage unit is determined as the proportion of the amount of active drug substance released from the dosage unit over a specified time by a test method conducted under standardized conditions. The physiological fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.

Although there are many diverse factors which influence the dissolution of a drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from a specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in this steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiological conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium, providing for a steady state absorption.

The transport across a tissue absorption site in the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane, since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e. the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the gastrointestinal tract into the blood stream.

Notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, in many cases an important correlation can be established between the in vitro dissolution time determined for a dosage form and the in vivo bioavailability. This correlation is so firmly established in the art that dissolution time has become generally descriptive of bioavailability potential for many classes of active components contained in a particular dosage form. In view of this relationship, the dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating whether a controlled release formulation should be tested in vivo.

With the above in mind, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%

In certain preferred embodiments of the present invention, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0–45%
1	10–50%
4	30–80%
8	NLT 65%
12	NLT 80%

Sustained Release Coatings

In certain preferred embodiments, the drug is incorporated into or onto a substrate and a sustained release coating is applied thereto. For example, the drug may be contained within or on a substrate as follows: (i) incorporated into matrix spheroids (e.g., together with a pharmaceutically acceptable spheronizing agent such as microcrystalline cellulose), (ii) coated into inert pharmaceutically acceptable beads (e.g., nonpareil beads); (iii) incorporated into a normal release tablet core; or (iv) incorporated into a tablet core which comprises a matrix including an sustained release carrier material. Thereafter, a sustained release coating is applied into substrates such as those mentioned in (i)–(iv) above. The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid A pH-dependent coating serves to release the drug in desired areas of the gastrointestinal (GI) tract, e.g., the stomach or small intestine. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) comprising the drug is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Such formulations are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference. The particles are preferably film coated with a material that permits release of the drug so as to achieve, in combination with the other stated properties, a desired in-vitro release rate and in-vivo plasma levels. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Acrylic Polymers

The hydrophobic material comprising the controlled release coating may comprise a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate)copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly (methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in

accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® Rs, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material such as an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When the aqueous dispersion of hydrophobic material is used to coat a substrate including the drug, for example, inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. Alternatively, the substrate may be a tablet core coated with the sustained release coating, and optionally a further film-forming agent or colorant, such as Opadry®.

In formulations where an aqueous dispersion of an hydrophobic polymer such as an alkylcellulose is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60° C. and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

In formulations where an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45° C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

The sustained release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the drug to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropyhnethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethyl-cellulose, such as Aquacoat® or Surelease®, may be used. If Surelease is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

The plasticized aqueous dispersion of hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined sustained release of the therapeutically active agent (i.e., drug) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the drug from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropyl-methylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The substrate of the present invention may be prepared by a spheronizing agent together with the active agent ingredient that can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredients and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer or ethyl cellulose. In such embodiments, the sustained-release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

In a particular preferred embodiment of the invention, the controlled/modified release methylphenidate formulation is prepared as a multilayered release (MLR) formulation comprising coated inert beads. A summary of one method of manufacturing such a formulation is outlined as follows. First, immediate release (IR) drug-coated beads are prepared by spraying a solution of methylphenidate in water over sugar beads in a fluid bed dryer with a drug load of about 8%. The spray process is carried out in a fluid bed dryer, equipped with a Wurster column. A clear overcoat of HPMC is applied using an Opadry® material (e.g., Opadry® Clear (Formula No: YS-1-7006)), to a weight gain of about 1%. Next, a controlled release coating is applied to the IR beads, which converts the same into controlled release (CR) beads. This is accomplished by spraying a solution of Eudragit®

RS 30 D, triethyl citrate (plasticizer) and talc (glidant), onto the IR beads. Next, the coated beads are cured in order to obtain a stabilized release rate of the therapeutically active agent. In preferred embodiments of the present invention where the CR coating utilizes an acrylic resin to control the release of the drug, the CR beads at this stage are subjected to oven curing at a temperature above the Tg of the plasticized acrylic polymer of the required time period, the optimum values of the temperature and time for the particular formulation being determined experimentally. In certain embodiments of the present invention, the stabilized products is obtained via oven curing conducted at a temperature of about 40–50° C. for a time period of about 12 to about 24 hours or longer. An enteric coating is then applied onto the CR beads to convert the same into enteric coated CR (ECCR) beads. This is accomplished by spraying a solution of Eudragit® L 30 D-55 dispersion, triethyl citrate (plasticizer) and talc (glidant) onto the CR beads. Finally, an immediate release coating is applied onto the ECCR beads (referred to as, e.g., an IR Topcoat). This is accomplished by spraying a solution of methylphenidate in water over EC CR beads.

Results of initial studies show that this formulation is stable under room temperature (25° C., 60% RH) and accelerated conditions (40° C., 75% RH).

In certain preferred embodiments of the present invention, an effective amount of the drug in immediate release form is included in the drug formulation. The immediate release form of the drug is included in an amount which is effective to shorten the time to maximum concentration of the drug in the blood (e.g., plasma), such that time to T_{max} is shortened to a time of, e.g., from about 0.5 to about 2 hours. By including an amount of immediate release drug in the formulation, the time to onset of action is significantly reduced, and is the same or earlier than that of the reference standard immediate release treatment (e.g., Ritalin IR). In such embodiments, an effective amount of the drug in immediate release form may be coated onto the substrates (e.g., multiparticulates or tablets) of the present invention. For example, where the extended release of the drug from the formulation is due to a controlled release coating, the immediate release layer can be overcoated on top of the controlled release coating. On the other hand, the immediate release layer may be coated onto the surface of substrates wherein the drug is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising an effective unit dose of the drug (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the drug dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release drug as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the drug. One skilled in the art would recognize still other alternative manners of incorporating the immediate release drug portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Methylphenidate HCl Immediate Release Beads

TABLE 1

Ingredients	%
Methylphenidate hydrochloride	15.0
Sugar bead 14/18	80.0
Opadry ® clear YS-1-7006	5.0
Water	q.s.
Total	100.0

1. Charge Niro-Aeromatic Strea 1 Fluid Bed Wurster Coater with 14/18 mesh Nupareil® PG (sugar spheres NF).
2. Coat the beads at 60° C. by spraying a solution of methylphenidate hydrochloride (12% w/w) and Opadry clear (4% w/w) in water.
3. Once the coating is completed, allow the beads to dry at 60° C. for 2 or 3 minutes.
4. Cool the beads in a shallow pan at room temperature.
5. Break agglomerates, if any.
6. Sift the beads through Tyler 10 mesh sieve (1.77 mm opening) and then through Tyler 20 mesh sieve (850 micrometer opening) to remove fines.
7. Apply top coat to beads by spraying a solution of coloured Opadry clear solution (4% w/w) to a theoretical weight gain of 1% w/w.

After the completion of the topcoat, the beads are then filled into hard gelatin capsules at a strength of 20 mg.

Dissolution testing was conducted on the bead filled IR capsules using USP Apparatus 1 (basket method) in 500 mL of simulated gastric juice without enzyme, 100 rpm at 37° C. The results are as follows:

TABLE 2

Time (minutes)	% Methylphenidate HCl dissolved
10	92.7
20	95.7
30	97.7
45	98.5

The dissolution results as set forth in the above table indicate that 98.5% of the methylphenidate hydrochloride was dissolved in 45 minutes.

EXAMPLE 2

Methylphenidate HCl Controlled-Release (CR) Beads with Acrylic Polymer Coating

TABLE 3

Ingredients	%
Methylphenidate IR beads	86.20
Eudragit ® RS 30 D	8.63
Triethyl citrate	1.72
Talc	3.45
Water	q.s.
Total	100.0

The controlled-release coating is manufactured as follows:

1. The Eudragit® RS 30 D is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the IR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~8%.
3. Upon completion of the coating, the beads are cured for 24 hours at 40–45° C.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR capsules using the following USP Apparatus (basket method). The capsules were placed into 500 mL of simulated gastric juice without enzyme, for first 2 hours at 100 rpm and 37° C. and then placed into 500 mL simulated intestinal fluid without enzyme for the remainder of the testing period. The results are as follows:

TABLE 4

Time (hours)	Methylphenidate HCl dissolved
1	6.9
2	16.2
3	26.1
4	35.7
6	59.8
8	74.7
12	75.4
18	82.5
24	92.8

The dissolution results as set forth in the above table indicate that 92.8% of methylphenidate hydrochloride dissolved in 24 hours.

EXAMPLES 3 & 4

Dependence of Release Rate of Methylphenidate HCl From Controlled-Release (CR) Beads on Amount of Acrylic Polymer Coating

By adjusting the amount of Eudragit® RS 30 D applied, the release rate can be adjusted. This effect is illustrated in Examples 3 and 4 below:

TABLE 5

	%	
Ingredients	Example 3	Example 4
Methylphenidate HCl IR Bead	91.2	94.0
Eudragit ® RS 30 D	5.8	3.9
Triethyl citrate	1.0	0.7
Talc	2.0	1.4
Water	—	—
Total	100.0	100.0

The method of manufacturing the controlled-release beads in Examples 3 and 4 is similar to the method described under Example 2, by varying the proportion of beads and Eudragit® RS 30D.

The cured beads were filled into hard gelatin capsules at a strength of 20 mg.

The dissolution results, conducted under conditions identical to those found under Example 2, are shown below:

TABLE 6

Time	% Methylphenidate HCl dissolved	
(hours)	Example 3	Example 4
1	18.7	49.5
2	35.1	73.3
3	49.0	81.5
4	60.6	85.2
6	75.7	90.4
8	77.3	90.7
12	82.1	92.8

The dissolution results as set forth in the above table, indicate that 82.1% and 92.8% respectively of methylphenidate hydrochloride is dissolved in 12 hours. However, the release of drug form Example 4 was significantly faster at time points 1, 2, 3, 4, 6 and 8 hours.

EXAMPLE 5

Enteric Coated (EC) Coated Release (CR) Beads—EC•CR Beads

TABLE 7

Ingredients	%
Methylphenidate CR beads	83.2
Eudragit ® L 30 D55	9.9
Triethyl citrate	2.0
Talc	4.9
Water	q.s.
Total	100.0

The enteric coating procedure is described below:

1. The Eudragit® L 30 D 55 is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the methylphenidate CR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~9%.
3. Upon completion of the coating, the beads are cured for 18 hours at 40° C.
4. The cured beads are then sieved through Tyler 10 mesh (1.7 mm opening) and Tyler 20 mesh (850 micorometer opening) sieves to remove any fines.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR filled capsules using USP Apparatus 1 (basket method) 500 mL at 100 rpm and 37° C. using SGF without enzyme for the first 2 hours and SIF without enzyme for the rest of the testing period. Results are shown below:

TABLE 8

Time	% Methylphenidate HCl dissolved		
(hours)	Lot 1	Lot 2	Lot 3
1	0.4	1.0	2.0
2	2.2	5.4	7.4
3	18.8	27.8	61.3
4	36.7	48.3	87.0
6	59.5	75.5	98.8
8	76.9	90.1	100.0
12	82.3	99.6	—

The dissolution results as set forth in the above table indicate that very little drug is dissolved in gastric juice after enteric coating and that the dissolution profile of the CR beads has been modified.

EXAMPLE 6

Formulations for Clinical Trials

Examples 6A, 6B and 6C below set forth the formulations developed and tested in clinical studies.

EXAMPLE 6A

(IR•EC•CR Beads)

Immediate Release (IR) Coating of Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The (IR•EC•CR Beads) formulation, hereinafter referred to as Formulation 1, is a capsule containing multi-layer release beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption equal to or greater than Ritalin® IR immediate release tablets. The immediate release component represent 40% of the total dose per bead and the controlled release component represents 60%.

TABLE 9

Ingredients	%
Enteric coated Controlled Release Methylphenidate HCl beads	91.4
Methylphenidate hydrochloride USP	6.5
Opadry ® clear YS-1-7006	2.1
Water	q.s.
Total	100.0

The application of an immediate release coat on the top of Enteric Coated CR beads is described below:

1. Dissolve methylphenidate HCl USP and Opadry in water with stirring.
2. Load ECCR beads into a Wurster insert of an Aeromatic Fluid Bed Dryer.
3. Spray the beads with the coating solution using a 1 mm spray nozzle at a temperature of not more than 50° C.
4. Once the coating is completed, cool the beads at room temperature and pass through Tyler sieves 10 and 20 mesh to remove fines.

The beads were then filled into a hard gelatin capsule to a 20 mg strength.

Dissolution testing was conducted on the bead filled capsules of Formulation 1 using USP Apparatus 1 (basket method) 100 rpm, 500 mL at 37° C.—simulated gastric juice without enzyme 1st and 2nd hours; 3rd hour onwards simulated intestinal fluid without enzyme.

The results are as follows;

TABLE 10

Time (hours)	% Methylphenidate HCl dissolved
5 minutes	37.0
10 minutes	38.0
15 minutes	39.0
30 minutes	40.0
60 minutes	40.0
2	40.1
3	51.4
4	61.0
6	75.6
8	87.0
12	87.5

The dissolution results as set forth in the above table indicate a rapid onset on dissolution, followed by prolonged action.

EXAMPLE 6B

(IR+EC•CR Blend)

Combination of Immediate Release Methylphenidate Beads (IR) and Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The enteric-coated controlled release beads (EC•CR) beads described in Example 5 may be mixed with the immediate release (IR) beads described in Example 1 in varying proportions and placed in capsules to obtain the final blended dosage form, (IR+EC•CR Blend), hereinafter referred to as Formulation 2. Formulation 1 was designed to provide a faster rate of absorption of the controlled release portion than Formulation 1. The immediate release component represents 35% of the total dose per capsule and the controlled release component represents 65%.

Dissolution testing was performed and the comparative results are shown in Table 11 below.

EXAMPLE 6C

(IR•CR Beads)

Immediate Release (R) Coating of Controlled-Release (CR) Methylphenidate Beads

The IR•CR Beads formulation, hereinafter referred to as Formulation 3, is a capsule containing single beads made up of an immediate release topcoat and a controlled release core, and is designed to provide an intermediate rate of absorption of the controlled release portion between that of the controlled release formulations of Formulations 1 and 2. The immediate release component represents 30% of the total dose per bead and the controlled release component represents 70%.

The immediate release topcoat is applied to CR beads as described in Example 6A for Formulation 1.

The dissolution profiles of Formulations 1–3 and Ritalin® SR, used as a comparator, are shown in Table 11 below. Hours 1 and 2 are in 500 ml of simulated gastric fluid. Simulated intestinal fluid (500 ml) is used from the third hour onwards. The results of the dissolution firmed the anticipated in vitro dissolution profile.

TABLE 11

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
10 min	21.4	38.0	32.0	28.6
30 min	31.4	40.0	36.7	34.0
1	45.7	40.0	38.2	40.5
2	62.3	40.1	40.4	57.6
3	75.8	51.4	68.1	70.6
4	79.5	61.0	86.4	79.5
6	88.0	75.6	95.4	89.6
8	90.7	87.0	96.2	92.7
12	91.3	87.5	97.0	93.1

EXAMPLE 7

Four Way Comparison of Single Dose Formulation 1 (Fed and Fasted) with Two Doses of Ritulin IR (Fed and Fasted)

The bioavailability of Methylphenidate MLR capsules was investigated in a four-way blind study which compared the Formulation 1 20 mg single dosage formulation under fed and fasted conditions with two doses (4 hours apart) of Ritalin® IR.

Healthy male volunteers were given a single dose of 20 mg Formulation 1 or two doses of immediate release methylphenidate 10 mg administered four hours apart under both fed and fasting conditions (n=12). "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 4 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, under fasting conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, administered 5 minutes after a high fat breakfast.

Treatment 4: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, administered 5 minutes after a high fat breakfast.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Formulation 1 and at pre-dose, 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Ritulin® IR. Plasma was harvested from each blood sample and stored in a −20° C. freezer until assayed for plasma methylphenidate concentration. Assay of plasma methylphenidate concentrations was performed using gas chromatography/mass spectrometry (GC/MS).

The mean plasma concentrations, standard deviations and coefficients of variation are shown as a function of time in Tables 12 and 13, for fasting and fed conditions, respectively.

This data is presented graphically in FIGS. **1**–**4**. FIG. **1** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fasting conditions. FIG. **2** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fed conditions. FIG. **3** presents the mean plasma concentration versus time for Formulation 1 under fed and fasting conditions. FIG. **4** presents the mean plasma concentration versus time for Ritalin® under fed and fasting conditions.

TABLE 12

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fasting)

Sample	Formulation 1			Ritalin		
Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	—
0.250	0.00	0.00	—	0.00	0.00	—
0.500	817.53	801.84	98.08	883.96	686.65	77.68
0.750	2268.79	1128.12	49.72	2485.74	828.38	33.33
1.00	3108.79	756.66	24.34	3468.74	1172.28	33.80
1.50	3597.88	740.36	20.58	4388.04	998.86	22.76
2.00	3675.60	1315.29	35.78	4289.39	1144.40	26.68
2.50	3469.81	882.62	25.44	4121.37	1014.57	24.62
3.00	3573.56	1031.61	28.87	3528.56	863.25	24.46
3.50	3637.01	1008.73	27.74	3020.93	716.36	23.71
4.00	3604.03	1071.59	29.73	2747.91	698.95	25.44
4.50	3494.44	1069.13	30.60	2958.49	799.89	27.04
5.00	3446.41	1069.50	31.03	4394.22	1603.40	36.49
5.50	—	—	—	5525.84	1766.58	31.97
6.00	3421.13	1166.25	34.09	5927.06	1955.99	33.00
6.50	—	—	—	5528.41	1758.49	31.81
7.00	3422.32	958.42	28.00	4860.45	1482.24	30.50
8.00	3338.59	724.49	21.70	3795.34	1500.79	39.54
10.0	2858.42	612.21	21.42	2223.48	926.11	41.65
12.0	2073.97	536.08	25.85	1334.71	523.37	39.21
16.0	1180.67	502.11	42.53	455.86	237.79	63.13
24.0	275.87	201.51	73.04	55.10	99.99	181.46

TABLE 13

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fed)

Sample	Formulation 1			Ritalin		
Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	—
0.250	0.00	0.00	—	53.12	133.84	251.95
0.500	291.66	271.58	93.11	1256.61	1602.66	127.54
0.750	910.22	653.80	71.83	2984.60	3406.53	114.14
1.00	1580.66	983.13	62.20	3400.39	2301.87	67.69
1.50	2760.68	797.24	28.88	5205.16	1882.17	36.16
2.00	3098.73	874.49	28.22	5146.55	1617.43	31.43
2.50	3655.68	982.31	26.87	5157.11	1227.99	23.81
3.00	3625.88	797.55	22.00	4546.61	932.94	20.52
3.50	3717.71	951.58	25.60	4184.34	1080.71	25.83
4.00	3650.63	875.97	23.99	3652.57	1023.22	28.01
4.50	3627.41	835.40	23.03	3811.27	1103.83	28.96
5.00	3430.14	783.72	22.85	5158.45	1714.53	33.24
5.50	—	—	—	5982.98	1618.65	27.05
6.00	3418.03	937.07	27.42	6228.81	1591.64	25.55
6.50	—	—	—	6054.32	1919.95	31.71
7.00	4218.94	775.86	18.39	5538.57	1741.02	31.43
8.00	4679.67	1126.52	24.07	4350.90	1611.95	37.05
10.0	3858.58	1045.56	27.10	2577.66	896.59	34.78
12.0	2610.98	902.53	34.57	1521.52	611.54	40.19
16.0	1372.86	737.71	53.74	577.90	334.26	57.84
24.0	334.79	306.63	91.59	94.23	144.99	153.86

EXPERIMENTAL RESULTS

Pharmacokinetic parameters were calculated based on the data from the four-way study. AUC_{0-t} (pg•h/mL), AUC_{0-inf} (pg•h/mL), $AUC_{t/inf}$(%), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours) were calculated as described below.

For purposes of the present invention, the following terms are meant to have the following meanings:

Analysis of Pharmacokinetic Data and Statistical Analysis

AUC_{0-t} Area under the concentration-time curve from time zero to the time of the last non-zero concentration (this corresponds to the area under the concentration-time curve, over the dosing interval of the test formulation for both controlled-release and immediate-release formulations)

AUC_{0-inf} Area under the concentration-time curve from time zero to infinity

C.I. Confidence interval

CV Coefficient of variation

C_{max} Maximum observed concentration

K_{el} Elimination rate constant

LQCT The last quantifable concentration time

SD Standard deviation

TLIN The time point where log-linear elimination begins

$T_{1/2\ el}$ Time for observed C_{max}

Sampling Time Time post dose of plasma collection based on parameters to be studied

Scheduled Time The predetermined (clock) time at which the samples are to be taken

Actual time The exact (clock) time at which the sample was taken

Time deviations during sampling for drugs with a $T_{max} \leqq 4$ hours were treated as follows: between 0 and 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of blood collection was<10%. Above 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of plasma collection was<15%. When sampling times were used when previously described acceptance criteria, the corrected sampling items were used when performing pharmacokinetic parameters calculations. Sampling times are present in concentration tables and graphs of statistical report.

The mean, standard deviation (SD), and coefficient of variation (CV) were calculated for plasma concentrations of methylphenidate for each sampling time and treatment. As well, the mean, SD, and CV were calculated for the AUC_{0-t} (pg•h/mL), AUC_{0-inf}(pg•h/mL), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours). The calculation of these pharmacokinetic parameters is explained below.

Areas under the Concentration-Time Curves

AUC_{0-t} was calculated using the linear trapezoidal rule.

The AUC_{0-t} was derived where t is the time (t) of the last measurable (non-zero) concentration (C_t) for each treatment.

The AUC_{0-inf} was calculated as:

$$AUC_{0-t} + \frac{C_t}{K_{el}}$$

Where C_t=the last non-zero concentration for that treatment, AUC_{0-t}=the AUC from time zero to the time of the last non-zero concentration for that treatment and K_{el}=the elimination rate constant.

Maximum Observed Concentration and Time of Observed Peak Concentration

The maximum observed concentration, C_{max} and the observed time to reach peak concentration, T_{max}, was determined for each subject and for each treatment.

Half-Life and Elimination Rate Constant

To calculate the elimination rate constant (K_{el}), linear regression analyses were performed on the natural log (Ln) of plasma concentration values (y) versus time (x). Calculations were made between a time point where log-linear elimination phase begins (LQCT) occurred. The K_{el} was taken as the slope multiplied by (−1) and the apparent half-life ($T_{1/2\ el}$) as $0.693/K_{el}$.

TLIN and LQCT

TLIN, the time point where log-linear elimination begins, and LQCT, the last quantifiable concentration time were determined for each subject and for each treatment.

Percent Drug Absorbed

Percent drug absorbed was calculated at each sampling time (t) by Modified Wagner-Nelson's method, as implemented in Kinetica software, version 2.0.1 according to the following formula:

$$\frac{C_t + (K_{el} \times AUC_{0-t})}{(K_{el} \times AUC_{0-inf})} \times 100$$

All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.050. Based on the pairwise comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} data, the relative ratios of the geometric means, calculated according to the formulation "$e^{(X-Y)} \times 100$", as well as the 90% geometric confidence intervals were determined.

The plasma concentration of unchanged methylphenidate following administration of the controlled release formulation Formulation 1 reached the maximum concentration (C_{max}) at a mean of 3.27 hours under fasting conditions and 7.29 hours under fed conditions reflecting a biphasic absorption profile. The plasma concentration of unchanged methylphenidate following administration of two doses of the immediate release formulation (Ritalin® IR) reached the maximum concentration (C_{max}) at 5.96 hours under fasting conditions and 3.54 hours under fed conditions. When the determination of C_{max} was restricted to the first dose of immediate release methylphenidate, the T_{max} was 1.71 hours under fasting conditions and 1.63 hours under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg Formulation 1 and immediate release methylphenidate 10 mg (Ritalin® IR) under fed and fasted conditions are summarized in Tables 14 and 15 below.

TABLE 14

Pharmacokinetic Parameters for Formulation 1

Parameters	Formulation 1 (fasting) Mean ± SD	CV (%)	Formulation 1 (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	48493.80 ± 13430.27	27.69	54686.38 ± 15118.66	27.65
AUC_{0-inf} (pg · h/mL)	51213.86 ± 13260.14	26.59	57931.47 ± 16762.54	28.94
C_{max} (pg/mL)	4410.25 ± 1188.68	26.95	4879.37 ± 1027.85	21.07
T_{max} (h)	3.27 ± 2.54	77.64	7.29 ± 1.29	17.65
K_{el} (h^{-1})	0.1672 ± 0.0339	20.25	0.1812 ± 0.0392	21.65
$T_{1/2\ el}$ (h)	4.32 ± 0.96	22.18	4.06 ± 1.25	30.91

TABLE 15

Pharmacokinetic Parameters for Ritalin ® IR

Parameters	RITALIN ® (fasting) Mean ± SD	CV (%)	RITALIN ® (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	44644.22 ± 13806.82	30.93	52781.49 ± 15194.94	28.79
AUC_{0-inf} (pg · h/mL)	46466.23 ± 14012.73	30.16	54783.17 ± 15311.08	27.95
C_{max} (pg/mL)	6536.04 ± 1669.29	25.54	7571.74 ± 1534.58	20.27
T_{max} (h)	5.96 ± 0.54	9.09	3.54 ± 2.42	68.43
K_{el} (h^{-1})	0.2481 ± 0.0550	22.17	0.2449 ± 0.0719	29.37
$T_{1/2\ el}$ (h)	2.93 ± 0.71	24.10	3.08 ± 0.96	31.26

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatment 1 was significantly different from the AUC_{0-t} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized in Table 16 below:

TABLE 16

AUC_{0-t} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	109.90%	104.08%	88.65%
90% Geometric C.I.	102.59% to 117.74%	97.15% to 111.50%	82.75% to 94.97%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatment 1 was significantly different from the AUC_{0-inf} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized below in Table 17:

TABLE 17

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	111.65%	105.86%	88.85%
90% Geometric C.I.	104.09% to 119.95%	98.70% to 113.55%	82.84% to 95.30%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 1 was not significantly different from the C_{max} of treatment 3. However, Duncan's Multiple Range Test detected statistically significant differences for C_{max} when comparing treatments 1 and 2 and treatments 3 and 4. The statistical analyses performed on the data are summarized below in Table 18:

TABLE 18

C_{max} (pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	67.48%	64.38%	89.37%
90% Geometric C.I.	60.28% to 75.54%	57.51% to 72.07%	79.83% to 100.04%

The ANOVA and Duncan's Multiple Range Test performed on the T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 3 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 3 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 and treatments 3 and 4 for this parameter.

The results of the ANOVA and Duncan's Multiple Range Test performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were detected by Duncan's Multiple Range Test between treatments 1 and 2 and treatments 3 and 4, but not for treatments 1 and 3.

Summary and Analysis

The AUC and C_{max} ratios of controlled release methylphenidate 20 mg Formulation 1 under fed and fasted conditions are summarized in Table 500 below. A comparison of the AUC and C_{max} ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fasting conditions are summarized in Table 20 below. Table 21 shows the comparative ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fed conditions.

Treatment 1 (Formulation 1, Fasting) Versus Treatment 3 (Formulation 1, fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 3 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed K_{el} and $T_{1/2\ el}$. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test product (Formulation 1, fasting) to reference product (Formulation 1, fed) were found to be within 80 to 125%. This is summarized in Table 19 below:

TABLE 19

Formulation 1 (Fed) vs. Formulation 1 (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.80%	112.54%	111.90%
90% Geometric C.I.[2]	105.29%–120.84%	104.93%–120.71%	99.96%–125.27%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1(fed)} - \text{Formulation 1 (fasting)}]} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 1, Fasting) Versus Treatment 2 (Ritalin®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for all parameters. With the exception of C_{max}, all formulation ratios as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80 to 125%. This is summarized in Table 20 below:

TABLE 20

Formulation 1 (Fast) vs Ritalin ® (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.90%	111.65%	67.48%
90% Geometric C.I.[2]	102.59%–117.74%	104.09%–119.75%	60.28%–75.54%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1 (fast)} - \text{Ritalin IR (fast)}]} \times 100$
[2]90% Geometric Confidence Interval using log-transformed data

Treatment 3 (Formulation 1, Fed) Versus Treatment 4 (Ritalin® , Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for all parameters with the exception of ln-transformed AUC_{0-t} and AUC_{0-inf}. With the exception of C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80% to 125%. This is summarized in Table 21 below:

TABLE 21

Formulation 1 (Fed) vs. Ritalin ® IR (Fed)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.08%	105.86%	64.38%
90% Geometric C.I.[2]	97.15%–111.50%	98.70%–113.55%	57.51%–72.07%

[1]Calculated using geometric means according to the formula: $e^{[\text{Formulation 1 (fed)}-\text{Ritalin IR (fed)}]} \times 100$
[2]90% Geometric Confidence Interval using log-transformed data

CONCLUSIONS

Review of individual plasma MPH time curves indicates the following:

Plasma MPH concentrations at 12 hours were higher on Formulation 1 than on Ritalin IR in all subjects, under both fed and fasted conditions.

A biphasic profile was apparent under fasted conditions in 7–10/12 subjects and in 8–10/12 under fed conditions. The mean curve showing a stable plateau under fasted conditions is therefore not fully representative of the individual profiles. The enteric coat therefore gave rise to a biphasic profile in some subjects even under fasted conditions.

Under fasted conditions the apparent rate of rise of plasma MPH was equivalent to, or faster than, that of Ritalin IR in 8/12 subjects under fasted conditions and 4–5/12 subjects under fed conditions. The mean curves which demonstrate an equivalent rate of rise under fasted conditions and a slower rise under fed conditions were therefore largely reflective of the individual profiles.

The bioavailability of Formulation 1 relative to Ritalin IR was acceptable under both fed and fasted conditions (Relative AUC_{inf} 106% and 112%). There was an increase in AUC of both

Formulation 1 and Ritalin when given with food (13.1% and 17.9% respectively).

Formulation 1 had a more prolonged mean plasma MPH concentration time profile than two doses of Ritalin IR. An across study comparison indicates that Formulation 1 also has a more prolonged profile than Ritalin SR.

Under fasted conditions Formulation 1 had a mean initial rate of rise of plasma MPH that is similar to Ritalin IR and a relatively flat plateau until 8 hours post-dose.

Under fed conditions, the initial rise in plasma MPH from Formulation 1 was slower than under fasted conditions and the plateau showed a biphasic profile. This was consistent with predictions that the enteric coat would delay release of the controlled release component and that this delay would be longer under fed conditions (allowing the initial plasma

concentration peak, due to the IR component, to fall prior to the start of release from the controlled release component).

Formulation 1 results in both a fast initial rate of rise of plasma methylphenidate concentration, and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Formulation 1 therefore has the potential to meet the dual objectives of rapid onset and prolonged duration that are considered desirable characteristics of a controlled release methylphenidate formulation for the treatment of ADD/ADHD.

An initial pilot bioavailability study completed in adult healthy volunteers has confirmed that a single 20 mg dose of this formulation has an equivalent extent of absorption to two doses of immediate release methylphenidate (10 mg) given 4 hours apart. Maximal plasma concentrations with the controlled release formulation are similar to those attained with the first dose of immediate release methylphenidate and from approximately 10 hours post-dose, are higher than those following the second dose of immediate release methylphenidate.

The results indicate the potential for a single morning dose of this formulation to produce clinical effects that are at least equivalent to those of two doses of immediate-release methylphenidate given at breakfast and lunchtime, with a duration of action that may reduce the need for a third dose of immediate release methylphenidate later in the day.

EXAMPLE 8

Five-Way Comparison of Single Dose Formulation 1 (Fed and Fasted), Single Dose Formulation 3 (Fed and Fasted) and Single Dose Ritalin SR (Fasted)

A five-way blind study was conducted which compared a single dose of Formulation 2, 20 mg, both fed and fasted, a single dose of Formulation 3, 20 mg, both fed and fasted, and Ritalin SR 20 mg single dose fasted. According to the published literature and anecdotal comments from physicians, Ritalin SR is used in less than 20% of methylphenidate treated patients.

Twelve healthy male volunteers were given a single dose of either 20 mg Formulation 1 or Formulation 3 administered four hours apart under both fed and fasting conditions (n=12), or slow-release 20 mg methylphenidate (Ritalin SR) under fasting conditions. "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 5 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning, under fed conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fasting conditions.

Treatment 4: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fed conditions.

Treatment 5: Reference Product: methylphenidate slow-release 20 mg tablet Ritalin SR (Novartis) under fasting conditions.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose. Plasma was harvested from each blood sample and stored in a −20 C. freezer until assayed for plasma methylphenidate concentration.

The data is presented graphically in FIGS. **5**–**8**. FIG. **5** presents the mean plasma concentration versus time for Formulation 1 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **6** presents the mean plasma concentration versus time for Formulation 3 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **7** presents the mean plasma concentration versus time for Formulations 2 and 3 under fasting conditions. FIG. **8** presents the mean plasma concentration versus time for Formulations 2 and 3 under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg (Formulation 1 and 3) under fed and fasting conditions, and for slow release methylphenidate 20 mg (Ritalin® SR) under fasting conditions are summarized in Tables 22–24 below.

TABLE 22

Pharmacokinetic Parameters for Formulation 2

	Treatment 1, Fasting		Treatment 2, Fed	
Parameters	Means ± SD	CV (%)	Mean ± SD	CV (%)
AUC_{0-t} (pg.h/mL)	48190.73 ± 11668.71	24.21	53452.63 ± 12820.39	23.98
AUC_{0-inf} (pg.h/mL)	49787.07 ± 12053.23	24.21	55690.49 ± 12691.52	22.79
C_{max} (pg.h/mL)	7498.57 ± 1968.38	26.25	6879.09 ± 1486.53	21.61
T_{max} (h)	3.63 ± 0.57	15.70	6.42 ± 1.08	16.89
K_{el} (h^{-1})	0.2391 ± 0.0428	17.91	0.2321 ± 0.0342	14.75
$T_{1/2}$ (h)	3.00 ± 0.64	21.32	3.05 ± 0.48	15.74

TABLE 23

Pharmacokinetic Parameters for Formulation 3

	Treatment 3, Fasting		Treatment 4, Fed	
Parameters	Means ± SD	CV (%)	Mean ± SD	CV (%)
AUC_{0-t} (pg.h/mL)	48057.06 ± 14743.87	30.68	54128.75 ± 14787.94	27.32
AUC_{0-inf} (pg.h/mL)	49984.68 ± 14873.03	29.76	56315.66 ± 14779.59	26.24
C_{max} (pg.h/mL)	6080.97 ± 2048.60	33.69	6959.07 ± 1559.34	22.41
T_{max} (h)	3.46 ± 0.89	25.76	4.42 ± 0.56	12.62
K_{el} (h^{-1})	0.2009 ± 0.0468	23.32	0.2057 ± 0.0390	18.97
$T_{1/2}$ (h)	3.65 ± 0.97	26.52	3.49 ± 0.70	20.01

TABLE 24

Pharmacokinetic Parameters for Ritalin SR ®

Parameters	Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	47404.51 ± 12754.66	26.91
AUC_{0-inf} (pg · h/mL)	49252.17 ± 12841.52	26.07
C_{max} (pg/mL)	6783.09 ± 1496.65	22.06

TABLE 24-continued

Pharmacokinetic Parameters for Ritalin SR ®		
Parameters	Mean ± SD	CV (%)
T_{max} (h)	3.50 ± 0.43	12.18
K_{el} (h^{-1})	0.2282 ± 0.0320	14.01
$T_{1/2\ el}$ (h)	3.10 ± 0.47	15.14

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 3 was significantly different from the C_{max} of treatments 4 and 5. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for C_{max} when comparing treatment 1 vs. treatment 2 or treatment 1 vs treatment 5. The statistical analyses performed on the data are summarized in Table 25 below:

TABLE 25

C_{max} (pg/ML)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	103.73%	84.78%	109.25%	87.40%
90% Geometric C.I.	98.94% to 115.14%	78.59% to 91.45%	101.28% to 117.85%	81.05% to 94.26%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, and treatments 3 and 4 for this parameter. Duncan's Multiple Range Test did not detect statistically significant differences between treatments for T_{max} when comparing treatments 1 vs. 3 or treatments 3 vs. 5.

The ANOVA performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 5 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were not detected by Duncan's Multiple Range Test, between treatments for K_{el} when comparing treatments 1 and 2, treatments 3 and 4, or treatments 1 and 5. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatments 1 and 3 was significantly different from the AUC_{0-t} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-t} when comparing treatment 1 vs treatment 5, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 26:

TABLE 26

AUC_{0-t} (pg · h/mL)	Treatment 1 vs. Treatment 2	Treatment 3 vs. Treatment 4	Treatment 1 vs. Treatment 5	Treatment 3 vs. Treatment 5
Ratio	89.21%	88.23%	101.82%	100.63%
90% Geometric C.I.	84.03% to 94.71%	83.10% to 93.67%	95.91% to 108.10%	94.81% to 106.81%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatments 1 and 3 was significantly different from the AUC_{0-inf} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-inf} when comparing treatment 1 vs treatment 3, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 27:

TABLE 27

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	88.33%	88.14%	101.14%	100.82%
90% Geometric C.I.	83.50% to 93.44%	83.32% to 93.24%	95.61% to 106.99%	95.33% to 106.63%

Treatment 1 (Formulation 2, Fasting) vs. Treatment 2 (Formulation 2, Fed)

The ANOVAs detected statistically significant differences between fed and fasting conditions, treatments 1 and 2, for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2\ el}$, and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for ln-transformed AUC_{0-t}, and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed $T_{1/2\ el}$ and K_{el}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 28 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 2. However, this food effect was less than 20% on average.

TABLE 28

Formulation 2, Fed versus Fasting			
	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.09%	113.21%	93.69%
90% Geometric C.I.[2]	105.58% to 119.00%	107.03% to 119.76%	86.85% to 101.07%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 2(Fed)}-\text{Formulation 2 (Fasting)})} \times 100$

[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 4 (Formulation 3, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and

C_{max} and untransformed T_{max}, $T_{1/2\ el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for untransformed $T_{1/2\ el}$ and K_{el} . With the exception of lower 90% geometric confidence interval for C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 29 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 3. However, this food effect was less than 20% on average.

TABLE 29

Formulation 3, Fed versus Fasting

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	113.35%	113.45%	117.96%
90% Geometric C.I.[2]	106.76% to 120.33%	107.25% to 120.01%	109.35% to 127.25%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 3 (fed)}-\text{Formulation 3 (Fasting)})} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 2, Fasting) vs. Treatment 5 (Ritalin SR® , Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2\ el}$ and K_{el} Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 5 for all parameters. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 30 below. Thus, Formulation 1 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 30

Formulation 2 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.82%	101.14%	106.99%
90% Geometric C.I.[2]	95.91% to 108.10%	95.61% to 106.99%	101.28 to 117.85%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation 2 (fast)}-\text{Ritalin SR (Fast)})} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2\ el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for ln-transformed C_{max} and untransformed $T_{1/2\ el}$ and K_{el}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 31 below. Thus, Formulation 3 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 31

Formulation 3 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.63%	100.82%	87.40%
90% Geometric C.I.[2]	94.81% to 106.81%	95.33% to 106.63%	81.05 to 94.26%

[1]Calculated using geometric means according to the formula: $e^{(\text{Formulation (fast)}-\text{Ritalin SR (Fast)})} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

CONCLUSIONS

The bioavailability of Formulation 1 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 101%-Fed conditions not tested)

The bioavailability of Ritalin SR® under fasted conditions is similar to that of Ritalin® IR, as discussed in Example 7 (AUC_{inf} 29.2 vs. 46.5 ng•h/mL, respectively). Literature data which indicates that Ritalin® IR and SR are absorbed at equivalent rates suggests that comparisons between the studies presented in Examples 7 and 8 are reasonable.

Bioavailability of Formulations 1 and 2 are similar under fasted and fed conditions (fasted: 49.8 vs. 51.2 ng•h/mL; fed: 55.7 vs. 57.9 ng•h/mL).

From the mean curves of Formulation 1 and Ritalin SR®, the initial rate of rise of plasma MPH concentration is slightly faster for Formulation 1 compared to Ritalin SR®. Under fed conditions, the rate of rise of plasma MPH with Formulation 1 decreased and T_{max} was delayed in comparison to both Formulation 1 fasted and Ritalin SR® fasted.

Bioavailability of Formulation 3 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 100.8%-fed conditions not tested).

Bioavailability of Formulations 1 and 3 are similar under fasted and fed conditions (fasted: 50.0 versus 51.2ng/hmL; fed: 56.3 versus 57.9ng•h/mL). Note also that Formulations 2 and 3 have almost identical AUC values.

From the mean curves for Formulation 3 and Ritalin SR®, the initial rate of rise of plasma MPH concentrations is slightly faster for Formulation 3 compared to Ritalin SR®.

In contrast to Formulation 2, the effect of food on the initial rate of concentration rise is minimal. Since Formulation 3 does not contain an enteric coat, this suggests that food slows the initial release from the IR component of formulations that contain an enteric coat, both when the enteric coat is part of the same bead (underneath the IR coat in the case of Formulation 1) and when it is in a separate bead (as for Formulation 2).

Also in contrast to Formulation 2, the T_{max} of the mean curve of Formulation 3 occurs at a similar time to that of Ritalin SR® under fed and fasted conditions. For Formulation 1 (and Formulation 1) the T_{max} of the second absorption phase under fed conditions is substantially delayed relative to Ritalin SR®.

CONCLUSIONS—EXAMPLES 7 AND 8

1. Formulation 1 has both a fast initial rate of rise, at least under fasted conditions and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Since these conditions represent the extremes of "food stress", one might predict that administration in association with normal meals and times would provide an intermediate profile. It is also possible that gastric emptying in children on a normal meal schedule will be faster than in adults fed a high fat meal—this will tend to make the second absorption phase occur earlier and produce lower concentrations from 12 hours onwards. Formulation 1 therefore meets the dual objectives of rapid onset and prolonged duration.
2. Formulation 1 is also very similar to Ritalin SR® under fasted conditions but shows a delayed peak under fed conditions such that plasma MPH concentrations are higher than Ritalin SR®(fasted) from 6 hours post dose onwards. The controlled release component in Formulation 2 is faster releasing than the one in Formulation 1 and plasma MPH concentrations are lower for Formulation 1 from about 10 hours post dose.
3. Overall, Formulation 3 (non-enteric coated) has a profile very similar to Ritalin SR® under both fed and fasted conditions. The IR component of Formulation 3 provides some increase in initial absorption rate relative to Ritalin SR® under fasted conditions. Since concentrations later in the day are similar for the two formulations, this confirms the concept that a fast initial rise and higher concentrations later in the day are not possible at the same dose, unless a delay is introduced into the release of a component of the total dose.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. An oral controlled release formulation which provides a rapid onset of therapeutic effect and a rapid drop in plasma concentration after a prolonged period of therapeutic effect, comprising

a plurality of substrates comprising a portion of an effective dose of methylphenidate hydrochloride in immediate release form,

a hydrophobic material comprising an acrylic polymer, coated onto the surface of said substrates in an amount sufficient to retard the release of said drug,

an enteric coating applied over said hydrophobic coating in an amount sufficient to substantially delay the release of said drug from said substrate until after said formulation passes through the stomach, wherein said enteric coating is derived from an aqueous dispersion comprising an acrylic/methacrylic copolymer, a plasticizer and a glidant,

the formulation further comprising the remaining portion of said methylphenidate hydrochloride in immediate release form, and

wherein the formulation provides a time to maximum plasma concentration of said methylphenidate hydrochloride at about 0.5 to about 4 hours after oral administration.

2. The formulation of claim **1**, wherein said remaining portion of said methylphenidate or a pharmaceutically acceptable salt thereof is applied to said substrates over said enteric coating.

3. The formulation of claim **1**, wherein a unit dose comprises said plurality of substrates contained within a gelatin capsule, and said remaining portion of said methylphenidate or pharmaceutically acceptable salt thereof is contained within said gelatin capsule in a form selected from the group consisting of an immediate release powder, an immediate release granulate, immediate release matrix spheroids, immediate release beads, and as a coating applied onto the surface of said enteric coated substrates.

4. The formulation of claim **1**, wherein said hydrophobic material comprises a plasticized aqueous dispersion of an acrylic polymer which is sprayed onto the surface of said substrates.

5. The formulation of claim **4**, wherein said substrates are subjected to oven curing at a temperature above the glass transition temperature of the plasticized acrylic polymer at a temperature from about 40 to about 50°C. for a time period of at least about 12 hours prior to the application of said enteric coating.

6. The formulation of claim **1**, which provides a peak plasma concentration of the methylphenidate or a pharmaceutically acceptable salt thereof which is from about 1.0 to about 2.0 times the plasma concentration of the methylphenidate or a pharmaceutically acceptable salt thereof provided by the formulation at about 9 hours after oral administration.

7. The formulation of claim **6**, wherein the duration of effect provided by the methylphenidate or a pharmaceutically acceptable salt thereof contained in the formulation falls below effective plasma concentrations at about 8 to about 12 hours after oral administration.

8. The formulation of claim **7**, wherein the oral dosage form provides a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration.

9. The formulation of claim **6**, wherein the peak plasma concentration is from about 1.0 to about 1.7 times the plasma concentration of methylphenidate or a pharmaceutically acceptable salt thereof provided by the formulation at about 9 hours after oral administration.

10. The formulation of claim **6**, wherein the duration of effect provided by the methylphenidate or a pharmaceutically acceptable salt thereof contained in the oral dosage form falls below effective plasma concentrations at about 8 to about 10 hours after oral administration.

11. The formulation of claim **10**, which provides a "square wave" plasma profile.

12. The formulation of claim **10**, which provides an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate Dissolved
0.25	0–45%
1	5–50%
4	40–90%
8	NLT 60%
12	NLT 80%.

* * * * *

EXHIBIT D

US008580310B2

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

(10) **Patent No.: US 8,580,310 B2**
(45) **Date of Patent: *Nov. 12, 2013**

(54) **CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS**

(75) Inventors: **Thinnayam N. Krishnamurthy**, Scarborough (CA); **Andrew Darke**, Newmarket (CA)

(73) Assignee: **Purdue Pharma**, Pickering, Ontario (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 848 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/283,431**

(22) Filed: **Sep. 11, 2008**

(65) **Prior Publication Data**

US 2009/0123554 A1 May 14, 2009

Related U.S. Application Data

(63) Continuation of application No. 11/879,646, filed on Jul. 18, 2007, now Pat. No. 7,438,930, which is a continuation of application No. 10/156,622, filed on May 28, 2002, now Pat. No. 7,247,318, which is a continuation of application No. 09/465,159, filed on Dec. 16, 1999, now Pat. No. 6,419,960.

(60) Provisional application No. 60/112,617, filed on Dec. 17, 1998.

(51) **Int. Cl.**

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A61K 9/20	(2006.01)
A61K 9/26	(2006.01)
A61K 9/48	(2006.01)
A61K 9/50	(2006.01)

(52) **U.S. Cl.**
USPC **424/490**; 424/451; 424/458; 424/464; 424/474

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

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Primary Examiner — Susan Tran
(74) *Attorney, Agent, or Firm* — Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

The invention is directed to oral modified/controlled release drug formulations which provide a rapid initial onset of effect and a prolonged duration of effect. Preferably, the peak concentration is lower than that provided by the reference standard for immediate release formulations of the drug, and the duration of effect falls rapidly at the end of the dosing interval.

7 Claims, 8 Drawing Sheets

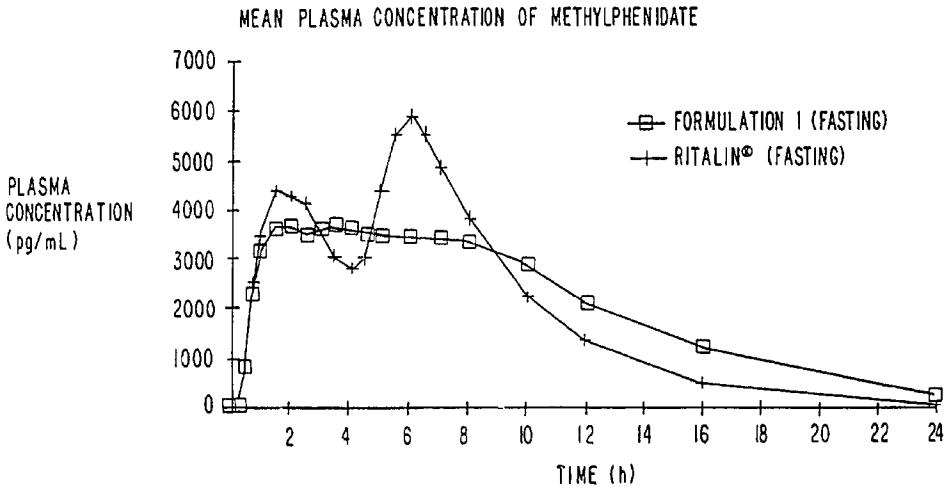

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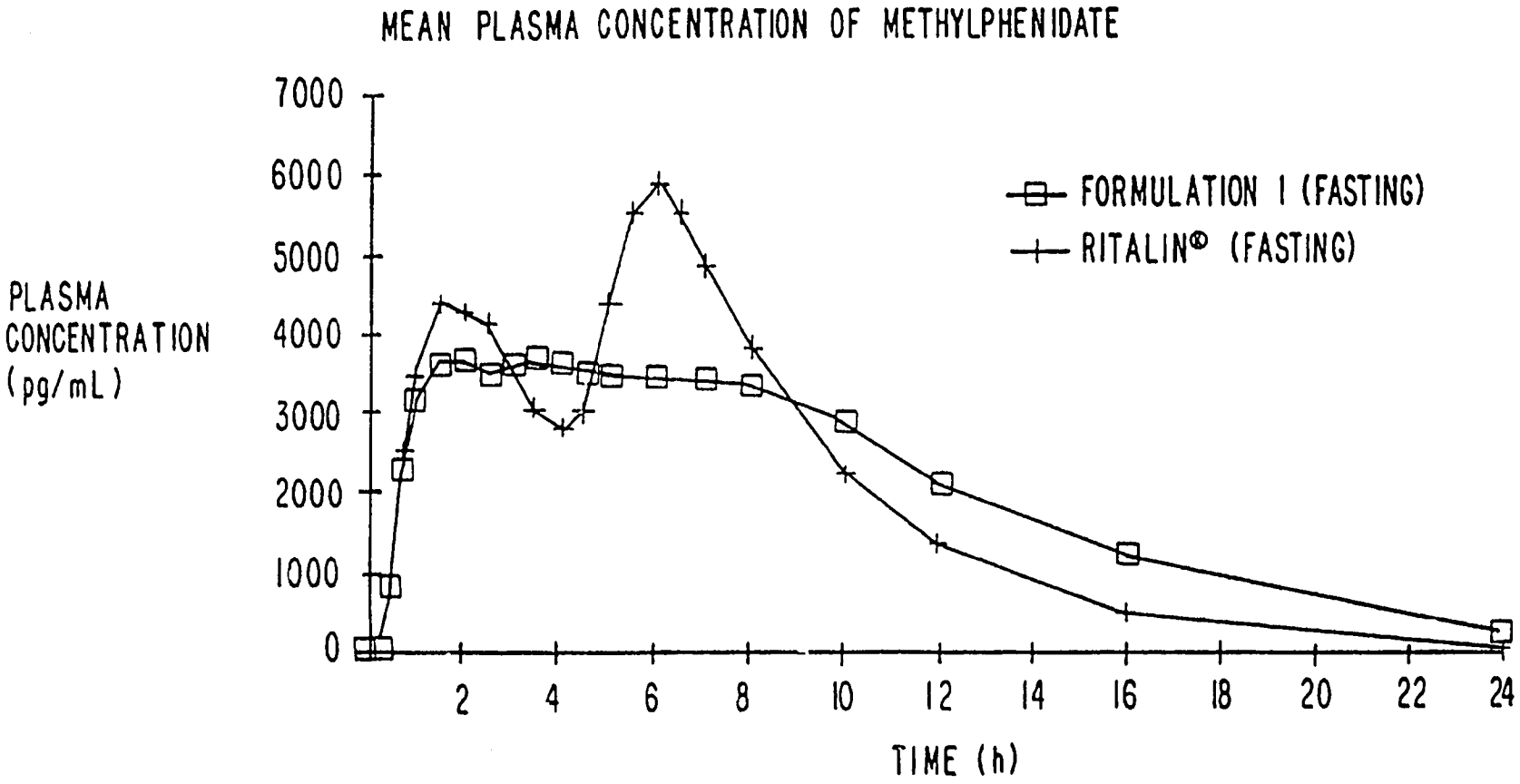
FIG. 1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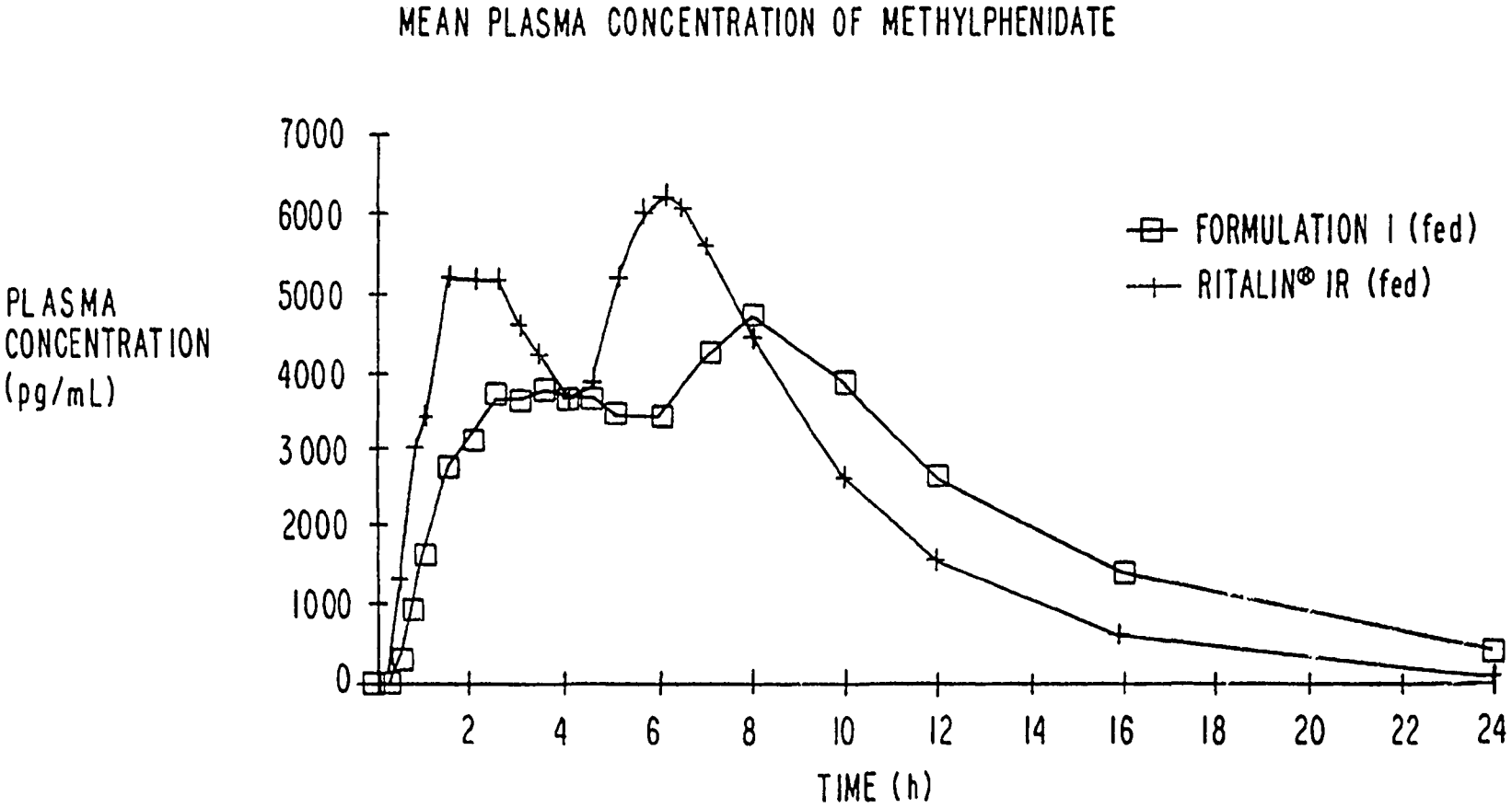
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (FASTING)
RITALIN® (FASTING)

FIG. 2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PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (fed)
RITALIN® IR (fed)

FIG.3

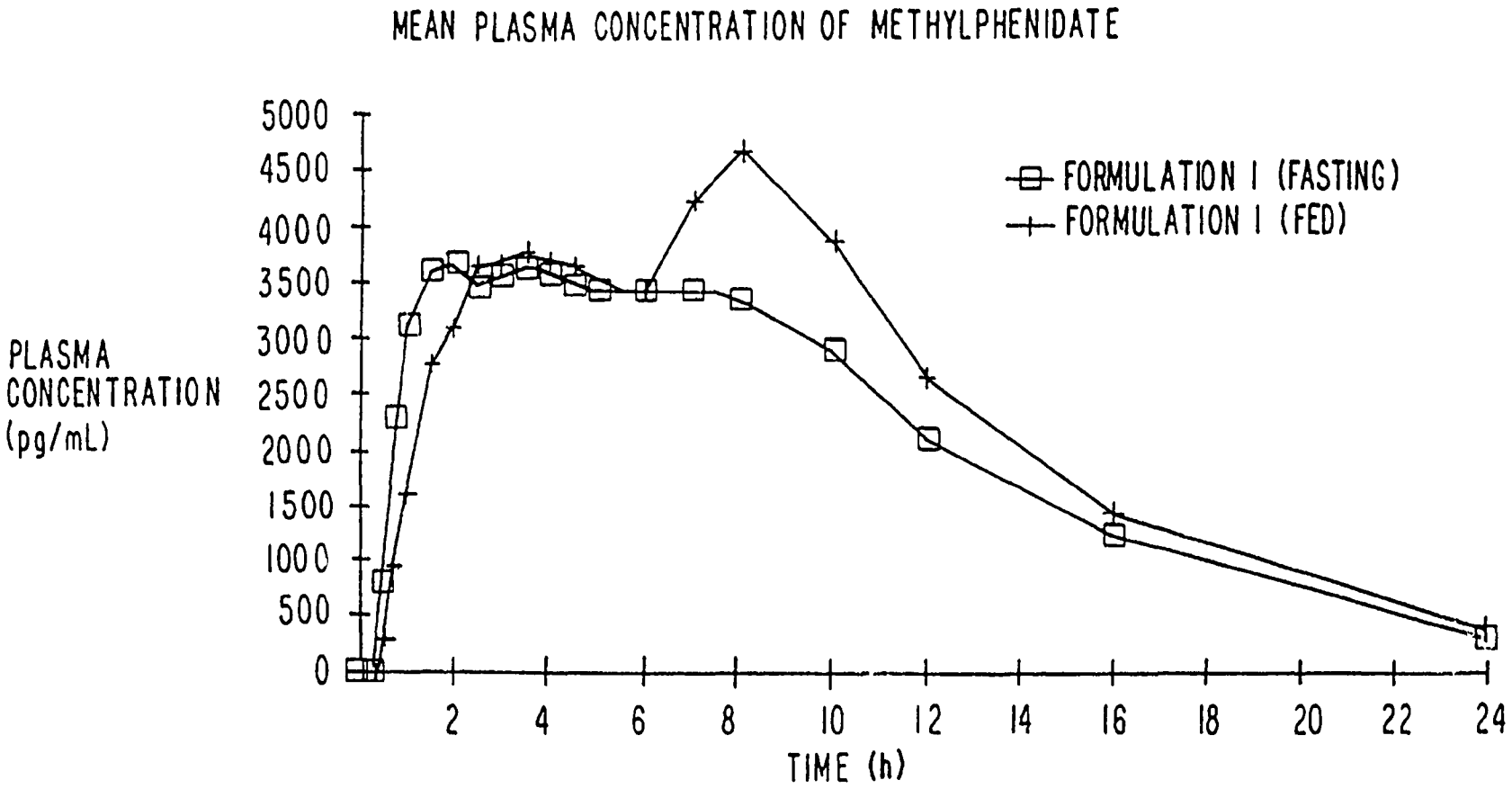

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (FASTING)
FORMULATION I (FED)

FIG. 4

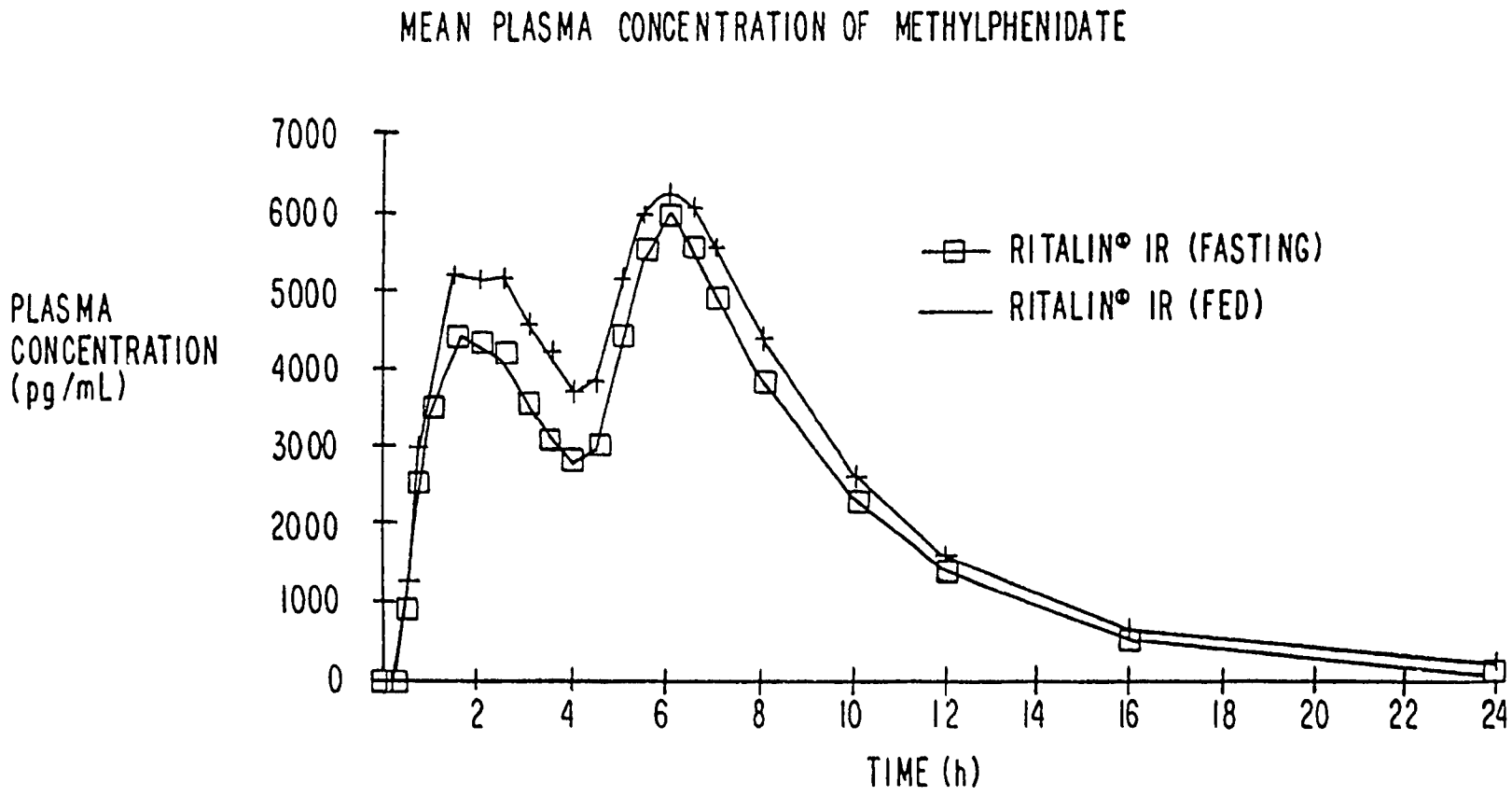

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
RITALIN® IR (FASTING)
RITALIN® IR (FED)

FIG.5

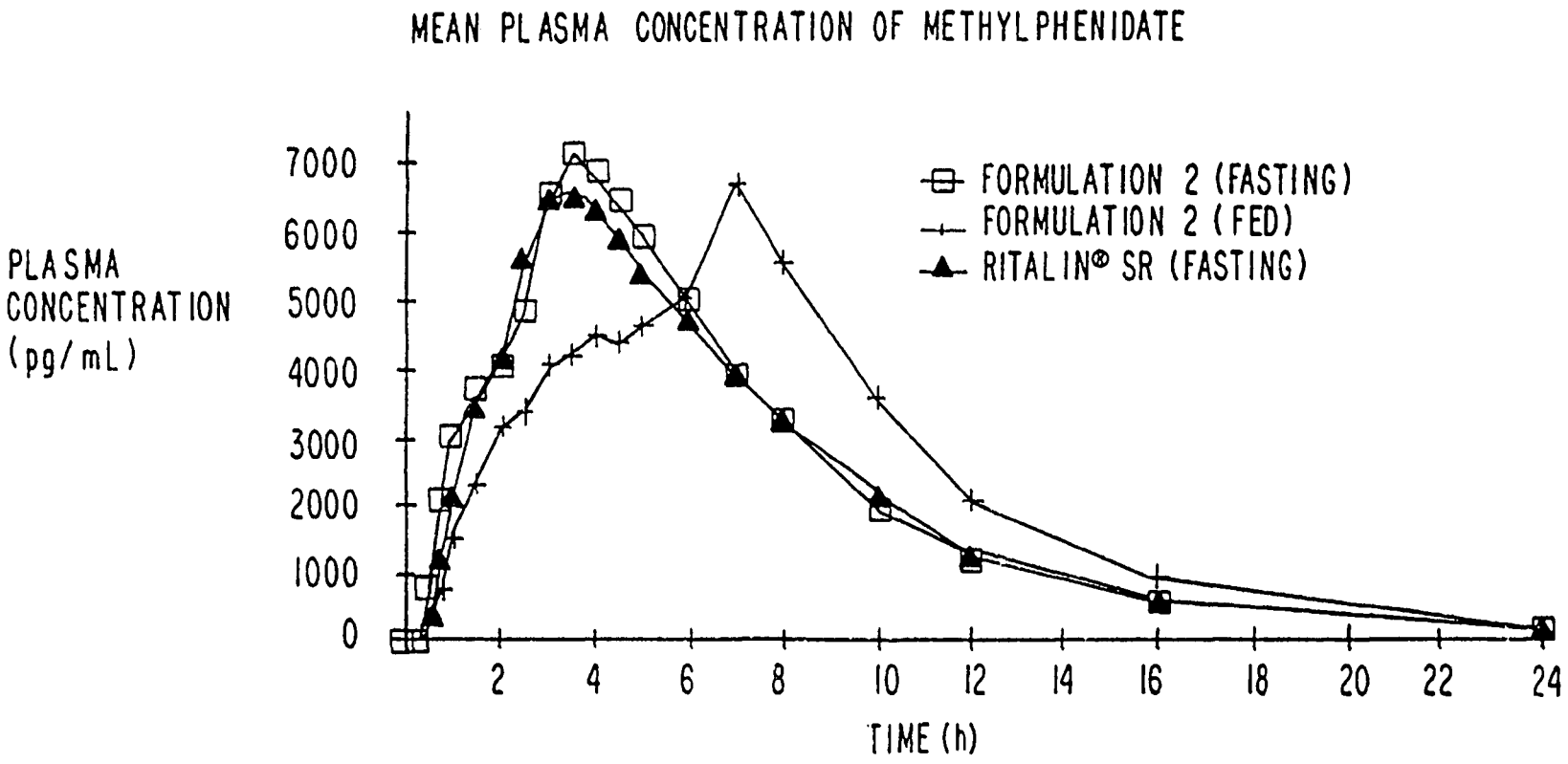

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FASTING)
FORMULATION 2 (FED)
RITALIN® SR (FASTING)

FIG.6

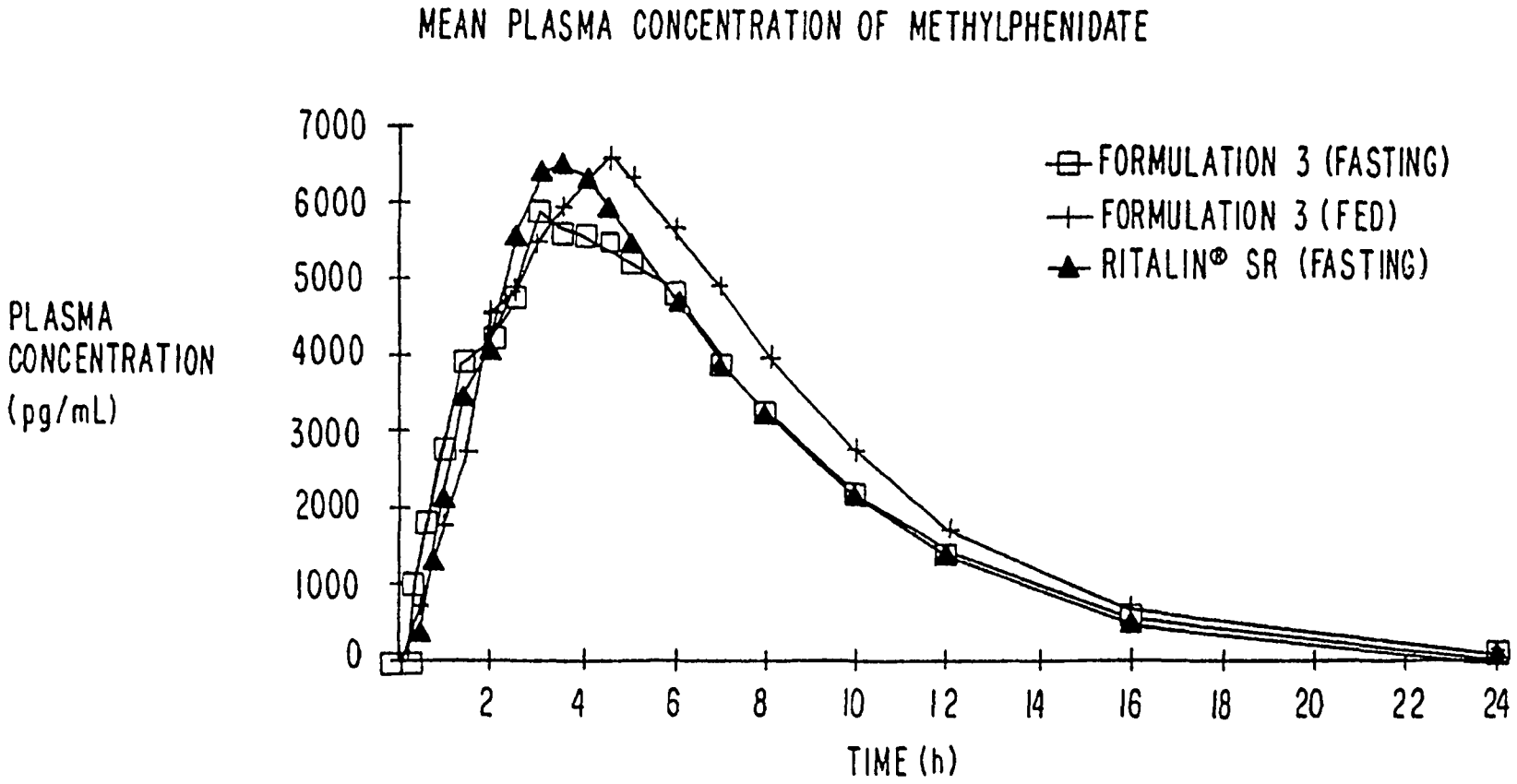

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 3 (FASTING)
FORMULATION 3 (FED)
RITALIN® SR (FASTING)

FIG. 7

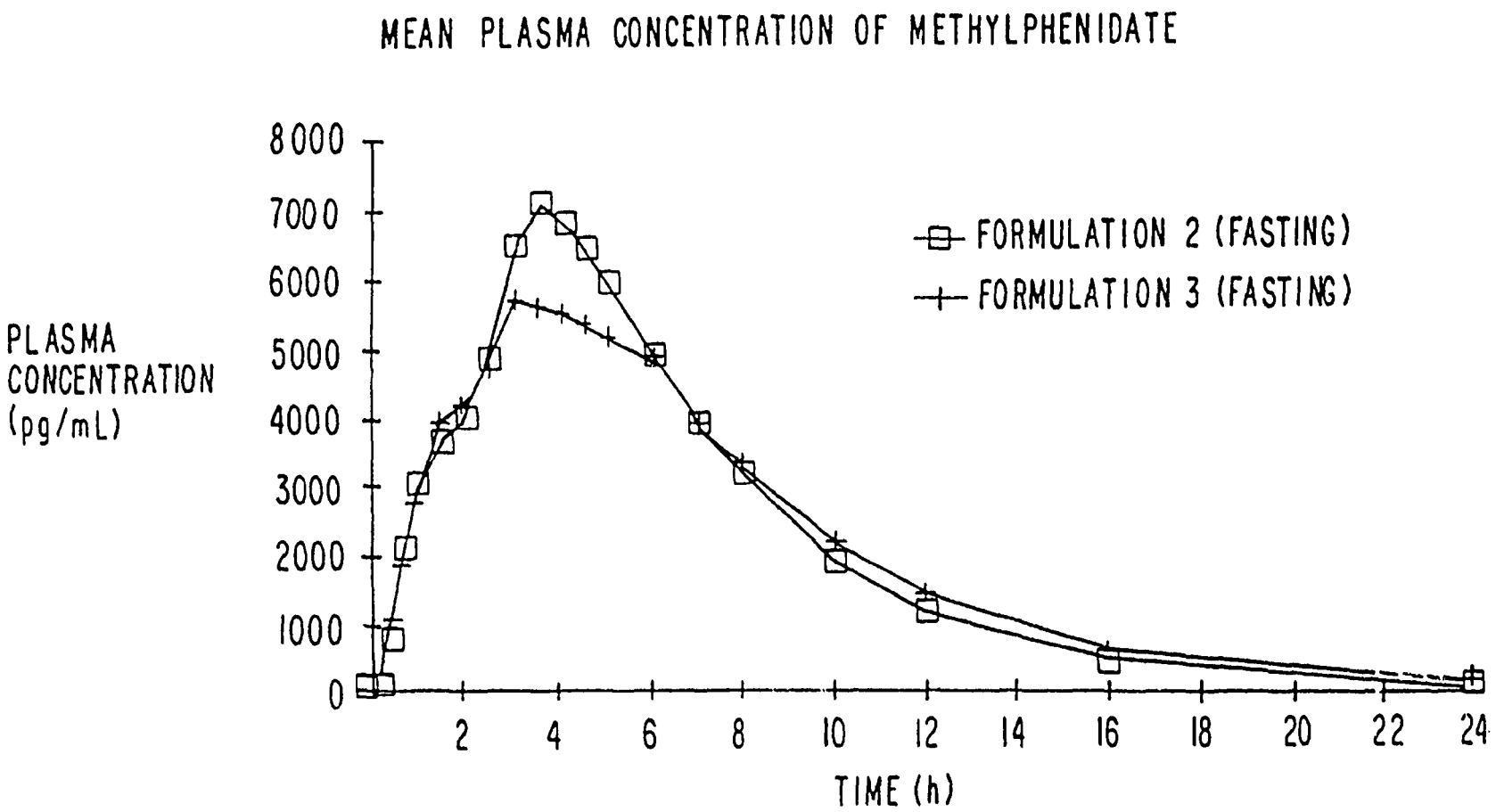
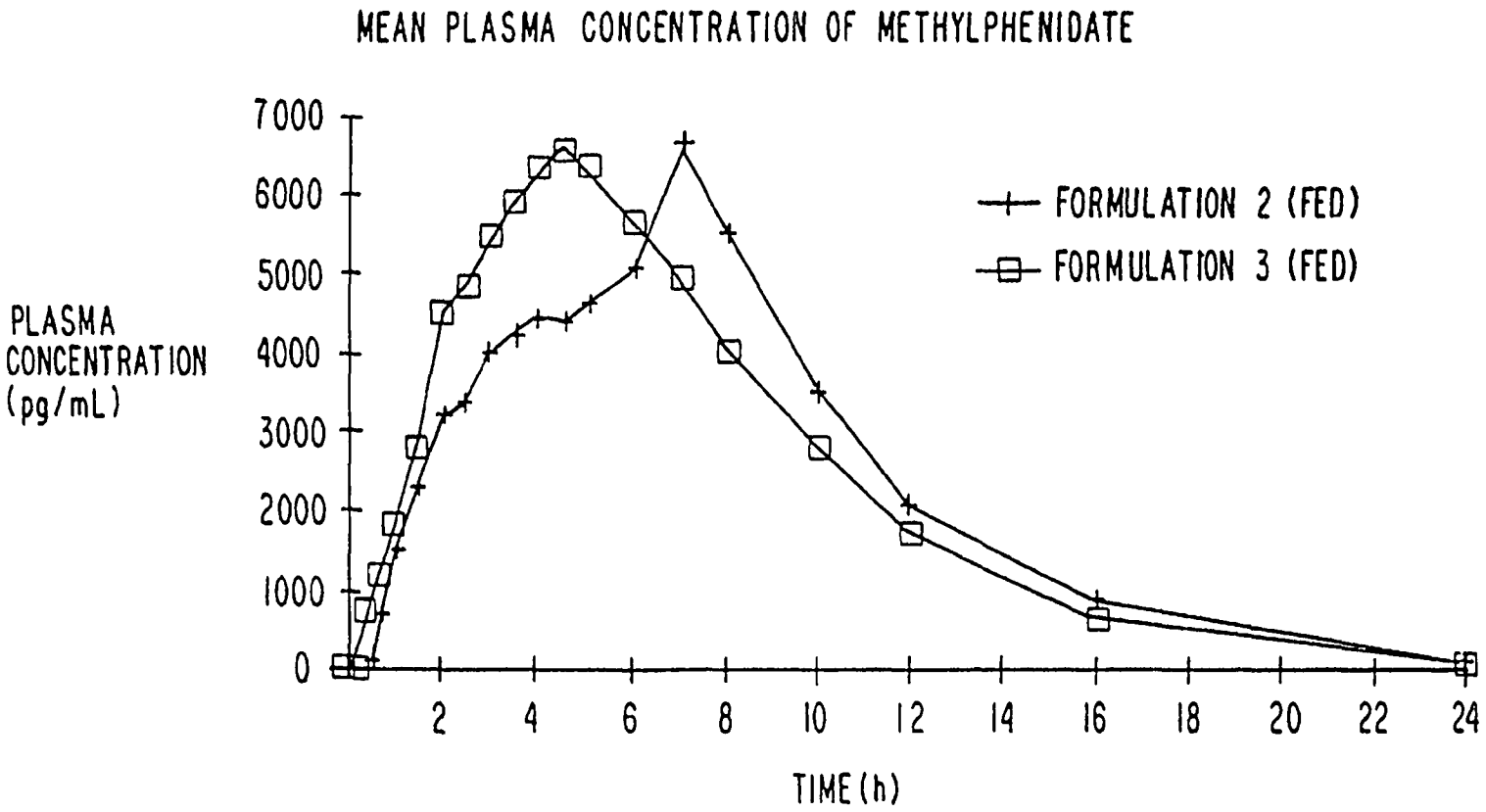

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
8000
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FASTING)
FORMULATION 3 (FASTING)

FIG. 8


MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FED)
FORMULATION 3 (FED)

CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS

This application is a continuation of U.S. application Ser. No. 11/879,646, filed on Jul. 18, 2007, now U.S. Pat. No. 7,438,930; which is a continuation of U.S. application Ser. No. 10/156,622, filed May 28, 2002, now U.S. Pat. No. 7,247,318; which is a continuation of U.S. application Ser. No. 09/465,159, filed Dec. 16, 1999, now U.S. Pat. No. 6,419,960, which claims priority to U.S. Provisional Application No. 60/112,617, filed Dec. 17, 1998, the disclosures of which are hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. It is the intent of all sustained release formulations to provide a longer period of pharmacologic action after administration than is ordinarily obtained after administration of immediate-release dosage forms. Sustained release compositions may be used to delay absorption of a medicament until it has reached certain portions of the alimentary tract, and maintain a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered. Such longer periods of response provide for many therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. Thus, therapy may be continued without interrupting the sleep of the patient, which is of special importance, for example, when treating a patient for moderate to severe pain (e.g., a post-surgery patient, a cancer patient, etc.), or for those patients who experience migraine headaches on awakening, as well as for the debilitated patient for whom sleep is essential. A further general advantage of longer acting drug preparations is improved patient compliance resulting from the avoidance of missed doses through patient forgetfulness.

Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occurs because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance therapy of the patient. In view of this, it is considered a goal of many skilled in the art that a controlled release dosage form will ideally provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ratio. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

It is known in the pharmaceutical art to prepare compositions which provide for sustained release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Sustained release formulations known in the art include specially coated pellets, coated tablets and capsules, and ion exchange resins, wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ration. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

Controlled release formulations known in the art include specially coated beads or pellets, coated tablets and ion exchange resins, wherein the slow release of the active drug is brought about through selective breakdown of the coating of the preparation or through formulation with a special matrix to affect the release of the drug. Some controlled release formulations provide for sequential release of a single dosage of an active medicament at predetermined periods after administration.

While controlled and/or sustained release compositions have constituted a definite advance in the art, improvements in these compositions have been sought, particularly for preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD), diabetes etc.

Attention Deficit Disorders are the most common psychiatric disorders in children (Campbell et al. 1992) with reported rates ranging from 4% to 9% (Aman et al. 1983). Attention Deficit Disorder (ADD) is characterized by inattention and impulsivity and may be present with hyperactivity (ADHD) (Shaywitz et al. 1984). Other characteristics may include aggressiveness, stealing, lying, truancy, setting fires, running away, explosiveness, cognitive and learning problems as well as poor social skills (Campbell et al. 1992). It is four to five times more frequent in boys than girls (Campbell et al. 1992).

Stimulant medication, such as amphetamines, have been shown to be the most effective agents in the treatment of children with disorders of activity modulation and attention regulation and result in significant improvement in 70 to 80 percent of affected children (Shaywitz et al. 1984). Positive effects of stimulants have been documented in a variety of areas including behavioral, social, perceptual performance, motor activity, impulse control, attention regulation and cognitive performance (Barkley 1977, Kavale 1983, Offenbacher et al. 1983, Rosenthal et al 1978).

Methylphenidate {dl-threo-methyl-2-phenyl-2-(2-piperidyl)acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The efficacy of methylphenidate ("MPH") in improving attention and behavioral symptoms has been supported by many studies.

Immediate release methylphenidate preparations, because of their short half-life, require frequent administration at short intervals to ensure adequate treatment throughout a child's school day. The rapid onset and offset of immediate release methylphenidate preparations means that a medicated child with attention deficit disorder will be maximally affected only for relatively brief periods during the day. Due to its short half-life, MPH is usually given twice per day, usually once after breakfast and once during the school day, an event that some children and some school personnel apparently avoid, resulting in poor compliance with prescribed regimens (Brown et al., 1985; Firestone 1982). Compliance is a major problem for children who require a midday or midafternoon dose as many schools prohibit children from taking medica-

tions during the school day and others often insist that all medications be given by a nurse. Poor compliance in taking medication may explain, in part, the variable and conflicting results reported in many studies of the effect of medication on improving the behavior of hyperactive children. These limitations of immediate release methylphenidate led to interest in products with longer effective periods of action. These limitations of immediate release methylphenidate preparations led to interest in products with longer effective periods of action.

A sustained release form of methylphenidate (Ritalin® SR) is commercially available. As a result of many clinical trials, various opinion leaders in treatment of attention deficit hyperactivity disorder have made the following comments regarding Ritalin® SR (sustained release methylphenidate) produced by Ciba-Geigy: (i) Ritalin® SR does not have a sufficiently early onset of effect to allow for behavioral management in the early morning; (ii) Ritalin® SR does not have the beneficial late effects that would be produced by a lunch time dose of immediate release methylphenidate, thus defeating the purpose of using an SR formulation; (iii) The effects of Ritalin® SR are inconsistent or erratic over the course of the day.

There is a need in the art to develop drug formulations which provide a rapid onset, a prolonged action, followed by rapid offset of effect in order to overcome the deficiencies of the current state of the art.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which results in improved patient compliance.

It is an object of the present invention to provide new oral dosage formulations which represent improvements over currently available preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD).

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which ensure adequate treatment throughout a child's school day.

It is an object of the present invention to provide new oral dosage formulations which allow a child with attention deficit disorder to be maximally treated throughout the daytime, while being administered only once, i.e., in the morning.

It is a further object of the present invention to provide new controlled/modified release oral dosage formulations which provide a rapid onset and rapid offset with an extended release of active medicaments incorporated therein.

It is yet another object of the present invention to provide new controlled/modified release oral dosage formulations which are useful in all types of pharmaceutically active ingredients and which can extend the time of release of all such ingredients.

It is yet another object of the present invention to provide an oral controlled release formulation which combines both a rapid onset and sustained plasma concentrations throughout the day, followed by a rapid drop-off of plasma concentrations of drug to below minimum effective concentrations.

It is yet another object of the present invention to provide a "multi-layer release" (MLR) technology which is useful for all types of pharmaceutically active ingredients and which can extend the duration of action for a desired length of time.

To address the above-mentioned deficiencies as well as other goals, the present invention is directed in part to a controlled release product which is intended to combined

both a rapid onset and sustained plasma concentrations throughout the day. Significantly, the formulations of the present invention provide a rapid onset, a prolonged action, followed by rapid offset of effect, i.e., a "square wave" profile.

The invention is directed in part to controlled/modified release formulations based on a multi-layered release ("MLR") technology. The drug product can be in a tablet or a multiparticulate formulation contained within an oral gelatin capsule.

In the case of beads, encapsulated in a capsule, each bead contains a series of layers with different characteristics—an outer immediate release layer, a release delaying layer (enteric coat), a controlled release layer over an immediate release layer. The MLR formulation is designed such that upon oral administration, the formulation provides a rapid dissolution and absorption of the outer layer of the formulation which contains a portion of the drug in immediate release form, thereby resulting in a rapid rise of the drug to therapeutic plasma levels. This is followed by a period of no absorption (due to an enteric coating), followed thereafter by a controlled release of the drug from the formulation to maintain plasma levels. After absorption of the drug from an immediate release core, plasma levels then rapidly decrease. By virtue of the release of the drug from the MLR formulation, the plasma level of the drug, when plotted on a time/concentration curve, takes the appearance of a "square wave".

In certain further preferred embodiments, the formulation provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and provides effective blood levels for at least about 6 hours after administration.

In certain further preferred embodiments, the formulation exhibits a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit a "plateau" which lasts from about 6 hours to about 12 hours. The "plateau" is characterized by a stabilized plasma concentration, wherein the plasma level at the end of the measured interval does not differ by more than 20%, preferably by no more than 10% of the plasma concentration at the beginning of the measured interval.

In certain further preferred embodiments, the formulation exhibits a bimodal release of active agent from the dosage form. Bimodal release of the active agent is characterized by the active agent being release from the dosage form by more than one distinct release rate. In some embodiments, the release rates can be separated by a no-release or a substantially no-release interval, although this is not always necessary.

In certain further preferred embodiments, the formulation exhibits a biphasic absorption of the active agent. Biphasic absorption of the active agent is characterized by the active agent being absorbed through a natural barrier (e.g. the mucosal lining of the gastro-intestinal tract) by more than one distinct absorption rate. In some embodiments, the absorption rates can be separated by a no-absorption or a substantially no-absorption interval, although this is not always necessary. A formulation can exhibit both biphasic absorption and bimodal release of the active agent, with the biphasic absorption being a function of the bimodal release rate. However, biphasic absorption is not always attributed to release rate and can occur in a formulation not exhibiting bimodal release.

In other preferred embodiments the formulation exhibits bimodal release and/or biphasic absorption to provide a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit bimodal release and/or biphasic absorption to provide a "plateau"

which lasts from about 6 hours to about 12 hours. Other embodiments maintain effective plasma levels of the active agent for about 16 to about 18 hours after administration of the dosage form.

In certain preferred embodiments, an acrylic resin is utilized to provide the controlled slow release of therapeutically active ingredients over a predetermined or a specified period of time, the acrylic resin thereby comprising a significant part of the "base composition". Base compositions prepared from such acrylic resins provide sustained release of therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration, generally oral administration, in humans or animals.

In other embodiments of the invention, the formulations of the invention are composed of:

(i) a mixture of immediate release particles (e.g., beads) and enteric coated immediate release particles (e.g., beads); (ii) a mixture of immediate release particles (e.g., beads) and enteric coated controlled release particles (e.g., beads) or (iii) a mixture of immediate release particles (e.g., beads) and controlled release particles (e.g., beads). In each such instance, the mixture of particles possessing different release properties are blended together and filled into hard gelatin capsules.

In certain preferred embodiments, the controlled/modified release drug formulations of the invention consist of a plurality of beads, each containing an immediate-release component in combination with an enteric coated controlled-release component to produce a delay in the absorption process. The drug product is an oral capsule containing beads. Each bead contains a series of layers with different release characteristics—an outer immediate release layer; a release delaying layer; a controlled release layer; and an immediate release core. The final product is a capsule containing multi-layer release (MLR) beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption of the drug. In certain embodiments, the immediate release component represents 40% of the total dose per bead and the controlled release component represents 60%. This formulation is designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug. The results of a bioavailability study of this formulation indicate a biphasic release profile that is consistent with the pharmaceutical rationale discussed herein.

In other embodiments of the invention, the bead size of the formulations can be adjusted in order to obtain a desired pharmacokinetic profile based on the correlation between gastric emptying and bead size. A smaller bead size exhibits faster gastric emptying as compared to a larger bead size.

Other objects and advantages of the present invention will be apparent from the further reading of the specification and of the appended claims.

The term "pH-dependent" for purposes of the present invention is defined as having characteristics (e.g. dissolution) which vary according to environmental pH (e.g., due to changes in the in-vitro dissolution media, or due to passage of the dosage form through the gastrointestinal tract.

The term "pH-independent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH, in that a difference, at any given time, between an amount of methylphenidate released at one pH and an amount released at any other pH, when measured in-vitro using the USP Paddle Method of U.S. Pharmacopeia XXII (1990) at 100 rpm in 900 ml aqueous buffer, is no greater than 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. **1** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fasting conditions.

FIG. **2** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fed conditions.

FIG. **3** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 as a function of time when given under fasting and fed conditions.

FIG. **4** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Ritalin® as a function of time when given under fasting and fed conditions.

FIG. **5** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 2 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **6** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 3 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **7** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fasting conditions as a function of time.

FIG. **8** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fed conditions as a function of time.

DETAILED DESCRIPTION

The drug used in the formulations of the invention may be selected from a wide variety of pharmaceutically active drugs such as diabetes drugs, attention deficit hyperactivity controlled drugs, analgesics, anti-obesity preparations, anti-inflammatories, antihistamines, antitussives, decongestants, antinausea agents, narcotics, bronchodilators, cardiovasculars, central nervous system (CNS) drugs, nicotine replacement therapy, nitrates, sleeping aids/sedatives, vitamins, etc.

The controlled/modified release preparations of the present invention may be used in conjunction with any multiparticulate system, such as granules, spheroids, beads, pellets, ion-exchange resin beads, and other multiparticulate systems in order to obtain a desired sustained-release of the therapeutically active agent. Beads, granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable unit dosage form. An amount of the multiparticulates effective to provide the desired dose of drug over time may be placed in a capsule,

may be contained in a packet and sprinkled onto food, or may be incorporated in any other suitable oral solid form, such as a tablet. On the other hand, the present invention can be in the form of a matrix tablet. With respect to all such optional formulations, it is desired that the formulation be prepared such that an initial immediate release of drug provides an early onset of effect, which onset is analogous to an immediate release formulation, and that the formulation further provide a sustained release component which maintains therapeutically effective levels of the drug in the plasma for the desired amount of time, followed by a relatively rapid drop-off in blood plasma levels relative to typical sustained release formulations. Viewed as an in vivo time/concentration plot, the plasma level of the drug from the formulations of the present invention have the appearance of a "square wave". The immediate release component preferably represents from about 30% to about 40% of the total dose and the controlled release component preferably represents from about 60% to about 70% of the total dose of methylphenidate contained in the formulations of the present invention. In certain preferred embodiments, including the MLR embodiments of the invention, the immediate release component represents about 40% of the total dose and the controlled release component represents about 60% of the total dose of methylphenidate contained in the formulation.

In the case of methylphenidate, it is desired that the onset of action occurs from about 0.5 to about 4 hours, and preferably from about 0.5 to about 2 hours after the oral dosage form is administered, and it is further desired that the dosage form no longer provides effective plasma levels of methylphenidate from about 8 to about 12, more preferably from about 8 to about 10 hours, after oral administration of the dose. In this manner, the dose of methylphenidate can be administered to a child in the morning before school begins, provides the desired effect at the start of the school day, with the pharmacologic action of the drug not waning until after the school day ends, and preferably before dinner so that the drug does not have the side effect of acting as an appetite suppressant.

The formulations of the present invention are designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug.

It is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability. Bioavailability, in a more meaningful sense, is the degree, or amount, to which a drug substance is absorbed into the systemic circulation in order to be available to a target tissue site. To be absorbed, an active drug substance must be in a solution. The time required for a given proportion of an active drug substance contained in a dosage unit to enter into solution in appropriate physiological fluids is known as the dissolution time. The dissolution time for an active substance from a dosage unit is determined as the proportion of the amount of active drug substance released from the dosage unit over a specified time by a test method conducted under standardized conditions. The physiological fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.

Although there are many diverse factors which influence the dissolution of a drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from a specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in this steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiological conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium, providing for a steady state absorption.

The transport across a tissue absorption site in the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane, since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e. the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the gastrointestinal tract into the blood stream.

Notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, in many cases an important correlation can be established between the in vitro dissolution time determined for a dosage form and the in vivo bioavailability. This correlation is so firmly established in the art that dissolution time has become generally descriptive of bioavailability potential for many classes of active components contained in a particular dosage form. In view of this relationship, the dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating whether a controlled release formulation should be tested in vivo.

With the above in mind, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0-45%
1	5-50%
4	40-90%
8	NLT 60%
12	NLT 80%

In certain preferred embodiments of the present invention, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0-45%
1	10-50%
4	30-80%
8	NLT 65%
12	NLT 80%

Sustained Release Coatings

In certain preferred embodiments, the drug is incorporated into or onto a substrate and a sustained release coating is applied thereto. For example, the drug may be contained within or on a substrate as follows: (i) incorporated into matrix spheroids (e.g., together with a pharmaceutically acceptable spheronizing agent such as microcrystalline cellulose), (ii) coated onto inert pharmaceutically acceptable beads (e.g., nonpareil beads); (iii) incorporated into a normal release tablet core; or (iv) incorporated into a tablet core which comprises a matrix including a sustained release carrier material. Thereafter, a sustained release coating is applied onto substrates such as those mentioned in (i)-(iv) above. The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastro-intestinal fluid. A pH-dependent coating serves to release the drug in desired areas of the gastro-intestinal (GI) tract, e.g., the stomach or small intestine. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) comprising the drug is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Such formulations are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference. The particles are preferably film coated with a material that permits release of the drug so as to achieve, in combination with the other stated properties, a desired in-vitro release rate and in-vivo plasma levels. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Acrylic Polymers

The hydrophobic material comprising the controlled release coating may comprise a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these poly-

mers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material such as an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When the aqueous dispersion of hydrophobic material is used to coat a substrate including the drug, for example, inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. Alternatively, the substrate may be a tablet core coated with the sustained release coating, and optionally a further film-forming agent or colorant, such as Opadry®.

In formulations where an aqueous dispersion of an hydrophobic polymer such as an alkylcellulose is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60° C. and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

In formulations where an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45° C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

The sustained release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the drug to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from

the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethyl-cellulose, such as Aquacoat® (or Surelease®, may be used. If Surelease is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

The plasticized aqueous dispersion of hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined sustained release of the therapeutically active agent (i.e., drug) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the drug from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The substrate of the present invention may be prepared by a spheronizing agent together with the active agent ingredient that can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredients and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer or ethyl cellulose. In such embodiments, the sustained-release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

In a particular preferred embodiment of the invention, the controlled/modified release methylphenidate formulation is prepared as a multilayered release (MLR) formulation comprising coated inert beads. A summary of one method of manufacturing such a formulation is outlined as follows. First, immediate release (IR) drug-coated beads are prepared by spraying a solution of methylphenidate in water over sugar beads in a fluid bed dryer with a drug load of about 8%. The spray process is carried out in a fluid bed dryer, equipped with a Wurster column. A clear overcoat of HPMC is applied using an Opadry® material (e.g., Opadry® Clear (Formula No: YS-1-7006)), to a weight gain of about 1%. Next, a controlled release coating is applied to the IR beads, which converts the same into controlled release (CR) beads. This is accomplished by spraying a solution of Eudragit® RS 30 D, triethyl citrate (plasticizer) and talc (glidant), onto the IR beads. Next, the coated beads are cured in order to obtain a stabilized release rate of the therapeutically active agent. In preferred embodiments of the present invention where the CR coating utilizes an acrylic resin to control the release of the drug, the CR beads at this stage are subjected to oven curing at a temperature above the Tg of the plasticized acrylic polymer of the required time period, the optimum values of the temperature and time for the particular formulation being determined experimentally. In certain embodiments of the present invention, the stabilized products is obtained via oven curing conducted at a temperature of about 40-50° C. for a time period of about 12 to about 24 hours or longer. An enteric coating is then applied onto the CR beads to convert the same into enteric coated CR (ECCR) beads. This is accomplished by spraying a solution of Eudragit® L 30 D-55 dispersion,

triethyl citrate (plasticizer) and talc (glidant) onto the CR beads. Finally, an immediate release coating is applied onto the ECCR beads (referred to as, e.g., an IR Topcoat). This is accomplished by spraying a solution of methylphenidate in water over EC CR beads.

Results of initial studies show that this formulation is stable under room temperature (25° C., 60% RH) and accelerated conditions (40° C., 75% RH).

In certain preferred embodiments of the present invention, an effective amount of the drug in immediate release form is included in the drug formulation. The immediate release form of the drug is included in an amount which is effective to shorten the time to maximum concentration of the drug in the blood (e.g., plasma), such that time to T_{max} is shortened to a time of, e.g., from about 0.5 to about 2 hours. By including an amount of immediate release drug in the formulation, the time to onset of action is significantly reduced, and is the same or earlier than that of the reference standard immediate release treatment (e.g., Ritalin IR). In such embodiments, an effective amount of the drug in immediate release form may be coated onto the substrates (e.g., multiparticulates or tablets) of the present invention. For example, where the extended release of the drug from the formulation is due to a controlled release coating, the immediate release layer can be overcoated on top of the controlled release coating. On the other hand, the immediate release layer may be coated onto the surface of substrates wherein the drug is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising an effective unit dose of the drug (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the drug dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release drug as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the drug. One skilled in the art would recognize still other alternative manners of incorporating the immediate release drug portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

Example 1

Methylphenidate HCl Immediate Release Beads

TABLE 1

Ingredients	%
Methylphenidate hydrochloride	15.0
Sugar bead 14/18	80.0
Opadry ® clear YS-1-7006	5.0
Water	q.s.
Total	100.0

1. Charge Niro-Aeromatic Strea 1 Fluid Bed Wurster Coater with 14/18 mesh Nupareil® PG (sugar spheres NF).
2. Coat the beads at 60° C. by spraying a solution of methylphenidate hydrochloride (12% w/w) and Opadry clear (4% w/w) in water.
3. Once the coating is completed, allow the beads to dry at 60° C. for 2 or 3 minutes.
4. Cool the beads in a shallow pan at room temperature.
5. Break agglomerates, if any.
6. Sift the beads through Tyler 10 mesh sieve (1.77 mm opening) and then through Tyler 20 mesh sieve (850 micrometer opening) to remove fines.
7. Apply top coat to beads by spraying a solution of coloured Opadry clear solution (4% w/w) to a theoretical weight gain of 1% w/w.

After the completion of the overcoat, the beads are then filled into hard gelatin capsules at a strength of 20 mg.

Dissolution-testing was conducted on the bead filled IR capsules using USP Apparatus 1 (basket method) in 500 mL of simulated gastric juice without enzyme, 100 rpm at 37° C. The results are as follows:

TABLE 2

Time (minutes)	% Methylphenidate HCl dissolved
10	92.7
20	95.7
30	97.7
45	98.5

The dissolution results as set forth in the above table indicate that 98.5% of the methylphenidate hydrochloride was dissolved in 45 minutes.

Example 2

Methylphenidate HCl Controlled-Release (CR) Beads with Acrylic Polymer Coating

TABLE 3

Ingredients	%
Methylphenidate IR beads	86.20
Eudragit ® RS 30 D	8.63
Triethyl citrate	1.72
Talc	3.45
Water	q.s.
Total	100.0

The controlled-release coating is manufactured as follows:

1. The Eudragit® RS 30 D is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the IR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~8%.
3. Upon completion of the coating, the beads are cured for 24 hours at 40-45° C.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR capsules using the following USP Apparatus (basket method). The capsules were placed into 500 mL of simulated gastric juice without enzyme, for first 2 hours at 100 rpm and 37° C. and then placed into 500 mL simulated intestinal fluid without enzyme for the remainder of the testing period. The results are as follows:

TABLE 4

Time (hours)	Methylphenidate HCl dissolved
1	6.9
2	16.2
3	26.1
4	35.7
6	59.8
8	74.7
12	75.4
18	82.5
24	92.8

The dissolution results as set forth in the above table indicate that 92.8% of methylphenidate hydrochloride dissolved in 24 hours.

Examples 3 & 4

Dependence of Release Rate of Methylphenidate HCl from Controlled-Release (CR) Beads on Amount of Acrylic Polymer Coating

By adjusting the amount of Eudragit® RS 30 D applied, the release rate can be adjusted. This effect is illustrated in Examples 3 and 4 below:

TABLE 5

	%	
Ingredients	Example 3	Example 4
Methylphenidate HCl IR Bead	91.2	94.0
Eudragit ® RS 30 D	5.8	3.9
Triethyl citrate	1.0	0.7
Talc	2.0	1.4
Water	—	—
Total	100.0	100.0

The method of manufacturing the controlled-release beads in Examples 3 and 4 is similar to the method described under Example 2, by varying the proportion of beads and Eudragit® RS 30D.

The cured beads were filled into hard gelatin capsules at a strength of 20 mg.

The dissolution results, conducted under conditions identical to those found under Example 2, are shown below:

TABLE 6

Time	% Methylphenidate HCl dissolved	
(hours)	Example 3	Example 4
1	18.7	49.5
2	35.1	73.3
3	49.0	81.5
4	60.6	85.2
6	75.7	90.4
8	77.3	90.7
12	82.1	92.8

The dissolution results as set forth in the above table, indicate that 82.1% and 92.8% respectively of methylphenidate hydrochloride is dissolved in 12 hours. However, the release of drug from Example 4 was significantly faster at time points 1, 2, 3, 4, 6 and 8 hours.

Example 5

Enteric Coated (EC) Coated Release (CR) Beads—EC•CR Beads

TABLE 7

Ingredients	%
Methylphenidate CR beads	83.2
Eudragit ® L 30 D55	9.9
Triethyl citrate	2.0
Talc	4.9
Water	q.s.
Total	100.0

The enteric coating procedure is described below:

1. The Eudragit® L 30 D 55 is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the methylphenidate CR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~9%.
3. Upon completion of the coating, the beads are cured for 18 hours at 40° C.
4. The cured beads are then sieved through Tyler 10 mesh (1.7 mm opening) and Tyler 20 mesh (850 micrometer opening) sieves to remove any fines.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR filled capsules using USP Apparatus 1 (basket method) 500 mL at 100 rpm and 37° C. using SGF without enzyme for the first 2 hours and SIF without enzyme for the rest of the testing period. Results are shown below:

TABLE 8

Time	% Methylphenidate HCl dissolved		
(hours)	Lot 1	Lot 2	Lot 3
1	0.4	1.0	2.0
2	2.2	5.4	7.4
3	18.8	27.8	61.3
4	36.7	48.3	87.0
6	59.5	75.5	98.8
8	76.9	90.1	100.0
12	82.3	99.6	—

The dissolution results as set forth in the above table indicate that very little drug is dissolved in gastric juice after enteric coating and that the dissolution profile of the CR beads has been modified.

Example 6

Formulations for Clinical Trials

Examples 6A, 6B and 6C below set forth the formulations developed and tested in clinical studies.

Example 6A

IR•EC•CR Beads

Immediate Release (IR) Coating of Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The (IR•EC•CR Beads) formulation, hereinafter referred to as Formulation 1, is a capsule containing multi-layer release beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption equal to or greater than Ritalin® IR immediate release tablets. The immediate release component represent 40% of the total dose per bead and the controlled release component represents 60%.

TABLE 9

Ingredients	%
Enteric coated Controlled Release Methylphenidate HCl beads	91.4
Methylphenidate hydrochloride USP	6.5
Opadry ® clear YS-1-7006	2.1
Water	q.s.
Total	100.0

The application of an immediate release coat on the top of Enteric Coated CR beads is described below:

1. Dissolve methylphenidate HCl USP and Opadry in water with stirring.
2. Load EC•CR beads into a Wurster insert of an Aeromatic Fluid Bed Dryer.
3. Spray the beads with the coating solution using a 1 mm spray nozzle at a temperature of not more than 50° C.
4. Once the coating is completed, cool the beads at room temperature and pass through Tyler sieves 10 and 20 mesh to remove fines.

The beads were then filled into a hard gelatin capsule to a 20 mg strength.

Dissolution testing was conducted on the bead filled capsules of Formulation 1 using USP Apparatus 1 (basket method) 100 rpm, 500 mL at 37° C. —simulated gastric juice without enzyme 1st and 2nd hours; 3rd hour onwards simulated intestinal fluid without enzyme.

The results are as follows:

TABLE 10

Time (hours)	% Methylphenidate HCl dissolved
5 minutes	37.0
10 minutes	38.0
15 minutes	39.0
30 minutes	40.0
60 minutes	40.0
2	40.1
3	51.4
4	61.0
6	75.6
8	87.0
12	87.5

The dissolution results as set forth in the above table indicate a rapid onset on dissolution, followed by prolonged action.

Example 6B

IR+EC•CR Blend

Combination of Immediate Release Methylphenidate Beads (IR) and Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The enteric-coated controlled release beads (EC•CR) beads described in Example 5 may be mixed with the immediate release (IR) beads described in Example 1 in varying proportions and placed in capsules to obtain the final blended dosage form, (IR+EC•CR Blend), hereinafter referred to as Formulation 2. Formulation 2 was designed to provide a faster rate of absorption of the controlled release portion than Formulation 1. The immediate release component represents 35% of the total dose per capsule and the controlled release component represents 65%:

Dissolution testing was performed and the comparative results are shown in Table 11 below.

Example 6C

IR•CR Beads

Immediate Release (IR) Coating of Controlled-Release (CR) Methylphenidate Beads

The IR•CR Beads formulation, hereinafter referred to as Formulation 3, is a capsule containing single beads made up of an immediate release topcoat and a controlled release core, and is designed to provide an intermediate rate of absorption of the controlled release portion between that of the controlled release formulations of Formulations 1 and 2. The immediate release component represents 30% of the total dose per bead and the controlled release component represents 70%.

The immediate release topcoat is applied to CR beads as described in Example 6A for Formulation 1.

The dissolution profiles of Formulations 1-3 and Ritalin® SR, used as a comparator, are shown in Table 11 below. Hours 1 and 2 are in 500 ml of simulated gastric fluid. Simulated intestinal fluid (500 ml) is used from the third hour onwards. The results of the dissolution testing confirmed the anticipated in vitro dissolution profile.

TABLE 11

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
10 min	21.4	38.0	32.0	28.6
30 min	31.4	40.0	36.7	34.0

TABLE 11-continued

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
1	45.7	40.0	38.2	40.5
2	62.3	40.1	40.4	57.6
3	75.8	51.4	68.1	70.6
4	79.5	61.0	86.4	79.5
6	88.0	75.6	95.4	89.6
8	90.7	87.0	96.2	92.7
12	91.3	87.5	97.0	93.1

Example 7

Four Way Comparison of Single Dose Formulation 1 (Fed and Fasted) with Two Doses of Ritulin IR (Fed and Fasted)

The bioavailability of Methylphenidate MLR capsules was investigated in a four-way blind study which compared the Formulation 1 20 mg single dosage formulation under fed and fasted conditions with two doses (4 hours apart) of Ritalin® IR.

Healthy male volunteers were given a single dose of 20 mg Formulation 1 or two doses of immediate release methylphenidate 10 mg administered four hours apart under both fed and fasting conditions (n=12). "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 4 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, under fasting conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, administered 5 minutes after a high fat breakfast.

Treatment 4: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, administered 5 minutes after a high fat breakfast.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Formulation 1 and at pre-dose, 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Ritulin® IR. Plasma was harvested from each blood sample and stored in a −20° C. freezer until assayed for plasma methylphenidate concentration. Assay of plasma methylphenidate concentrations was performed using gas chromatography/mass spectrometry (GC/MS).

The mean plasma concentrations, standard deviations and coefficients of variation are shown as a function of time in Tables 12 and 13, for fasting and fed conditions, respectively.

This data is presented graphically in FIGS. **1-4**. FIG. **1** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fasting conditions. FIG. **2** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fed conditions. FIG. **3** presents the mean plasma concentration versus time for Formulation 1 under fed and fasting conditions. FIG. **4** presents the mean plasma concentration versus time for Ritalin® under fed and fasting conditions.

TABLE 12

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fasting)

Sample	Formulation 1			Ritalin		
Time (h)	Concentrations	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00		0.00	0.00	
0.250	0.00	0.00	—	0.00	0.00	
0.500	817.53	801.84	98.08	883.96	686.65	77.68
0.750	2268.79	1128.12	49.72	2485.74	828.38	33.33
1.00	3108.79	756.66	24.34	3468.74	1172.28	33.80
1.50	3597.88	740.36	20.58	4388.04	998.86	22.76
2.00	3675.60	1315.29	35.78	4289.39	1144.40	26.68
2.50	3469.81	882.62	25.44	4121.37	1014.57	24.62
3.00	3573.56	1031.61	28.87	3528.56	863.25	24.46
3.50	3637.01	1008.73	27.74	3020.93	716.36	23.71
4.00	3604.03	1071.59	29.73	2747.91	698.95	25.44
4.50	3494.44	1069.13	30.60	2958.49	799.89	27.04
5.00	3446.41	1069.50	31.03	4394.22	1603.40	36.49
5.50	—	—	—	5525.84	1766.58	31.97
6.00	3421.13	1166.25	34.09	5927.06	1955.99	33.00
6.50		—	—	5528.41	1758.49	31.81
7.00	3422.32	958.42	28.00	4860.45	1482.24	30.50
8.00	3338.59	724.49	21.70	3795.34	1500.79	39.54
10.0	2858.42	612.21	21.42	2223.48	926.11	41.65
12.0	2073.97	536.08	25.85	1334.71	523.37	39.21
16.0	1180.67	502.11	42.53	455.86	287.79	63.13
24.0	275.87	201.51	73.04	55.10	99.99	181.46

TABLE 13

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fed)

Sample	Formulation 1			Ritalin		
Time (h)	Concentration	SD. (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	
0.250	0.00	0.00	—	53.12	133.84	251.95
0.500	291.66	271.58	93.11	1256.61	1602.66	127.54
0.750	910.22	653.80	71.83	2984.60	3406.53	114.14
1.00	1580.66	983.13	62.20	3400.39	2301.87	67.69
1.50	2760.68	797.24	28.88	5205.16	1882.17	36.16
2.00	3098.73	874.49	28.22	5146.55	1617.43	31.43
2.50	3655.68	982.31	26.87	5157.11	1227.99	23.81
3.00	3625.88	797.55	22.00	4546.61	932.94	20.52
3.50	3717.71	951.58	25.60	4184.34	1080.71	25.83
4.00	3650.63	875.97	23.99	3652.57	1023.22	28.01
4.50	3627.41	835.40	23.03	3811.27	1103.83	28.96
5.00	3430.14	783.72	22.85	5158.45	1714.53	33.24
5.50	—	—	—	5982.98	1618.65	27.05
6.00	3418.03	937.07	27.42	6228.81	1591.64	25.55
6.50	—	—	—	6054.32	1919.95	31.71
7.00	4218.94	775.86	18.39	5538.57	1741.02	31.43
8.00	4679.67	1126.52	24.07	4350.90	1611.95	37.05
10.0	3858.58	1045.56	27.10	2577.66	896.59	34.78
12.0	2610.98	902.53	34.57	1521.52	611.54	40.19
16.0	1372.86	737.71	53.74	577.90	334.26	57.84
24.0	334.79	306.63	91.59	94.23	144.99	153.86

Experimental Results

Pharmacokinetic parameters were calculated based on the data from the four-way study. AUC_{0-t} (pg·h/mL), AUC_{0-inf} (pg·h/mL), $AUC_{t/inf}$ (%), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours) were calculated as described below.

For purposes of the present invention, the following terms are meant to have the following meanings:

Analysis of Pharmacokinetic Data and Statistical Analysis

AUC_{0-t} Area under the concentration-time curve from time zero to the time of the last non-zero concentration (this corresponds to the area under the concentration-time curve, over the dosing interval of the test formulation for both controlled-release and immediate-release formulations)

AUC_{0-inf} Area under the concentration-time curve from time zero to infinity

C.I. Confidence interval

CV Coefficient of variation

C_{max} Maximum observed concentration

K_{el} Elimination rate constant

LQCT The last quantifable concentration time

SD Standard deviation

TLIN The time point where log-linear elimination begins

$T_{1/2\ el}$ Time for observed C_{max}

Sampling Time Time post dose of plasma collection based on parameters to be studied

Scheduled Time The predetermined (clock) time at which the samples are to be taken

Actual time The exact (clock) time at which the sample was taken

Time deviations during sampling for drugs with a $T_{max} \leq 4$ hours were treated as follows: between 0 and 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of blood collection was <10%. Above 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of plasma collection was <15%. When sampling times were used when previously described acceptance criteria, the corrected sampling items were used when performing pharmacokinetic parameters calculations. Sampling times are present in concentration tables and graphs of statistical report.

The mean, standard deviation (SD), and coefficient of variation (CV) were calculated for plasma concentrations of methylphenidate for each sampling time and treatment. As well, the mean, SD, and CV were calculated for the AUC_{0-t} (pg·h/mL), AUC_{0-inf} (pg·h/mL), C_{max}(pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours). The calculation of these pharmacokinetic parameters is explained below.

Areas Under the Concentration-Time Curves

AUC_{0-t} was calculated using the linear trapezoidal rule.

The AUC_{0-t} was derived where t is the time (t) of the last measurable (non-zero) concentration (C_t) for each treatment.

The AUC_{0-inf} was calculated as:

$$AUC_{0-t} + \frac{C_t}{K_{el}}$$

Where C_t=the last non-zero concentration for that treatment, AUC_{0-t}=the AUC from time zero to the time of the last non-zero concentration for that treatment and K_{el}=the elimination rate constant.

Maximum Observed Concentration and Time of Observed Peak Concentration

The maximum observed concentration, C_{max}, and the observed time to reach peak concentration, T_{max}, was determined for each subject and for each treatment.

Half-Life and Elimination Rate Constant

To calculate the elimination rate constant (K_{el}), linear regression analyses were performed on the natural log (Ln) of plasma concentration values (y) versus time (x). Calculations were made between a time point where log-linear elimination phase begins (LQCT) occurred. The K_{el} was taken as the slope multiplied by (−1) and the apparent half-life ($T_{1/2\ el}$) as $0.693/K_{el}$.

TLIN and LQCT

TLIN, the time point where log-linear elimination begins, and LQCT, the last quantifiable concentration time were determined for each subject and for each treatment.

Percent Drug Absorbed

Percent drug absorbed was calculated at each sampling time (t) by Modified Wagner-Nelson's method, as implemented in Kinetica software, version 2.0.1 according to the following formula:

$$\frac{C_t + (K_{el} \times AUC_{0-t})}{(K_{el} \times AUC_{0-inf})} \times 100$$

All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.050. Based on the pairwise comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} data, the relative ratios of the geometric means, calculated according to the formulation "$e^{(X-Y)} \times 100$", as well as the 90% geometric confidence intervals were determined.

The plasma concentration of unchanged methylphenidate following administration of the controlled release formulation Formulation 1 reached the maximum concentration (C_{max}) at a mean of 3.27 hours under fasting conditions and 7.29 hours under fed conditions reflecting a biphasic absorption profile. The plasma concentration of unchanged methylphenidate following administration of two doses of the immediate release formulation (Ritalin® IR) reached the maximum concentration (C_{max}) at 5.96 hours under fasting conditions and 3.54 hours under fed conditions. When the determination of C_{max} was restricted to the first dose of immediate release methylphenidate, the T_{max} was 1.71 hours under fasting conditions and 1.63 hours under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg Formulation 1 and immediate release methylphenidate 10 mg (Ritalin® IR) under fed and fasted conditions are summarized in Tables 14 and 15 below.

TABLE 14

Pharmacokinetic Parameters for Formulation 1

Parameters	Formulation 1 (fasting) Mean ± SD	CV (%)	Formulation 1 (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	48493.80 ± 13430.27	27.69	54686.38 ± 15118.66	27.65
AUC_{0-inf} (pg · h/mL)	51213.86 ± 13260.14	26.59	57931.47 ± 16762.54	28.94
C_{max} (pg/mL)	4410.25 ± 1188.68	26.95	4879.37 ± 1027.85	21.07
T_{max} (h)	3.27 ± 2.54	77.64	7.29 ± 1.29	17.65

TABLE 14-continued

Pharmacokinetic Parameters for Formulation 1

Parameters	Formulation 1 (fasting) Mean ± SD	CV (%)	Formulation 1 (fed) Mean ± SD	CV (%)
K_{el} (h^{-1})	0.1672 ± 0.0339	20.25	0.1812 ± 0.0392	21.65
$T_{1/2\ el}$ (h)	4.32 ± 0.96	22.18	4.06 ± 1.25	30.91

TABLE 15

Pharmacokinetic Parameters for Ritalin ® IR

Parameters	RITALIN ® (fasting) Mean ± SD	CV (%)	RITALIN ® (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	44644.22 ± 13806.82	30.93	52781.49 ± 15194.94	28.79
AUC_{0-inf} (pg · h/mL)	46466.23 ± 14012.73	30.16	54783.17 ± 15311.08	27.95
C_{max} (pg/mL)	6536.04 ± 1669.29	25.54	7571.74 ± 1534.58	20.27
T_{max} (h)	5.96 ± 0.54	9.09	3.54 ± 2.42	68.43
K_{el} (h^{-1})	0.2481 ± 0.0550	22.17	0.2449 ± 0.0719	29.37
$T_{1/2\ el}$ (h)	2.93 ± 0.71	24.10	3.08 ± 0.96	31.26

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatment 1 was significantly different from the AUC_{0-t}, of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized in Table 16 below:

TABLE 16

AUC_{0-t} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	109.90%	104.08%	88.65%
90% Geometric C.I.	102.59% to 117.74%	97.15% to 111.50%	82.75% to 94.97%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatment 1 was significantly different from the AUC_{0-t} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized below in Table 17:

TABLE 17

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	111.65%	105.86%	88.85%
90% Geometric C.I.	104.09% to 119.95%	98.70% to 113.55%	82.84% to 95.30%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 1 was not significantly different from the C_{max} of treatment 3. However, Duncan's Multiple Range Test detected statistically significant differences for C_{max} when comparing treatments 1 and 2 and treatments 3 and 4. The statistical analyses performed on the data are summarized below in Table 18:

TABLE 18

C_{max} (pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	67.48%	64.38%	89.37%
90% Geometric C.I.	60.28% to 75.54%	57.51% to 72.07%	79.83% to 100.04%

The ANOVA and Duncan's Multiple Range Test performed on the T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 3 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 3 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 and treatments 3 and 4 for this parameter.

The results of the ANOVA and Duncan's Multiple Range Test performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were detected by Duncan's Multiple Range Test between treatments 1 and 2 and treatments 3 and 4, but not for treatments 1 and 3.

Summary and Analysis

The AUC and C_{max} ratios of controlled release methylphenidate 20 mg Formulation 1 under fed and fasted conditions are summarized in Table 19 below. A comparison of the AUC and C_{max} ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fasting conditions are summarized in Table 20 below. Table 21 shows the comparative ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fed conditions.

Treatment 1 (Formulation 1, Fasting) Versus Treatment 3 (Formulation 1, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 3 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed K_{el} and $T_{1/2\ el}$. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test product (Formulation 1, fasting) to reference product (Formulation 1, fed) were found to be within 80 to 125%. This is summarized in Table 19 below:

TABLE 19

Formulation 1 (Fed) vs. Formulation 1 (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.80%	112.54%	111.90%
90% Geometric C.I.[2]	105.29%-120.84%	104.93%-120.71%	99.96%-125.27%

[1]Calculated using geometric means according to the formula: $e^{[Formulation\ 1\ (fed) - Formulation\ 1\ (fasting)]} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 1, Fasting) Versus Treatment 2 (Ritalin®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for all parameters. With the exception of C_{max}, all formulation ratios as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80 to 125%. This is summarized in Table 20 below:

TABLE 20

Formulation 1 (Fast) vs Ritalin ® (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.90%	111.65%	67.48%
90% Geometric C.I.[2]	102.59%-117.74%	104.09%-119.75%	60.28%-75.54%

[1]Calculated using geometric means according to the formula: $e^{[Formulation\ 1\ (fast) - Ritalin\ IR\ (fast)]} \times 100$
[2]90% Geometric Confidence Interval using log-transformed data

Treatment 3 (Formulation 1, Fed) Versus Treatment 4 (Ritalin®, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for all parameters with the exception of ln-transformed AUC_{0-t} and AUC_{0-inf}. With the exception of C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80% to 125%. This is summarized in Table 21 below:

TABLE 21

Formulation 1 (Fed) vs. Ritalin ® IR (Fed)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.08%	105.86%	64.38%
90% Geometric C.I.[2]	97.15%-111.50%	98.70%-113.55%	57.51%-72.07%

[1]Calculated using geometric means according to the formula: $e^{[Formulation\ 1\ (fed) - Ritalin\ IR\ (fed)]} \times 100$
[2]90% Geometric Confidence Interval using log-transformed data

Conclusions

Review of individual plasma MPH time curves indicates the following:

Plasma MPH concentrations at 12 hours were higher on Formulation 1 than on Ritalin IR in all subjects, under both fed and fasted conditions.

A biphasic profile was apparent under fasted conditions in 7-10/12 subjects and in 8-10/12 under fed conditions. The mean curve showing a stable plateau under fasted conditions is therefore not fully representative of the individual profiles. The enteric coat therefore gave rise to a biphasic profile in some subjects even under fasted conditions.

Under fasted conditions the apparent rate of rise of plasma MPH was equivalent to, or faster than, that of Ritalin IR in 8/12 subjects under fasted conditions and 4-5/12 subjects under fed conditions. The mean curves which demonstrate an equivalent rate of rise under fasted conditions and a slower rise under fed conditions were therefore largely reflective of the individual profiles.

The bioavailability of Formulation 1 relative to Ritalin IR was acceptable under both fed and fasted conditions (Relative AUC_{inf} 106% and 112%). There was an increase in AUC of both Formulation 1 and Ritalin when given with food (13.1% and 17.9% respectively).

Formulation 1 had a more prolonged mean plasma MPH concentration time profile than two doses of Ritalin IR. An across study comparison indicates that Formulation 1 also has a more prolonged profile than Ritalin SR.

Under fasted conditions Formulation 1 had a mean initial rate of rise of plasma MPH that is similar to Ritalin IR and a relatively flat plateau until 8 hours post-dose.

Under fed conditions, the initial rise in plasma MPH from Formulation 1 was slower than under fasted conditions and the plateau showed a biphasic profile. This was consistent with predictions that the enteric coat would delay release of the controlled release component and that this delay would be longer under fed conditions (allowing the initial plasma concentration peak, due to the IR component, to fall prior to the start of release from the controlled release component).

Formulation 1 results in both a fast initial rate of rise of plasma methylphenidate concentration, and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Formulation 1 therefore has the potential to meet the dual objectives of rapid onset and prolonged duration that are considered desirable characteristics of a controlled release methylphenidate formulation for the treatment of ADD/ADHD.

An initial pilot bioavailability study completed in adult healthy volunteers has confirmed that a single 20 mg dose of this formulation has an equivalent extent of absorption to two doses of immediate release methylphenidate (10 mg) given 4 hours apart. Maximal plasma concentrations with the controlled release formulation are similar to those attained with the first dose of immediate release methylphenidate and from

approximately 10 hours post-dose, are higher than those following the second dose of immediate release methylphenidate.

The results indicate the potential for a single morning dose of this formulation to produce clinical effects that are at least equivalent to those of two doses of immediate-release methylphenidate given at breakfast and lunchtime, with a duration of action that may reduce the need for a third dose of immediate release methylphenidate later in the day.

Example 8

Five-Way Comparison of Single Dose Formulation 2 (Fed and Fasted), Single Dose Formulation 3 (Fed and Fasted) and Single Dose Ritulin SR (Fasted)

A five-way blind study was conducted which compared a single dose of Formulation 2, 20 mg, both fed and fasted, a single dose of Formulation 3, 20 mg, both fed and fasted, and Ritalin SR 20 mg single dose fasted. According to the published literature and anecdotal comments from physicians, Ritalin SR is used in less than 20% of methylphenidate treated patients.

Twelve healthy male volunteers were given a single dose of either 20 mg Formulation 2 or Formulation 3 administered four hours apart under both fed and fasting conditions (n=12), or slow-release 20 mg methylphenidate (Ritalin SR) under fasting conditions. "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 5 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning, under fed conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fasting conditions.

Treatment 4: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fed conditions.

Treatment 5: Reference Product: methylphenidate slow-release 20 mg tablet Ritalin SR (Novartis) under fasting conditions.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose. Plasma was harvested from each blood sample and stored in a −20 C freezer until assayed for plasma methylphenidate concentration.

The data is presented graphically in FIGS. **5-8**. FIG. **5** presents the mean plasma concentration versus time for Formulation 2 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **6** presents the mean plasma concentration versus time for Formulation 3 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **7** presents the mean plasma concentration versus time for Formulations 2 and 3 under fasting conditions. FIG. **8** presents the mean plasma concentration versus time for Formulations 2 and 3 under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg (Formulation 2 and 3) under fed and fasting conditions, and for slow release methylphenidate 20 mg (Ritalin® SR) under fasting conditions are summarized in Tables 22-24 below.

TABLE 22

Pharmacokinetic Parameters for Formulation 2

Parameters		Treatment 1, Fasting Means ± SD	CV(%)	Treatment 2, Fed Mean ± SD	CV(%)
AUC_{0-t}	(pg · h/mL)	48190.73 ± 11668.71	24.21	53452.63 ± 12820.39	23.98
AUC_{0-inf}	(pg · h/mL)	49787.07 ± 12053.23	24.21	55690.49 ± 12691.52	22.79
C_{max}	(pg · h/mL)	7498.57 ± 1968.38	26.25	6879.09 ± 1486.53	21.61
T_{max}	(h)	3.63 ± 0.57	15.70	6.42 ± 1.08	16.89
K_{el}	(h^{-1})	0.2391 ± 0.0428	17.91	0.2321 ± 0.0342	14.75
$T_{1/2}$	(h)	3.00 ± 0.64	21.32	3.05 ± 0.48	15.74

TABLE 23

Pharmacokinetic Parameters for Formulation 3

Parameters		Treatment 3, Fasting Means ± SD	CV(%)	Treatment 4, Fed Mean ± SD	CV(%)
AUC_{0-t}	(pg · h/mL)	48057.06 ± 14743.87	30.68	54128.75 ± 14787.94	27.32
AUC_{0-inf}	(pg · h/mL)	49984.68 ± 14873.03	29.76	56315.66 ± 14779.59	26.24
C_{max}	(pg · h/mL)	6080.97 ± 2048.60	33.69	6959.07 ± 1559.34	22.41
T_{max}	(h)	3.46 ± 0.89	25.76	4.42 ± 0.56	12.62
K_{el}	(h^{-1})	0.2009 ± 0.0468	23.32	0.2057 ± 0.0390	18.97
$T_{1/2}$	(h)	3.65 ± 0.97	26.52	3.49 ± 0.70	20.01

TABLE 24

Pharmacokinetic Parameters for Ritalin SR ®

Parameters	Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	47404.51 ± 12754.66	26.91
AUC_{0-inf} (pg · h/mL)	49252.17 ± 12841.52	26.07
C_{max} (pg/mL)	6783.09 ± 1496.65	22.06
T_{max} (h)	3.50 ± 0.43	12.18
K_{el} (h^{-1})	0.2282 ± 0.0320	14.01
$T_{1/2\ el}$ (h)	3.10 ± 0.47	15.14

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 3 was significantly different from the C_{max} of treatments 4 and 5. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for C_{max} when comparing treatment 1 vs. treatment 2 or treatment 1 vs treatment 5. The statistical analyses performed on the data are summarized in Table 25 below:

TABLE 25

C_{max} (pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	103.73%	84.78%	109.25%	87.40%
90% Geometric C.I.	98.94% to 115.14%	78.59% to 91.45%	101.28% to 117.85%	81.05% to 94.26%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, and treatments 3 and 4 for this parameter. Duncan's Multiple Range Test did not detect statistically significant differences between treatments for T_{max} when comparing treatments 1 vs. 3 or treatments 3 vs. 5.

The ANOVA performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 5 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were not detected by Duncan's Multiple Range Test, between treatments for K_{el} when comparing treatments 1 and 2, treatments 3 and 4, or treatments 1 and 5. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatments 1 and 3 was significantly different from the AUC_{0-t} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-t} when comparing treatment 1 vs treatment 5, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 26:

TABLE 26

AUC_{0-t} (pg · h/mL)	Treatment 1 vs. Treatment 2	Treatment 3 vs. Treatment 4	Treatment 1 vs. Treatment 5	Treatment 3 vs. Treatment 5
Ratio	89.21%	88.23%	101.82%	100.63%
90% Geometric C.I.	84.03% to 94.71%	83.10% to 93.67%	95.91% to 108.10%	94.81% to 106.81%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatments 1 and 3 was significantly different from the AUC_{0-inf} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-inf} when comparing treatment 1 vs treatment 3, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 27:

TABLE 27

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	88.33%	88.14%	101.14%	100.82%
90% Geometric C.I.	83.50% to 93.44%	83.32% to 93.24%	95.61% to 106.99%	95.33% to 106.63%

Treatment 1 (Formulation 2, Fasting) vs. Treatment 2 (Formulation 2, Fed)

The ANOVAs detected statistically significant differences between fed and fasting conditions, treatments 1 and 2, for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed $T_{1/2el}$ and K_{el}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 28 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 2. However, this food effect was less than 20% on average.

TABLE 28

Formulation 2, Fed versus Fasting

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.09%	113.21%	93.69%
90% Geometric C.I.[2]	105.58% to 119.00%	107.03% to 119.76%	86.85% to 101.07%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ 2(Fed) - Formulation\ 2\ (Fasting))} \times 100$

[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 4 (Formulation 3, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}. However, Dun-

can's Multiple Range Test detected no statistically significant differences between treatments for untransformed $T_{1/2el}$ and K_{el}. With the exception of lower 90% geometric confidence interval for C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 29 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 3. However, this food effect was less than 20% on average.

TABLE 29

Formulation 3, Fed versus Fasting

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	113.35%	113.45%	117.96%
90% Geometric C.I.[2]	106.76% to 120.33%	107.25% to 120.01%	109.35% to 127.25%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ 3\ (fed) - Formulation\ 3\ (Fasting))} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 2, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2\ el}$ and K_{el}. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 5 for all parameters. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 30 below. Thus, Formulation 2 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 30

Formulation 2 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.82%	101.14%	106.99%
90% Geometric C.I.[2]	95.91% to 108.10%	95.61% to 106.99%	101.28 to 117.85%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ 2\ (fast) - Ritalin\ SR\ (Fast))} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for ln-transformed C_{max} and untransformed $T_{1/2el}$ and K_{el}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 31 below. Thus, Formulation 3 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 31

Formulation 3 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.63%	100.82%	87.40%
90% Geometric C.I.[2]	94.81% to 106.81%	95.33% to 106.63%	81.05 to 94.26%

[1]Calculated using geometric means according to the formula: $e^{(Formulation(fast) - Ritalin\ SR\ (Fast))} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Conclusions

The bioavailability of Formulation 2 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 101%—Fed conditions not tested)

The bioavailability of Ritalin SR® under fasted conditions is similar to that of Ritalin® IR, as discussed in Example 7 (AUC_{inf} 29.2 vs. 46.5 ng·h/mL, respectively). Literature data which indicates that Ritalin® IR and SR are absorbed at equivalent rates suggests that comparisons between the studies presented in Examples 7 and 8 are reasonable.

Bioavailability of Formulations 1 and 2 are similar under fasted and fed conditions (fasted: 49.8 vs. 51.2 ng·h/mL; fed: 55.7 vs. 57.9 ng·h/mL).

From the mean curves of Formulation 2 and Ritalin SR®, the initial rate of rise of plasma MPH concentration is slightly faster for Formulation 2 compared to Ritalin SR®. Under fed conditions, the rate of rise of plasma MPH with Formulation 2 decreased and T_{max} was delayed in comparison to both Formulation 2 fasted and Ritalin SR® fasted.

Bioavailability of Formulation 3 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 100.8%—fed conditions not tested).

Bioavailability of Formulations 1 and 3 are similar under fasted and fed conditions (fasted: 50.0 versus 51.2 ng/hmL; fed: 56.3 versus 57.9 ng·h/mL). Note also that Formulations 2 and 3 have almost identical AUC values.

From the mean curves for Formulation 3 and Ritalin SR®, the initial rate of rise of plasma MPH concentrations is slightly faster for Formulation 3 compared to Ritalin SR®.

In contrast to Formulation 2, the effect of food on the initial rate of concentration rise is minimal. Since Formulation 3 does not contain an enteric coat, this suggests that food slows the initial release from the IR component of formulations that contain an enteric coat, both when the enteric coat is part of the same bead (underneath the IR coat in the case of Formulation 1) and when it is in a separate bead (as for Formulation 2).

Also in contrast to Formulation 2, the T_{max} of the mean curve of Formulation 3 occurs at a similar time to that of Ritalin SR® under fed and fasted conditions. For Formulation 2 (and Formulation 1) the T_{max} of the second absorption phase under fed conditions is substantially delayed relative to Ritalin SR®.

Conclusions—Examples 7 and 8

1. Formulation 1 has both a fast initial rate of rise, at least under fasted conditions and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Since these conditions represent the extremes of "food stress", one might predict that administration in association with normal meals and times would provide an intermediate profile. It is also possible that gastric emptying in children on a normal meal schedule will be faster than in adults fed a high fat meal—this will tend to make the second absorption phase occur earlier and produce lower concentrations from 12 hours

onwards. Formulation 1 therefore meets the dual objectives of rapid onset and prolonged duration.

2. Formulation 2 is also very similar to Ritalin SR® under fasted conditions but shows a delayed peak under fed conditions such that plasma MPH concentrations are higher than Ritalin SR® (fasted) from 6 hours post dose onwards. The controlled release component in Formulation 2 is faster releasing than the one in Formulation 1 and plasma MPH concentrations are lower for Formulation 2 from about 10 hours post dose.

3. Overall, Formulation 3 (non-enteric coated) has a profile very similar to Ritalin SR® under both fed and fasted conditions. The IR component of Formulation 3 provides some increase in initial absorption rate relative to Ritalin SR® under fasted conditions. Since concentrations later in the day are similar for the two formulations, this confirms the concept that a fast initial rise and higher concentrations later in the day are not possible at the same dose, unless a delay is introduced into the release of a component of the total dose.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. An oral controlled release formulation comprising a plurality of multi-layer release beads, each bead comprising:

(i) an immediate release core comprising a first portion of an effective dose of methylphenidate or a pharmaceutically acceptable salt thereof coated over an inert pharmaceutically acceptable bead;

(ii) a controlled release layer coated over the core, the controlled release layer comprising a hydrophobic material in an amount sufficient to provide a controlled release of the first portion of the methylphenidate over a predetermined period of time, the hydrophobic material selected from the group consisting of an alkylcellulose, an acrylic polymer and mixtures thereof;

(iii) a release delaying layer coated over the controlled release layer, the release delaying layer comprising a pH-dependent polymer in an amount sufficient to delay release of the first portion of the effective dose of methylphenidate or the pharmaceutically acceptable salt thereof until after the formulation passes through the stomach; and

(iv) an outer layer coated over the release delaying layer, the outer layer comprising a second portion of the effective dose of methylphenidate or the pharmaceutically acceptable salt thereof; wherein the formulation provides:

(a) a maximum plasma concentration of methylphenidate at about 0.5 to about 4 hours after an oral administration to a human patient,

(b) a plasma concentration of methylphenidate which does not differ by more than 20% during a measuring interval, wherein the measuring interval is from about 2 hours to about 6 hours,

(c) the plasma concentration of methylphenidate which is below effective plasma concentrations in said human patient at about 8 to 12 hours after the oral administration, and

(d) an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate Dissolved
0.25	0-45%
1	5-50%
4	40-90%
8	NLT 60%
12	NLT 80%.

2. The formulation of claim **1**, wherein the formulation exhibits biphasic absorption through a mucosal lining of the gastrointestinal tract of said human patient.

3. The formulation of claim **1**, which provides the maximum plasma concentration of methylphenidate which is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after the oral administration.

4. The formulation of claim **3**, wherein the formulation provides the maximum plasma concentration at about 0.5 to about 2 hours after the oral administration.

5. The formulation of claim **4**, wherein the maximum plasma concentration is from about 1.0 to about 1.7 times the plasma concentration of the methylphenidate provided by the formulation at about 9 hours after the oral administration.

6. The formulation of claim **1**, wherein the plasma concentration the methylphenidate falls below effective plasma concentrations at about 8 to about 10 hours after the oral administration.

7. The formulation of claim **1**, comprising a gelatin capsule containing a unit dose of said multi-layer release beads.

* * * * *

EXHIBIT E

US009066869B2

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

(10) **Patent No.: US 9,066,869 B2**
(45) **Date of Patent: *Jun. 30, 2015**

(54) **CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS**

(71) Applicant: **PURDUE PHARMA**, Pickering Ontario (CA)

(72) Inventors: **Thinnayam N. Krishnamurthy**, Scarborough (CA); **Andrew Darke**, Newmarket (CA)

(73) Assignee: **Purdue Pharma**, Pickering, Ontario (CA)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/049,677**

(22) Filed: **Oct. 9, 2013**

(65) **Prior Publication Data**

US 2014/0099361 A1 Apr. 10, 2014

Related U.S. Application Data

(63) Continuation of application No. 12/283,431, filed on Sep. 11, 2008, now Pat. No. 8,580,310, which is a continuation of application No. 11/879,646, filed on Jul. 17, 2007, now Pat. No. 7,438,930, which is a continuation of application No. 10/156,622, filed on May 28, 2002, now Pat. No. 7,247,318, which is a continuation of application No. 09/465,159, filed on Dec. 16, 1999, now Pat. No. 6,419,960.

(60) Provisional application No. 60/112,617, filed on Dec. 17, 1998.

(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61K 9/20	(2006.01)
A61K 9/26	(2006.01)
A61K 9/48	(2006.01)
A61K 9/50	(2006.01)
A61K 9/16	(2006.01)
A61K 31/4458	(2006.01)

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

CPC ***A61K 9/167*** (2013.01); ***A61K 9/2081*** (2013.01); ***A61K 9/5078*** (2013.01); ***A61K 9/5084*** (2013.01); ***A61K 31/4458*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Susan Tran

(74) *Attorney, Agent, or Firm* — Davidson, Davidson & Kappel, LLC

(57) **ABSTRACT**

The invention is directed to oral modified/controlled release drug formulations which provide a rapid initial onset of effect and a prolonged duration of effect. Preferably, the peak concentration is lower than that provided by the reference standard for immediate release formulations of the drug, and the duration of effect falls rapidly at the end of the dosing interval.

20 Claims, 8 Drawing Sheets

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FIG. 1

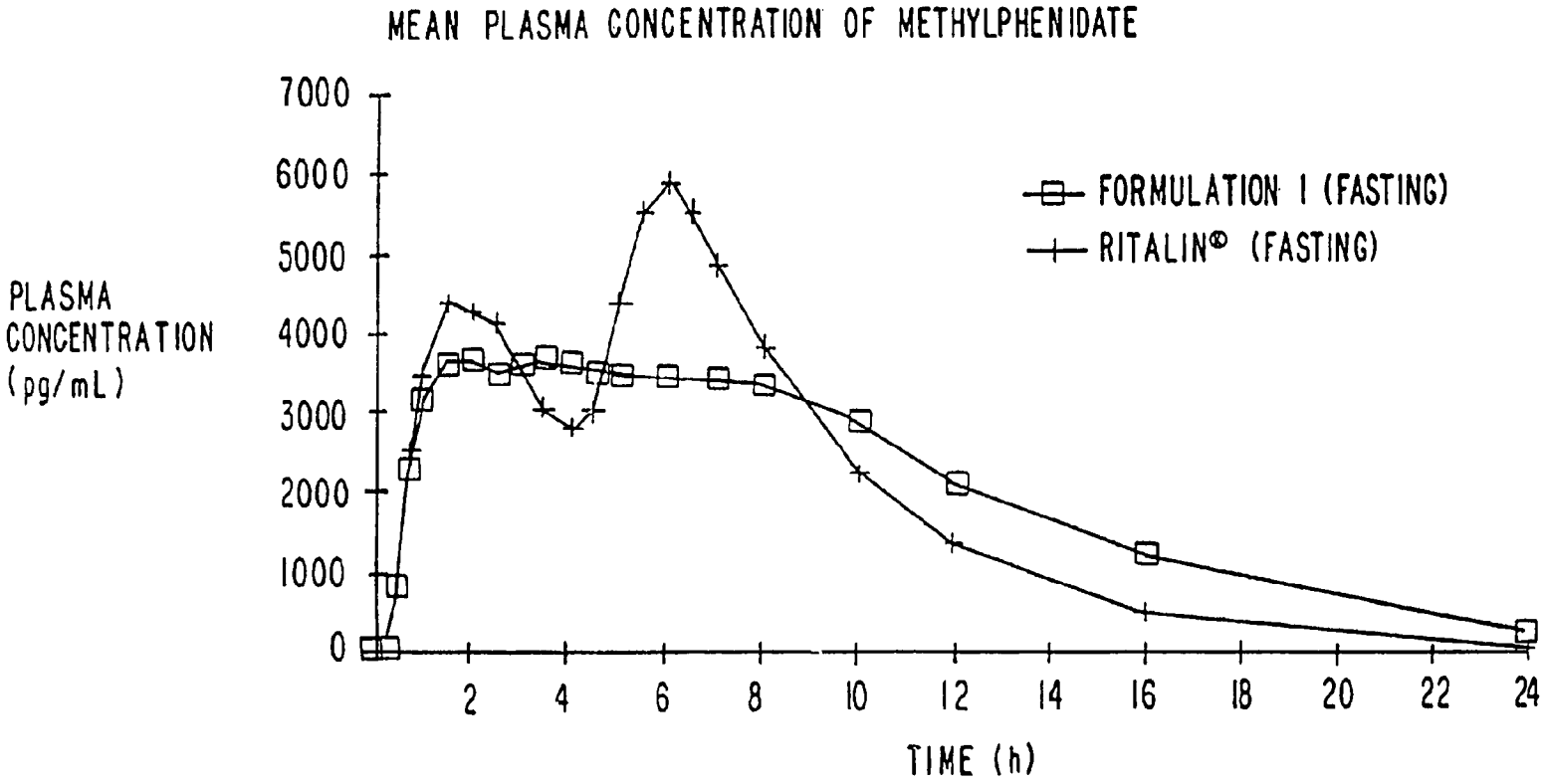

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (FASTING)
RITALIN® (FASTING)

FIG. 2

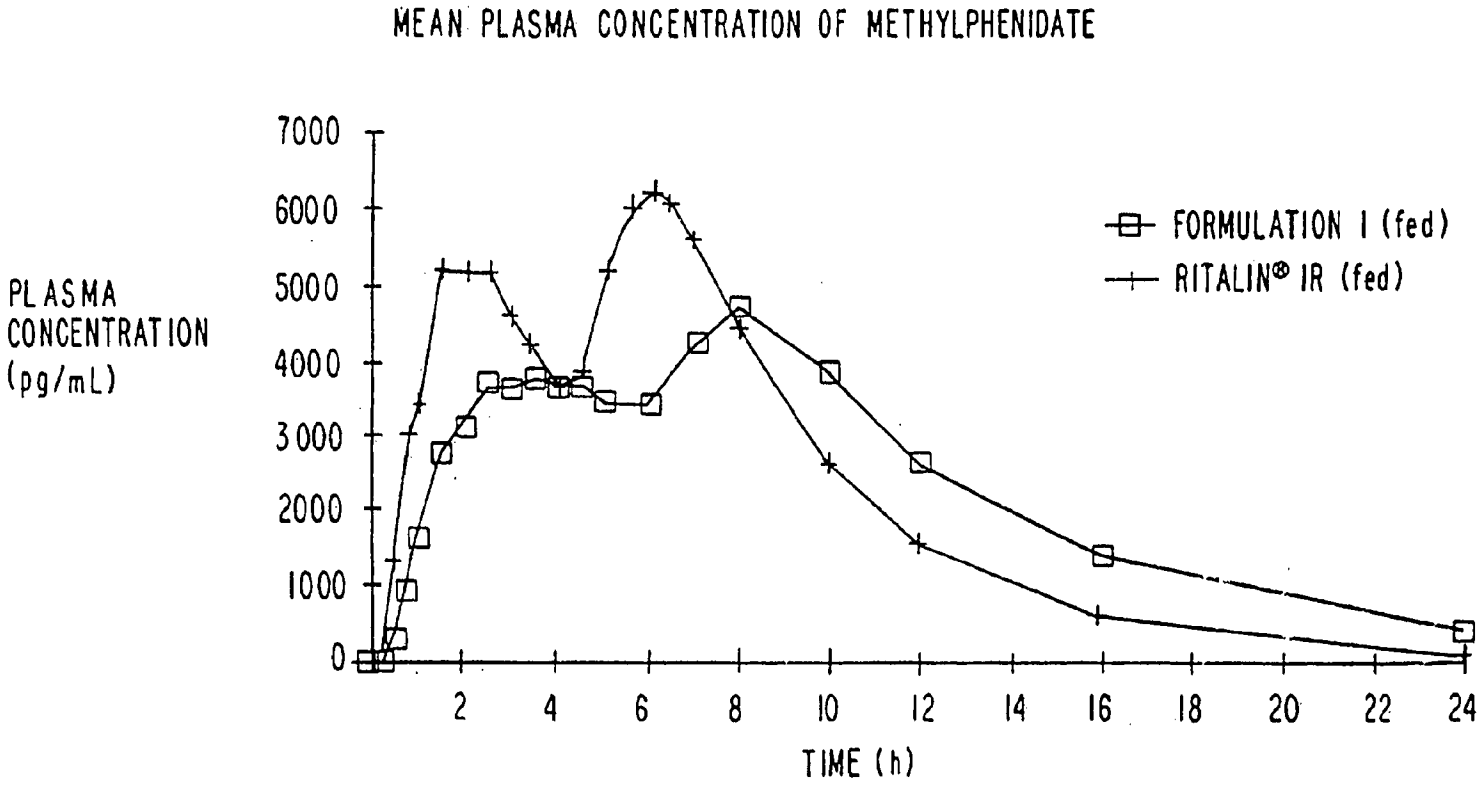

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (fed)
RITALIN® IR (fed)

FIG.3

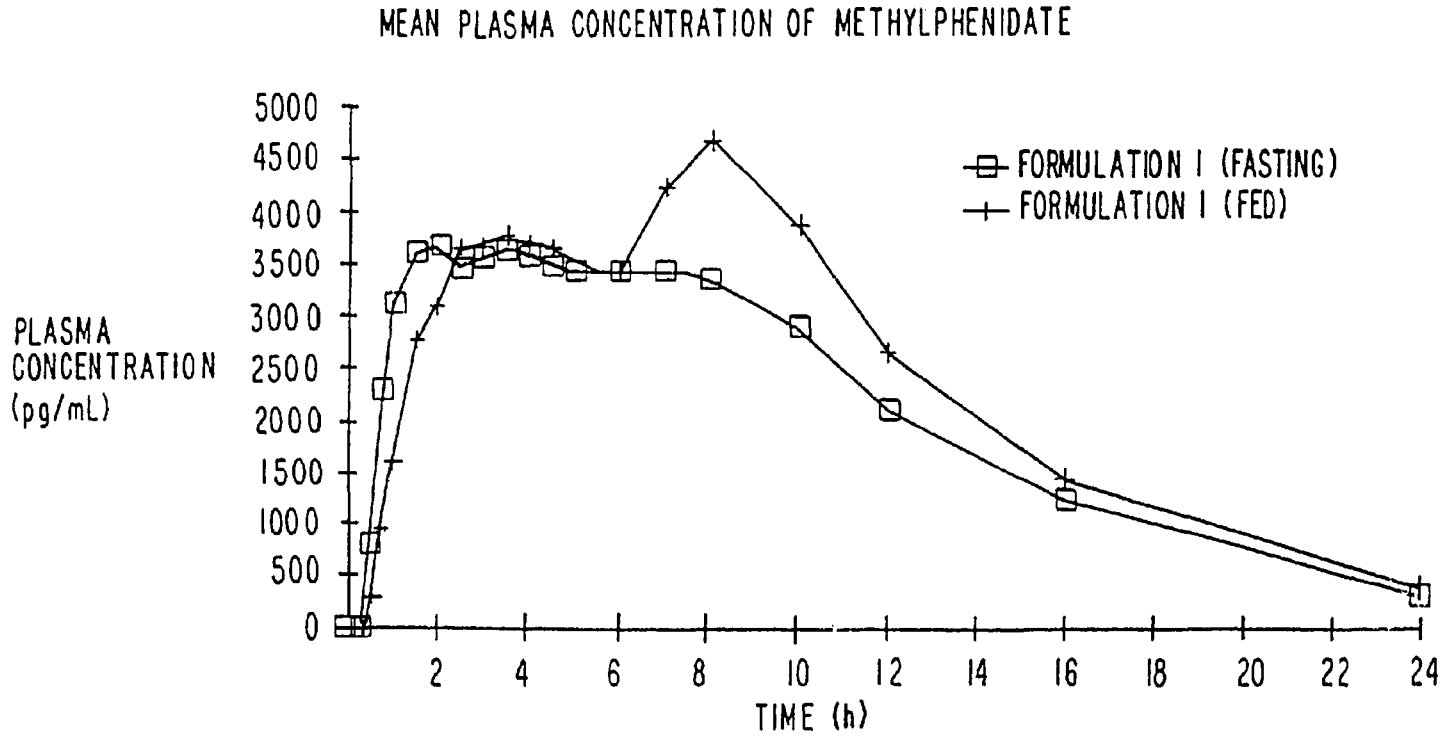

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION I (FASTING)
FORMULATION I (FED)

FIG. 4

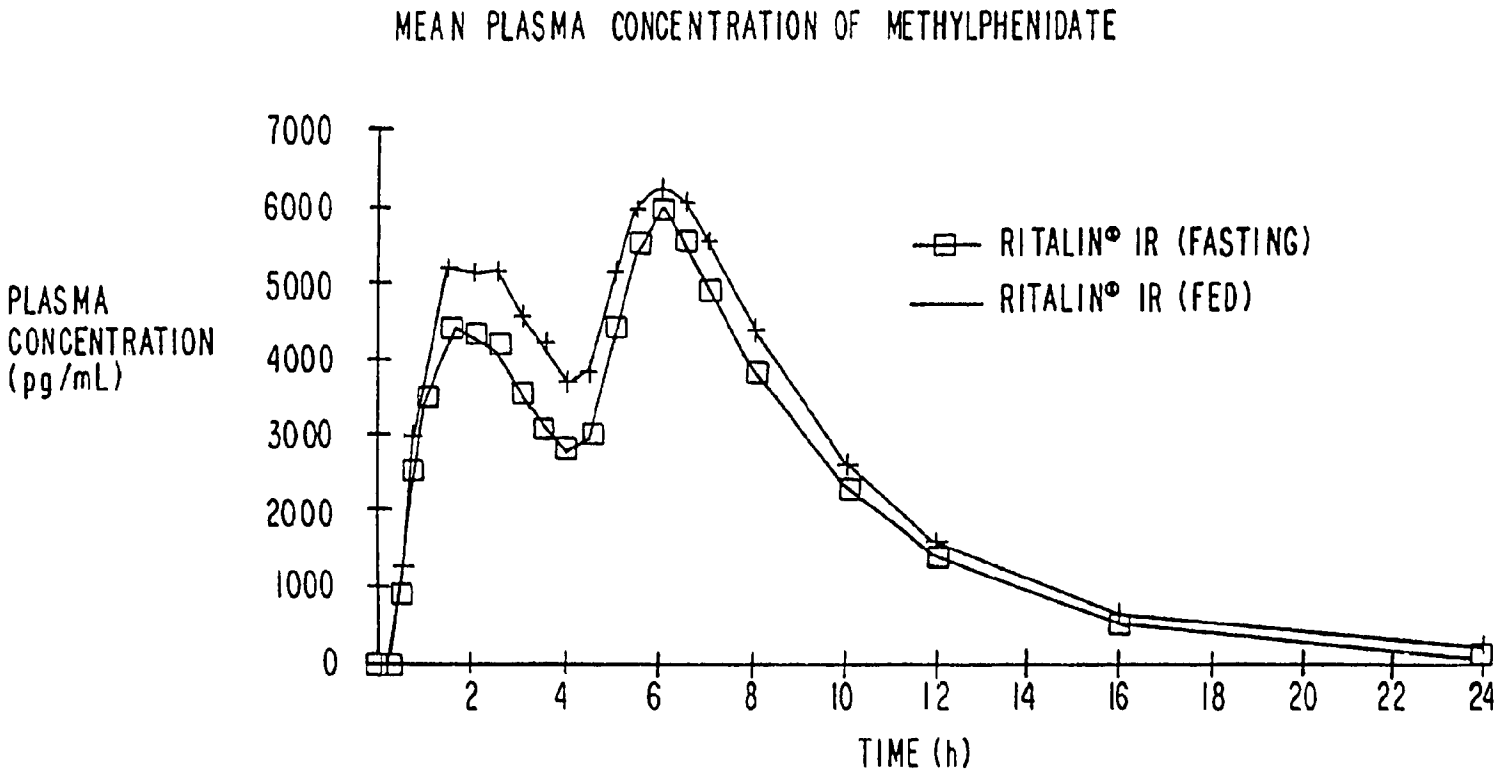

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
RITALIN® IR (FASTING)
RITALIN® IR (FED)

FIG.5

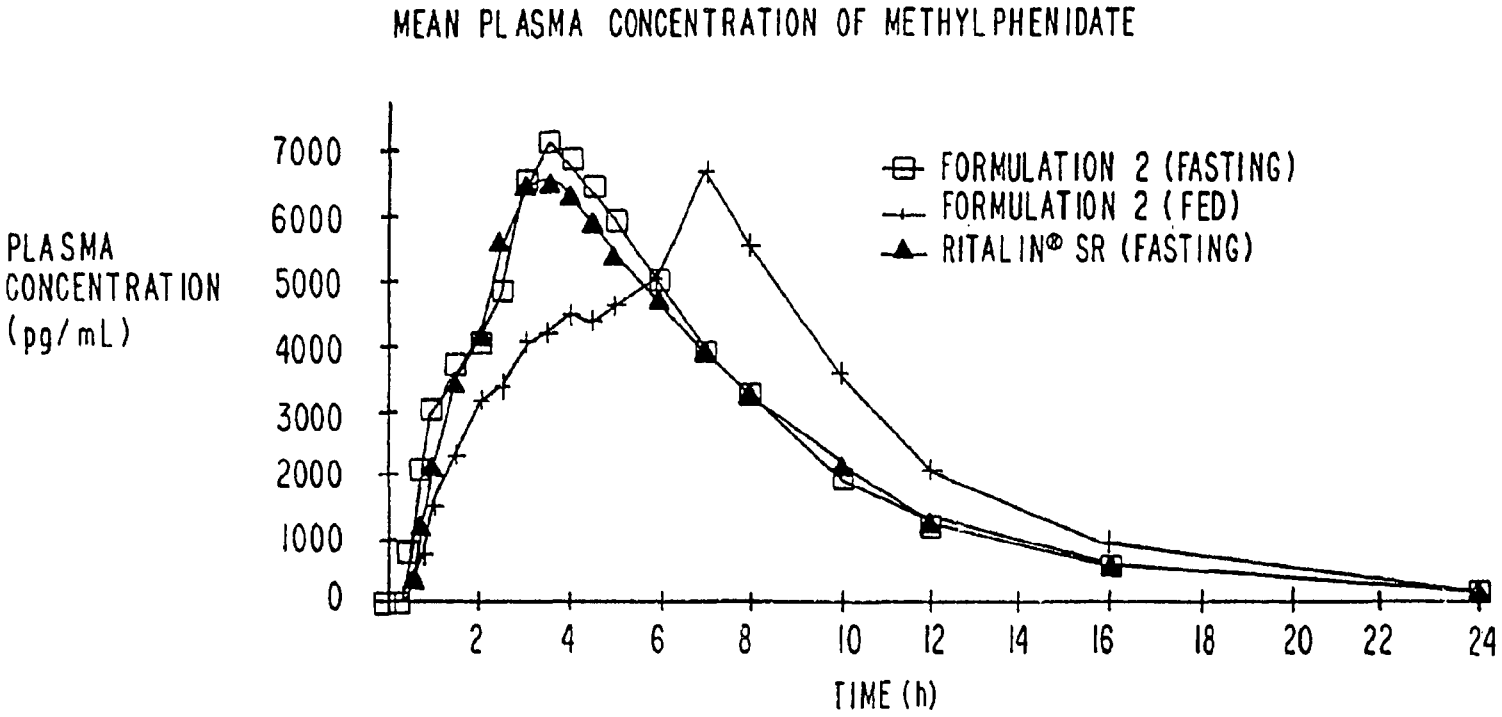

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FASTING)
FORMULATION 2 (FED)
RITALIN® SR (FASTING)

FIG.6

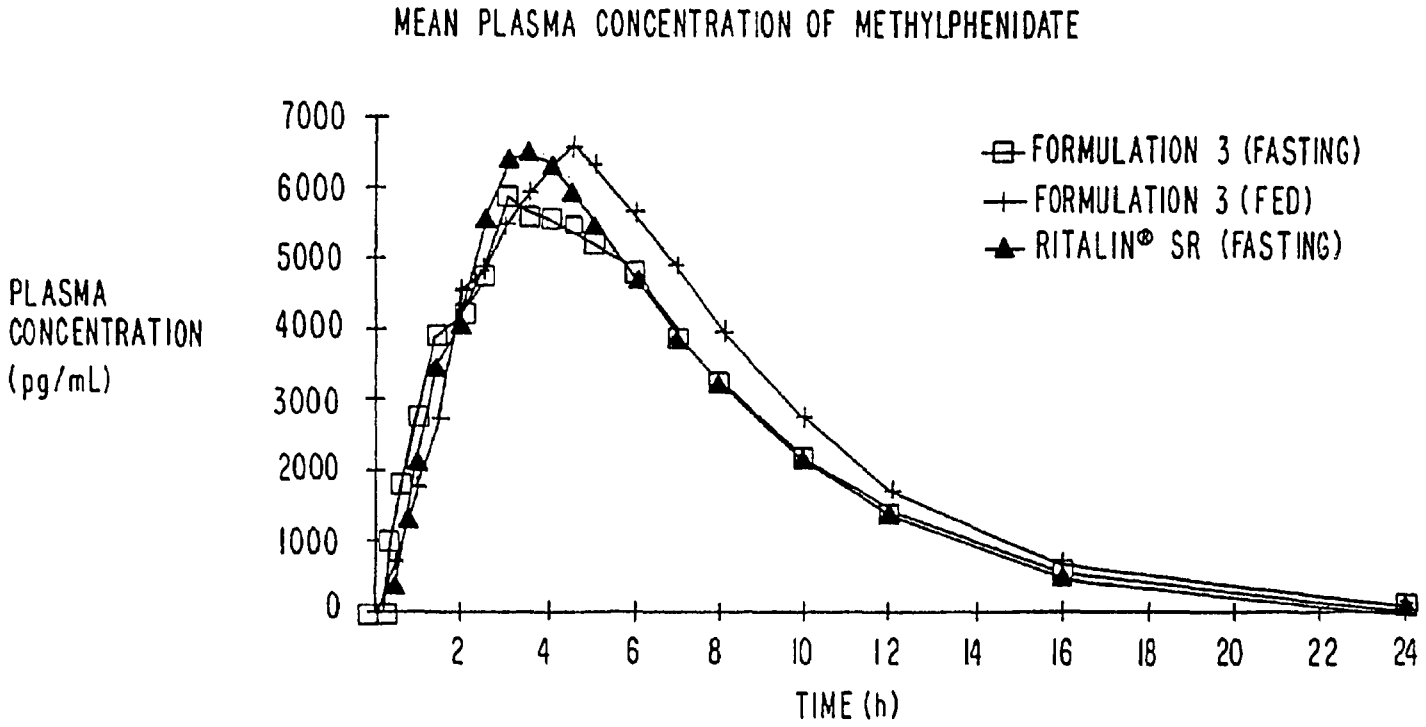

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 3 (FASTING)
FORMULATION 3 (FED)
RITALIN® SR (FASTING)

FIG. 7

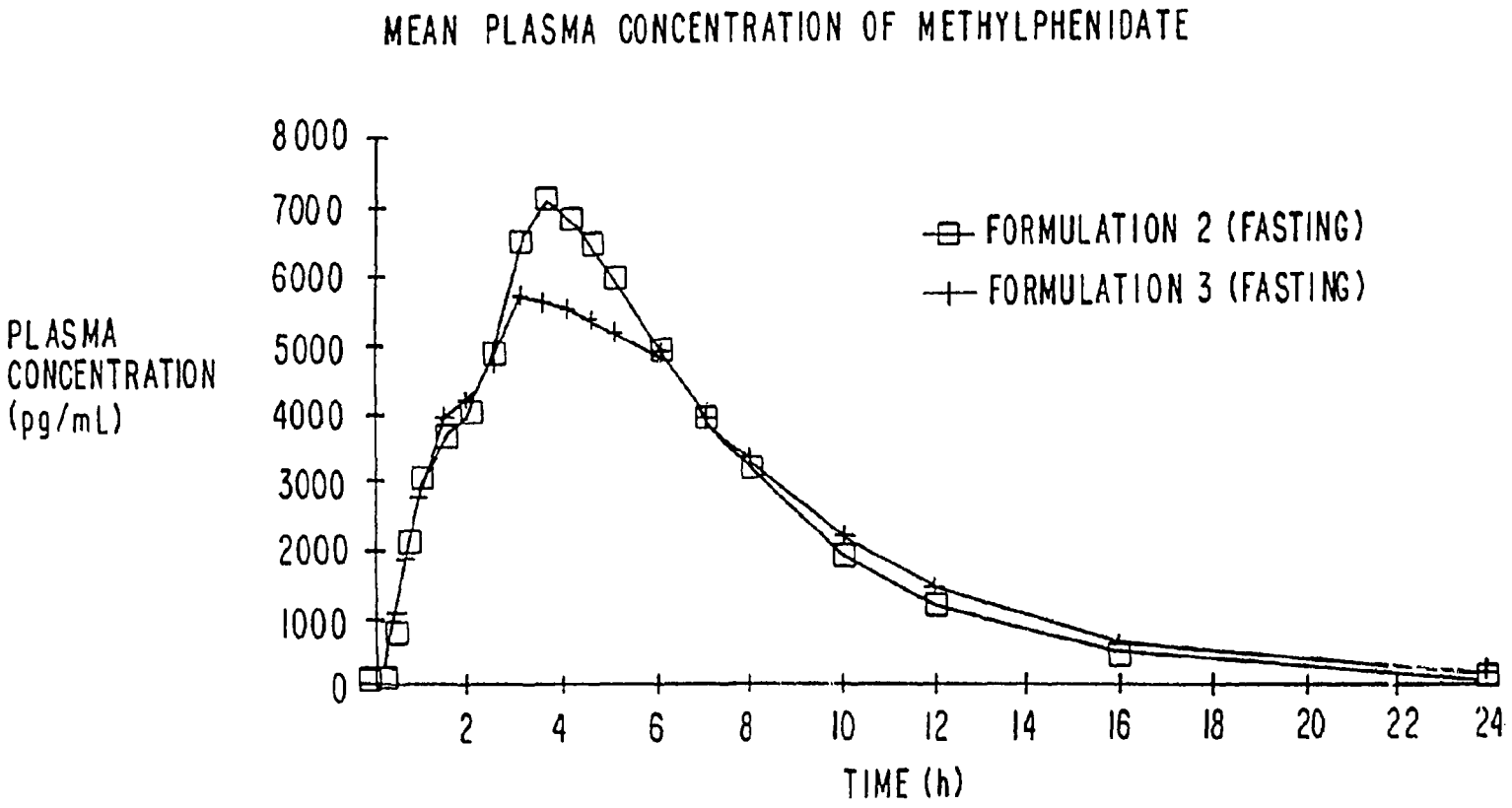
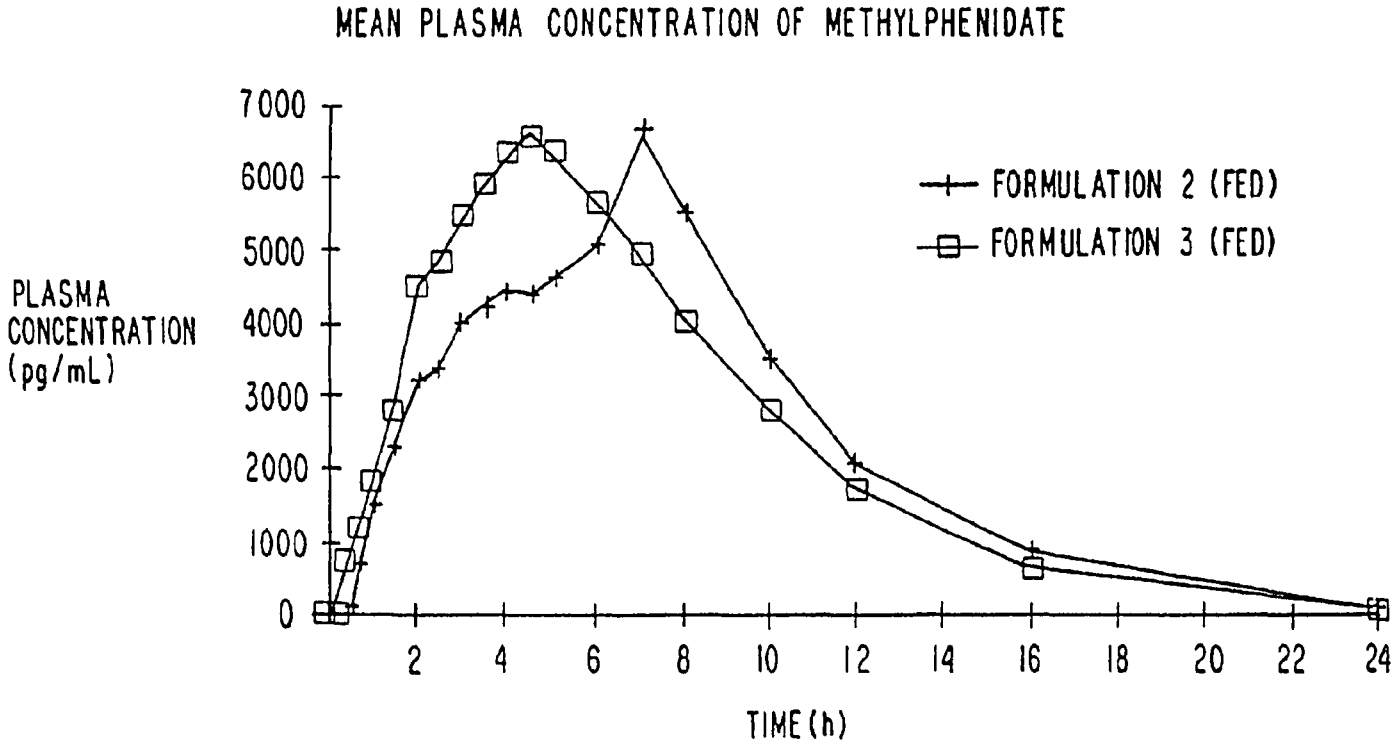

MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
8000
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FASTING)
FORMULATION 3 (FASTING)

FIG. 8


MEAN PLASMA CONCENTRATION OF METHYLPHENIDATE
PLASMA CONCENTRATION (pg/mL)
7000
6000
5000
4000
3000
2000
1000
0
2
4
6
8
10
12
14
16
18
20
22
24
TIME (h)
FORMULATION 2 (FED)
FORMULATION 3 (FED)

CONTROLLED RELEASE FORMULATIONS HAVING RAPID ONSET AND RAPID DECLINE OF EFFECTIVE PLASMA DRUG CONCENTRATIONS

This application is a continuation of U.S. application Ser. No. 12/283,431, filed Sep. 11, 2008, which is a continuation of U.S. application Ser. No. 11/879,646, filed on Jul. 18, 2007, now U.S. Pat. No. 7,438,930; which is a continuation of U.S. application Ser. No. 10/156,622, filed May 28, 2002, now U.S. Pat. No. 7,247,318; which is a continuation of U.S. application Ser. No. 09/465,159, filed Dec. 16, 1999, now U.S. Pat. No. 6,419,960, which claims priority to U.S. Provisional Application No. 60/112,617, filed Dec. 17, 1998, the disclosures of which are hereby incorporated by reference in their entireties.

BACKGROUND OF THE INVENTION

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. It is the intent of all sustained release formulations to provide a longer period of pharmacologic action after administration than is ordinarily obtained after administration of immediate-release dosage forms. Sustained release compositions may be used to delay absorption of a medicament until it has reached certain portions of the alimentary tract, and maintain a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered. Such longer periods of response provide for many therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. Thus, therapy may be continued without interrupting the sleep of the patient, which is of special importance, for example, when treating a patient for moderate to severe pain (e.g., a post-surgery patient, a cancer patient, etc.), or for those patients who experience migraine headaches on awakening, as well as for the debilitated patient for whom sleep is essential. A further general advantage of longer acting drug preparations is improved patient compliance resulting from the avoidance of missed doses through patient forgetfulness.

Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occurs because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance therapy of the patient. In view of this, it is considered a goal of many skilled in the art that a controlled release dosage form will ideally provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ratio. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

It is known in the pharmaceutical art to prepare compositions which provide for sustained release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Sustained release formulations known in the art include specially coated pellets, coated tablets and capsules, and ion exchange resins, wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

Sustained release dosage forms are central in the search for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a controlled release dosage form will provide therapeutic concentration of the drug in blood that is maintained throughout the dosing interval with a reduction in the peak/trough concentration ration. Central to the development process are the many variables that influence the in vivo release and subsequent absorption of the active ingredients from the gastrointestinal tract.

Controlled release formulations known in the art include specially coated beads or pellets, coated tablets and ion exchange resins, wherein the slow release of the active drug is brought about through selective breakdown of the coating of the preparation or through formulation with a special matrix to affect the release of the drug. Some controlled release formulations provide for sequential release of a single dosage of an active medicament at predetermined periods after administration.

While controlled and/or sustained release compositions have constituted a definite advance in the art, improvements in these compositions have been sought, particularly for preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD), diabetes etc.

Attention Deficit Disorders are the most common psychiatric disorders in children (Campbell et al. 1992) with reported rates ranging from 4% to 9% (Aman et al. 1983). Attention Deficit Disorder (ADD) is characterized by inattention and impulsivity and may be present with hyperactivity (ADHD) (Shaywitz et al. 1984). Other characteristics may include aggressiveness, stealing, lying, truancy, setting fires, running away, explosiveness, cognitive and learning problems as well as poor social skills (Campbell et al. 1992). It is four to five times more frequent in boys than girls (Campbell et al. 1992).

Stimulant medication, such as amphetamines, have been shown to be the most effective agents in the treatment of children with disorders of activity modulation and attention regulation and result in significant improvement in 70 to 80 percent of affected children (Shaywitz et al. 1984). Positive effects of stimulants have been documented in a variety of areas including behavioral, social, perceptual performance, motor activity, impulse control, attention regulation and cognitive performance (Barkley 1977, Kavale 1983, Offenbacher et al. 1983, Rosenthal et al 1978).

Methylphenidate {dl-threo-methyl-2-phenyl-2-(2-piperidyl)acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The efficacy of methylphenidate ("MPH") in improving attention and behavioral symptoms has been supported by many studies.

Immediate release methylphenidate preparations, because of their short half-life, require frequent administration at short intervals to ensure adequate treatment throughout a child's school day. The rapid onset and offset of immediate release methylphenidate preparations means that a medicated child with attention deficit disorder will be maximally affected only for relatively brief periods during the day. Due to its short half-life, MPH is usually given twice per day, usually once after breakfast and once during the school day, an event that some children and some school personnel apparently avoid, resulting in poor compliance with prescribed regimens

(Brown et al., 1985; Firestone 1982). Compliance is a major problem for children who require a midday or midafternoon dose as many schools prohibit children from taking medications during the school day and others often insist that all medications be given by a nurse. Poor compliance in taking medication may explain, in part, the variable and conflicting results reported in many studies of the effect of medication on improving the behavior of hyperactive children. These limitations of immediate release methylphenidate led to interest in products with longer effective periods of action. These limitations of immediate release methylphenidate preparations led to interest in products with longer effective periods of action.

A sustained release form of methylphenidate (Ritalin® SR) is commercially available. As a result of many clinical trials, various opinion leaders in treatment of attention deficit hyperactivity disorder have made the following comments regarding Ritalin® SR (sustained release methylphenidate) produced by Ciba-Geigy: (i) Ritalin® SR does not have a sufficiently early onset of effect to allow for behavioral management in the early morning; (ii) Ritalin® SR does not have the beneficial late effects that would be produced by a lunch time dose of immediate release methylphenidate, thus defeating the purpose of using an SR formulation; (iii) The effects of Ritalin® SR are inconsistent or erratic over the course of the day.

There is a need in the art to develop drug formulations which provide a rapid onset, a prolonged action, followed by rapid offset of effect in order to overcome the deficiencies of the current state of the art.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which results in improved patient compliance.

It is an object of the present invention to provide new oral dosage formulations which represent improvements over currently available preparations available for conditions such as Attention Deficit Hyperactivity Disorder (ADHD).

It is an object of the present invention to provide new oral dosage formulations of methylphenidate or similarly acting drugs which ensure adequate treatment throughout a child's school day.

It is an object of the present invention to provide new oral dosage formulations which allow a child with attention deficit disorder to be maximally treated throughout the daytime, while being administered only once, i.e., in the morning.

It is a further object of the present invention to provide new controlled/modified release oral dosage formulations which provide a rapid onset and rapid offset with an extended release of active medicaments incorporated therein.

It is yet another object of the present invention to provide new controlled/modified release oral dosage formulations which are useful in all types of pharmaceutically active ingredients and which can extend the time of release of all such ingredients.

It is yet another object of the present invention to provide an oral controlled release formulation which combines both a rapid onset and sustained plasma concentrations throughout the day, followed by a rapid drop-off of plasma concentrations of drug to below minimum effective concentrations.

It is yet another object of the present invention to provide a "multi-layer release" (MLR) technology which is useful for all types of pharmaceutically active ingredients and which can extend the duration of action for a desired length of time.

To address the above-mentioned deficiencies as well as other goals, the present invention is directed in part to a controlled release product which is intended to combined both a rapid onset and sustained plasma concentrations throughout the day. Significantly, the formulations of the present invention provide a rapid onset, a prolonged action, followed by rapid offset of effect, i.e., a "square wave" profile.

The invention is directed in part to controlled/modified release formulations based on a multi-layered release ("MLR") technology. The drug product can be in a tablet or a multiparticulate formulation contained within an oral gelatin capsule.

In the case of beads, encapsulated in a capsule, each bead contains a series of layers with different characteristics—an outer immediate release layer, a release delaying layer (enteric coat), a controlled release layer over an immediate release layer. The MLR formulation is designed such that upon oral administration, the formulation provides a rapid dissolution and absorption of the outer layer of the formulation which contains a portion of the drug in immediate release form, thereby resulting in a rapid rise of the drug to therapeutic plasma levels. This is followed by a period of no absorption (due to an enteric coating), followed thereafter by a controlled release of the drug from the formulation to maintain plasma levels. After absorption of the drug from an immediate release core, plasma levels then rapidly decrease. By virtue of the release of the drug from the MLR formulation, the plasma level of the drug, when plotted on a time/concentration curve, takes the appearance of a "square wave".

In certain further preferred embodiments, the formulation provides a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration and provides effective blood levels for at least about 6 hours after administration.

In certain further preferred embodiments, the formulation exhibits a "plateau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit a "plateau" which lasts from about 6 hours to about 12 hours. The "plateau" is characterized by a stabilized plasma concentration, wherein the plasma level at the end of the measured interval does not differ by more than 20%, preferably by no more than 10% of the plasma concentration at the beginning of the measured interval.

In certain further preferred embodiments, the formulation exhibits a bimodal release of active agent from the dosage form. Bimodal release of the active agent is characterized by the active agent being release from the dosage form by more than one distinct release rate. In some embodiments, the release rates can be separated by a no-release or a substantially no-release interval, although this is not always necessary.

In certain further preferred embodiments, the formulation exhibits a biphasic absorption of the active agent. Biphasic absorption of the active agent is characterized by the active agent being absorbed through a natural barrier (e.g. the mucosal lining of the gastro-intestinal tract) by more than one distinct absorption rate. In some embodiments, the absorption rates can be separated by a no-absorption or a substantially no-absorption interval, although this is not always necessary. A formulation can exhibit both biphasic absorption and bimodal release of the active agent, with the biphasic absorption being a function of the bimodal release rate. However, biphasic absorption is not always attributed to release rate and can occur in a formulation not exhibiting bimodal release.

In other preferred embodiments the formulation exhibits bimodal release and/or biphasic absorption to provide a "pla-

teau" in the blood plasma curve which lasts from about 2 hours to about 6 hours. Other embodiments exhibit bimodal release and/or biphasic absorption to provide a "plateau" which lasts from about 6 hours to about 12 hours. Other embodiments maintain effective plasma levels of the active agent for about 16 to about 18 hours after administration of the dosage form.

In certain preferred embodiments, an acrylic resin is utilized to provide the controlled slow release of therapeutically active ingredients over a predetermined or a specified period of time, the acrylic resin thereby comprising a significant part of the "base composition". Base compositions prepared from such acrylic resins provide sustained release of therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration, generally oral administration, in humans or animals.

In other embodiments of the invention, the formulations of the invention are composed of:

(i) a mixture of immediate release particles (e.g., beads) and enteric coated immediate release particles (e.g., beads); (ii) a mixture of immediate release particles (e.g., beads) and enteric coated controlled release particles (e.g., beads) or (iii) a mixture of immediate release particles (e.g., beads) and controlled release particles (e.g., beads). In each such instance, the mixture of particles possessing different release properties are blended together and filled into hard gelatin capsules.

In certain preferred embodiments, the controlled/modified release drug formulations of the invention consist of a plurality of beads, each containing an immediate-release component in combination with an enteric coated controlled-release component to produce a delay in the absorption process. The drug product is an oral capsule containing beads. Each bead contains a series of layers with different release characteristics—an outer immediate release layer; a release delaying layer; a controlled release layer; and an immediate release core. The final product is a capsule containing multi-layer release (MLR) beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption of the drug. In certain embodiments, the immediate release component represents 40% of the total dose per bead and the controlled release component represents 60%. This formulation is designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug. The results of a bioavailability study of this formulation indicate a biphasic release profile that is consistent with the pharmaceutical rationale discussed herein.

In other embodiments of the invention, the bead size of the formulations can be adjusted in order to obtain a desired pharmacokinetic profile based on the correlation between gastric emptying and bead size. A smaller bead size exhibits faster gastric emptying as compared to a larger bead size.

Other objects and advantages of the present invention will be apparent from the further reading of the specification and of the appended claims.

The term "pH-dependent" for purposes of the present invention is defined as having characteristics (e.g. dissolution) which vary according to environmental pH (e.g., due to changes in the in-vitro dissolution media, or due to passage of the dosage form through the gastrointestinal tract.

The term "pH-independent" for purposes of the present invention is defined as having characteristics (e.g., dissolution) which are substantially unaffected by pH, in that a difference, at any given time, between an amount of methylphenidate released at one pH and an amount released at any other pH, when measured in-vitro using the USP Paddle Method of U.S. Pharmacopeia XXII (1990) at 100 rpm in 900 ml aqueous buffer, is no greater than 10%.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. **1** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fasting conditions.

FIG. **2** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 and Ritalin® as a function of time when given under fed conditions.

FIG. **3** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 1 as a function of time when given under fasting and fed conditions.

FIG. **4** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Ritalin® as a function of time when given under fasting and fed conditions.

FIG. **5** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 2 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **6** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulation 3 under fasting and fed conditions, and Ritalin® SR under fasting conditions, as a function of time.

FIG. **7** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fasting conditions as a function of time.

FIG. **8** is a graphical comparison of the mean plasma concentration of methylphenidate when test subjects are treated with Formulations 2 and 3 under fed conditions as a function of time.

DETAILED DESCRIPTION

The drug used in the formulations of the invention may be selected from a wide variety of pharmaceutically active drugs such as diabetes drugs, attention deficit hyperactivity controlled drugs, analgesics, anti-obesity preparations, anti-inflammatories, antihistamines, antitussives, decongestants, antinausea agents, narcotics, bronchodilators, cardiovasculars, central nervous system (CNS) drugs, nicotine replacement therapy, nitrates, sleeping aids/sedatives, vitamins, etc.

The controlled/modified release preparations of the present invention may be used in conjunction with any multiparticulate system, such as granules, spheroids, beads, pellets, ion-exchange resin beads, and other multiparticulate systems in order to obtain a desired sustained-release of the therapeutically active agent. Beads, granules, spheroids, or pellets, etc., prepared in accordance with the present invention can be presented in a capsule or in any other suitable unit dosage

form. An amount of the multiparticulates effective to provide the desired dose of drug over time may be placed in a capsule, may be contained in a packet and sprinkled onto food, or may be incorporated in any other suitable oral solid form, such as a tablet. On the other hand, the present invention can be in the form of a matrix tablet. With respect to all such optional formulations, it is desired that the formulation be prepared such that an initial immediate release of drug provides an early onset of effect, which onset is analogous to an immediate release formulation, and that the formulation further provide a sustained release component which maintains therapeutically effective levels of the drug in the plasma for the desired amount of time, followed by a relatively rapid drop-off in blood plasma levels relative to typical sustained release formulations. Viewed as an in vivo time/concentration plot, the plasma level of the drug from the formulations of the present invention have the appearance of a "square wave". The immediate release component preferably represents from about 30% to about 40% of the total dose and the controlled release component preferably represents from about 60% to about 70% of the total dose of methylphenidate contained in the formulations of the present invention. In certain preferred embodiments, including the MLR embodiments of the invention, the immediate release component represents about 40% of the total dose and the controlled release component represents about 60% of the total dose of methylphenidate contained in the formulation.

In the case of methylphenidate, it is desired that the onset of action occurs from about 0.5 to about 4 hours, and preferably from about 0.5 to about 2 hours after the oral dosage form is administered, and it is further desired that the dosage form no longer provides effective plasma levels of methylphenidate from about 8 to about 12, more preferably from about 8 to about 10 hours, after oral administration of the dose. In this manner, the dose of methylphenidate can be administered to a child in the morning before school begins, provides the desired effect at the start of the school day, with the pharmacologic action of the drug not waning until after the school day ends, and preferably before dinner so that the drug does not have the side effect of acting as an appetite suppressant.

The formulations of the present invention are designed to produce a rapid rise to therapeutic plasma levels after oral administration, due to the rapid dissolution and absorption of the outer layer, followed by a period of reduced absorption and then controlled release of the immediate release core, to maintain therapeutic plasma levels. After absorption of the immediate release core, plasma levels would then decrease according to the elimination kinetics of the drug.

It is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability. Bioavailability, in a more meaningful sense, is the degree, or amount, to which a drug substance is absorbed into the systemic circulation in order to be available to a target tissue site. To be absorbed, an active drug substance must be in a solution. The time required for a given proportion of an active drug substance contained in a dosage unit to enter into solution in appropriate physiological fluids is known as the dissolution time. The dissolution time for an active substance from a dosage unit is determined as the proportion of the amount of active drug substance released from the dosage unit over a specified time by a test method conducted under standardized conditions. The physiological fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.

Although there are many diverse factors which influence the dissolution of a drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from a specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in this steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiological conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium, providing for a steady state absorption.

The transport across a tissue absorption site in the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane, since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e. the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the gastrointestinal tract into the blood stream.

Notwithstanding the diverse factors influencing both dissolution and absorption of a drug substance, in many cases an important correlation can be established between the in vitro dissolution time determined for a dosage form and the in vivo bioavailability. This correlation is so firmly established in the art that dissolution time has become generally descriptive of bioavailability potential for many classes of active components contained in a particular dosage form. In view of this relationship, the dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating whether a controlled release formulation should be tested in vivo.

With the above in mind, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0-45%
1	5-50%
4	40-90%
8	NLT 60%
12	NLT 80%

In certain preferred embodiments of the present invention, the in-vitro dissolution of the drug at various time points for formulations in accordance with the present invention is provided below:

Time (hours)	% Drug Dissolved
0.25	0-45%
1	10-50%
4	30-80%
8	NLT 65%
12	NLT 80%

Sustained Release Coatings

In certain preferred embodiments, the drug is incorporated into or onto a substrate and a sustained release coating is applied thereto. For example, the drug may be contained within or on a substrate as follows: (i) incorporated into matrix spheroids (e.g., together with a pharmaceutically acceptable spheronizing agent such as microcrystalline cellulose), (ii) coated onto inert pharmaceutically acceptable beads (e.g., nonpareil beads); (iii) incorporated into a normal release tablet core; or (iv) incorporated into a tablet core which comprises a matrix including a sustained release carrier material. Thereafter, a sustained release coating is applied onto substrates such as those mentioned in (i)-(iv) above. The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the drug in desired areas of the gastro-intestinal (GI) tract, e.g., the stomach or small intestine. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) comprising the drug is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Such formulations are described, e.g., in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, assigned to the Assignee of the present invention and hereby incorporated by reference. The particles are preferably film coated with a material that permits release of the drug so as to achieve, in combination with the other stated properties, a desired in-vitro release rate and in-vivo plasma levels. The sustained release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Other examples of sustained release formulations and coatings which may be used in accordance with the present invention include Assignee's U.S. Pat. Nos. 5,324,351; 5,356,467, and 5,472,712, hereby incorporated by reference in their entirety.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Acrylic Polymers

The hydrophobic material comprising the controlled release coating may comprise a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Röhm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit® S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these poly-

mers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material such as an alkylcellulose or an acrylic polymer, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol; diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When the aqueous dispersion of hydrophobic material is used to coat a substrate including the drug, for example, inert pharmaceutical beads such as nu pariel 18/20 beads, a plurality of the resultant stabilized solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. Alternatively, the substrate may be a tablet core coated with the sustained release coating, and optionally a further film-forming agent or colorant, such as Opadry®.

In formulations where an aqueous dispersion of an hydrophobic polymer such as an alkylcellulose is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer and at a relative humidity above ambient conditions, until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, in such formulations the curing time is about 24 hours or more, and the curing conditions may be, for example, about 60° C. and 85% relative humidity. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,273,760; 5,681,585; and 5,472,712; all of which are hereby incorporated by reference in their entireties.

In formulations where an aqueous dispersion of an acrylic polymer is applied to the substrate, it is preferred that the coated substrate is cured at a temperature above the glass transition temperature of the plasticized polymer until an endpoint is reached at which the coated formulation attains a dissolution profile which is substantially unaffected by exposure to storage conditions, e.g., of elevated temperature and/or humidity. Generally, the curing time is about 24 hours or more, and the curing temperature may be, for example, about 45° C. Detailed information concerning the stabilization of such formulations is set forth in U.S. Pat. Nos. 5,286,493; 5,580,578; and 5,639,476; all of which are hereby incorporated by reference in their entireties.

The sustained release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of hydrophobic material, altering the manner in which the plasticizer is added to the aqueous dispersion of hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the drug to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from

the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethyl-cellulose, such as Aquacoat® or Surelease®, may be used. If Surelease is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

The plasticized aqueous dispersion of hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the aqueous dispersion of hydrophobic material to obtain a predetermined sustained release of the therapeutically active agent (i.e., drug) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the drug from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semipermeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The substrate of the present invention may be prepared by a spheronizing agent together with the active agent ingredient that can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredients and spheronizing agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer or ethyl cellulose. In such embodiments, the sustained-release coating will generally include a water insoluble material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

In a particular preferred embodiment of the invention, the controlled/modified release methylphenidate formulation is prepared as a multilayered release (MLR) formulation comprising coated inert beads. A summary of one method of manufacturing such a formulation is outlined as follows. First, immediate release (IR) drug-coated beads are prepared by spraying a solution of methylphenidate in water over sugar beads in a fluid bed dryer with a drug load of about 8%. The spray process is carried out in a fluid bed dryer, equipped with a Wurster column. A clear overcoat of HPMC is applied using an Opadry® material (e.g., Opadry® Clear (Formula No: YS-1-7006)), to a weight gain of about 1%. Next, a controlled release coating is applied to the IR beads, which converts the same into controlled release (CR) beads. This is accomplished by spraying a solution of Eudragit® RS 30 D, triethyl citrate (plasticizer) and talc (glidant), onto the IR beads. Next, the coated beads are cured in order to obtain a stabilized release rate of the therapeutically active agent. In preferred embodiments of the present invention where the CR coating utilizes an acrylic resin to control the release of the drug, the CR beads at this stage are subjected to oven curing at a temperature above the Tg of the plasticized acrylic polymer of the required time period, the optimum values of the temperature and time for the particular formulation being determined experimentally. In certain embodiments of the present invention, the stabilized products is obtained via oven curing conducted at a temperature of about 40-50° C. for a time period of about 12 to about 24 hours or longer. An enteric coating is then applied onto the CR beads to convert the same into enteric coated CR (ECCR) beads. This is accomplished by spraying a solution of Eudragit® L 30 D-55 dispersion,

triethyl citrate (plasticizer) and talc (glidant) onto the CR beads. Finally, an immediate release coating is applied onto the ECCR beads (referred to as, e.g., an IR Topcoat). This is accomplished by spraying a solution of methylphenidate in water over EC CR beads.

Results of initial studies show that this formulation is stable under room temperature (25° C., 60% RH) and accelerated conditions (40° C., 75% RH).

In certain preferred embodiments of the present invention, an effective amount of the drug in immediate release form is included in the drug formulation. The immediate release form of the drug is included in an amount which is effective to shorten the time to maximum concentration of the drug in the blood (e.g., plasma), such that time to T_{max} is shortened to a time of, e.g., from about 0.5 to about 2 hours. By including an amount of immediate release drug in the formulation, the time to onset of action is significantly reduced, and is the same or earlier than that of the reference standard immediate release treatment (e.g., Ritalin IR). In such embodiments, an effective amount of the drug in immediate release form may be coated onto the substrates (e.g., multiparticulates or tablets) of the present invention. For example, where the extended release of the drug from the formulation is due to a controlled release coating, the immediate release layer can be overcoated on top of the controlled release coating. On the other hand, the immediate release layer may be coated onto the surface of substrates wherein the drug is incorporated in a controlled release matrix. Where a plurality of the sustained release substrates comprising an effective unit dose of the drug (e.g., multiparticulate systems including pellets, spheres, beads and the like) are incorporated into a hard gelatin capsule, the immediate release portion of the drug dose may be incorporated into the gelatin capsule via inclusion of the sufficient amount of immediate release drug as a powder or granulate within the capsule. Alternatively, the gelatin capsule itself may be coated with an immediate release layer of the drug. One skilled in the art would recognize still other alternative manners of incorporating the immediate release drug portion into the unit dose. Such alternatives are deemed to be encompassed by the appended claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Methylphenidate HCl Immediate Release Beads

TABLE 1

Ingredients	%
Methylphenidate hydrochloride	15.0
Sugar bead 14/18	80.0
Opadry ® clear YS-1-7006	5.0
Water	q.s.
Total	100.0

1. Charge Niro-Aeromatic Strea 1 Fluid Bed Wurster Coater with 14/18 mesh Nupareil® PG (sugar spheres NF).
2. Coat the beads at 60° C. by spraying a solution of methylphenidate hydrochloride (12% w/w) and Opadry clear (4% w/w) in water.
3. Once the coating is completed, allow the beads to dry at 60° C. for 2 or 3 minutes.
4. Cool the beads in a shallow pan at room temperature.
5. Break agglomerates, if any.
6. Sift the beads through Tyler 10 mesh sieve (1.77 mm opening) and then through Tyler 20 mesh sieve (850 micrometer opening) to remove fines.
7. Apply top coat to beads by spraying a solution of coloured Opadry clear solution (4% w/w) to a theoretical weight gain of 1% w/w.

After the completion of the overcoat, the beads are then filled into hard gelatin capsules at a strength of 20 mg.

Dissolution testing was conducted on the bead filled IR capsules using USP Apparatus 1 (basket method) in 500 mL of simulated gastric juice without enzyme, 100 rpm at 37° C. The results are as follows:

TABLE 2

Time (minutes)	% Methylphenidate HCl dissolved
10	92.7
20	95.7
30	97.7
45	98.5

The dissolution results as set forth in the above table indicate that 98.5% of the methylphenidate hydrochloride was dissolved in 45 minutes.

EXAMPLE 2

Methylphenidate HCl Controlled-Release (CR) Beads with Acrylic Polymer Coating

TABLE 3

Ingredients	%
Methylphenidate IR beads	86.20
Eudragit ® RS 30 D	8.63
Triethyl citrate	1.72
Talc	3.45
Water	q.s.
Total	100.0

The controlled-release coating is manufactured as follows:

1. The Eudragit® RS 30 D is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the IR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~8%.
3. Upon completion of the coating, the beads are cured for 24 hours at 40-45° C.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR capsules using the following USP Apparatus (basket method). The capsules were placed into 500 mL of simulated gastric juice without enzyme, for first 2 hours at 100 rpm and 37° C. and then placed into 500 mL simulated intestinal fluid without enzyme for the remainder of the testing period. The results are as follows:

TABLE 4

Time (hours)	Methylphenidate HCl dissolved
1	6.9
2	16.2
3	26.1
4	35.7
6	59.8
8	74.7
12	75.4
18	82.5
24	92.8

The dissolution results as set forth in the above table indicate that 92.8% of methylphenidate hydrochloride dissolved in 24 hours.

EXAMPLES 3 & 4

Dependence of Release Rate of Methylphenidate HCl from Controlled-Release (CR) Beads on Amount of Acrylic Polymer Coating

By adjusting the amount of Eudragit® RS 30 D applied, the release rate can be adjusted. This effect is illustrated in Examples 3 and 4 below:

TABLE 5

	%	
Ingredients	Example 3	Example 4
Methylphenidate HCl IR Bead	91.2	94.0
Eudragit ® RS 30 D	5.8	3.9
Triethyl citrate	1.0	0.7
Talc	2.0	1.4
Water	—	—
Total	100.0	100.0

The method of manufacturing the controlled-release beads in Examples 3 and 4 is similar to the method described under Example 2, by varying the proportion of beads and Eudragit® RS 30D.

The cured beads were filled into hard gelatin capsules at a strength of 20 mg.

The dissolution results, conducted under conditions identical to those found under Example 2, are shown below:

TABLE 6

Time	% Methylphenidate HCl dissolved	
(hours)	Example 3	Example 4
1	18.7	49.5
2	35.1	73.3
3	49.0	81.5
4	60.6	85.2
6	75.7	90.4
8	77.3	90.7
12	82.1	92.8

The dissolution results as set forth in the above table, indicate that 82.1% and 92.8% respectively of methylphenidate hydrochloride is dissolved in 12 hours. However, the release of drug from Example 4 was significantly faster at time points 1, 2, 3, 4, 6 and 8 hours.

EXAMPLE 5

Enteric Coated (EC) Coated Release (CR) Beads—EC•CR Beads

TABLE 7

Ingredients	%
Methylphenidate CR beads	83.2
Eudragit ® L 30 D55	9.9
Triethyl citrate	2.0
Talc	4.9
Water	q.s.
Total	100.0

The enteric coating procedure is described below:

1. The Eudragit® L 30 D 55 is plasticized with triethyl citrate and talc approximately 30 minutes.
2. A load of the methylphenidate CR beads is charged into a Wurster insert of an Aeromatic Fluid Bed Dryer with 1 mm spray nozzle and the beads are coated to a weight gain of ~9%.
3. Upon completion of the coating, the beads are cured for 18 hours at 40° C.
4. The cured beads are then sieved through Tyler 10 mesh (1.7 mm opening) and Tyler 20 mesh (850 micrometer opening) sieves to remove any fines.

The beads were then filled into hard gelatin capsules at a 20 mg strength.

Dissolution testing was conducted on the bead filled CR filled capsules using USP Apparatus 1 (basket method) 500 mL at 100 rpm and 37° C. using SGF without enzyme for the first 2 hours and SIF without enzyme for the rest of the testing period. Results are shown below:

TABLE 8

Time	% Methylphenidate HCl dissolved		
(hours)	Lot 1	Lot 2	Lot 3
1	0.4	1.0	2.0
2	2.2	5.4	7.4
3	18.8	27.8	61.3
4	36.7	48.3	87.0
6	59.5	75.5	98.8
8	76.9	90.1	100.0
12	82.3	99.6	—

The dissolution results as set forth in the above table indicate that very little drug is dissolved in gastric juice after enteric coating and that the dissolution profile of the CR beads has been modified.

EXAMPLE 6

Formulations for Clinical Trials

Examples 6A, 6B and 6C below set forth the formulations developed and tested in clinical studies.

EXAMPLE 6A

IR•EC•CR Beads

Immediate Release (IR) Coating of Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The (IR•EC•CR Beads) formulation, hereinafter referred to as Formulation 1, is a capsule containing multi-layer release beads which have both immediate release and controlled release components. It is made up of a controlled release bead which is enteric coated to delay dissolution until after gastric emptying. The enteric coated controlled release bead has an immediate release topcoat to provide an initial rate of absorption equal to or greater than Ritalin® IR immediate release tablets. The immediate release component represent 40% of the total dose per bead and the controlled release component represents 60%.

TABLE 9

Ingredients	%
Enteric coated Controlled Release Methylphenidate HCl beads	91.4
Methylphenidate hydrochloride USP	6.5
Opadry ® clear YS-1-7006	2.1
Water	q.s.
Total	100.0

The application of an immediate release coat on the top of Enteric Coated CR beads is described below:

1. Dissolve methylphenidate HCl USP and Opadry in water with stirring.
2. Load EC•CR beads into a Wurster insert of an Aeromatic Fluid Bed Dryer.
3. Spray the beads with the coating solution using a 1 mm spray nozzle at a temperature of not more than 50° C.
4. Once the coating is completed, cool the beads at room temperature and pass through Tyler sieves 10 and 20 mesh to remove fines.

The beads were then filled into a hard gelatin capsule to a 20 mg strength.

Dissolution testing was conducted on the bead filled capsules of Formulation 1 using USP Apparatus 1 (basket method) 100 rpm, 500 mL at 37° C.—simulated gastric juice without enzyme 1st and 2nd hours; 3rd hour onwards simulated intestinal fluid without enzyme.

The results are as follows:

TABLE 10

Time (hours)	% Methylphenidate HCl dissolved
5 minutes	37.0
10 minutes	38.0
15 minutes	39.0
30 minutes	40.0
60 minutes	40.0
2	40.1
3	51.4
4	61.0
6	75.6
8	87.0
12	87.5

The dissolution results as set forth in the above table indicate a rapid onset on dissolution, followed by prolonged action.

EXAMPLE 6B

IR+EC•CR Blend

Combination of Immediate Release Methylphenidate Beads (IR) and Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

The enteric-coated controlled release beads (EC•CR) beads described in Example 5 may be mixed with the immediate release (IR) beads described in Example 1 in varying proportions and placed in capsules to obtain the final blended dosage form, (IR+EC•CR Blend), hereinafter referred to as Formulation 2. Formulation 2 was designed to provide a faster rate of absorption of the controlled release portion than Formulation 1. The immediate release component represents 35% of the total dose per capsule and the controlled release component represents 65%:

Dissolution testing was performed and the comparative results are shown in Table 11 below.

EXAMPLE 6C

IR•CR Beads

Immediate Release (IR) Coating of Controlled-Release (CR) Methylphenidate Beads

The IR•CR Beads formulation, hereinafter referred to as Formulation 3, is a capsule containing single beads made up of an immediate release topcoat and a controlled release core, and is designed to provide an intermediate rate of absorption of the controlled release portion between that of the controlled release formulations of Formulations 1 and 2. The immediate release component represents 30% of the total dose per bead and the controlled release component represents 70%.

The immediate release topcoat is applied to CR beads as described in Example 6A for Formulation 1.

The dissolution profiles of Formulations 1-3 and Ritalin® SR, used as a comparator, are shown in Table 11 below. Hours 1 and 2 are in 500 ml of simulated gastric fluid. Simulated intestinal fluid (500 ml) is used from the third hour onwards. The results of the dissolution testing confirmed the anticipated in vitro dissolution profile.

TABLE 11

Comparative Dissolution of Formulations

Time (Hours)	Ritalin SR	Formulation 1	Formulation 2	Formulation 3
10 min	21.4	38.0	32.0	28.6
30 min	31.4	40.0	36.7	34.0
1	45.7	40.0	38.2	40.5
2	62.3	40.1	40.4	57.6
3	75.8	51.4	68.1	70.6
4	79.5	61.0	86.4	79.5
6	88.0	75.6	95.4	89.6
8	90.7	87.0	96.2	92.7
12	91.3	87.5	97.0	93.1

EXAMPLE 7

Four Way Comparison of Single Dose Formulation 1 (Fed and Fasted) With Two Doses of Ritulin IR (Fed and Fasted)

The bioavailability of Methylphenidate MLR capsules was investigated in a four-way blind study which compared the

Formulation 1 20 mg single dosage formulation under fed and fasted conditions with two doses (4 hours apart) of Ritalin® IR.

Healthy male volunteers were given a single dose of 20 mg Formulation 1 or two doses of immediate release methylphenidate 10 mg administered four hours apart under both fed and fasting conditions (n=12). "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 4 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, under fasting conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 1, 20 mg capsule, administered 5 minutes after a high fat breakfast.

Treatment 4: Reference Product: methylphenidate immediate-release, Ritalin® (Novartis), 10 mg tablet in the morning and 4 hours later, administered 5 minutes after a high fat breakfast.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Formulation 1 and at pre-dose, 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose for the Ritulin® IR. Plasma was harvested from each blood sample and stored in a −20° C. freezer until assayed for plasma methylphenidate concentration. Assay of plasma methylphenidate concentrations was performed using gas chromatography/mass spectrometry (GC/MS).

The mean plasma concentrations, standard deviations and coefficients of variation are shown as a function of time in Tables 12 and 13, for fasting and fed conditions, respectively.

This data is presented graphically in FIGS. **1-4**. FIG. **1** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fasting conditions. FIG. **2** presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fed conditions. FIG. **3** presents the mean plasma concentration versus time for Formulation 1 under fed and fasting conditions. FIG. **4** presents the mean plasma concentration versus time for Ritalin® under fed and fasting conditions.

TABLE 12

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fasting)

	Formulation 1			Ritalin		
Sample Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00		0.00	0.00	
0.250	0.00	0.00	—	0.00	0.00	
0.500	817.53	801.84	98.08	883.96	686.65	77.68
0.750	2268.79	1128.12	49.72	2485.74	828.38	33.33
1.00	3108.79	756.66	24.34	3468.74	1172.28	33.80

TABLE 12-continued

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fasting)

	Formulation 1			Ritalin		
Sample Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
1.50	3597.88	740.36	20.58	4388.04	998.86	22.76
1.00	3675.60	1315.29	35.78	4289.39	1144.40	26.68
2.50	3469.81	882.62	25.44	4121.37	1014.57	24.62
3.00	3573.56	1031.61	28.87	3528.56	863.25	24.46
3.50	3637.01	1008.73	27.74	3020.93	716.36	23.71
4.00	3604.03	1071.59	29.73	2747.91	698.95	25.44
4.50	3494.44	1069.13	30.60	2958.49	799.89	27.04
5.00	3446.41	1069.50	31.03	4394.22	1603.40	36.49
5.50	—	—	—	5525.84	1766.58	31.97
6.00	3421.13	1166.25	34.09	5927.06	1955.99	33.00
6.50		—	—	5528.41	1758.49	31.81
7.00	3422.32	958.42	28.00	4860.45	1482.24	30.50
8.00	3338.59	724.49	21.70	3795.34	1500.79	39.54
10.0	2858.42	612.21	21.42	2223.48	926.11	41.65
12.0	2073.97	536.08	25.85	1334.71	523.37	39.21
16.0	1180.67	502.11	42.53	455.86	287.79	63.13
24.0	275.87	201.51	73.04	55.10	99.99	181.46

TABLE 13

Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin ® IR (fed)

	Formulation 1			Ritalin		
Sample Time (h)	Concentration	SD (±)	CV (%)	Concentration	SD (±)	CV (%)
0.000	0.00	0.00	—	0.00	0.00	
0.250	0.00	0.00	—	53.12	133.84	251.95
0.500	291.66	271.58	93.11	1256.61	1602.66	127.54
0.750	910.22	653.80	71.83	2984.60	3406.53	114.14
1.00	1580.66	983.13	62.20	3400.39	2301.87	67.69
1.50	2760.68	797.24	28.88	5205.16	1882.17	36.16
2.00	3098.73	874.49	28.22	5146.55	1617.43	31.43
2.50	3655.68	982.31	26.87	5157.11	1227.99	23.81
3.00	3625.88	797.55	22.00	4546.61	932.94	20.52
3.50	3717.71	951.58	25.60	4184.34	1080.71	25.83
4.00	3650.63	875.97	23.99	3652.57	1023.22	28.01
4.50	3627.41	835.40	23.03	3811.27	1103.83	28.96
5.00	3430.14	783.72	22.85	5158.45	1714.53	33.24
5.50	—	—	—	5982.98	1618.65	27.05
6.00	3418.03	937.07	27.42	6228.81	1591.64	25.55
6.50	—	—	—	6054.32	1919.95	31.71
7.00	4218.94	775.86	18.39	5538.57	1741.02	31.43
8.00	4679.67	1126.52	24.07	4350.90	1611.95	37.05
10.0	3858.58	1045.56	27.10	2577.66	896.59	34.78
12.0	2610.98	902.53	34.57	1521.52	611.54	40.19
16.0	1372.86	737.71	53.74	577.90	334.26	57.84
24.0	334.79	306.63	91.59	94.23	144.99	153.86

Experimental Results

Pharmacokinetic parameters were calculated based on the data from the four-way study. AUC_{0-t} (pg·h/mL), AUC_{0-inf} (pg·h/mL), $AUC_{t/inf}$ (%), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TUN (hours) and LQCT (hours) were calculated as described below.

For purposes of the present invention, the following terms are meant to have the following meanings:

Analysis of Pharmacokinetic Data and Statistical Analysis

AUC_{0-t}	Area under the concentration-time curve from time zero to the time of the last non-zero concentration (this corresponds to the area under the concentration-time curve, over the dosing interval of the test formulation for both controlled-release and immediate-release formulations)
AUC_{0-inf}	Area under the concentration-time curve from time zero to infinity
C.I.	Confidence interval
CV	Coefficient of variation
C_{max}	Maximum observed concentration
K_{el}	Elimination rate constant
LQCT	The last quantifable concentration time
SD	Standard deviation
TLIN	The time point where log-linear elimination begins
$T_{1/2\ el}$	Time for observed C_{max}
Sampling Time	Time post dose of plasma collection based on parameters to be studied
Scheduled Time	The predetermined (clock) time at which the samples are to be taken
Actual time	The exact (clock) time at which the sample was taken

Time deviations during sampling for drugs with a $T_{max} \leq 4$ hours were treated as follows: between 0 and 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of blood collection was <10%. Above 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of plasma collection was <15%. When sampling times were used when previously described acceptance criteria, the corrected sampling items were used when performing pharmacokinetic parameters calculations. Sampling times are present in concentration tables and graphs of statistical report.

The mean, standard deviation (SD), and coefficient of variation (CV) were calculated for plasma concentrations of methylphenidate for each sampling time and treatment. As well, the mean, SD, and CV were calculated for the AUC_{0-t} (pg·h/mL), AUC_{0-inf} (pg·h/mL), C_{max} (pg/mL), T_{max} (hours), $T_{1/2\ el}$ (hours), K_{el} ($hour^{-1}$), TLIN (hours) and LQCT (hours). The calculation of these pharmacokinetic parameters is explained below.

Areas Under the Concentration-Time Curves

AUC_{0-t} was calculated using the linear trapezoidal rule.

The AUC_{0-t} was derived where t is the time (t) of the last measurable (non-zero) concentration (C_t) for each treatment.

The AUC_{0-inf} was calculated as:

$$AUC_{0-t} + \frac{C_t}{K_{el}}$$

Where C_t=the last non-zero concentration for that treatment, AUC_{0-t}=the AUC from time zero to the time of the last non-zero concentration for that treatment and K_{el}=the elimination rate constant.

Maximum Observed Concentration and Time of Observed Peak Concentration

The maximum observed concentration, C_{max}, and the observed time to reach peak concentration, T_{max}, was determined for each subject and for each treatment.

Half-Life and Elimination Rate Constant

To calculate the elimination rate constant (K_{el}), linear regression analyses were performed on the natural log (Ln) of plasma concentration values (y) versus time (x). Calculations were made between a time point where log-linear elimination phase begins (LQCT) occurred. The K_{el} was taken as the slope multiplied by (−1) and the apparent half-life ($T_{1/2\ el}$) as $0.693/K_{el}$.

TLIN and LQCT

TLIN, the time point where log-linear elimination begins, and LQCT, the last quantifiable concentration time were determined for each subject and for each treatment.

Percent Drug Absorbed

Percent drug absorbed was calculated at each sampling time (t) by Modified Wagner-Nelson's method, as implemented in Kinetica software, version 2.0.1 according to the following formula:

$$\frac{C_t + (K_{el} \times AUC_{0-t})}{(K_{el} \times AUC_{0-inf})} \times 100$$

All ANOVAs were performed with the SAS General Linear Models Procedure (GLM). For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.050. Based on the pairwise comparisons of the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} data, the relative ratios of the geometric means, calculated according to the formulation "$e^{(X-Y)} \times 100$", as well as the 90% geometric confidence intervals were determined.

The plasma concentration of unchanged methylphenidate following administration of the controlled release formulation Formulation 1 reached the maximum concentration (C_{max}) at a mean of 3.27 hours under fasting conditions and 7.29 hours under fed conditions reflecting a biphasic absorption profile. The plasma concentration of unchanged methylphenidate following administration of two doses of the immediate release formulation (Ritalin® IR) reached the maximum concentration (C_{max}) at 5.96 hours under fasting conditions and 3.54 hours under fed conditions. When the determination of C_{max} was restricted to the first dose of immediate release methylphenidate, the T_{max} was 1.71 hours under fasting conditions and 1.63 hours under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg Formulation 1 and immediate release methylphenidate 10 mg (Ritalin® IR) under fed and fasted conditions are summarized in Tables 14 and 15 below.

TABLE 14

Pharmacokinetic Parameters for Formulation 1

Parameters	Formulation 1 (fasting) Mean ± SD	CV (%)	Formulation 1 (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	48493.80 ± 13430.27	27.69	54686.38 ± 15118.66	27.65
AUC_{0-inf} (pg · h/mL)	51213.86 ± 13260.14	26.59	57931.47 ± 16762.54	28.94
C_{max} (pg/mL)	4410.25 ± 1188.68	26.95	4879.37 ± 1027.85	21.07
T_{max} (h)	3.27 ± 2.54	77.64	7.29 ± 1.29	17.65
K_{el} (h^{-1})	0.1672 ± 0.0339	20.25	0.1812 ± 0.0392	21.65
$T_{1/2\ el}$ (h)	4.32 ± 0.96	22.18	4.06 ± 1.25	30.91

TABLE 15

Pharmacokinetic Parameters for Ritalin ® IR

Parameters	RITALIN ® (fasting) Mean ± SD	CV (%)	RITALIN ® (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	44644.22 ± 13806.82	30.93	52781.49 ± 15194.94	28.79
AUC_{0-inf} (pg · h/mL)	46466.23 ± 14012.73	30.16	54783.17 ± 15311.08	27.95
C_{max} (pg/mL)	6536.04 ± 1669.29	25.54	7571.74 ± 1534.58	20.27
T_{max} (h)	5.96 ± 0.54	9.09	3.54 ± 2.42	68.43
K_{el} (h^{-1})	0.2481 ± 0.0550	22.17	0.2449 ± 0.0719	29.37
$T_{1/2\ el}$ (h)	2.93 ± 0.71	24.10	3.08 ± 0.96	31.26

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatment 1 was significantly different from the AUC_{0-t} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized in Table 16 below:

TABLE 16

AUC_{0-t} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	109.90%	104.08%	88.65%
90% Geometric C.I.	102.59% to 117.74%	97.15% to 111.50%	82.75% to 94.97%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatment 1 was significantly different from the AUC_{0-inf} of treatments 2 and 3. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments 3 and 4 for this parameter. The statistical analyses performed on the data are summarized below in Table 17:

TABLE 17

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	111.65%	105.86%	88.85%
90% Geometric C.I.	104.09% to 119.95%	98.70% to 113.55%	82.84% to 95.30%

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 1 was not significantly different from the C_{max} of treatment 3. However, Duncan's Multiple Range Test detected statistically significant differences for C_{max} when comparing treatments 1 and 2 and treatments 3 and 4. The statistical analyses performed on the data are summarized below in Table 18:

TABLE 18

C_{max} (pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 3
Ratio	67.48%	64.38%	89.37%
90% Geometric C.I.	60.28% to 75.54%	57.51% to 72.07%	79.83% to 100.04%

The ANOVA and Duncan's Multiple Range Test performed on the T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 3 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 3 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 and treatments 3 and 4 for this parameter.

The results of the ANOVA and Duncan's Multiple Range Test performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were detected by Duncan's Multiple Range Test between treatments 1 and 2 and treatments 3 and 4, but not for treatments 1 and 3.

Summary and Analysis

The AUC and C_{max} ratios of controlled release methylphenidate 20 mg Formulation 1 under fed and fasted conditions are summarized in Table 19 below. A comparison of the AUC and C_{max} ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fasting conditions are summarized in Table 20 below. Table 21 shows the comparative ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fed conditions.

Treatment 1 (Formulation 1, Fasting) Versus Treatment 3 (Formulation 1, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 3 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed K_{el} and $T_{1/2\ el}$. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test product (Formulation 1, fasting) to reference product (Formulation 1, fed) were found to be within 80 to 125%. This is summarized in Table 19 below:

TABLE 19

Formulation 1 (Fed) vs. Formulation 1 (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.80%	112.54%	111.90%
90% Geometric C.I.[2]	105.29%-120.84%	104.93%-120.71%	99.96%-125.27%

[1]Calculated using geometric means according to the formula: $e^{[Formulation\ 1\ (fed) - Formulation\ 1\ (fasting)]} \times 100$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 1, Fasting) Versus Treatment 2 (Ritalin®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, K_{el}, $T_{1/2el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for all parameters. With the exception of C_{max}, all formulation ratios as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80 to 125%. This is summarized in Table 20 below:

TABLE 20

Formulation 1 (Fast) vs Ritalin ® (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.90%	111.65%	67.48%
90% Geometric C.I.[2]	102.59%-117.74%	104.09%-119.75%	60.28%-75.54%

[1]Calculated using geometric means according to the formula: $e^{[Formulation\ 1\ (fast) - Ritalin\ IR\ (fast)]} \times 100$
[2]90% Geometric Confidence Interval using log-transformed data

Treatment 3 (Formulation 1, Fed) Versus Treatment 4 (Ritalin®, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max}, and untransformed T_{max}, K_{el}, $T_{1/2\ el}$. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for all parameters with the exception of ln-transformed AUC_{0-t} and AUC_{0-inf}. With the exception of C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t} and AUC_{0-inf} of the test product (Formulation 1) to reference product (Ritalin) were found to be within the 80% to 125%. This is summarized in Table 21 below:

TABLE 21

Formulation 1 (Fed) vs. Ritalin ® IR (Fed)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.08%	105.86%	64.38%
90% Geometric C.I.[2]	97.15%-111.50%	98.70%-113.55%	57.51%-72.07%

[1]Calculated using geometric means according to the formula: $e^{[Formulation\ 1\ (fed) - Ritalin\ IR\ (fed)]} \times 100$
[2]90% Geometric Confidence Interval using log-transformed data

Conclusions

Review of individual plasma MPH time curves indicates the following:

Plasma MPH concentrations at 12 hours were higher on Formulation 1 than on Ritalin IR in all subjects, under both fed and fasted conditions.

A biphasic profile was apparent under fasted conditions in 7-10/12 subjects and in 8-10/12 under fed conditions. The mean curve showing a stable plateau under fasted conditions is therefore not fully representative of the individual profiles. The enteric coat therefore gave rise to a biphasic profile in some subjects even under fasted conditions.

Under fasted conditions the apparent rate of rise of plasma MPH was equivalent to, or faster than, that of Ritalin IR in 8/12 subjects under fasted conditions and 4-5/12 subjects under fed conditions. The mean curves which demonstrate an equivalent rate of rise under fasted conditions and a slower rise under fed conditions were therefore largely reflective of the individual profiles.

The bioavailability of Formulation 1 relative to Ritalin IR was acceptable under both fed and fasted conditions (Relative AUC_{inf} 106% and 112%). There was an increase in AUC of both Formulation 1 and Ritalin when given with food (13.1% and 17.9% respectively).

Formulation 1 had a more prolonged mean plasma MPH concentration time profile than two doses of Ritalin IR. An across study comparison indicates that Formulation 1 also has a more prolonged profile than Ritalin SR.

Under fasted conditions Formulation 1 had a mean initial rate of rise of plasma MPH that is similar to Ritalin IR and a relatively flat plateau until 8 hours post-dose.

Under fed conditions, the initial rise in plasma MPH from Formulation 1 was slower than under fasted conditions and the plateau showed a biphasic profile. This was consistent with predictions that the enteric coat would delay release of the controlled release component and that this delay would be longer under fed conditions (allowing the initial plasma concentration peak, due to the IR component, to fall prior to the start of release from the controlled release component).

Formulation 1 results in both a fast initial rate of rise of plasma methylphenidate concentration, and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Formulation 1 therefore has the potential to meet the dual objectives of rapid onset and prolonged duration that are considered desirable characteristics of a controlled release methylphenidate formulation for the treatment of ADD/ADHD.

An initial pilot bioavailability study completed in adult healthy volunteers has confirmed that a single 20 mg dose of this formulation has an equivalent extent of absorption to two doses of immediate release methylphenidate (10 mg) given 4 hours apart. Maximal plasma concentrations with the controlled release formulation are similar to those attained with the first dose of immediate release methylphenidate and from approximately 10 hours post-dose, are higher than those following the second dose of immediate release methylphenidate.

The results indicate the potential for a single morning dose of this formulation to produce clinical effects that are at least equivalent to those of two doses of immediate-release methylphenidate given at breakfast and lunchtime, with a duration of action that may reduce the need for a third dose of immediate release methylphenidate later in the day.

EXAMPLE 8

Five-Way Comparison of Single Dose Formulation 2 (Fed and Fasted), Single Dose Formulation 3 (Fed and Fasted) and Single Dose Ritulin SR (Fasted)

A five-way blind study was conducted which compared a single dose of Formulation 2, 20 mg, both fed and fasted, a single dose of Formulation 3, 20 mg, both fed and fasted, and Ritalin SR 20 mg single dose fasted. According to the published literature and anecdotal comments from physicians, Ritalin SR is used in less than 20% of methylphenidate treated patients.

Twelve healthy male volunteers were given a single dose of either 20 mg Formulation 2 or Formulation 3 administered four hours apart under both fed and fasting conditions (n=12), or slow-release 20 mg methylphenidate (Ritalin SR) under fasting conditions. "Fed" conditions indicates the test formulation was given to the subjects after they had eaten a high-fat breakfast. Following an overnight fast of at least 10.0 hours, each of the normal, healthy, non-smoking, male subjects were given the following treatments according to Williams design 5 treatment randomization scheme.

Treatment 1: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning under fasting conditions.

Treatment 2: Test Product: methylphenidate controlled-release, Formulation 2, 20 mg capsule, in the morning, under fed conditions.

Treatment 3: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fasting conditions.

Treatment 4: Test Product: methylphenidate controlled-release, Formulation 3, 20 mg capsule, under fed conditions.

Treatment 5: Reference Product: methylphenidate slow-release 20 mg tablet Ritalin SR (Novartis) under fasting conditions.

There was a seven day washout period between the study periods. During each study period, blood samples (1×5 mL each) were taken from each subject within one hour prior to dosing and at 0.250, 0.500, 0.750, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 16.0, 24.0 hours post-dose. Plasma was harvested from each blood sample and stored in a −20 C freezer until assayed for plasma methylphenidate concentration.

The data is presented graphically in FIGS. **5-8**. FIG. **5** presents the mean plasma concentration versus time for Formulation 2 under fasting and fed conditions and Ritalin® under fasting conditions. FIG. **6** presents the mean plasma concentration versus time for Formulation 3 under fasting and fed conditions and Ritalin® under fasting conditions; FIG. **7** presents the mean plasma concentration versus time for Formulations 2 and 3 under fasting conditions. FIG. **8** presents the mean plasma concentration versus time for Formulations 2 and 3 under fed conditions.

The complete pharmacokinetic parameters of controlled release methylphenidate 20 mg (Formulation 2 and 3) under fed and fasting conditions, and for slow release methylphenidate 20 mg (Ritalin® SR) under fasting conditions are summarized in Tables 22-24 below.

TABLE 22

Pharmacokinetic Parameters for Formulation 2

Parameters		Treatment 1, Fasting Means ± SD	CV (%)	Treatment 2, Fed Mean ± SD	CV (%)
AUC_{0-t}	(pg · h/mL)	48190.73 ± 11668.71	24.21	53452.63 ± 12820.39	23.98
AUC_{0-inf}	(pg · h/mL)	49787.07 ± 12053.23	24.21	55690.49 ± 12691.52	22.79
C_{max}	(pg · h/mL)	7498.57 ± 1968.38	26.25	6879.09 ± 1486.53	21.61
T_{max}	(h)	3.63 ± 0.57	15.70	6.42 ± 1.08	16.89
K_{el}	(h^{-1})	0.2391 ± 0.0428	17.91	0.2321 ± 0.0342	14.75
$T_{1/2}$	(h)	3.00 ± 0.64	21.32	3.05 ± 0.48	15.74

TABLE 23

Pharmacokinetic Parameters for Formulation 3

Parameters		Treatment 3, Fasting Means ± SD	CV (%)	Treatment 4, Fed Mean ± SD	CV (%)
AUC_{0-t}	(pg · h/mL)	48057.06 ± 14743.87	30.68	54128.75 ± 14787.94	27.32
AUC_{0-inf}	(pg · h/mL)	49984.68 ± 14873.03	29.76	56315.66 ± 14779.59	26.24
C_{max}	(pg · h/mL)	6080.97 ± 2048.60	33.69	6959.07 ± 1559.34	22.41
T_{max}	(h)	3.46 ± 0.89	25.76	4.42 ± 0.56	12.62
K_{el}	(h^{-1})	0.2009 ± 0.0468	23.32	0.2057 ± 0.0390	18.97
$T_{1/2}$	(h)	3.65 ± 0.97	26.52	3.49 ± 0.70	20.01

TABLE 24

Pharmacokinetic Parameters for Ritalin SR ®

Parameters	Mean ± SD	CV (%)
AUC_{0-t} (pg · h/mL)	47404.51 ± 12754.66	26.91
AUC_{0-inf} (pg · h/mL)	49252.17 ± 12841.52	26.07
C_{max} (pg/mL)	6783.09 ± 1496.65	22.06
T_{max} (h)	3.50 ± 0.43	12.18
K_{el} (h^{-1})	0.2282 ± 0.0320	14.01
$T_{1/2\ el}$ (h)	3.10 ± 0.47	15.14

The results of the ANOVA and Duncan's Multiple Range Test performed on the ln-transformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 3 was significantly different from the C_{max} of treatments 4 and 5. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for C_{max} when comparing treatment 1 vs. treatment 2 or treatment 1 vs treatment 5. The statistical analyses performed on the data are summarized in Table 25 below:

TABLE 25

C_{max} (pg/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	103.73%	84.78%	109.25%	87.40%
90% Geometric C.I.	98.94% to 115.14%	78.59% to 91.45%	101.28% to 117.85%	81.05% to 94.26%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed T_{max} data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2, and treatments 3 and 4 for this parameter. Duncan's Multiple Range Test did not detect statistically significant differences between treatments for T_{max} when comparing treatments 1 vs. 3 or treatments 3 vs. 5.

The ANOVA performed on the $T_{1/2\ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 5 for $T_{1/2\ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA performed on the K_{el} data show a statistically significant difference between treatments for this parameter. Statistically significant differences were not detected by Duncan's Multiple Range Test, between treatments for K_{el} when comparing treatments 1 and 2, treatments 3 and 4, or treatments 1 and 5. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-t} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-t} of treatments 1 and 3 was significantly different from the AUC_{0-t} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-t} when comparing treatment 1 vs treatment 5, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 26:

TABLE 26

AUC_{0-t} (pg · h/mL)	Treatment 1 vs. Treatment 2	Treatment 3 vs. Treatment 4	Treatment 1 vs. Treatment 5	Treatment 3 vs. Treatment 5
Ratio	89.21%	88.23%	101.82%	100.63%
90% Geometric C.I.	84.03% to 94.71%	83.10% to 93.67%	95.91% to 108.10%	94.81% to 106.81%

The ANOVA and Duncan's Multiple Range Test performed on the ln-transformed AUC_{0-inf} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the AUC_{0-inf} of treatments 1 and 3 was significantly different from the AUC_{0-inf} of treatments 2 and 4 respectively. However, Duncan's Multiple Range Test did not detect statistically significant differences between treatments for AUC_{0-inf} when comparing treatment 1 vs treatment 3, or treatment 3 vs treatment 5. The statistical analyses performed on the data are summarized below in Table 27:

TABLE 27

AUC_{0-inf} (pg · h/mL)	TRT 1 vs. TRT 2	TRT 3 vs. TRT 4	TRT 1 vs. TRT 5	TRT 3 vs. TRT 5
Ratio	88.33%	88.14%	101.14%	100.82%
90% Geometric C.I.	83.50% to 93.44%	83.32% to 93.24%	95.61% to 106.99%	95.33% to 106.63%

Treatment 1 (Formulation 2, Fasting) Vs. Treatment 2 (Formulation 2, Fed)

The ANOVAs detected statistically significant differences between fed and fasting conditions, treatments 1 and 2, for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test

detected statistically significant differences between treatments 1 and 2 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed $T_{1/2el}$ and K_{el}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 28 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 2. However, this food effect was less than 20% on average.

TABLE 28

Formulation 2, Fed versus Fasting

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	112.09%	113.21%	93.69%
90% Geometric C.I.[2]	105.58% to 119.00%	107.03% to 119.76%	86.85% to 101.07%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ 2(Fed) - Formulation\ 2\ (Fasting)) \times 100}$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) Vs. Treatment 4 (Formulation 3, Fed)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 4 for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for untransformed $T_{1/2el}$ and K_{el}. With the exception of lower 90% geometric confidence interval for C_{max}, all formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 29 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 3. However, this food effect was less than 20% on average.

TABLE 29

Formulation 3, Fed versus Fasting

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	113.35%	113.45%	117.96%
90% Geometric C.I.[2]	106.76% to 120.33%	107.25% to 120.01%	109.35% to 127.25%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ 3\ (fed) - Formulation\ 3\ (Fasting)) \times 100}$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 1 (Formulation 2, Fasting) Vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 5 for all parameters. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 30 below. Thus, Formulation 2 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 30

Formulation 2 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.82%	101.14%	106.99%
90% Geometric C.I.[2]	95.91% to 108.10%	95.61% to 106.99%	101.28 to 117.85%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ 2\ (fast) - Ritalin\ SR\ (Fast)) \times 100}$
[2]90% Geometric Confidence Interval using ln-transformed data

Treatment 3 (Formulation 3, Fasting) Vs. Treatment 5 (Ritalin SR®, Fasting)

The ANOVAs detected statistically significant differences between treatments for ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for ln-transformed C_{max} and untransformed $T_{1/2el}$ and K_{el}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} of the test to reference product were found to be within the 80% to 125%, as shown in Table 31 below. Thus, Formulation 3 is bioequivalent to the reference product Ritalin SR® under fasting conditions.

TABLE 31

Formulation 3 (Fasting) versus Ritalin SR (Fasting)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	101.63%	100.82%	87.40%
90% Geometric C.I.[2]	94.81% to 106.81%	95.33% to 106.63%	81.05 to 94.26%

[1]Calculated using geometric means according to the formula: $e^{(Formulation\ (fast) - Ritalin\ SR\ (Fast)) \times 100}$
[2]90% Geometric Confidence Interval using ln-transformed data

Conclusions

The bioavailability of Formulation 2 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 101%—Fed conditions not tested)

The bioavailability of Ritalin SR® under fasted conditions is similar to that of Ritalin® IR, as discussed in Example 7 (AUC_{inf} 29.2 vs. 46.5 ng·h/mL, respectively). Literature data which indicates that Ritalin® IR and SR are absorbed at equivalent rates suggests that comparisons between the studies presented in Examples 7 and 8 are reasonable.

Bioavailability of Formulations 1 and 2 are similar under fasted and fed conditions (fasted: 49.8 vs. 51.2 ng·h/mL; fed: 55.7 vs. 57.9 ng·h/mL).

From the mean curves of Formulation 2 and Ritalin SR®, the initial rate of rise of plasma MPH concentration is slightly faster for Formulation 2 compared to Ritalin SR®. Under fed conditions, the rate of rise of plasma MPH with Formulation 2 decreased and T_{max} was delayed in comparison to both Formulation 2 fasted and Ritalin SR® fasted.

Bioavailability of Formulation 3 relative to Ritalin SR® is acceptable under fasted conditions (Relative AUC_{inf} 100.8%—fed conditions not tested).

Bioavailability of Formulations 1 and 3 are similar under fasted and fed conditions (fasted: 50.0 versus 51.2 ng/hmL; fed: 56.3 versus 57.9 ng·h/mL). Note also that Formulations 2 and 3 have almost identical AUC values.

From the mean curves for Formulation 3 and Ritalin SR®, the initial rate of rise of plasma MPH concentrations is slightly faster for Formulation 3 compared to Ritalin SR®.

In contrast to Formulation 2, the effect of food on the initial rate of concentration rise is minimal. Since Formulation 3 does not contain an enteric coat, this suggests that food slows the initial release from the IR component of formulations that contain an enteric coat, both when the enteric coat is part of the same bead (underneath the IR coat in the case of Formulation 1) and when it is in a separate bead (as for Formulation 2).

Also in contrast to Formulation 2, the T_{max} of the mean curve of Formulation 3 occurs at a similar time to that of Ritalin SR® under fed and fasted conditions. For Formulation 2 (and Formulation 1) the T_{max} of the second absorption phase under fed conditions is substantially delayed relative to Ritalin SR®.

Conclusions—Examples 7 and 8

1. Formulation 1 has both a fast initial rate of rise, at least under fasted conditions and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Since these conditions represent the extremes of "food stress", one might predict that administration in association with normal meals and times would provide an intermediate profile. It is also possible that gastric emptying in children on a normal meal schedule will be faster than in adults fed a high fat meal—this will tend to make the second absorption phase occur earlier and produce lower concentrations from 12 hours onwards. Formulation 1 therefore meets the dual objectives of rapid onset and prolonged duration.
2. Formulation 2 is also very similar to Ritalin SR® under fasted conditions but shows a delayed peak under fed conditions such that plasma MPH concentrations are higher than Ritalin SR® (fasted) from 6 hours post dose onwards. The controlled release component in Formulation 2 is faster releasing than the one in Formulation 1 and plasma MPH concentrations are lower for Formulation 2 from about 10 hours post dose.
3. Overall, Formulation 3 (non-enteric coated) has a profile very similar to Ritalin SR® under both fed and fasted conditions. The IR component of Formulation 3 provides some increase in initial absorption rate relative to Ritalin SR® under fasted conditions. Since concentrations later in the day are similar for the two formulations, this confirms the concept that a fast initial rise and higher concentrations later in the day are not possible at the same dose, unless a delay is introduced into the release of a component of the total dose.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. An oral controlled release formulation comprising a plurality of multi-layer release beads collectively comprising a dose of methylphenidate, each bead comprising:

(i) an outer immediate release layer comprising a portion of the dose of methylphenidate,

(ii) a release delaying layer under the outer immediate release layer, the release delaying layer comprising a pH-dependent polymer,

(iii) a controlled release layer under the release delaying layer, the controlled release layer comprising a hydrophobic material selected from the group consisting of an alkylcellulose, an acrylic polymer and mixtures thereof; and

(iv) an immediate release core under the controlled release layer, the immediate release core comprising a further portion of the dose of methylphenidate,

wherein from about 30% to about 40% of the dose of methylphenidate is in the outer immediate release layers of the beads and from about 60% to about 70% of the dose of methylphenidate is in the immediate release cores of the beads, and

the formulation provides

(a) a time to a maximum plasma concentration of methylphenidate at about 0.5 to about 4 hours after oral administration to a human patient,

(b) a plasma concentration of methylphenidate which does not differ by more than 10% during a measuring interval, wherein the measuring interval is from about 6 hours to about 12 hours, and

(c) an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate Dissolved
0.25	0-45%
1	5-50%
4	40-90%
8	NLT 60%
12	NLT 80%.

2. The formulation of claim **1**, wherein the formulation provides a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration.

3. The formulation of claim **1**, wherein about 40% of the dose of methylphenidate is in the outer immediate release layers of the beads and about 60% of the dose of methylphenidate is in the immediate release cores of the beads.

4. The formulation of claim **1**, wherein about 30% of the dose of methylphenidate is in the outer immediate release layers of the beads and about 70% of the dose of methylphenidate is in the immediate release cores of the beads.

5. The formulation of claim **1**, wherein the plurality of the multi-layer release beads is incorporated into a hard gelatin capsule.

6. The formulation of claim **1**, wherein the immediate release core further comprises a spheroid or a bead.

7. The formulation of claim **6**, wherein the spheroid or the bead is sprayed with the further portion of the dose of the methylphenidate.

8. The formulation of claim **1**, wherein each bead comprises a coat of a barrier agent between the immediate release core and the controlled release layer.

9. The formulation of claim **8**, wherein the barrier agent is hydroxypropylmethylcellulose.

10. The formulation of claim **1**, wherein the dose is 20 mg.

11. An oral controlled release formulation comprising a plurality of multi-layer release beads collectively comprising a dose of methylphenidate, each bead comprising:

(i) an outer immediate release layer comprising a portion of the dose of methylphenidate,

(ii) a release delaying layer under the outer immediate release layer, the release delaying layer comprising a pH-dependent polymer,

(iii) a controlled release layer under the release delaying layer, the controlled release layer comprising a hydrophobic material selected from the group consisting of an alkylcellulose, an acrylic polymer and mixtures thereof; and

(iv) an immediate release core under the controlled release layer, the immediate release core comprising a further portion of the dose of methylphenidate,

wherein from about 30% to about 40% of the dose of methylphenidate is in the outer immediate release layers of the beads and from about 60% to about 70% of the dose of methylphenidate is in the immediate release cores of the beads, and

the formulation provides

(a) a time to a maximum plasma concentration of methylphenidate at about 0.5 to about 2 hours after oral administration to a human patient,

(b) a plasma concentration of methylphenidate which does not differ by more than 10% during a measuring interval, wherein the measuring interval is from about 2 hours to about 6 hours, and

(c) an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate Dissolved
0.25	0-45%
1	5-50%
4	40-90%
8	NLT 60%
12	NLT 80%.

12. The formulation of claim **11**, wherein the immediate release core further comprises a spheroid or a bead.

13. The formulation of claim **12**, wherein the spheroid or the bead is sprayed with the further portion of the dose of the methylphenidate.

14. The formulation of claim **12**, wherein each bead comprises a coat of a barrier agent between the immediate release core and the controlled release layer.

15. The formulation of claim **11**, which provides effective plasma levels of methylphenidate for from about 8 to about 10 hours.

16. An oral controlled release formulation comprising a plurality of multi-layer release beads collectively comprising a dose of methylphenidate, each bead comprising:

(i) an outer immediate release layer comprising a portion of the dose of methylphenidate,

(ii) a release delaying layer under the outer immediate release layer, the release delaying layer comprising a pH-dependent polymer,

(iii) a controlled release layer under the release delaying layer, the controlled release layer comprising a hydrophobic material selected from the group consisting of an alkylcellulose, an acrylic polymer and mixtures thereof; and

(iv) an immediate release core under the controlled release layer, the immediate release core comprising a further portion of the dose of methylphenidate,

wherein from about 30% to about 40% of the dose of methylphenidate is in the outer immediate release layers of the beads and from about 60% to about 70% of the dose of methylphenidate is in the immediate release cores of the beads, and

the formulation provides

(a) a time to a maximum plasma concentration of methylphenidate at about 0.5 to about 2 hours after oral administration to a human patient,

(b) effective plasma levels of methylphenidate for from about 8 to about 10 hours, and

(c) an in-vitro dissolution as follows:

Time (hours)	% Methylphenidate Dissolved
0.25	0-45%
1	5-50%
4	40-90%
8	NLT 60%
12	NLT 80%.

17. The formulation of claim **16**, wherein the immediate release core further comprises a spheroid or a bead.

18. The formulation of claim **17**, wherein the spheroid or the bead is sprayed with the further portion of the dose of the methylphenidate.

19. The formulation of claim **16**, wherein each bead comprises a coat of a barrier agent between the immediate release core and the controlled release layer.

20. A method of treating Attention Deficit Hyperactivity Disorder in a child comprising: administering to the child once-a-day in the morning a formulation according to claim **1**.

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