Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, New Jersey 07102-5426
(973) 286-6700
clizza@saul.com

Attorneys for Plaintiff
Celgene Corporation

William J. O'Shaughnessy
Jonathan M.H. Short
MCCARTER & ENGLISH, LLP
Four Gateway Center
100 Mulberry Street
Newark, New Jersey 07102
(973) 639-2094
woshaughnessy@mccarter.com

Attorneys for Plaintiffs
Novartis Pharmaceuticals
Corporation and Novartis Pharma AG

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

CELGENE CORPORATION, NOVARTIS PHARMACEUTICALS CORPORATION and NOVARTIS PHARMA AG,	**Civil Action No. _____**
Plaintiffs,	**COMPLAINT FOR PATENT INFRINGEMENT**
v.	**(Filed Electronically)**
TEVA PHARMACEUTICALS USA, INC.,	
Defendant.	

Plaintiffs Celgene Corporation ("Celgene"), Novartis Pharmaceuticals Corporation and Novartis Pharma AG, (together, "Novartis") (collectively, "Plaintiffs"), by their attorneys, for their Complaint against defendant Teva Pharmaceuticals USA, Inc. ("Teva" or "Defendant"), allege as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 United States Code, arising from Defendant's filing of an Abbreviated New Drug Application ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to market a generic version of Novartis' patented FOCALIN XR® drug product in new, 25 mg and 35 mg dosage strengths prior to the expiration of Celgene's United States Patent Nos. 5,908,850 (the "'850 patent"), 6,355,656 (the "'656 patent"), 6,528,530 (the "'530 patent"), 5,837,284 (the "1998 '284 patent"), 6,635,284 (the "2003 '284 patent"), and 7,431,944 (the "'944 patent"), all of which cover the FOCALIN XR® products or their use (collectively, the "Patents-in-Suit").

The Parties

2. Plaintiff Celgene Corporation is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

3. Plaintiff Novartis Pharmaceuticals Corporation is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 59 Route 10, East Hanover, New Jersey 07936.

4. Plaintiff Novartis Pharma AG is a corporation organized and existing under the laws of Switzerland, having an office and place of business at Lichtstrasse 35, CH-4056 Basel, Switzerland.

5. Upon information and belief, Teva Pharmaceuticals USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1090 Horsham Road, P.O. Box 1090, North Wales, Pennsylvania 19454-1090.

6. Teva initially prepared and filed with the FDA, pursuant to 21 U.S.C. § 355(j), ANDA No. 78-908 concerning proposed generic versions of FOCALIN XR® in 5 mg, 10 mg, 15 mg, and 20 mg dosage strengths. Within forty-five (45) days of receiving notice of that ANDA filing, Celgene and Novartis instituted a lawsuit in this Court captioned *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 07-4459 (FLW)(TJB) (D.N.J.) (the "First Teva Litigation"). Pursuant to a confidential settlement agreement, the First Teva Litigation was resolved and dismissed without prejudice by this Court on February 1, 2010. The First Teva Litigation and the resulting settlement concerned only Teva's proposed 5 mg, 10 mg, 15 mg, and 20 mg products and did not concern any of the dosage strengths currently at issue in the present litigation. After the First Teva Litigation was resolved, Teva informed Celgene and Novartis, via a Paragraph IV notice dated March 11, 2011, that it had filed another ANDA, number 202731, concerning proposed generic versions of FOCALIN XR® in 30 mg and 40 mg dosage strengths. Teva's 30 mg and 40 mg products are the subject of an action currently pending before this Court captioned *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 11-2356 (SDW)(MCA) (D.N.J.), which was filed on April 25, 2011. By way of a Paragraph IV notice dated October 19, 2011, Teva informed Celgene and Novartis that it had amended its ANDA, number 202731, to include 25 mg and 35 mg dosage strengths of its proposed generic product ("Teva's 25 mg and 35 mg Products"). The present action concerns Teva's 25 mg and 35 mg Products and is filed within forty-five (45) days of Plaintiffs' receipt of that notice.

7. Upon information and belief, if ANDA No. 202731 is approved, it is the intention of Teva to commercially manufacture, use, and sell Teva's 25 mg and 35 mg Products in the United States.

Jurisdiction and Venue

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

9. This Court has personal jurisdiction over Teva by virtue of, *inter alia*, (i) Teva's continuous and systematic contacts with New Jersey, (ii) its sale of prescription drugs in New Jersey, (iii) its registration of prescription drugs in the New Jersey Generic Formulary of the New Jersey Department of Health and Senior Services, (iv) its consent to being sued in New Jersey as evidenced by its registration to do business in New Jersey and its appointment of a registered agent in New Jersey, (v) its regular and established facilities and places of business in New Jersey (including, for example, at 208 Passaic Avenue, Fairfield, New Jersey, and at 10 Gloria Lane, Fairfield, New Jersey), (vi) its performance of tortious acts that will result in foreseeable harm in New Jersey, and (vii) Teva's consent to jurisdiction in numerous actions in this district (including, for example, *Celgene Corporation, et al. v. Teva Pharmaceuticals USA, Inc.*, Civil Action Nos. 04-4030 and 06-6154 (FLW)(TJB), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 07-4459 (FLW)(TJB), and *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 11-2356 (SDW)(MCA)).

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patents-in-Suit and the FOCALIN XR® Drug Products

11. The '850 patent, entitled "Method of Treating Attention Deficit Disorders With D-Threo Methylphenidate," duly and legally issued to Celgene on June 1, 1999, by the United States Patent and Trademark Office ("PTO"). A copy of the '850 patent is attached hereto as Exhibit A. The '850 patent includes claims directed to methods of treatment using *d-threo* methylphenidate.

12. The '656 patent, entitled "Phenidate Drug Formulations Having Diminished Abuse Potential," originally duly and legally issued to Celgene on March 12, 2002, by the PTO. An *Ex Parte* Reexamination Certificate, which amended certain claims of the '656 patent and added new claims, issued on March 27, 2007, by the PTO. Copies of the '656 patent and the *Ex Parte* Reexamination Certificate for the '656 patent are attached hereto as Exhibit B. The '656 patent claims are directed to pharmaceutical unit dosages of *d-threo* methylphenidate.

13. The '530 patent, entitled "Phenidate Drug Formulations Having Diminished Abuse Potential," duly and legally issued to Celgene on March 4, 2003, by the PTO. A copy of the '530 patent is attached hereto as Exhibit C. The '530 patent includes claims directed to pharmaceutical unit dosages of *d-threo* methylphenidate.

14. The 1998 '284 patent, entitled "Delivery of Multiple Doses of Medications," duly and legally issued to Celgene on November 17, 1998, by the PTO. A copy of the 1998 '284 patent is attached hereto as Exhibit D. The 1998 '284 patent includes claims directed to extended release dosage forms of methylphenidate drug products.

15. The 2003 '284 patent, entitled "Delivery of Multiple Doses of Medications," duly and legally issued to Celgene on October 21, 2003, by the PTO. A copy of the 2003 '284 patent is attached hereto as Exhibit E. The 2003 '284 patent includes claims directed to an extended

release dosage form and claims directed to a method of treating disease with certain extended release dosage forms.

16. The '944 patent, entitled "Delivery of Multiple Doses of Medications," duly and legally issued to Celgene on October 7, 2008, by the PTO. A copy of the '944 patent is attached hereto as Exhibit F. The '944 patent includes claims directed to dosage forms for oral administration of a methylphenidate drug.

17. Celgene is the owner by assignment of all right, title and interest in the Patents-in-Suit. Novartis Pharma AG is the exclusive licensee, in certain fields of use, of the Patents-in-Suit.

18. Novartis Pharmaceuticals Corporation holds an approved New Drug Application for extended release capsules (including 25 mg and 35 mg dosage strengths) of the hydrochloride salt of *d-threo*-methylphenidate, also known as dexmethylphenidate hydrochloride, which it sells as commercial products under the trade name FOCALIN XR®. This commercial product or its use is covered by one or more claims of the Patents-in-Suit.

Acts Giving Rise To This Action

19. Plaintiffs received a letter from Teva dated October 19, 2011 (the "Notification Letter"), notifying them that Teva had filed ANDA No. 202731 with the FDA seeking approval to market 25 mg and 35 mg extended release dexmethylphenidate hydrochloride capsules. The Notification Letter informed Plaintiffs that Teva had submitted a certification to the FDA pursuant to 21 U.S.C. § 355(j)(2)(vii)(IV) ("Paragraph IV Certification") stating that, in Teva's opinion, all claims of the '850 patent, the '656 patent, the '530 patent, the 1998 '284 patent, the 2003 '284 patent, and the '944 patent are invalid, unenforceable, and/or not infringed by Teva's 25 mg and 35 mg Products.

20. Teva seeks approval to engage in the commercial manufacture, use and sale of Teva's 25 mg and 35 mg Products prior to the expiration of the Patents-in-Suit, which are listed in the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations," as being applicable to the patented FOCALIN XR® products.

21. Upon information and belief, Teva intends to engage, and will engage, in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products promptly upon receiving FDA approval to do so.

22. Upon information and belief, Teva's ANDA No. 202731 contains information showing that Teva's 25 mg and 35 mg Products (a) are bioequivalent to the patented FOCALIN XR® products, (b) have the same active ingredient as the patented FOCALIN XR® products, (c) have the same route of administration and strength as the patented FOCALIN XR® products, and (d) have the same, or substantially the same, dosage form and proposed labeling, and the same indication and usage, as the patented FOCALIN XR® products.

23. This action has been brought, pursuant to 21 U.S.C. § 355(j)(5)(B)(iii), before the expiration of forty-five (45) days from the date of receipt by Plaintiffs of the Notification Letter.

Count I: Teva's Filing of an ANDA for Teva's 25 mg and 35 mg Products Infringes the '850 Patent.

24. Plaintiffs repeat and reallege the allegations of paragraphs 1-23 as though fully set forth herein.

25. Teva's submission of ANDA No. 202731 to obtain approval to engage in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '850 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

26. Unless enjoined by this Court, upon FDA approval of ANDA No. 202731, Teva will infringe the '850 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling Teva's 25 mg and 35 mg Products in the United States.

27. Plaintiffs will be substantially and irreparably damaged and harmed if Teva's infringement of the '850 patent is not enjoined. Plaintiffs do not have an adequate remedy at law for this infringement.

Count II: Teva's Filing of an ANDA for Teva's 25 mg and 35 mg Products Infringes the '656 Patent.

28. Plaintiffs repeat and reallege the allegations of paragraphs 1-23 as though fully set forth herein.

29. Teva's submission of ANDA No. 202731 to obtain approval to engage in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '656 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

30. Unless enjoined by this Court, upon FDA approval of ANDA No. 202731, Teva will infringe the '656 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling Teva's 25 mg and 35 mg Products in the United States.

31. Plaintiffs will be substantially and irreparably damaged and harmed if Teva's infringement of the '656 patent is not enjoined. Plaintiffs do not have an adequate remedy at law for this infringement.

Count III: Teva's Filing of an ANDA for Teva's 25 mg and 35 mg Products Infringes the '530 Patent.

32. Plaintiffs repeat and reallege the allegations of paragraphs 1-23 as though fully set forth herein.

33. Teva's submission of ANDA No. 202731 to obtain approval to engage in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '530 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

34. Unless enjoined by this Court, upon FDA approval of ANDA No. 202731, Teva will infringe the '530 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling Teva's 25 mg and 35 mg Products in the United States.

35. Plaintiffs will be substantially and irreparably damaged and harmed if Teva's infringement of the '530 patent is not enjoined. Plaintiffs do not have an adequate remedy at law for this infringement.

Count IV: Teva's Filing of an ANDA for Teva's 25 mg and 35 mg Products Infringes the 1998 '284 Patent.

36. Plaintiffs repeat and reallege the allegations of paragraphs 1-23 as though fully set forth herein.

37. Teva's submission of ANDA No. 202731 to obtain approval to engage in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the 1998 '284 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

38. Unless enjoined by this Court, upon FDA approval of ANDA No. 202731, Teva will infringe the 1998 '284 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling Teva's 25 mg and 35 mg Products in the United States.

39. Plaintiffs will be substantially and irreparably damaged and harmed if Teva's infringement of the 1998 '284 patent is not enjoined. Plaintiffs do not have an adequate remedy at law for this infringement.

Count V: Teva's Filing of the ANDA for Teva's 25 mg and 35 mg Products Infringes the 2003 '284 Patent.

40. Plaintiffs repeat and reallege the allegations of paragraphs 1-23 as though fully set forth herein.

41. Teva's submission of ANDA No. 202731 to obtain approval to engage in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the 2003 '284 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

42. Unless enjoined by this Court, upon FDA approval of ANDA No. 202731, Teva will infringe the 2003 '284 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling Teva's 25 mg and 35 mg Products in the United States.

43. Plaintiffs will be substantially and irreparably damaged and harmed if Teva's infringement of the 2003 '284 patent is not enjoined. Plaintiffs do not have an adequate remedy at law for this infringement.

Count VI: Teva's Filing of the ANDA for Teva's 25 mg and 35 mg Products Infringes the '944 Patent.

44. Plaintiffs repeat and reallege the allegations of paragraphs 1-23 as though fully set forth herein.

45. Teva's submission of ANDA No. 202731 to obtain approval to engage in the commercial manufacture, use or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '944 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

46. Unless enjoined by this Court, upon FDA approval of ANDA No. 202731, Teva will infringe the '944 patent under 35 U.S.C. § 271 by making, using, offering to sell, importing, or selling Teva's 25 mg and 35 mg Products in the United States.

47. Plaintiffs will be substantially and irreparably damaged and harmed if Teva's infringement of the '944 patent is not enjoined. Plaintiffs do not have an adequate remedy at law for this infringement.

Prayer For Relief

WHEREFORE, Plaintiffs respectfully request the following relief:

(A) A Judgment declaring that Teva has infringed one or more claims of the '850 patent;

(B) A Judgment declaring that Teva has infringed one or more claims of the '656 patent;

(C) A Judgment declaring that Teva has infringed one or more claims of the '530 patent;

(D) A Judgment declaring that Teva has infringed one or more claims of the 1998 '284 patent;

(E) A Judgment declaring that Teva has infringed one or more claims of the 2003 '284 patent;

(F) A Judgment declaring that Teva has infringed one or more claims of the '944 patent;

(G) An Order that the effective date of any FDA approval of ANDA No. 202731 be a date which is not earlier than the later of the expiration of the '850 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(H) An Order that the effective date of any FDA approval of ANDA No. 202731 be a date which is not earlier than the later of the expiration of the '656 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(I) An Order that the effective date of any FDA approval of ANDA No. 202731 be a

date which is not earlier than the later of the expiration of the '530 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(J) An Order that the effective date of any FDA approval of ANDA No. 202731 be a date which is not earlier than the later of the expiration of the 1998 '284 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(K) An Order that the effective date of any FDA approval of ANDA No. 202731 be a date which is not earlier than the later of the expiration of the 2003 '284 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(L) An Order that the effective date of any FDA approval of ANDA No. 202731 be a date which is not earlier than the later of the expiration of the '944 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(M) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing into the United States Teva's 25 mg and 35 mg Products until after the expiration of the '850 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(N) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing into the United States Teva's 25 mg and 35 mg Products until after the expiration of the '656 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(O) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using,

selling, offering to sell, or importing into the United States Teva's 25 mg and 35 mg Products until after the expiration of the '530 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(P) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing into the United States Teva's 25 mg and 35 mg Products until after the expiration of the 1998 '284 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(Q) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing into the United States Teva's 25 mg and 35 mg Products until after the expiration of the 2003 '284 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(R) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing into the United States Teva's 25 mg and 35 mg Products until after the expiration of the '944 patent, or any expiration of exclusivity to which Plaintiffs are or become entitled;

(S) A Declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Teva's 25 mg and 35 mg Products will directly infringe or induce and/or contribute to infringement of the '850 patent;

(T) A Declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Teva's 25 mg and 35 mg Products will directly infringe or

induce and/or contribute to infringement of the '656 patent;

(U) A Declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Teva's 25 mg and 35 mg Products will directly infringe or induce and/or contribute to infringement of the '530 patent;

(V) A Declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Teva's 25 mg and 35 mg Products will directly infringe or induce and/or contribute to infringement of the 1998 '284 patent;

(W) A Declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Teva's 25 mg and 35 mg Products will directly infringe or induce and/or contribute to infringement of the 2003 '284 patent;

(X) A Declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Teva's 25 mg and 35 mg Products will directly infringe or induce and/or contribute to infringement of the '944 patent;

(Y) If Teva engages in the commercial manufacture, use, importation into the United States, offering to sell, or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '850 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed, together with interest;

(Z) If Teva engages in the commercial manufacture, use, importation into the United States, offering to sell, or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '656 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed, together with interest;

(AA) If Teva engages in the commercial manufacture, use, importation into the United States, offering to sell, or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the

'530 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed, together with interest;

(BB) If Teva engages in the commercial manufacture, use, importation into the United States, offering to sell, or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the 1998 '284 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed, together with interest;

(CC) If Teva engages in the commercial manufacture, use, importation into the United States, offering to sell, or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the 2003 '284 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed, together with interest;

(DD) If Teva engages in the commercial manufacture, use, importation into the United States, offering to sell, or sale of Teva's 25 mg and 35 mg Products prior to the expiration of the '944 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed, together with interest;

(EE) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § § 271(e)(4) and 285, entitling Plaintiffs to their reasonable attorneys' fees;

(FF) Costs and expenses in this action; and

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

Dated: December 2, 2011

Respectfully submitted,

By: s/ William J. O'Shaughnessy
William J. O'Shaughnessy
Jonathan M.H. Short
McCARTER & ENGLISH, LLP
Four Gateway Center
100 Mulberry Street
Newark, New Jersey 07102
(973) 639-2094
woshaughnessy@mccarter.com

OF COUNSEL:

Henry J. Renk
Tara A. Byrne
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104
(212) 218-2100

Attorneys for Plaintiffs
Novartis Pharmaceuticals Corporation
and Novartis Pharma AG

By: s/ Charles M. Lizza
Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, New Jersey 07102-5426
(973) 286-6700
clizza@saul.com

OF COUNSEL:

Anthony M. Insogna
Lester J. Savit
JONES DAY
12265 El Camino Real, Suite 200
San Diego, California 92130-4096
(858) 314-1200

Jason G. Winchester
JONES DAY
77 West Wacker
Chicago, Illinois 60601-1692
(312) 782-3939

Attorneys for Plaintiff
Celgene Corporation

CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1

I hereby certify that the matter captioned *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*, Civil Action No. 11-2356 (SDW)(MCA) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same Plaintiffs, the same Defendant, the same ANDA, and the same six patents.

I hereby further certify that the matters captioned (i) *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. IntelliPharmaCeutics Corp.*, Civil Action No. 11-1736 (ES)(CLW) (D.N.J.), (ii) *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Mylan Pharmaceuticals Inc.*, Civil Action No. 11-1882 (SDW)(MCA) (D.N.J.), (iii) *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Actavis South Atlantic LLC*, Civil Action No. 11-2162 (SDW)(MCA) (D.N.J.), (iv) *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Par Pharmaceutical, Inc.*, Civil Action No. 11-3094 (SDW)(MCA) (D.N.J.), (v) *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Actavis South Atlantic LLC*, Civil Action No. 11-6519 (SDW)(MCA), and (vi) *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Par Pharmaceutical, Inc.*, Civil Action No. 11-6640 (SDW)(MCA) (D.N.J.), are related to the matter in controversy because the matter in controversy involves the same Plaintiffs and the same six patents.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: December 2, 2011

Respectfully submitted,

By: s/ William J. O'Shaughnessy

William J. O'Shaughnessy
Jonathan M.H. Short
McCARTER & ENGLISH, LLP
Four Gateway Center
100 Mulberry Street
Newark, New Jersey 07102
(973) 639-2094
woshaughnessy@mccarter.com

OF COUNSEL:

Henry J. Renk
Tara A. Byrne
FITZPATRICK, CELLA, HARPER & SCINTO
1290 Avenue of the Americas
New York, New York 10104
(212) 218-2100

Attorneys for Plaintiffs
Novartis Pharmaceuticals Corporation
and Novartis Pharma AG

By: s/ Charles M. Lizza

Charles M. Lizza
William C. Baton
SAUL EWING LLP
One Riverfront Plaza, Suite 1520
Newark, New Jersey 07102-5426
(973) 286-6700
clizza@saul.com

OF COUNSEL:

Anthony M. Insogna
Lester J. Savit
JONES DAY
12265 El Camino Real, Suite 200
San Diego, California 92130-4096
(858) 314-1200

Jason G. Winchester
JONES DAY
77 West Wacker
Chicago, Illinois 60601-1692
(312) 782-3939

Attorneys for Plaintiff
Celgene Corporation

EXHIBIT A

US005908850A

United States Patent [19]

Zeitlin et al.

[11] Patent Number: 5,908,850

[45] Date of Patent: Jun. 1, 1999

[54] METHOD OF TREATING ATTENTION DEFICIT DISORDERS WITH D-THREO METHYLPHENIDATE

[75] Inventors: **Andrew L. Zeitlin**, Millington; **Maghsoud M. Dariani**, Fanwood; **David I. Stirling**, Branchburg, all of N.J.

[73] Assignee: **Celgene Corporation**, Warren, N.J.

[21] Appl. No.: **08/827,230**

[22] Filed: **Apr. 2, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/567,131, Dec. 4, 1995, abandoned.

[51] **Int. Cl.**[6] **A61K 31/445**

[52] **U.S. Cl.** **514/315**

[58] **Field of Search** 514/315

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,507,631	5/1950	Hartmann et al.	260/294
2,957,880	10/1960	Rometsch	546/233
4,992,445	2/1991	Lawter et al.	514/279
5,104,899	4/1992	Young et al.	514/646
5,114,946	5/1992	Lawter et al.	514/279
5,217,718	6/1993	Colley et al.	424/449
5,283,193	2/1994	Yamamoto et al.	435/280
5,284,769	2/1994	Evans et al. .	
5,331,000	7/1994	Young et al.	514/570
5,362,755	11/1994	Barberich et al.	514/649
5,375,693	12/1994	Woosley et al.	514/317
5,449,743	9/1995	Kobayashi et al.	528/355

FOREIGN PATENT DOCUMENTS

WO 97/03671	2/1997	WIPO .
WO 97/03672	2/1997	WIPO .
WO 97/03673	2/1997	WIPO .

OTHER PUBLICATIONS

Angrist et al. *Journal of Clinical Phsychopharmacology,* 1992 12:268–272.

Barkley et al. *Pediatrics* 1990 86:184–192.

Barkley et al. *Pediatrics* 1991 87:519–531.

Golinko *Neuro–Psychopharmacol. & Biol Phsychiat* 1984 8:1–8.

Greenhill *Pediatric Psychopharmacology* 1992 15:1–27.

Scott *Drug Safety* 1993 8:149–159.

White et al. *J. Clin. Phsychiatry* 1992 53:153–156.

Biosis Abstract No.: 87129969 Holmes et al. Psychostimulant Response in Aids–Related Complex Patients *J. Clin. Psychiatry* 50(1):5–8 (1989).

Biosis Abstract No.: 95066168 Srinivas et al. Enantioselective Pharmacolinetics and Pharmacodynamics of Racemic Threo–Methylphenidate in Children with Attention Deficit Hyperactivity Disorder *Clin. Pharmacol. Ther* 52(2):561–568 (1990).

Bowden et al. Reactions of Carbonyl COmpounds in Basic SOlutions The Alkaline Hydrolysis of N–Methyl, N–Phenyl, and Bicyclo Lactams Penicillins, and N–Alkyl–N–methylacetamides *J. Chem. Soc. Perkin Trans.* 1990 12:2111–2116.

Ding et al., Cis– and trans–Axetidin–2–ones from Nitrones and Copper Acetylide *J. Chem. Soc. Perkin* 1976 22:2382–2386.

Brown, C. Chirality in Drug Design and Synthesis Academic Press Inc. 1990 4–7.

Klibanov A.M. Asymmetric Transformations Catalyzed by Enzymes in Organic Solvents *Acc. Chem. Res.* 1990 23:114–120.

Earle et al. J. Chem. Soc. 1969:2093 (1980).

Srinivas et al. Enantiomeric Gas Chromatography Assay with Electron Capture Detection for d–Ritalinic Acid in Plasma, J. Chromatagraph 1990 530:327–336.

Srinivas et al. Sterioselective Disposition of Methylphenidate in Children with Attention Deficit Disorder J. Pharmacol. Exp. Ther. 1987 241:300–306.

Corey et al. J. Amer. Chem. Soc 1965 87:2518.

Moll F. Naturforsch Teil B. 1966 21.297.

Greenhill Pediatric Psychopharmacology 1992 15:1–27.

Scott Drug Safety 1993 8:149–159.

White et al. J. Clin. Psychiatry 1992 53:153–156.

Greenhill L. Attention–Deficit Hyperactivity Disorder Child & Adol. Psych. Clin. N.A., 1995 4:123–165.

Navia et al. Annals of Neurology 1986 19:517–524.

Douzenis et al. Proc 7th. Int'l. Conf. AIDS 1991 1:2135–2215.

Aoyama et al. Pharmacolinetics and pharmacodynamics of (+)–threo–methylphenidate enantiomer in patients with hypersomnia Clin. Pharmacol. Ther 1994 55:270–276.

Uetrecht et al. Pharmacol Res. 1989 6:265–273.

Staal et al. Lancet 1992 339:909–912.

Rieder et al. Ann. Intern Med. 1989 110:286–289.

Patrick et al. J. Pharmacol & Exp. Terhap. 1987 241:152–158.

Srinivas et al. Pharmacol Res. 1993 10:14–21.

Brown G. Int'l J. Psychiatry Med. 1995 25:21–37.

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

[57] **ABSTRACT**

Methods for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS while minimizing drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential by administration of d-threo-methylphenidate or pharmaceutically acceptable salts thereof.

4 Claims, No Drawings

METHOD OF TREATING ATTENTION DEFICIT DISORDERS WITH D-THREO METHYLPHENIDATE

This is a continuation of application Ser. No. 08/567,131, filed Dec. 4, 1995, now abandoned, disclosure of which is herein incorporated by reference.

The present invention relates to methods of treating certain Central Nervous System disorders such as Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS cognitive decline, and AIDS Dementia Complex with decreased side effects, reduced euphoric effect, and reduced drug abuse potential.

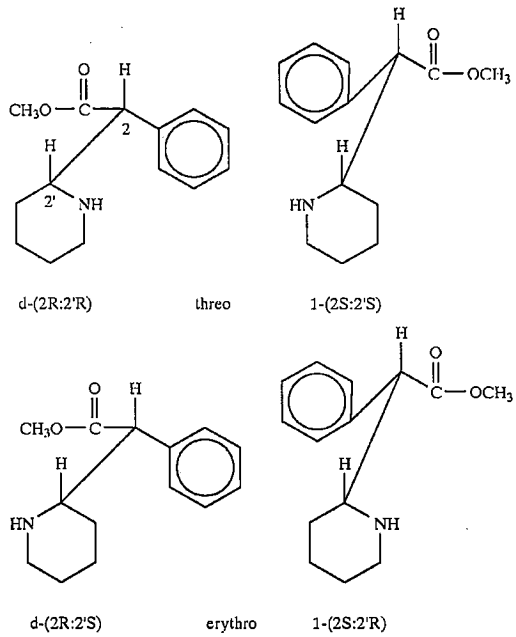
BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD) is the most commonly diagnosed illness in children. Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1987). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by increased symptoms of hyperactivity in patients. Racemic methylphenidate (e.g., Ritalin®) is a mild Central Nervous System stimulant with pharmacological activity qualitatively similar to amphetamines, and has been the drug of choice for symptomatic treatment of ADD in children. Greenhill, L., *Child & Adol. Psych. Clin. N.A.,* Vol. 4, Number 1:123–165 (1995). Current administration of racemic methylphenidate, however, results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia et al., *Annals of Neurology,* 19:517–524 (1986). Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, personality change, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th Int'l. Conf. AIDS,* 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., *Intl. J. Psych. Med.* 25(1): 21–37 (1995). As described above, racemic methylphenidate which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse in AIDS patients.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.,* 6:265–273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet,* 339:909–912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.,* 110:286–289 (1989). It is therefore desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

Methylphenidate possesses two centers of chirality and thus can exist as four separate optical isomers. The four isomers of methylphenidate are as follows:



Diastereomers are known in the art to possess differing physical properties, such as melting point and boiling point. For example, while the threo- racemate of methylphenidate produces the desired Central Nervous System action, the erythro- racemate contributes to hypertensive side effects and exhibits lethality in rats.

Additional studies in animals, children and adults have demonstrated pharmacological activity in the d-threo isomer of methylphenidate (2R:2'R) . See Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1987). Although the role of the l-isomer in toxicity or adverse side effects has not been thoroughly examined, the potential for isomer ballast in methylphenidate is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

Although l-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration, intravenous administration or inhalation results in high l-threo-methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.,* 10:14–21 (1993). Intravenous administration and inhalation are the methods of choice by drug abusers of current methylphenidate formulations. The present invention postulates that the euphoric effect produced by current formulations of methylphenidate is due to the action of l-threo-methylphenidate.

Accordingly, it has been discovered that the use of the d-threo isomer (2R:2'R) of methylphenidate, substantially free of the l-threo isomer produces a methylphenidate medication which retains high activity levels and simultaneously possesses reduced euphoric effect and reduced potential for abuse among patients.

U.S. Pat. No. 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same.

U.S. Pat. No. 2,957,880, to Rometsch et al. describes the conversion of α-aryl-α-piperidyl-(2)-acetic acids and

derivatives thereof (including methylphenidate) into their respective racemates.

Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989) reported on the use of racemic methylphenidate (Ritaline®) and dextroamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp. Therap.,* 241:300–306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et al., *Clin. Pharmacol. Ther.,* 52:561–568 (1992) studied the administration of dl-threo, d-threo and l-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of the l-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below ½ of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152–158 (1986) examined the pharmacology of the enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., *Intl. J. Psych. Med.,* 25(1):21–37 (1995) reported the use of racemic methylphenidate for the treatment of AIDS cognitive decline.

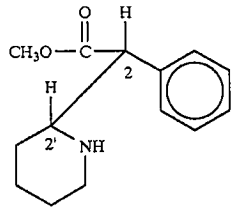
Patrick et al., *Psychopharmacology: The Third Generation of Progress,* Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Patrick noted the d-threo isomer possesses higher activity than the l-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

Aoyama et al., *Clin. Pharmacol. Ther.,* 55:270–276 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama et al. describe a correlation between sleep latency in patients and plasma concentration or (+)-threo-methylphenidate.

SUMMARY OF THE INVENTION

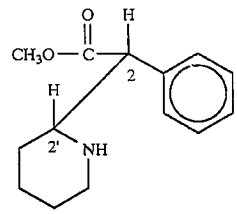
The present invention is based on the discovery that d-threo-methylphenidate (2R:2'R) possesses enhanced therapeutic activity with reduced side effects, and l-threo-methylphenidate produces undesirable side effects, euphoria and drug abuse potential in patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex.

The present invention thus relates to methods of treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse potential through administration of d-threo-methylphenidate (2R:2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the l-threo isomer.

The invention further relates to methods of treating AIDS-related dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of d-threo-methylphenidate (2R:2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the l-threo isomer.

Prescription of methylphenidate to treat AIDS cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry. Med.,* 25:21–37 (1995). The d-threo isomer use of the present invention thus enables a lowered dosing therapy resulting in improved efficacy for diseased patients and particularly HIV-infected patients.

Moreover, administration of the d-threo isomer to patients will result in decreased side effects, reduced euphoric effect, and substantially reduce the potential for abuse of the product.

DETAILED DESCRIPTION OF THE INVENTION

Racemic methylphenidate and its individual isomers are known. See U.S. Pat. Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be obtained from a variety of commercial sources.

The d-threo isomer of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped compressed pharmaceutical forms. Isotonic saline solutions containing 20–100 milligrams/milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

The dosage employed must be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 5–50 mg/day, but the actual decision as to dosage must be made by the attending physician.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of d-threo-methylphenidate substantially free of the l-threo isomer.

The invention further provides for treatment of AIDS-related dementia and related cognitive disorders with d-threo-methylphenidate substantially free of the l-threo isomer while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential.

The term, "substantially free of the l-threo-isomer" means that the composition contains at least 90% by weight of d-threo-methylphenidate, and 10% by weight of l-threo-methylphenidate. In the most preferred embodiment, the term "substantially free of the l-threo isomer" means that the composition contains at least 99% by weight of d-threo-methylphenidate and 1% or less of l-threo-methylphenidate.

The following examples will serve to further typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLE 1

Tablets for chewing, each containing 5 milligrams of d-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 tablets)	
d-threo-methylphenidate	5.00 grams
mannitol	15.33 grams
lactose	10.00 grams
talc	1.40 grams
glycine	0.83 grams
stearic acid	0.66 grams
saccharin	0.10 grams
5% gelatin solution q.s.	

All the solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50° C. and again forced through a sieve of 1.7 mm mesh width. The d-threo-methylphenidate, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

EXAMPLE 2

Tablets, each containing 10 milligrams of d-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 tablets)	
d-threo-methylphenidate	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water q.s.	

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

EXAMPLE 3

Gelatin dry-filled capsules, each containing 20 milligrams of d-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 capsules)	
d-threo-methylphenidate	20.0 grams
microcrystalline cellulose	6.0 grams
sodium lauryl sulfate	0.4 grams
magnesium stearate	1.6 grams

The sodium lauryl sulfate is sieved into the d-threo-methylphenidate through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 28 milligrams each into size 0 (elongated) gelatin dry-fill capsules.

EXAMPLE 4

A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

d-threo-methylphenidate	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water to 2500 mL.	

The d-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 mL of H_2O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare dosage unit forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 milligrams of d-threo-methylphenidate).

What is claimed is:

1. A method of treating at least one of Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder and

providing enhanced therapeutic activity, reduced side effects euphoric effect, or potential for drug abuse as compared to racemic threo methylphenidate, said method comprising administering to a human exhibiting symptoms of such disorder therapeutically effective amounts of D-threo methylphenidate or pharmaceutically acceptable salt thereof, substantially free of L-threo methylphenidate, on a daily basis.

2. The method according to claim 1 wherein the amount administered is 5 mg to 50 mg per day.

3. The method according to claim 1 wherein the amount of d-threo-methylphenidate or a pharmaceutically acceptable salt thereof is greater than 99% by weight.

4. The method according to claim 1 wherein said D-threo methylphenidate is administered together with a pharmaceutically acceptable carrier.

* * * * *

EXHIBIT B

US006355656B1

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

(10) **Patent No.: US 6,355,656 B1**
(45) **Date of Patent: *Mar. 12, 2002**

(54) **PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL**

(75) Inventors: **Andrew L. Zeitlin**, Millington; **Maghsoud M. Dariani**, Fanwood, both of NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/318,151**

(22) Filed: **May 25, 1999**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation-in-part of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned, and a continuation-in-part of application No. 08/583,317, filed on Jan. 5, 1996, now Pat. No. 5,733,756.

(51) **Int. Cl.**[7] **A61K 31/445**
(52) **U.S. Cl.** **514/317**
(58) **Field of Search** 514/317

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,507,631 A		5/1950	Hartmann et al.	260/294
2,957,880 A		10/1960	Rometsch	546/233
4,992,445 A		2/1991	Lawter et al.	514/279
5,104,899 A		4/1992	Young et al.	514/646
5,114,946 A		5/1992	Lawter et al.	514/279
5,217,718 A		6/1993	Colley et al.	424/449
5,283,193 A		2/1994	Yamamoto et al.	435/280
5,284,769 A		2/1994	Evans et al.	435/280
5,331,000 A		7/1994	Young et al.	514/570
5,362,755 A		11/1994	Barberich et al.	514/649
5,375,693 A		12/1994	Woosley et al.	514/317
5,449,743 A		9/1995	Hartmann et al.	528/355
5,773,478 A	*	6/1998	Richards et al.	514/649
5,837,284 A	*	11/1998	Mehta et al.	424/459
5,874,090 A	*	2/1999	Baker et al.	424/600
5,908,850 A		6/1999	Zeitlin et al.	514/315

FOREIGN PATENT DOCUMENTS

WO	WO 97/03671	2/1997
WO	WO 97/03672	2/1997
WO	WO 97/03673	2/1997

OTHER PUBLICATIONS

Angrist et al., *J. Chin. Psychopharma.*, 1992, 12, 268–272.

Barkley et al., *Pediatrics*, 1990, 86, 184–192.

Barkley et al., *Pediatrics*, 1991, 87, 519–531.

Golinko, *Prog. Neuro–Psychopharmacol. & Biol. Phsychiat.*, 1984, 8, 1–8.

Aoyama et al., "Pharmacolinetics and pharmacodynamics of (+)–threo–methylphenidate enantiomer in patients with hypersomnia", *Clin. Pharmacol. Ther.*, 1994, 55(3), 270–276.

Bowden et al., "Reactions of Carbonyl Compounds in Basic Solutions the Alkaline Hydrolysis of N–Methyl, N–Phenyl, and Bicyclo Lactams Penicillins, and N–Alkyl–N–methylacetamides", *J. Chem. Soc. Perkin Trans.*, 1990, 12, 2111–2116.

Brown, "Pharmacological Action and Drug Development", *Chirality in Drug Design and Synthesis*, Academic Press Inc., 1990, 4–7.

Brown G., "The Use of Methylphenidate for Cognitive Decline Associated with HIV Disease", *Int'l J. Psychiatry Med.*, 1995, 25(1), 21–37.

Corey et al., "A New Synthetic Approach to the Penicillins", *J. Am. Chem. Soc.*, 1965, 87(11), 2518–2519.

Ding et al., "Cis–and trans–Axetidin–2–ones from Nitrones and Copper Acetylide", *J. Chem. Soc. Perkin*, 1976, 22, 2382–2386.

Douzenis et al., "Phychiatric Disorder in HIV Disease: Description of 200 Referrals to a Liaison psychiatry Service", *Proc 7th. Int'l Conf. AIDS*, 1991, 215 (M.B.2135—Summary).

Earle et al., "Synthesis and Hydrolysis of some Fused–ring β–Lactams", *J. Chem. Soc.*, 1969, 2093–2098.

Greenhill L., "Attention–Deficit Hyperactivity Disorder", *Child & Adol. Psych. Clin. N.A.*, 1995, 4(1), 123–168.

Greenhill, "Pharmacologic Treatment of Attention Deficit Hyperactivity Disorder", *Pediatric Psychopharmacology*, 1992, 15(1), 1–27.

Holmes et al., "Psychostimulant Response in Aids–Related Complex Patients", *J. Clin. Psychiatry*, 1989, 50(1), 5–8 (Biosis Abstract No. 87129969).

Klibanov, "Asymmetric Transformations Catalyzed by Enzymes in Organic Solvents", *Acc. Chem. Res.*, 1990, 23, 114–120.

Moll F., "Darstellung von 1–Aza–bicyclo[4.2.0] octan–2–on", *Naturforsch Teil B.*, 1966, 21, 297.

Navia et al., "The AIDS Dementia Complex: I. Clinical Features", *Annals of Neurology*, 1986, 19, 517–524.

(List continued on next page.)

Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

4 Claims, No Drawings

OTHER PUBLICATIONS

Patrick et al., "Pharmacology of the Enantiomers of threo–Methylphenidate", *J. Pharmacol & Exp. Terhap.*, 1987, 241, 152–158.

Rieder et al., "Diagnosis of Sulfonamide Hypersensitivity Reactions by In–Vitro "Rechallenge" with Hydroxylamine Metabolites", *Ann. Intern Med.*, 1989, 110, 286–289.

Scott, "Stereoisomers and Drug Toxicity", *Drug Safety*, 1993, 8(2), 149–159.

Srinivas et al., "Enantioselective Pharmacokinetics of dl–threo–Methylphenidate in Humans", *Pharmacol Res.*, 1993, 10(1), 14–21.

Srinivas et al., "Enantioselective Pharmacolinetics and Pharmacodynamics of Racemic Threo–Methylphenidate in Children with Attention Deficit Hyperactivity Disorder", *Clin. Pharmacol.*, 1992, 52(5), 561–568 (Biosis Abstract No. 95066168).

Srinivas et al., "Enantiomeric Gas Chromatography Assay with Electron Capture Detection for d–Ritalinic Acid in Plasma", *J. Chromatagraph*, 1990, 530, 327–336.

Srinivas et al., "Sterioselective Disposition of Methylphenidate in Children with Attention Deficit Disorder", *J. Pharmacol. Exp. Ther.*, 1987, 241(1), 300–306.

Staal et al., "Glutathione deficiency and human immunodeficiency virus infection", *Lancet*, 1992, 339, 909–912.

Uetrecht et al., "Idiosyncratic Drug Reactions: Possible Role of Reactive Metabolites Generated by Leukocytes", *Pharmacol Res.*, 1989, 6(4), 265–273.

White et al., "Methylphenidate as a Treatment for Depression in Acquired Immunodeficiency Syndrome: An n–of–1 Trial", *J. Clin. Psychiatry*, 1992, 53(5), 153–156.

* cited by examiner

PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL

This application is a continuation-in-part of Ser. No. 08/827,230, filed Apr. 2, 1997, now U.S. Pat. No. 5,908,850 which is a continuation-in-part of Ser. No. 08/567,131 filed Dec. 4, 1995, now abandoned and Ser. No. 08/583,317, filed Jan. 5, 1996, now U.S. Pat. No. 5,733,756 both assigned to the assignee hereof. The foregoing applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to phenidate drug compositions for treating certain Central Nervous System disorders such as Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS cognitive decline, and AIDS Dementia Complex. This invention features such drugs having decreased side effects, reduced euphoric effect, and reduced drug abuse potential.

BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD) is the most commonly diagnosed nervous system illness in children. Patrick et al., J. Phamacol. & Exp. Therap., 241:152–158 (1987). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by increased symptoms of hyperactivity in patients. Racemic methylphenidate (e.g., Ritalin®) is a mild Central Nervous System stimulant with pharmacological activity qualitatively similar to amphetamines, and has long been the drug of choice for symptomatic treatment of ADD in children. Greenhill, L., Child & Adol. Psych. Clin. N.A., Vol. 4, Number 1:123–165 (1995).

Current administration of racemic methylphenidate, however, often results in notable side effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia et al., *Annals of Neurology*, 19:517–524 (1986). Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th Int'l. Conf. AIDS*, 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry*, 50:5–8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., Intl. *J. Psych. Med.* 25(1): 21–37 (1995). As described above, racemic methylphenidate, a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse.

U.S. Pat. No. 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same. U.S. Pat. No. 2,957,880, to Rometsch et al. describes the conversion of α-aryl-α-piperidyl-(2)-acetic acids and derivatives thereof (including methylphenidate) into their respective racemates. Each of these patents is incorporated herein by reference.

Holmes et al., *J. Clin. Psychiatry*, 50:5–8 (1989) reported on the use of racemic methylphenidate (Ritalin®) and dexamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp. Therap.*, 241:300306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et: al., *Clin. Pharmacol. Ther.*, 52:561–568 (1992) studied the administration of dl-threo, d-threo and l-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of the l-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below ½ of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152158 (1986) examined the pharmacology of the enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., Intl. *J. Psych. Med.*, 25 (1): 21–37 (1995) reported the use of racemic methylphenidate for the treatment of AIDS 'cognitive decline.

Patrick et al., Psychopharmacology: The Third Generation of Progress, Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Patrick noted the d-threo isomer possesses higher activity than the l-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

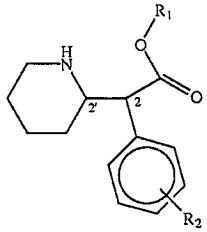
Aoyama et al., *Clin. Pharmacol. Ther.*, 55:270–276 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama at al. describe a correlation between sleep latency in patients and plasma concentration of (+)-threo-methylphenidate.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.*, 6:265–273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet*, 339:909–912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.*, 110:286–289 (1989). It is desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

There is a long-felt and very intense need for phenidate drug compositions, especially methyl phenidate, which are less susceptible to unlawful abuse and which exhibit diminished side effects while retaining therapeutic efficacy.

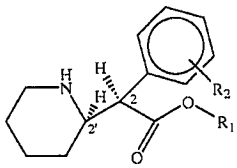
SUMMARY OF INVENTION

Phenidate drugs in accordance with this invention have the structure:

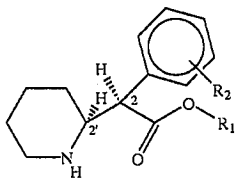


where R_1 is C_1–C_4 alkyl and R_2 is either C_1–C_4 alkyl or hydrogen. Of this family of drugs, methylphenidate, where R_1 is methyl and R_2 is hydrogen, is the most well known, having long been prescribed under the trade mark Ritalin®. Phenidate drugs are α-aryl-α-piperidyl-2-acetic acids and comprise two centers of asymmetry, existing as four separate optical isomers as follows:

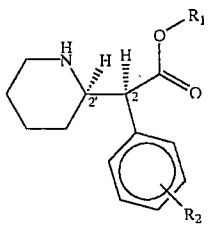
2R, 2'R; D-THREO



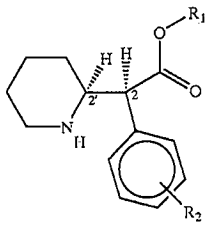
2R, 2'S; D-ERYTHRO



2S, 2'R; L-ERYTHRO



2S, 2'S; L-THREO



It is known that certain physiological properties of methylphenidate and other phenidate drugs are dependent upon stereochemistry. Thus, while the threo racemate of methylphenidate is understood to produce the desired central nervous system action, the erythro racemate is thought to contribute to hypertensive side effects.

It is now believed, however, that another stereochemical distinction also applies. Studies in animals, children and adults have demonstrated pharmacological activity in the

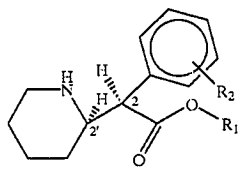
D-threo isomer of methylphenidate (2R,2'R). See Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152–158 (1987). The role of the L-threo isomer in toxicity or adverse side effects has not been examined heretofore although the potential for isomer ballast in methylphenidate and other phenidate drugs is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

Although L-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration by extensive first pass metabolism, intravenous administration or inhalation results in high L-threo methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.*, 10:14–21 (1993). Intravenous administration and inhalation are methods of choice by drug abusers of current, racemic methylphenidate formulations. It is now believed that the euphoric effect produced by current formulations of methylphenidate is due to the action of L-threo-methylphenidate, rather than the pharmaceutically efficacious D-threo compound.

Accordingly, it has now been discovered that the incorporation into pharmaceutical formulations of the D-threo isomer (2R,2'R) of a phenidate drug, especially methylphenidate, with the substantial exclusion of the other three isomers of the phenidate, especially the L-threo isomer, produces a phenidate medication dosage form which retains high pharmaceutical efficacy levels upon administration to patients, while simultaneously possessing fewer or reduced side-effects, reduced euphoric effect and reduced potential for abuse.

Patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex are benefitted by receiving phenidate drug, especially the preferred methylphenidate, in a dosage form which substantially excludes three of the four stereoisomers, D erythro, Lerythro, and L-threo. Stated alternatively, such dosage forms comprise D-threo phenidate in the substantial absence of L-threo and both erythro stereoisomers.

The present invention also provides dosage forms of phenidate drugs for treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse. This is accomplished by formulating dosage forms for administration to patients comprising D-threo-phenidate or a pharmaceutically acceptable salt thereof, substantially free of the L-threo isomer and both erythro isomers. The invention further provides methods of treating AIDS-related dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential comprising administering D-threo-phenidate (2R, 2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the other three stereoisomeric forms of the drug.

In accordance with the invention, R_1 is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl. It is preferred that R_1 be methyl. R_2 may be hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl and may appear either ortho, meta or para to the acetic acid moiety.

Additional substitutients may also appear in the phenidate drug molecule, either in the aryl ring, in the pipiridine heterocycle of in the ester function, however, extensive substitution is not preferred.

Salts of phenidates, such as the conventional hydrochloride salts, are also within the spirit of the invention and all such salts are specifically contemplated hereby.

Preferably, R_1 is methyl and R_2 is hydrogen such that the phenidate drug is methylphenidate.

Prescription of methylphenidate to treat AIDS cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry. Med.*, 25:21–37 (1995). The exclusive D-threo isomer formulations of the present invention enable a lowered dosing therapy with avoidance of the administration of the stereoisomer believed to be responsible for adverse side effects and abuse potential resulting in improved efficacy for diseased patients and particularly HIV-infected patients.

Racemic methylphenidate and its individual isomers are known. See U.S. Pat. Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be obtained from a variety of commercial sources. Moreover, the D-threo- isomer of methylphenidate and other phenidate drugs can be prepared in accordance with Ser. No. 08/583,317 filed Jan. 5, 1996, which application forms a parent to this application and has been incorporated herein by reference. Examples forming part of this application set forth certain preferred synthetic routes to the phenidate compounds useful in the practice of this invention. Persons of ordinary skill will be able to modify such procedures to prepare the lower alkyl substituted phenyl derivatives and lower alkyl esters contemplated herein without undue experimentation. Thus, preparation of ethyl, propyl, isopropyl etc. esters is a simple matter in view of the synthetic schemes set forth. Likewise, substituting the phenyl ring with one or more alkyl or other substituients may also be accomplished.

The dosage forms of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and other conventional, pharmaceutical forms. Isotonic saline solutions, conveniently containing about 1–40 milligrams of drug per milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes. Rectal administration can conveniently be effected through the use of suppositories such as can easily be formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

The dosage employed should be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 1–50 mg/day, but the actual decision as to dosage will depend upon the exact phenidate drug being employed and will be made by the attending physician as a matter of routine. Such physician can, however, determine an appropriate regime employing well-known medical considerations. Such persons will appreciate that the overall dosage amount will be significantly smaller than that used with the corresponding racemic drug, since the undesired enantiomers are not included in the present dosage forms.

Accordingly, a pharmaceutically effective amount of a phenidate drug in accordance with this invention will be understood by persons of ordinary skill in the art to be that amount of the selected D-threo phenidate which, upon administration to a patient, would result in a sensible and therapeutically useful effect.

When phenidates other than methylphenidate are to be administered, it will be appreciated that the effective amount of drug will likely be different than for methylphenidate. Determination of such amount, however, is well within the routine skill of the practitioner. In accordance with preferred embodiments, from 1 to about 50 mg will be administered to patients, with from about 2 to about 20 mg per day being still more preferred. In still more preferred embodiments, patients will receive from about 2½ to about 12 mg per day.

It is desirable to provide unit dosage forms for administration of compounds of the invention comprising from about 1 to about 50 mg of drug, with amounts of from about 2 to about 20 and particularly from about 2½ to about 12 mg being still more preferred. Oral administration is the protocol of choice, however other routes of administration, such as intravenous, intraperitoneal, rectal and the like may also be employed in formulating the unit dosage forms of this invention. Carriers, diluents and excipients are conventionally employed in formulating unit dosage forms and the same are selected as a matter of routine depending upon the selected route of administration. For oral administration, formulation into tablets using tabletting excipients are conveniently employed, although capsular and other oral forms are also useful.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of D-threo-methylphenidate substantially free of the L-threo and other isomers. The invention gives rise to methods of treatment of AIDS related dementia and related cognitive disorders with D-threo-methylphenidate substantially free of the remaining isomers.

The term, "substantially free as it applies to a stereoisomer in accordance with a composition of this invention means that the composition contains no more than 10% by weight of the isomer in question. It is preferred that such composition have less than about 2% of the unwanted isomers and even more preferred that less than 1% be present. When applied to a plurality of stereoisomers, then all of the isomers, taken together, comprise no more than 10% by weight of the composition and preferrably less than 2%. It is preferred that compositions characterized as being "substantially free" of all stereoisomers but the D-threo isomer comprise no more than about 5% of other isomers. It is still more preferred that no more than 1% of the undesired isomers be present.

The following examples will serve to further typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLES

A suitable salt medium for the microbiological transformations described in the following examples has been denominated "media A" and has the following composition:

$MgSO_4$	1.00 g/L
$CaCl_2$	0.021 g/L
$ZnSO_4.7H_2O$	0.20 mg/L
$MnSO_4.4H2O$	0.10 mg/L
H_3BO_3	0.02 mg/L
$CUSO_4.5H2O$	0.10 mg/L
$CoCL_2.6H_2O$	0.05 mg/L
$NiCl_2.6H2O$	0.01 mg/L
$FeSO_4$	1.50 mg/L
$NaMoO_4$	2.00 mg/L
Fe EDTA	5.00 mg/L
KH_2PO_4	20.00 mg/L
NaOH	to pH 7

Example 1

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one

Preparation of Biocatalyst

Lactamase is obtained from Pseudomonas cepacia grown on 1–2% penicillin as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 2 g/l of penicillin is inoculated with *Pseudomonas cepacia*. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 2 g/l penicillin. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic (+/−)trans-7-phenyl-1-azabicyclo (4,2,0)octan-8-one (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract of lactamase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 3 hours under these conditions. A lactamase with opposite stereoselectivity obtained from a microorganism such as Rhodococcus rhodochrous can be used to resolve (+/−)trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one to L-ritalinic acid and the D-trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one. This lactam is then hydrolyzed to the D-ritalinic acid by conventional means.

Trans-7-phenyl-i-azabicyclo(4,2,0)-octan-8-one may be prepared by the method of Corey, Mol, or Earle (Corey et al., *J. Amer. Chem. Soc.*, 87:2518 (1965); Earle et al., *J. Chem. Soc. C.*, 2093 (1969);Moll F. *Naturforsch., Teil B*, 21:297 (1966).

Isolation of D-lactam.

The reaction mixture prepared above is extracted with methylene chloride and the organic layer is dried with $MgSO_4$. The organic layer is then filtered and concentrated by rotary evaporation at 30° with reduced pressure, to yield an oil product. The oil product may be further purified by column chromatography.

Example 2

Preparation of D-threo-2-(piperid-2-yl)-2-phenylacetic acid from threo-2-(piperid-2-yl)-2-phenyl-2-acetamide

Preparation of Amidase

Amidase is obtained from Acinetobacter baumanni grown on 30 mM 2-cyanobutane as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with Acinetobacter baumanni. After the mixture in incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetamide (0.5 g) prepared by, e.g. the method of Hartmann, U.S. Pat. No. 2,507,631, is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of amidase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions. An amidase with opposite stereoselectivity obtained from a microorganism such as Rhodococcus rhodochrous can be used to resolve DL-threo-2-(piperid-2-yl)-2-phenyl-acetamide to L-ritalinic acid and the D-threo-2-(piperid-2-yl)-2-phenyl-acetamide. This amide is then hydrolyzed to the D-ritalinic acid by conventional means.

Example 3

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one.

Racemic trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one (0.5 g) is added to a mixture of 20 ml 50 mM phosphate buffer pH 7.5 and 1 ml of Pseudomonas putida cell extract. The reaction is maintained at 30° C. until the enantiomeric excess as determined by chiral chromatography is no less than 98% D-ritalinic acid, generally about 24 hours under these conditions. Alternatively, a cell extract containing an amidase of opposite stereoselectivity may be used to effect a resolution of racemic trans-7-phenyl-1-aza-bicyclo(4,2,0)-octan-8-one where L-ritalinic acid is produced and the D-lactam is isolated as the product.

Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer dried with $MgSO_4$. The organic layer is then filtered and concentration by rotary evaporation at 30° with reduced pressure, to yield an oil. The oil product may be further purified by column chromatography.

Example 4

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from threo-2-(piperid-2-yl)-2-phenyl-acetonitrile

Nitrile hydratase and amidase are obtained from Alcaligenes faecalis grown on 30 mM 2-cyanobutane or 2-phenylacetonitrile as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with Alcaligenes faccalis.

After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane or 2-phenylacetonitrile. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetonitrile (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of Alcaligenes faecalis with nitrile hydratase and amidase activity. The reaction is maintained at 30° C. until the enantiomer excess

as-determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions.

Example 5

The use of an esterase/lipase for the stereoselective enrichment of DL-threo-α-phenyl-α-piperidyl-acetic acid methyl ester

A microbial source of a stereoselective esterase or lipase may be obtained from commercial sources such as Novo Nordisk's "Humicola lipolase" or an ATCC Pseudomonas strain 31809 or 31808. Esterase/lipase is obtained from Pseudomonas sp. ATCC strain 31809 grown on 1% olive oil in media A supplemented with 8 g/l nutrient broth. Fifty ml of media A containing the 1% olive oil and 8 g/l nutrient broth is inoculated with Pseudomonas sp. ATCC strain 31809. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of media with 1% olive oil supplemented with 8 g/l nutrient broth. After 24 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer, pH 7.5 and again concentrated to a paste. Cells are ruptured as above.

DL-threo-α-phenyl-α-piperidylacetic acid methyl ester (0.5 g) prepared by the method of Hartmann is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract. The reaction is maintained at 30° C. until the enantiomeric excess, as determined by chiral chromatography, is no less than 98% D-threo-methylphenidate, generally in about 25 hours under these conditions.

PREPARATION OF EXEMPLARY DOSAGE FORMS

Example 6

Tablets for chewing, each containing 5 milligrams of D-threo-methylphenidate, can be prepared in the following manner: Composition (for 1000 tablets)

D-threo-methylphenidate	5.00 grams
mannitol	15.33 grams
lactose	10.00 grams
talc	1.40 grams
glycine	0.83 grams
stearic acid	0.66 grams
saccharin	0.10 grams
5% gelatin solution q.s.	

The solid ingredients are each forced through a 0.25 mm mesh sieve. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a 2 mm mesh sieve, dried at 50° C. and forced through a 1.7 mm mesh sieve. The D-threo-methylphenidate, glycine and saccharin are carefully mixed, the granulated mannitol and lactose, stearic acid and talc added and the whole mixed thoroughly. The mass is compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking groove on the one side.

Example 7

Tablets, each containing 10 milligrams of D-threo-methylphenidate, can be prepared in the following manner: Composition (for 1000 tablets)

D-threo-methylphenidate	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water q.s.	

The solid ingredients are first forced through a 0.6 mm mesh sieve. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh and compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 8

Gelatin dry-filled capsules, each containing 20 milligrams of D-threo-methylphenidate, can be prepared in the following manner: Composition (for 1000 capsules)

D-threo-methylphenidate	20.0 grams
microcrystalline cellulose	6.0 grams
sodium lauryl sulfate	0.4 grams
magnesium stearate	1.6 grams

The sodium lauryl sulfate is sieved into the D-threo-methylphenidate through a 0.2 mm mesh sieve and the two components intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a 0.9 mm mesh sieve and the whole again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a 0.8 mm mesh sieve and, after mixing for a further 3 minutes, the mixture is introduced in portions of 28 milligrams each into gelatin dry-fill capsules.

Example 9

A 0.2% injectable or infusible solution can be prepared, in the following exemplary manner:

D-threo-methylphenidate	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water to	2500 ml.

The D-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 ml of H_2O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare unit dosage forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules such that each contains, respectively 2.0 or 5.0 milligrams of D-threo-methylphenidate.

What is claimed is:

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of D-threo-methylphenidate or a

pharmaceutically acceptable salt thereof said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

2. The unit dosage of claim 1 comprising from about 2 to about 20 milligrams of D-threo-methylphenidate.

3. The unit dosage of claim 1 comprising from about 2½ to about 12 milligrams of D-threo-methylphenidate.

4. The unit dosage of claim 1 in a form suitable for oral administration.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,355,656 B1
DATED : March 12, 2002
INVENTOR(S) : Andrew L. Zeitlin et al.

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

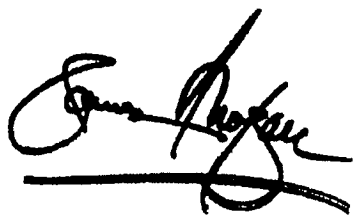
Column 1,
Lines 7 and 8, delete "and Ser. No. 08/583,317, filed, Jan. 5, 1996, now U.S. Pat. No. 5,733,756 both".
Line 9, "application are" and insert therefor -- application is --.

Column 5,
Line 3, delete "of in" and insert therefor -- or in --.

Column 6,
Line 44, after "free", insert quotation marks -- " --.

Signed and Sealed this

Twenty-ninth Day of July, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

US006355656C1

(12) EX PARTE REEXAMINATION CERTIFICATE (5729th)
United States Patent
Zeitlin et al.

(10) Number: US 6,355,656 C1
(45) Certificate Issued: *Mar. 27, 2007

(54) PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL

(75) Inventors: **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

Reexamination Request:
No. 90/007,177, Aug. 18, 2004

Reexamination Certificate for:

Patent No.:	**6,355,656**
Issued:	**Mar. 12, 2002**
Appl. No.:	**09/318,151**
Filed:	**May 25, 1999**

(*) Notice: This patent is subject to a terminal disclaimer.

Certificate of Correction issued Jul. 29, 2003.

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation-in-part of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned.

(51) **Int. Cl.**
A61K 31/445 (2006.01)

(52) **U.S. Cl.** **514/317**
(58) **Field of Classification Search** 514/317
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,838,519	A *	6/1958	Rometsch	546/238
2,957,880	A	10/1960	Rometsch et al.	260/294
4,137,300	A	1/1979	Sheth et al.	424/460
5,733,756	A	3/1998	Zeitlin et al.	435/122
5,773,478	A *	6/1998	Richards et al.	514/649
5,908,850	A	6/1999	Zeitlin et al.	514/315
6,221,883	B1	4/2001	Baldessarini	514/317
6,395,752	B1	5/2002	Midha et al.	514/317

FOREIGN PATENT DOCUMENTS

WO 96/41617 A1 12/1996

OTHER PUBLICATIONS

Patrick et al., "Distribution of Methylphenidate and P-Hydroxymethylphenidate in Rats", Journal of Pharmacology and Experimental Therapeutics, 1984, vol. 231, No. 1, pp. 61–65.*

Aoyama et al., Kinetic Analysis of Enantiomers of threo-Methylphenidate and Its Metabolite in Two Healthy Subjects after Oral Administration as Determined by a Gas Chromatographic-Mass Spectrometric Method, 1990, vol. 79, No. 6, pp. 465–469.*

Aoyama, T. et al., "Pharmacodynamic Modeling for Change of Locomotor Activity by Methyllphenidate in Rats," *Pharmaceutical Research*, 1997, 14(11), 1601–1606.

Aoyama, T. et al., "Pharmacokinetics and pharmacodynamics of methylphenidate enantiomers in rats," *Psychopharmacology*, 1996, 127, 117–122.

Aoyama, T., et al., "Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers," *Eur. J. Clin. Pharmacol.*, 1993, 44, 79–84.

Barkley, R. A., et al., "The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study," *J. Am. Acad. Adolesc. Psychiatry.*, 1990, 29(4), 546–557.

Baughman, Jr., F. A., "Treatment of Attention-Deficit/Hyperactivity Disorder," *JAMA.*, Apr. 28, 1999, 218(16), 1490–1491.

Bruera, E., and Neumann, C. M., "The uses of psychotropics in symptom management in advanced cancer," *Psycho-Oncology.*, 1998, 7, 346–358.

Carey, W. B., "What the multimodal treatment study of children with attention-deficit/hyperactivity disorder did and did not say about the use of methylphenidate for attention deficits," *Pediatrics*, 2000, 863–864.

Challman, T.D., et al., "Methylphenidate: its pharmacology and uses," *Mayo Clin Proc.*, 2000, 75, 711–721.

Chapin, R. et al., "*Methylphenidate hydrochloride*," Environmental Health Perspectives, 1997, 105 (supp 1), 319.

Coyle, J. T., "Psychotic drug use in very young children," *J. Am. Med. Assn.*, 2000, 283(8), 1059–1060.

Davids, E. et al., "Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning," *Psychopharmacology*, 2002, 160, 92–98.

Ding, Y.-S. et al., "Chiral drugs: comparison of the pharmacokinetics of [11C]d-threo and l-threo-methylphenidate in the human and baboon brain," *Psychopharmacology*, 1997, 131, 71–78.

Ding, Y.-S. et al., "Is the L-threo Enantiomer of Methylphenidate (Ritalin) Inactive in the Brain when the Drug is Given Orally?" *ACNP 41st Annual Meeting*, Dec. 8–12, 2002, Scientific Abstract No. 119.

Ding, Y-S. et al., "Brain Kinetics of Methylphenidate (Ritalin) Enantiomers After Oral Administration," *Synapse*, Sep. 2004, 53, 168–175.

Garland, E. J., "Pharmacotherapy of adolescent attention deficit hyperactivity disorder: challenges, choices and caveats," *J. Psychopharmacology.*, 1998, 12(4), 385–395.

Golden, G. S., "Role of attention deficit hyperactivity disorder in learning disabilities," *Seminars in Neurology.*, 1991, 11(1), 35–41.

(Continued)

Primary Examiner—Dwayne C. Jones

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

OTHER PUBLICATIONS

Goldman, L. S., et al., "Diagnosis and treatment of attention–deficit/hyperactivity disorder in children and adolescents," *J. Am. Med. Assn.*, 1998, 279(14), 1100–1107.

Jadad, A. R., et al., "Review: Pharmacologic interventions are more effective than non–pharmacologic for attention–deficit hyperactivity disorder," *Therapeutics, ACP Journal Club.*, Nov./Dec. 2000, 110.

Jensen, P. S., et al., "Are stimulants over–prescribed? Treatment of ADHD in four U.S. communities," *J. Am. Acad. Adolesc. Psychiatry*, 1999, 37(7), 797–804.

Jonkman, L.M. et al., "Differences in plasma concentrations of the D– and L–threo methylphenidate enantiomers in responding and non–responding children with attention–deficit hyperactivity disorder," *Psychiatry Research*, 1998, 78, 115–118.

Kimko, H. C., et al., "Pharmacokinetics and Clinical effectiveness of methylphenidate," *Clin. Pharmacokinetics*, 1999, 37(6), 457–470.

LeFever, G. B., et al., "The extent of drug therapy for attention dificit–hyperactivity disorder among children in public schools," *American Journal of Public Health*, (Sep. 1999), (89)9, 1359–1364.

Lin, J. H., and Lu, A. H., "Role of pharmacokinetics and Metabolism in drug discovery and development," *Pharmacological Reviews*, 1997, 49(4), 403–449.

Llana, M. E. and Crismon, M. L., "Methylphendiate: increased abuse or appropriate use?" *J. Amer. Pharmaceut. Assn.*, 1999, 39(4), 526–530.

MacDougall, M. K., et al., "Symptom control in the pregnant cancer patient," *Seminars in Oncology*, 2000, 27(6), 704–711.

Markowitz, J. S., et al., "Advances in the pharmacotherapy of attention–deficit–hyperactivity disorder: focus on methyl phenidate formulations," *Pharmacotherepy*, 2003, 23(10), 1281–1299.

McCarthy, M., "USA to improve care of children with ADHD," *The Lancet*, 2000, 355, 1161.

Mehta, M. A., et al., "Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain," *J. Neurosci.*, 2000, 20RC65: (1–6).

Modi, N. B. et al., "Dose–Proportional and Stereospecific Pharmacokinetics of Methylphenidate Delivered Using an Osmotic, Controlled–Release Oral Delivery System," *J. Clin. Pharmacol.*, 2000, 40, 1141–1149.

Patrick K S et al "The Absorption Of Sustained–Release Methylphenidate Formulations Compared To An Immediate–Release Formulation," Biopharmaceutics And Drug Disposition, Wiley, Chichester, US, vol. 10, No. 2, 1989, pp. 165–171.

Patrick, K.S. et al., "Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention–Deficit Hyperactivity Disorder," *Human Psychopharmacology*, 1997, 12, 527–546.

Patrick, K.S. et al., "Synthesis, Pharmacology and Human Metabolic Formation of Ethylphenidate: the Transesterification Product of Methylphenidate and Ethanol," *The 56th Southeast Regional Meeting 2004*, Nov. 10–13, 2004 1 page.

Patrick, K.S. et al., "New methylophenidate formulations for the treatment of attention–deficit/hyperactivity disorder," *Expert Opin. Drug Deliv.*, 2005, 2(1), 121–143.

Quinn, D.M.P., "Methylphenidate: The Role of the d–Isomer," undated, Department of Psychiatry, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, 369–373.

Rouhi, A.M, "Chirality of Work, " *C&EN*, May 5, 2003, 56–61.

Sarhill, N., et al., "Methylphenidate for fatigue in advanced cancer: a prospective open–label pilot study," *Am. J. of Hospice & Palliative Care*, 2001, 18(3), 187–192.

Schweitzer J. B., et al., "Attention deficit hyperactivity disorder," *Adv. Pathophysiol. And Treat. Psychiatric Disorders: Implications for Internal Med.*, 2001, 85(3), 757–777.

Shader R.I. et al., "Population Pharmacokinetics of Methylphenidate in Children with Attention–Deficit Hyperactivity Disorder," *J. Clin. Pharmacol.*, 1999, 39, 775–785.

Spencer, T., et al., "Pharmacotherapy of attention–deficit hyperactivity disorder across the life cycle," *J. Am. Acad. Adolesc. Psychiatry.*, 1996, 35(4), 409–432.

Srinivas, N.R. "Role of Stereoselective Assays in Bioequivalence Studies of Racemic Drugs: Have We Reached a Consensus?" *J. Clin. Pharmacol.*, Feb. 2004, 44, 115–119.

Srinivas, N.R., et al., "Enantiomeric Drug Development: Issues, Considerations, and Regulatory Requirements," *Journal of Pharmaceutical Sciences*, Sep. 2001, 90(9), 1205–1215.

Stein, M. A., et al., "Methylphenidate dosing: Twice daily versus three times daily," *Pediatrics*, 1996, 98(4), 784–756.

Sun, Z. et al., "Methylphenidate is Stereoselectively Hydrolzyed by Human Carboxylesterase CES1A1," *The Journal of Pharmacology and Experimental Therapeutics*, Aug. 2004, 310(2), 469–476.

Swanson, J. M., et al., "Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children," *Clin. Pharmacology and Therapeut.*, 1999, 66(3), 295–305.

Swanson, J. M., et al., "Analog classroom assessment of Adderall in children with ADHD," *J. Am. Acad. Adolesc. Psychiatry.*, 1998, 37(5), 519–525.

Taylor, M. A., "Attention–deficit hyperactivity disorder on the frontlines: Management in the primary care office," *Comp. Ther.*, 1999, 25(6/7), 313–325.

Teo, S. K., et al., "A 90–day oral gavage toxicity study of D–methylphenidate and D,L–methylphenidate in beagle dogs," *Internat. J. Toxicol.*, 2003, 22, 215–226.

Teo, S. K., et al., "A single–dose, two–way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects," *J. Clin. Pharmacol.*, Feb. 2004, 44, 173–178.

Teo, S. K., et al., "D–Methylphenidate and D,L–methylphenidate are not developmental toxicants in rats and rabbits," *Birth Defects Research (Part B)*, 2003, 68, 162–171.

Teo, S. K., et al., "D–Methylphenidate is non–genotoxic in *in vitro* and *in vivo* assays," *Mutation Research*, 2003, 537, 67–69.

Teo. S. K., et al., "Neurobehavioral effects of racemic threo–methylphenidate and its D and L enantiomers in rats," *Pharmacology, Biochemistry, and Behavior*, 2003, 74, 747–754.

Teo, S., et al., "A 90–day oral gavage toxicity study of D–methylphenidate and D,L–methylphenidate in Sprague–Dawley rats," *Toxicology*, 2002, 179, 183–196.

Teo, S.K. et al., "The perinatal and postnatal toxicity of D–methylphenidate and D,L–methylphenidate in rats," *Reproductive Toxicology*, 2002, 16, 353–366.

Thai, D.L., et al., "Comparative Pharmacokinetics and Tissue Distribution of the d–enantiomers of Para–substituted Methylphenidate Analogs," *Drug Metabolism and Disposition*, 1999, 27(6).

Thomson, M.R. et al., "Enantioselective Transesterification of Methylphenidate to Ethylphenidate After Coadministration with Ethanol," *Thirty–First Annual ACCP Meeting Abstracts*, Abstract No. 80, 2002.

Tripp, G. and Alsop, B., "Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder," *J. Clin. Child Psychology*, 1999, 28(3), 366–375.

Volkow, N. D. et al., "Mechanism of action of methylphenidate: Insights from PET imaging studies," *Journal of Attention Disorders*, 2002, 9(Suppl. 1/2002), S–31–S43.

Volkow, N.D. et al., "Effects of Methylphenidate on Regional Brain Glucose Metabolism in Humans: Relationship to Dopamine D_2 Receptors," *Am J Psychiatry*, Jan. 1997, 154(1), 50–55.

Volkow, N.D. et al., "Evidence That Methylphenidate Enhances the Saliency of a Mathematical Task by Increasing Dopamine in the Human Brain," *Am. J. Psychiatry*, Jul. 2004, 161(7), 1173–1180.

Volkow, N D. et al., "Temporal relationship between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects," *Psychopharmacology*, 1996, 123, 26–33.

Ward, M. F., et al., "The Wender Utah rating scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder," *Am. J. Psychiatry*, 1993, 150(6), 885–890.

Weiler, M. D., et al., "Mother and Teacher Reports of ADHD Symptoms: DSM–IV Questionnaire Data," *J. Am. Acad. Child Adolesc. Psychiatry*, Sep. 1999, 38(9), 1139–1147.

Weiss, M., et al., "A post hoc analysis of d–threo–methylphenidate hydrochloride (Focalin) versus d,l–threo–methylphenidate hydrochloride (Ritalin)," *J. Am. Acad, Adolesc. Psychiatry*, Nov. 2004, 43(11), 1415–1421.

Wigal, S., et al., "A double–blind, placebo–controlled trial of dexmethylphenidate hydrochloride and d,l–threo–methylphenidate hydrochlorid in children with attention–deficit/hyperactivity disorder," *J. Am. Acad. Adolesc. Psychiatry*, Nov. 2004, 43(11), 1406–1414.

Zametkin, A. J. and Ernst, M., "Problems in the management of attention–deficit/hyperactivity disorder," *New. Eng. Jour. Med.*, 1999, 340(1), 40–46.

Zito, J. M., et al., "Trends in the prescribing of psychotropic medications to preschoolers," *J. Am. Med. Assn.*, 2000, 283(8), 1025–1030.

Complaint, filed Aug. 19, 2004, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Answer and Counterclaim of Defendant Teva Pharmaceuticals USA, Inc., filed Nov. 9, 2004, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Plaintiffs' Reply to Defendant's Counterclaim, filed Nov. 29, 2004, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharm AG* v. *Teva Pharmaceuticals USA, Inc.*

Redacted Amended Answer and Counterclaims of Defendant Teva Pharmaceuticals USA, Inc., filed Nov. 9, 2005, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Plaintiffs' Reply to Defendant's Amended Counterclaims, filed Dec. 5, 2005, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Eckerman, D.A., et al., "Enantioselective behavioral effects of threo–methylphenidate in rats," *Pharmacology Biochemistry & Behavior*, 1991, 40, 875–880.

Patrick, K.S., et al., "Pharmacology of the enantiomers of threo–methylphenidate," *J. of Pharmacology and Experimental Therapeutics*, 1986, 152–158.

Srinivas, N.R., et al., "Enantioselective pharmacokinetics and pharmacodynamics of dl–threo–methylphenidate in children with attention deficit hyperactivity disorder," *Clinical Pharmacology & Therapeutics*, 1992, 52(2), 561–568.

Bioequivalence of Methylphenidate Immediate–Release Tablets Using a Replicated Study Design to Characterize Intrasubject Variability; Meyer et al., *Pharmaceutical Research*, vol. 17, No. 4 (2000).

Bioequivalence of Methylphenidate Tablets; Jarvi, et al., Abstract PPDM 8169, Pharmaceutical Research, vol. 7, No. 9 (1990).

Quinn et al., 2004, *J. Am. Child Adolesc. Psychiatry* 43(11):1422–1429.

Wigal et al., 2004, *J. Am. Child Adolesc. Psychiatry* 43(11):1406–1414.

Weiss et al., 2004, *J. Am. Child Adolesc. Psychiatry* 43(11):1415–1421.

Arnold et al., 2004, *J. Am. Child Adolesc. Psychopharmacol.* 14(4):542–554.

Silva et al., 2004, *J. Am. Child Adolesc. Psychopharmacol.* 14(4):555–563.

Jaffe, ed., 1992, *WIll the Real Ritalin Please Stand Up?, ADDendum* 10:1–3.

* cited by examiner

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim **1** is determined to be patentable as amended.

Claims **2, 3** and **4**, dependent on an amended claim, are determined to be patentable.

New claims **5–40** are added and determined to be patentable.

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof *mixed with a pharmaceutically acceptable carrier, diluent or excipient,* said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

5. The pharmaceutical unit dosage of claim 1 wherein said excipient is a tableting excipient.

6. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of mannitol, lactose, talc, glycine, stearic acid and saccharin.

7. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of lactose, corn starch, polyethylene glycol, talc and magnesium stearate.

8. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of microcrystalline cellulose, sodium lauryl sulfate and magnesium stearate.

9. The pharmaceutical unit dosage of claim 1 that comprises a pharmaceutically acceptable salt of D-threo-methylphenidate.

10. The pharmaceutical unit dosage of claim 9 that comprises a hydrochloride salt of D-threo-methylphenidate.

11. The pharmaceutical unit dosage of claim 4 that is a solid oral dosage form.

12. The pharmaceutical unit dosage of claim 11 that is a tablet.

13. The pharmaceutical unit dosage of claim 4 that is a capsule.

14. The pharmaceutical unit dosage of claim 4 that is a dragee.

15. The pharmaceutical unit dosage of claim 1 that is suitable for parenteral administration.

16. The pharmaceutical unit dosage of claim 1 that is suitable for transdermal administration.

17. The pharmaceutical unit dosage of claim 16 that is a transdermal patch.

18. A pharmaceutical unit dosage comprising 1 milligram of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

19. The pharmaceutical unit dosage of claim 18 that is a tablet.

20. The pharmaceutical unit dosage of claim 19 that comprises a hydrochloride salt of D-threo-methylphenidate.

21. A pharmaceutical unit dosage comprising 2 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

22. The pharmaceutical unit dosage of claim 21 that is a tablet.

23. The pharmaceutical unit dosage of claim 22 that comprises a hydrochloride salt of D-threo-methylphenidate.

24. A pharmaceutical unit dosage comprising 2½ milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

25. The pharmaceutical unit dosage of claim 24 that is a tablet.

26. The pharmaceutical unit dosage of claim 25 that comprises a hydrochloride salt of D-threo-methylphenidate.

27. A tablet comprising 5 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

28. The tablet of claim 27 that comprises a hydrochloride salt of D-threo-methylphenidate.

29. A pharmaceutical unit dosage comprising 10 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

30. The pharmaceutical unit dosage of claim 29 that is a tablet.

31. The pharmaceutical unit dosage of claim 30 that comprises a hydrochloride salt of D-threo-methylphenidate.

32. A pharmaceutical unit dosage comprising 12 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically

acceptable carrier, diluent or excipient, said dosage having less that 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

33. The pharmaceutical unit dosage of claim 32 that is a tablet.

34. The pharmaceutical unit dosage of claim 33 that comprises a hydrochloride salt of D-threo-methylphenidate.

35. A pharmaceutical unit dosage comprising 20 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

36. The pharmaceutical unit dosage of claim 35 that is a tablet.

37. The pharmaceutical unit dosage of claim 36 that comprises a hydrochloride salt of D-threo-methylphenidate.

38. A pharmaceutical unit dosage comprising 50 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

39. The pharmaceutical unit dosage of claim 38 that is a tablet.

40. The pharmaceutical unit dosage of claim 39 that comprises a hydrochloride salt of D-threo-methylphenidate.

* * * * *

US006355656C1

(12) EX PARTE REEXAMINATION CERTIFICATE (5729th)

United States Patent

Zeitlin et al.

(10) Number: US 6,355,656 C1
(45) Certificate Issued: *Mar. 27, 2007

(54) **PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL**

(75) Inventors: **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

Reexamination Request:
No. 90/007,177, Aug. 18, 2004

Reexamination Certificate for:
Patent No.: **6,355,656**
Issued: **Mar. 12, 2002**
Appl. No.: **09/318,151**
Filed: **May 25, 1999**

(*) Notice: This patent is subject to a terminal disclaimer.

Certificate of Correction issued Jul. 29, 2003.

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation-in-part of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned.

(51) **Int. Cl.**
A61K 31/445 (2006.01)

(52) **U.S. Cl.** **514/317**
(58) **Field of Classification Search** 514/317
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,838,519	A *	6/1958	Rometsch	546/238
2,957,880	A	10/1960	Rometsch et al.	260/294
4,137,300	A	1/1979	Sheth et al.	424/460
5,733,756	A	3/1998	Zeitlin et al.	435/122
5,773,478	A *	6/1998	Richards et al.	514/649
5,908,850	A	6/1999	Zeitlin et al.	514/315
6,221,883	B1	4/2001	Baldessarini	514/317
6,395,752	B1	5/2002	Midha et al.	514/317

FOREIGN PATENT DOCUMENTS

WO 96/41617 A1 12/1996

OTHER PUBLICATIONS

Patrick et al., "Distribution of Methylphenidate and P-Hydroxymethylphenidate in Rats", Journal of Pharmacology and Experimental Therapeutics, 1984, vol. 231, No. 1, pp. 61–65.*

Aoyama et al., Kinetic Analysis of Enantiomers of threo-Methylphenidate and Its Metabolite in Two Healthy Subjects after Oral Administration as Determined by a Gas Chromatographic–Mass Spectrometric Method, 1990, vol. 79, No. 6, pp. 465–469.*

Aoyama, T. et al., "Pharmacodynamic Modeling for Change of Locomotor Activity by Methyllphenidate in Rats," *Pharmaceutical Research*, 1997, 14(11), 1601–1606.

Aoyama, T. et al., "Pharmacokinetics and pharmacodynamics of methylphenidate enantiomers in rats," *Psychopharmacology*, 1996, 127, 117–122.

Aoyama, T., et al., "Nonlinear kinetics of threo–methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers," *Eur. J. Clin. Pharmacol.*, 1993, 44, 79–84.

Barkley, R. A., et al., "The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow–up study," *J. Am. Acad. Adolesc. Psychiatry.*, 1990, 29(4), 546–557.

Baughman, Jr., F. A., "Treatment of Attention–Deficit/Hyperactivity Disorder," *JAMA.*, Apr. 28, 1999, 218(16), 1490–1491.

Bruera, E., and Neumann, C. M., "The uses of psychotropics in symptom management in advanced cancer," *Psycho–Oncology.*, 1998, 7, 346–358.

Carey, W. B., "What the multimodal treatment study of children with attention–deficit/hyperactivity disorder did and did not say about the use of methylphenidate for attention deficits," *Pediatrics*, 2000, 863–864.

Challman, T.D., et al., "Methylphenidate: its pharmacology and uses," *Mayo Clin Proc.*, 2000, 75, 711–721.

Chapin, R. et al., "*Methylphenidate hydrochloride*," Environmental Health Perspectives, 1997, 105 (supp 1), 319.

Coyle, J. T., "Psychotic drug use in very young children," *J. Am. Med. Assn.*, 2000, 283(8), 1059–1060.

Davids, E. et al., "Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6–hydroxydopamine lesioning," *Psychopharmacology*, 2002, 160, 92–98.

Ding, Y.–S. et al., "Chiral drugs: comparison of the pharmacokinetics of [11C]d–threo and l–threo–methylphenidate in the human and baboon brain," *Psychopharmacology*, 1997, 131, 71–78.

Ding, Y.–S. et al., "Is the L–threo Enantiomer of Methylphenidate (Ritalin) Inactive in the Brain when the Drug is Given Orally?" *ACNP 41st Annual Meeting*, Dec. 8–12, 2002, Scientific Abstract No. 119.

Ding, Y–S. et al., "Brain Kinetics of Methylphenidate (Ritalin) Enantiomers After Oral Administration," *Synapse*, Sep. 2004, 53, 168–175.

Garland, E. J., "Pharmacotherapy of adolescent attention deficit hyperactivity disorder: challenges, choices and caveats," *J. Psychopharmacology.*, 1998, 12(4), 385–395.

Golden, G. S., "Role of attention deficit hyperactivity disorder in learning disabilities," *Seminars in Neurology.*, 1991, 11(1), 35–41.

(Continued)

Primary Examiner—Dwayne C. Jones

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

OTHER PUBLICATIONS

Goldman, L. S., et al., "Diagnosis and treatment of attention–deficit/hyperactivity disorder in children and adolescents," *J. Am. Med. Assn.*, 1998, 279(14), 1100–1107.

Jadad, A. R., et al., "Review: Pharmacologic interventions are more effective than non–pharmacologic for attention–deficit hyperactivity disorder," *Therapeutics, ACP Journal Club.*, Nov./Dec. 2000, 110.

Jensen, P. S., et al., "Are stimulants over–prescribed? Treatment of ADHD in four U.S. communities," *J. Am. Acad. Adolesc. Psychiatry*, 1999, 37(7), 797–804.

Jonkman, L.M. et al., "Differences in plasma concentrations of the D– and L–threo methylphenidate enantiomers in responding and non–responding children with attention–deficit hyperactivity disorder," *Psychiatry Research*, 1998, 78, 115–118.

Kimko, H. C., et al., "Pharmacokinetics and Clinical effectiveness of methylphenidate," *Clin. Pharmacokinetics*, 1999, 37(6), 457–470.

LeFever, G. B., et al., "The extent of drug therapy for attention dificit–hyperactivity disorder among children in public schools," *American Journal of Public Health*, (Sep. 1999), (89)9, 1359–1364.

Lin, J. H., and Lu, A. H., "Role of pharmacokinetics and Metabolism in drug discovery and development," *Pharmacological Reviews*, 1997, 49(4), 403–449.

Llana, M. E. and Crismon, M. L., "Methylphendiate: increased abuse or appropriate use?" *J. Amer. Pharmaceut. Assn.*, 1999, 39(4), 526–530.

MacDougall, M. K., et al., "Symptom control in the pregnant cancer patient," *Seminars in Oncology*, 2000, 27(6), 704–711.

Markowitz, J. S., et al., "Advances in the pharmacotherapy of attention–deficit–hyperactivity disorder: focus on methyl phenidate formulations," *Pharmacotherepy*, 2003, 23(10), 1281–1299.

McCarthy, M., "USA to improve care of children with ADHD," *The Lancet*, 2000, 355, 1161.

Mehta, M. A., et al., "Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain," *J. Neurosci.*, 2000, 20RC65: (1–6).

Modi, N. B. et al., "Dose–Proportional and Stereospecific Pharmacokinetics of Methylphenidate Delivered Using an Osmotic, Controlled–Release Oral Delivery System," *J. Clin. Pharmacol.*, 2000, 40, 1141–1149.

Patrick K S et al "The Absorption Of Sustained–Release Methylphenidate Formulations Compared To An Immediate–Release Formulation," Biopharmaceutics And Drug Disposition, Wiley, Chichester, US, vol. 10, No. 2, 1989, pp. 165–171.

Patrick, K.S. et al., "Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention–Deficit Hyperactivity Disorder," *Human Psychopharmacology*, 1997, 12, 527–546.

Patrick, K.S. et al., "Synthesis, Pharmacology and Human Metabolic Formation of Ethylphenidate: the Transesterification Product of Methylphenidate and Ethanol," *The 56th Southeast Regional Meeting 2004*, Nov. 10–13, 2004 1 page.

Patrick, K.S. et al., "New methylophenidate formulations for the treatment of attention–deficit/hyperactivity disorder," *Expert Opin. Drug Deliv.*, 2005, 2(1), 121–143.

Quinn, D.M.P., "Methylphenidate: The Role of the d–Isomer," undated, Department of Psychiatry, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, 369–373.

Rouhi, A.M, "Chirality of Work, " *C&EN*, May 5, 2003, 56–61.

Sarhill, N., et al., "Methylphenidate for fatigue in advanced cancer: a prospective open–label pilot study," *Am. J. of Hospice & Palliative Care*, 2001, 18(3), 187–192.

Schweitzer J. B., et al., "Attention deficit hyperactivity disorder," *Adv. Pathophysiol. And Treat. Psychiatric Disorders: Implications for Internal Med.*, 2001, 85(3), 757–777.

Shader R.I. et al., "Population Pharmacokinetics of Methylphenidate in Children with Attention–Deficit Hyperactivity Disorder," *J. Clin. Pharmacol.*, 1999, 39, 775–785.

Spencer, T., et al., "Pharmacotherapy of attention–deficit hyperactivity disorder across the life cycle," *J. Am. Acad. Adolesc. Psychiatry.*, 1996, 35(4), 409–432.

Srinivas, N.R. "Role of Stereoselective Assays in Bioequivalence Studies of Racemic Drugs: Have We Reached a Consensus?" *J. Clin. Pharmacol.*, Feb. 2004, 44, 115–119.

Srinivas, N.R., et al., "Enantiomeric Drug Development: Issues, Considerations, and Regulatory Requirements," *Journal of Pharmaceutical Sciences*, Sep. 2001, 90(9), 1205–1215.

Stein, M. A., et al., "Methylphenidate dosing: Twice daily versus three times daily," *Pediatrics*, 1996, 98(4), 784–756.

Sun, Z. et al., "Methylphenidate is Stereoselectively Hydrolzyed by Human Carboxylesterase CES1A1," *The Journal of Pharmacology and Experimental Therapeutics*, Aug. 2004, 310(2), 469–476.

Swanson, J. M., et al., "Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children," *Clin. Pharmacology and Therapeut.*, 1999, 66(3), 295–305.

Swanson, J. M., et al., "Analog classroom assessment of Adderall in children with ADHD," *J. Am. Acad. Adolesc. Psychiatry.*, 1998, 37(5), 519–525.

Taylor, M. A., "Attention–deficit hyperactivity disorder on the frontlines: Management in the primary care office," *Comp. Ther.*, 1999, 25(6/7), 313–325.

Teo, S. K., et al., "A 90–day oral gavage toxicity study of D–methylphenidate and D,L–methylphenidate in beagle dogs," *Internat. J. Toxicol.*, 2003, 22, 215–226.

Teo, S. K., et al., "A single–dose, two–way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects," *J. Clin. Pharmacol.*, Feb. 2004, 44, 173–178.

Teo, S. K., et al., "D–Methylphenidate and D,L–methylphenidate are not developmental toxicants in rats and rabbits," *Birth Defects Research (Part B)*, 2003, 68, 162–171.

Teo, S. K., et al., "D–Methylphenidate is non–genotoxic in *in vitro* and *in vivo* assays," *Mutation Research*, 2003, 537, 67–69.

Teo. S. K., et al., "Neurobehavioral effects of racemic threo–methylphenidate and its D and L enantiomers in rats," *Pharmacology, Biochemistry, and Behavior*, 2003, 74, 747–754.

Teo, S., et al., "A 90–day oral gavage toxicity study of D–methylphenidate and D,L–methylphenidate in Sprague–Dawley rats," *Toxicology*, 2002, 179, 183–196.

Teo, S.K. et al., "The perinatal and postnatal toxicity of D–methylphenidate and D,L–methylphenidate in rats," *Reproductive Toxicology*, 2002, 16, 353–366.

Thai, D.L., et al., "Comparative Pharmacokinetics and Tissue Distribution of the d–enantiomers of Para–substituted Methylphenidate Analogs," *Drug Metabolism and Disposition*, 1999, 27(6).

Thomson, M.R. et al., "Enantioselective Transesterification of Methylphenidate to Ethylphenidate After Coadministration with Ethanol," *Thirty–First Annual ACCP Meeting Abstracts*, Abstract No. 80, 2002.

Tripp, G. and Alsop, B., "Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder," *J. Clin. Child Psychology*, 1999, 28(3), 366–375.

Volkow, N. D. et al., "Mechanism of action of methylphenidate: Insights from PET imaging studies," *Journal of Attention Disorders*, 2002, 9(Suppl. 1/2002), S–31–S43.

Volkow, N.D. et al., "Effects of Methylphenidate on Regional Brain Glucose Metabolism in Humans: Relationship to Dopamine D_2 Receptors," *Am J Psychiatry*, Jan. 1997, 154(1), 50–55.

Volkow, N.D. et al., "Evidence That Methylphenidate Enhances the Saliency of a Mathematical Task by Increasing Dopamine in the Human Brain," *Am. J. Psychiatry*, Jul. 2004, 161(7), 1173–1180.

Volkow, N D. et al., "Temporal relationship between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects," *Psychopharmacology*, 1996, 123, 26–33.

Ward, M. F., et al., "The Wender Utah rating scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder," *Am. J. Psychiatry*, 1993, 150(6), 885–890.

Weiler, M. D., et al., "Mother and Teacher Reports of ADHD Symptoms: DSM–IV Questionnaire Data," *J. Am. Acad. Child Adolesc. Psychiatry*, Sep. 1999, 38(9), 1139–1147.

Weiss, M., et al., "A post hoc analysis of d–threo–methylphenidate hydrochloride (Focalin) versus d,l–threo–methylphenidate hydrochloride (Ritalin)," *J. Am. Acad, Adolesc. Psychiatry*, Nov. 2004, 43(11), 1415–1421.

Wigal, S., et al., "A double–blind, placebo–controlled trial of dexmethylphenidate hydrochloride and d,l–threo–methylphenidate hydrochlorid in children with attention–deficit/hyperactivity disorder," *J. Am. Acad. Adolesc. Psychiatry*, Nov. 2004. 43(11), 1406–1414.

Zametkin, A. J. and Ernst, M., "Problems in the management of attention–deficit/hyperactivity disorder," *New. Eng. Jour. Med.*, 1999, 340(1), 40–46.

Zito, J. M., et al., "Trends in the prescribing of psychotropic medications to preschoolers," *J. Am. Med. Assn.*, 2000, 283(8), 1025–1030.

Complaint, filed Aug. 19, 2004, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Answer and Counterclaim of Defendant Teva Pharmaceuticals USA, Inc., filed Nov. 9, 2004, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Plaintiffs' Reply to Defendant's Counterclaim, filed Nov. 29, 2004, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharm AG* v. *Teva Pharmaceuticals USA, Inc.*

Redacted Amended Answer and Counterclaims of Defendant Teva Pharmaceuticals USA, Inc., filed Nov. 9, 2005, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Plaintiffs' Reply to Defendant's Amended Counterclaims, filed Dec. 5, 2005, Civil Action No. 04–4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG* v. *Teva Pharmaceuticals USA, Inc.*

Eckerman, D.A., et al., "Enantioselective behavioral effects of threo–methylphenidate in rats," *Pharmacology Biochemistry & Behavior*, 1991, 40, 875–880.

Patrick, K.S., et al., "Pharmacology of the enantiomers of threo–methylphenidate," *J. of Pharmacology and Experimental Therapeutics*, 1986, 152–158.

Srinivas, N.R., et al., "Enantioselective pharmacokinetics and pharmacodynamics of dl–threo–methylphenidate in children with attention deficit hyperactivity disorder," *Clinical Pharmacology & Therapeutics*, 1992, 52(2), 561–568.

Bioequivalence of Methylphenidate Immediate–Release Tablets Using a Replicated Study Design to Characterize Intrasubject Variability; Meyer et al., *Pharmaceutical Research*, vol. 17, No. 4 (2000).

Biocquivalence of Methylphenidate Tablets; Jarvi, et al., Abstract PPDM 8169, Pharmaceutical Research, vol. 7, No. 9 (1990).

Quinn et al., 2004, *J. Am. Child Adolesc. Psychiatry* 43(11):1422–1429.

Wigal et al., 2004, *J. Am. Child Adolesc. Psychiatry* 43(11):1406–1414.

Weiss et al., 2004, *J. Am. Child Adolesc. Psychiatry* 43(11):1415–1421.

Arnold et al., 2004, *J. Am. Child Adolesc. Psychopharmacol.* 14(4):542–554.

Silva et al., 2004, *J. Am. Child Adolesc. Psychopharmacol.* 14(4):555–563.

Jaffe, ed., 1992, *WIll the Real Ritalin Please Stand Up?, ADDendum* 10:1–3.

* cited by examiner

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim **1** is determined to be patentable as amended.

Claims **2**, **3** and **4**, dependent on an amended claim, are determined to be patentable.

New claims **5–40** are added and determined to be patentable.

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof *mixed with a pharmaceutically acceptable carrier, diluent or excipient,* said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

5. The pharmaceutical unit dosage of claim 1 wherein said excipient is a tableting excipient.

6. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of mannitol, lactose, talc, glycine, stearic acid and saccharin.

7. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of lactose, corn starch, polyethylene glycol, talc and magnesium stearate.

8. The pharmaceutical unit dosage of claim 1 wherein the pharmaceutically acceptable carrier, diluent or excipient is selected from the group consisting of microcrystalline cellulose, sodium lauryl sulfate and magnesium stearate.

9. The pharmaceutical unit dosage of claim 1 that comprises a pharmaceutically acceptable salt of D-threo-methylphenidate.

10. The pharmaceutical unit dosage of claim 9 that comprises a hydrochloride salt of D-threo-methylphenidate.

11. The pharmaceutical unit dosage of claim 4 that is a solid oral dosage form.

12. The pharmaceutical unit dosage of claim 11 that is a tablet.

13. The pharmaceutical unit dosage of claim 4 that is a capsule.

14. The pharmaceutical unit dosage of claim 4 that is a dragee.

15. The pharmaceutical unit dosage of claim 1 that is suitable for parenteral administration.

16. The pharmaceutical unit dosage of claim 1 that is suitable for transdermal administration.

17. The pharmaceutical unit dosage of claim 16 that is a transdermal patch.

18. A pharmaceutical unit dosage comprising 1 milligram of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

19. The pharmaceutical unit dosage of claim 18 that is a tablet.

20. The pharmaceutical unit dosage of claim 19 that comprises a hydrochloride salt of D-threo-methylphenidate.

21. A pharmaceutical unit dosage comprising 2 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

22. The pharmaceutical unit dosage of claim 21 that is a tablet.

23. The pharmaceutical unit dosage of claim 22 that comprises a hydrochloride salt of D-threo-methylphenidate.

24. A pharmaceutical unit dosage comprising 2½ milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

25. The pharmaceutical unit dosage of claim 24 that is a tablet.

26. The pharmaceutical unit dosage of claim 25 that comprises a hydrochloride salt of D-threo-methylphenidate.

27. A tablet comprising 5 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

28. The tablet of claim 27 that comprises a hydrochloride salt of D-threo-methylphenidate.

29. A pharmaceutical unit dosage comprising 10 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

30. The pharmaceutical unit dosage of claim 29 that is a tablet.

31. The pharmaceutical unit dosage of claim 30 that comprises a hydrochloride salt of D-threo-methylphenidate.

32. A pharmaceutical unit dosage comprising 12 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically

acceptable carrier, diluent or excipient, said dosage having less that 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

33. The pharmaceutical unit dosage of claim 32 that is a tablet.

34. The pharmaceutical unit dosage of claim 33 that comprises a hydrochloride salt of D-threo-methylphenidate.

35. A pharmaceutical unit dosage comprising 20 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

36. The pharmaceutical unit dosage of claim 35 that is a tablet.

37. The pharmaceutical unit dosage of claim 36 that comprises a hydrochloride salt of D-threo-methylphenidate.

38. A pharmaceutical unit dosage comprising 50 milligrams of D-threo-methylphenidate or a pharmaceutically acceptable salt thereof mixed with a pharmaceutically acceptable carrier, diluent or excipient, said dosage having less than 10% by weight of other stereoisomers of methylphenidate or the salt thereof.

39. The pharmaceutical unit dosage of claim 38 that is a tablet.

40. The pharmaceutical unit dosage of claim 39 that comprises a hydrochloride salt of D-threo-methylphenidate.

* * * * *

EXHIBIT C

US006528530B2

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

(10) **Patent No.: US 6,528,530 B2**
(45) **Date of Patent: *Mar. 4, 2003**

(54) **PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL**

(75) Inventors: **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

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

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/955,556**

(22) Filed: **Sep. 18, 2001**

(65) **Prior Publication Data**

US 2002/0035126 A1 Mar. 21, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/318,151, filed on May 25, 1999, now Pat. No. 6,355,656, which is a continuation-in-part of application No. 08/827,230, filed on Apr. 2, 1997, now Pat. No. 5,908,850, which is a continuation of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned.

(51) **Int. Cl.**[7] **A61K 31/445**
(52) **U.S. Cl.** **514/317**
(58) **Field of Search** 514/317

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,507,631	A	5/1950	Hartmann et al.	260/294
2,957,880	A	10/1960	Rometsch	546/233
4,992,445	A	2/1991	Lawter et al.	514/279
5,104,899	A	4/1992	Young et al.	514/646
5,114,946	A	5/1992	Lawter et al.	514/279
5,217,718	A	6/1993	Colley et al.	424/449
5,283,193	A	2/1994	Yamamoto et al.	435/280
5,284,769	A	2/1994	Evans et al.	435/280
5,331,000	A	7/1994	Young et al.	514/570
5,362,755	A	11/1994	Barberich et al.	514/649
5,375,693	A	12/1994	Woosley et al.	514/317
5,449,743	A	9/1995	Hartmann et al.	528/355
5,773,478	A	6/1998	Richards et al.	514/649
5,837,284	A	11/1998	Mehta et al.	424/456
5,874,090	A	2/1999	Baker et al.	424/600
5,908,850	A	6/1999	Zeitlin et al.	514/315
6,255,325	B1 *	7/2001	Dariani et al.	514/317

FOREIGN PATENT DOCUMENTS

WO	WO 97/03671	2/1997
WO	WO 97/03672	2/1997
WO	WO 97/03673	2/1997
WO	WO 99/03471	1/1999

OTHER PUBLICATIONS

Angrist et al., *J. Clin. Psychopharma.*, 1992, 12, 268–272.
Barkley et al., *Pediatrics*, 1990, 86, 184–192.
Barkley et al., *Pediatrics*, 1991, 87, 519–531.
Golinko, *Prog. Neuro–Psychopharmacol. & Biol. Phsychiat.*, 1984, 8, 1–8.
Aoyama et al., "Pharmacolinetics and pharmacodynamics of (+)–threo–methylphenidate enantiomer in patients with hypersomnia", *Clin. Pharmacol. Ther.*, 1994, 55(3), 270–276.
Bowden et al., "Reactions of Carbonyl Compounds in Basic Solutions the Alkaline Hydrolysis of N–Methyl, N–Phenyl, and Bicyclo Lactams Penicillins, and N–Alkyl–N–methylacetamides", *J. Chem. Soc. Perkin Trans.*, 1990, 12, 2111–2116.
Brown, "Pharmacological Action and Drug Development", *Chirality in Drug Design and Synthesis*, Academic Press Inc., 1990, 4–7.
Brown G., "The Use of Methylphenidate for Cognitive Decline Associated with HIV Disease", *Int'l J. Psychiatry Med.*, 1995, 25(1), 21–37.
Corey et al., "A New Synthetic Approach to the Penicillins", *J. Am. Chem. Soc.*, 1965, 87(11), 2518–2519.
Ding et al., "Cis– and trans–Axetidin–2–ones from Nitrones and Copper Acetylide", *J. Chem. Soc. Perkin*, 1976, 22, 2382–2386.
Douzenis et al., "Phychiatric Disorder in HIV Disease: Description of 200 Referrals to a Liaison psychiatry Service", *Proc. 7th. Int'l Conf. AIDS*, 1991, 215 (M.B.2135—Summary).
Earle et al., "Synthesis and Hydrolysis of some Fused–ring β–Lactams", *J. Chem. Soc.*, 1969, 2093–2098.
Greenhill L., "Attention–Deficit Hyperactivity Disorder", *Child & Adol. Psych. Clin. N.A.*, 1995, 4(1), 123–168.
Greenhill, "Pharmacologic Treatment of Attention Deficit Hyperactivity Disorder", *Pediatric Psychopharmacology*, 1992, 15(1), 1–27.
Holmes et al., "Psychostimulant Response in Aids–Related Complex Patients", *J. Clin. Psychiatry*, 1989, 50(1), 5–8 (Biosis Abstract No. 87129969).
Klibanov, "Asymmetric Transformations Catalyzed by Enzymes in Organic Solvents", *Acc. Chem. Res.*, 1990, 23, 114–120.
Moll F., "Darstellung von 1–Aza–bicyclo[4.2.0] octan–2–on", *Naturforsch Teil B.*, 1966, 21, 297.
Navia et al., "The AIDS Dementia Complex: I. Clinical Features", *Annals of Neurology*, 1986, 19, 517–524.
Patrick et al., "Pharmacology of the Enantiomers of threo–Methylphenidate", *J. Pharmacol & Exp. Terhap.*, 1987, 241, 152–158.

(List continued on next page.)

Primary Examiner—Raymond Henley, III
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Phenidate drug formulations are provided having reduced potential for drug abuse. Dosage forms for treating Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS Dementia Complex and cognitive decline in HIV-AIDS are provided which minimize drug hypersensitivity, toxicity, side effects, euphoric effect, and drug abuse potential. Such dosage forms comprise D-threo stereoisomer of a phenidate in the substantial absence of all other stereoisomers.

4 Claims, No Drawings

OTHER PUBLICATIONS

Rieder et al., "Diagnosis of Sulfonamide Hypersensitivity Reactions by In–Vitro "Rechallenge" with Hydroxylamine Metabolites", *Ann. Intern. Med.*, 1989, 110, 286–289.
Scott, "Stereoisomers and Drug Toxicity", *Drug Safety*, 1993, 8(2), 149–159.
Srinivas et al., "Enantioselective Pharmacokinetics of dl–threo–Methylphenidate in Humans", *Pharmacol Res.*, 1993, 10(1), 14–21.
Srinivas et al., "Enantioselective Pharmacolinetics and Pharmacodynamics of Racemic Threo–Methylphenidate in Children with Deficit Hyperactivity Disorder", *Clin. Pharmacol.*, 1992, 52(5), 561–568 (Biosis Abstract No. 95066168).
Srinivas et al., "Enantiomeric Gas Chromatography Assay with Electron Capture Detection for d–Ritalinic Acid in Plasma", *J. Chromatagraph*, 1990, 530, 327–336.
Srinivas et al., "Sterioselective Disposition of Methylphenidate in Children with Attention Deficit Disorder", *J. Pharmacol. Exp. Ther.*, 1987, 241(1), 300–306.
Staal et al., "Glutathione deficiency and human immunodeficiency virus infection", *Lancet*, 1992, 339, 909–912.
Uetrecht et al., "Idiosyncratic Drug Reactions: Possible Role of Reactive Metabolites Generated by Leukocytes", *Pharmacol Res.*, 1989, 6(4), 265–273.
White et al., "Methylphenidate as a Treatment for Depression in Acquired Immunodeficiency Syndrome: An n–of–1 Trial", *J. Clin. Psychiatry*, 1992, 53(5), 153–156.

* cited by examiner

PHENIDATE DRUG FORMULATIONS HAVING DIMINISHED ABUSE POTENTIAL

This application is a continuation of U.S. application Ser. No. 09/318,151 filed May 25, 1999, now U.S. Pat. No. 6,355,656 which is a CIP of U.S. application Ser. No. 08/827,230 filed Apr. 2, 1997, now U.S. Pat. No. 5,908,850, which is a continuation of U.S. application Ser. No. 08/567,131 filed Dec. 4, 1995, now abandoned the contents of which are incorporated herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to phenidate drug compositions for treating certain Central Nervous System disorders such as Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD), HIV/AIDS cognitive decline, and AIDS Dementia Complex. This invention features such drugs having decreased side effects, reduced euphoric effect, and reduced drug abuse potential.

BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD) is the most commonly diagnosed nervous system illness in children. Patrick et al., J. Phamacol. & Exp. Therap., 241:152–158 (1987). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by increased symptoms of hyperactivity in patients. Racemic methylphenidate (e.g., Ritalin®) is a mild Central Nervous System stimulant with pharmacological activity qualitatively similar to amphetamines, and has long been the drug of choice for symptomatic treatment of ADD in children. Graenhill, L., Child & Adol. Psych. Clin. N.A., Vol. 4, Number 1:123–165 (1995).

Current administration of racemic methylphenidate, however, often results in notable aide effects such as anorexia, weight loss, insomnia, dizziness and dysphoria. Additionally, racemic methylphenidate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for substance abuse in patients.

At least 70% of HIV-infected individuals who have developed Acquired Immunodeficiency Syndrome (AIDS) eventually manifest cognitive defects, and many display signs and symptoms of dementia. See Navia at al., *Annals of Neurology,* 19:517–524 (1986). Complaints of forgetfulness, loss of concentration, fatigue, depression, loss of attentiveness, mood swings, and thought disturbance are common in patients with Human Immunodeficiency Virus (HIV) disease. Douzenis et al., *Proc. 7th int'l. Conf. AIDS,* 1, MB, 2135:215 (1991); Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989). Racemic methylphenidate has been used to treat cognitive decline in AIDS/ARC patients. Brown, G., Intl. *J. Psych. Med.* 25(1): 21–37 (1995). As described above, racemic methylphenidate, a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation, and thus carries a high potential for drug abuse.

U.S. Pat. No. 2,507,631, to Hartmann et al. describes methylphenidate and processes for making the same. U.S. Pat. No. 2,957,880, to Rometsch et al. describes the conversion of α-aryl-α-piperidyl-(2)-acetic acids and derivatives thereof (including methylphenidate) into their respective racemates. Each of these patents is incorporated herein by reference.

Holmes et al., *J. Clin. Psychiatry,* 50:5–8 (1989) reported on the use of racemic methylphenidate (Ritalin®) and dexamphetamines in the treatment of cognitive impairment in AIDS patients.

Srinivas et al., *J. Pharmacol. & Exp Therap.,* 241:300306 (1987) described use of racemic dl-threo-methylphenidate (Ritalin®) in the treatment of ADD in children. This study noted a 5-fold increase in plasma levels of d-threo-methylphenidate in children treated with racemic methylphenidate, but was otherwise inconclusive with regard to the efficacy of a single methylphenidate isomer at therapeutically significant doses.

Srinivas et: al., *Clin. Pharmacol. Ther.,* 52:561–568 (1992) studied the administration of dl-threo, d-threo and l-threo-methylphenidate to children suffering from ADHD. While Srinivas et al. reported the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer, this study investigated neither the adverse side effects of the l-threo isomer, nor the euphoric effects of the single isomers or racemate. Single isomer dosages below ½ of the racemate dosage were not studied.

Patrick et al., *J. Pharmacol. & Exp. Therap.,* 241:152158 (1986) examined the pharmacology of the enantiomers of threo-methylphenidate, and assessed the relative contribution of each isomer to central and peripheral actions of Ritalin®.

Brown, G., Intl. *J. Psych. Med.,* 25 (1) :21–37 (1995) reported the use of racemic methylphenidate for the treatment of AIDS' cognitive decline.

Patrick et al., Psychopharmacology: The Third Generation of Progress, Raven Press, N.Y. (1987) examined the pharmacokinetics and actions of methylphenidate in the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Patrick noted the d-threo isomer possesses higher activity than the l-threo isomer, and that d-threo methylphenidate may be responsible for the therapeutic activity in the racemic drug.

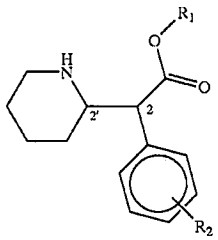
Aoyama et al., *Clin. Pharmacol. Ther.,* 55:270–276 (1994) reported on the use of (+)-threo-methylphenidate in the treatment of hypersomnia. Aoyama et al. describe a correlation between sleep latency in patients and plasma concentration of (+)-threo-methylphenidate.

Glutathione is an important antioxidative agent that protects the body against electrophilic reactive compounds and intracellular oxidants. It has been postulated that HIV-AIDS patients suffer from drug hypersensitivity due to drug overload and an acquired glutathione deficiency. See Uetrecht et al., *Pharmacol. Res.,* 6:265–273 (1989). Patients with HIV infection have demonstrated a reduced concentration of glutathione in plasma, cells and broncho-alveolar lavage fluid. Staal et al., *Lancet,* 339:909–912 (1992). Clinical data suggests that HIV-seropositive individuals display adverse reactions to the simultaneous administration of several otherwise therapeutic drugs. Rieder et al., *Ann. Intern. Med.,* 110:286–289 (1989). It is desirable to provide for the administration of methylphenidate in reduced dosages among patients with drug hypersensitivity due to HIV infection.

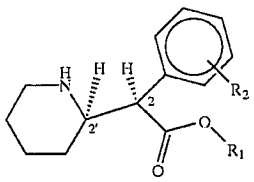
There is a long-felt and very intense need for phenidate drug compositions, especially methyl phenidate, which are less susceptible to unlawful abuse and which exhibit diminished side effects while retaining therapeutic efficacy.

SUMMARY OF INVENTION

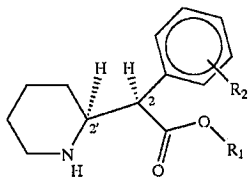
Phenidate drugs in accordance with this invention have the structure:



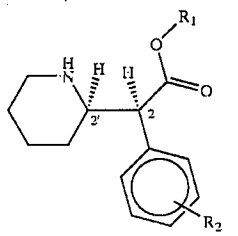
where R_1 is C_1–C_4 alkyl and R_2 is either C_1–C_4 alkyl or hydrogen. Of this family of drugs, methylphenidate, where R_1 is methyl and R_2 is hydrogen, is the most well known, having long been prescribed under the trade mark Ritalin®. Phenidate drugs are α-aryl-α-piperidyl-2-acetic acids and comprise two centers of asymmetry, existing as four separate optical isomers as follows:



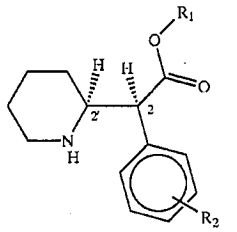
2R,2'R; D-THREO



2R,2'S; D-ERYTHRO



2S,2'R; L-ERYTHRO



2S,2'S; L-THREO

It is known that certain physiological properties of methylphenidate and other phenidate drugs are dependent upon stereochemistry. Thus, while the threo racemate of methylphenidate is understood to produce the desired central nervous system action, the erythro racemate is thought to contribute to hypertensive side effects.

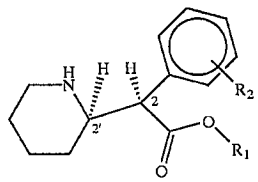
It is now believed, however, that another stereochemical distinction also applies. Studies in animals, children and adults have demonstrated pharmacological activity in the D-threo isomer of methylphenidate (2R,2'R). See Patrick et al., *J. Pharmacol. & Exp. Therap.*, 241:152–158 (1987). The role of the L-threo isomer in toxicity or adverse side effects has not been examined heretofore although the potential for isomer ballast in methylphenidate and other phenidate drugs is of concern for many patient groups, particularly those drug hypersensitive patients as described above.

Although L-threo-methylphenidate is rapidly and stereoselectively metabolized upon oral administration by extensive first pass metabolism, intravenous administration or inhalation results in high L-threo methylphenidate serum levels. Srinivas et al., *Pharmacol. Res.*, 10:14–21 (1993). Intravenous administration and inhalation are methods of choice by drug abusers of current, racemic methylphenidate formulations. It is now believed that the euphoric effect produced by current formulations of methylphenidate is due to the action of L-threo-methylphenidate, rather than the pharmaceutically efficacious D-threo compound.

Accordingly, it has now been discovered that the incorporation into pharmaceutical formulations of the D-threo isomer (2R,2'R) of a phenidate drug, especially methylphenidate, with the substantial exclusion of the other three isomers of the phenidate, especially the L-threo isomer, produces a phenidate medication dosage form which retains high pharmaceutical efficacy levels upon administration to patients, while simultaneously possessing fewer or reduced side-effects, reduced euphoric effect and reduced potential for abuse.

Patients suffering from Attention Deficit Disorder, Attention Deficit Hyperactivity Disorder, AIDS cognitive decline, and AIDS Dementia Complex are benefitted by receiving phenidate drug, especially the preferred methylphenidate, in a dosage form which substantially excludes three of the four stereoisomers, D erythro, Lerythro, and L-threo. Stated alternatively, such dosage forms comprise D-threo phenidate in the substantial absence of L-threo and both erythro stereoisomers.

The present invention also provides dosage forms of phenidate drugs for treating Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder in children and adults while providing for reduced side effects, reduced euphoric effect and reduced potential for abuse. This is accomplished by formulating dosage forms for administration to patients comprising D-threo-phenidate or a pharmaceutically acceptable salt thereof, substantially free of the L-threo isomer and both erythro isomers. The invention further provides methods of treating AIDS-related dementia and related cognitive disorders while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential comprising administering D-threo-phenidate (2R, 2'R) of the formula:



or a pharmaceutically acceptable salt thereof, substantially free of the other three stereoisomeric forms of the drug.

In accordance with the invention, R_1 is methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl. It is preferred that R_1 be methyl. R_2 may be hydrogen, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl or tert-butyl and may appear either ortho, meta or para to the acetic acid moiety. Additional substitutients may also appear in the phenidate drug molecule, either in the aryl ring, in the pipiridine heterocycle of in the ester function, however, extensive substitution is not preferred.

Salts of phenidates, such as the conventional hydrochloride salts, are also within the spirit of the invention and all such salts are specifically contemplated hereby.

Preferably, R_1 is methyl and R_2 is hydrogen such that the phenidate drug is methylphenidate.

Prescription of methylphenidate to treat AIDS cognitive decline and AIDS Dementia Complex associated with HIV infection is becoming increasingly popular. However, high doses in excess of 40 mg/day are not well tolerated by a substantial number of HIV-infected patients when treated over weeks or months. Brown, G., *Int'l J. Psychiatry. Med.*, 25:21–37 (1995). The exclusive D-threo isomer formulations of the present invention enable a lowered dosing therapy with avoidance of the administration of the stereoisomer

believed to be responsible for adverse side effects and abuse potential resulting in improved efficacy for diseased patients and particularly HIV-infected patients.

Racemic methylphenidate and its individual isomers are known. See U.S. Pat. Nos. 2,507,631 and 2,957,880. They can be prepared by conventional techniques, and can be obtained from a variety of commercial sources. Moreover, the D-threo-isomer of methylphenidate and other phenidate drugs can be prepared in accordance with Ser. No. 08/583,317 filed Jan. 5, 1996, which application forms a parent to this application and has been incorporated herein by reference. Examples forming part of this application set forth certain preferred synthetic routes to the phenidate compounds useful in the practice of this invention. Persons of ordinary skill will be able to modify such procedures to prepare the lower alkyl substituted phenyl derivatives and lower alkyl esters contemplated herein without undue experimentation. Thus, preparation of ethyl, propyl, isopropyl etc. esters is a simple matter in view of the synthetic schemes set forth. Likewise, substituting the phenyl ring with one or more alkyl or other substituients may also be accomplished.

The dosage forms of the present invention can be administered orally, rectally, parenterally, or transdermally, alone or in combination with other psychostimulants, antidepressants, and the like to a patient in need of treatment. Oral dosage forms include tablets, capsules, dragees, and other conventional, pharmaceutical forms. Isotonic saline solutions, conveniently containing about 1–40 milligrams of drug per milliliter can be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes. Rectal administration can conveniently be effected through the use of suppositories such as can easily be formulated from conventional carriers such as cocoa butter. Transdermal administration can be effected through the use of transdermal patch delivery systems and the like. The preferred routes of administration are oral and parenteral.

The dosage employed should be carefully titrated to the patient, considering age, weight, severity of the condition, and clinical-profile. Typically, the amount of d-threo-methylphenidate administered will be in the range of 1–50 mg/day, but the actual decision as to dosage will depend upon the exact phenidate drug being employed and will be made by the attending physician as a matter of routine. Such physician can, however, determine an appropriate regime employing well-known medical considerations. Such persons will appreciate that the overall dosage amount will be significantly smaller than that used with the corresponding racemic drug, since the undesired enantiomers are not included in the present dosage forms.

Accordingly, a pharmaceutically effective amount of a phenidate drug in accordance with this invention will be understood by persons of ordinary skill in the art to be that amount of the selected D-threo phenidate which, upon administration to a patient, would result in a sensible and therapeutically useful effect.

When phenidates other than methylphenidate are to be administered, it will be appreciated that the effective amount of drug will likely be different than for methylphenidate. Determination of such amount, however, is well within the routine skill of the practitioner. In accordance with preferred embodiments, from 1 to about 50 mg will be administered to patients, with from about 2 to about 20 mg per day being still more preferred. In still more preferred embodiments, patients will receive from about 2½ to about 12 mg per day.

It is desirable to provide unit dosage forms for administration of compounds of the invention comprising from about 1 to about 50 mg of drug, with amounts of from about 2 to about 20 and particularly from about 2½ to about 12 mg being still more preferred. Oral administration is the protocol of choice, however other routes of administration, such as intravenous, intraperitoneal, rectal and the like may also be employed in formulating the unit dosage forms of this invention. Carriers, diluents and excipients are conventionally employed in formulating unit dosage forms and the same are selected as a matter of routine depending upon the selected route of administration. For oral administration, formulation into tablets using tabletting excipients are conveniently employed, although capsular and other oral forms are also useful.

The present invention provides enhanced relief for patients suffering from Attention Deficit Disorder and Attention Deficit Hyperactivity Disorder while providing for reduced side effects, reduced euphoric effect, and reduced abuse potential through administration of D-threo-methylphenidate substantially free of the L-threo and other isomers. The invention gives rise to methods of treatment of AIDS related dementia and related cognitive disorders with D-threo-methylphenidate substantially free of the remaining isomers.

The term, "substantially free as it applies to a stereoisomer in accordance with a composition of this invention means that the composition contains no more than 10% by weight of the isomer in question. It is preferred that such composition have less than about 2% of the unwanted isomers and even more preferred that less than 1% be present. When applied to a plurality of stereoisomers, then all of the isomers, taken together, comprise no more than 10% by weight of the composition and preferrably less than 2%. It is preferred that compositions characterized as being "substantially free" of all stereoisomers but the D-threo isomer comprise no more than about 5% of other isomers. It is still more preferred that no more than 1% of the undesired isomers be present.

The following examples will serve to further typify the nature of the invention, but should not be construed as a limitation on the scope thereof, which is defined solely by the appended claims.

EXAMPLES

A suitable salt medium for the microbiological transformations described in the following examples has been denominated "media A" and has the following composition:

$MgSO_4$	1.00 g/L
$CaCl_2$	0.021 g/L
$ZnSO_4.7H_2O$	0.20 mg/L
$MnSO_4.4H_2O$	0.10 mg/L
H_3BO_3	0.02 mg/L
$CUSO_4.5H_2O$	0.10 mg/L
$CoCL_2.6H_2O$	0.05 mg/L
$NiCl_2.6H_2O$	0.01 mg/L
$FeSO_4$	1.50 mg/L
$NaMoO_4$	2.00 mg/L
Fe EDTA	5.00 mg/L
KH_2PO_4	20.00 mg/L
NaOH	to pH 7

Example 1

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one

Preparation of Biocatalyst

Lactamase is obtained from *Pseudomonas cepacia* grown on 1–2% penicillin as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 2 g/l of penicillin is inoculated with *Pseudomonas cepacia*. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 2 g/l penicillin. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic (+/−)trans-7-phenyl-1-azabicyclo(4,2,0)octan-8-one (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 7 and 1 ml cell extract of lactamase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 3 hours under these conditions. A lactamase with opposite stereoselectivity obtained from a microorganism such as *Rhodococcus rhodochrous* can be used to resolve (+/−)trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one to L-ritalinic acid and the D-trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one. This lactam is then hydrolyzed to the D-ritalinic acid by conventional means.

Trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one may be prepared by the method of Corey, Mol, or Earle (Corey et al., *J. Amer. Chem. Soc.*, 87:2518 (1965); Earle et al., *J. Chem. Soc. C.*, 2093 (1969); Moll F. *Naturforsch.*, Teil B, 21:297 (1996).

Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer is dried with $MgSO_4$. The organic layer is then filtered and concentrated by rotary evaporation at 30° with reduced pressure, to yield an oil product. The oil product may be further purified by column chromatography.

Example 2

Preparation of D-threo-2-(piperid-2-yl)-2-phenylacetic acid from threo-2-(piperid-2-yl)-2-phenyl-2-acetamide

Preparation of Amidase

Amidase is obtained from *Acinetobacter baumanni* grown on 30 mM 2-cyanobutane as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with *Acinetobacter baumanni*. After the mixture in incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane. After 40 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetamide (0.5 g) prepared by, e.g. the method of Hartmann, U.S. Pat. No. 2,507,631, is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of amidase. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions. An amidase with opposite stereoselectivity obtained from a microorganism such as *Rhodococcus rhodochrous* can be used to resolve DL-threo-2-(piperid-2-yl)-2-phenyl-acetamide to L-ritalinic acid and the D-threo-2-(piperid-2-yl)-2-phenyl-acetamide. This amide is then hydrolyzed to the D-ritalinic acid by conventional means.

Example 3

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl acetic acid from trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one

Racemic trans-7-phenyl-1-azabicyclo(4,2,0)-octan-8-one (0.5 g) is added to a mixture of 20 ml 50 mM phosphate buffer pH 7.5 and 1 ml of *Pseudomonas putida* cell extract. The reaction is maintained at 30° C. until the enantiomeric excess as determined by chiral chromatography is no less than 98% D-ritalinic acid, generally about 24 hours under these conditions. Alternatively, a cell extract containing an amidase of opposite stereoselectivity may be used to effect a resolution of racemic trans-7-phenyl-1-azabicyclo (4,2,0)-octan-8-one where L-ritalinic acid is produced and the D-lactamis isolated as the product.

Isolation of D-lactam

The reaction mixture prepared above is extracted with methylene chloride and the organic layer dried with $MgSO_4$. The organic layer is then filtered and concentration by rotary evaporation at 30° with reduced pressure, to yield an oil. The oil product may be further purified by column chromatography.

Example 4

Preparation of D-threo-2-(piperid-2-yl)-2-phenyl-acetic acid from threo-2-(piperid-2-yl)-2-phenyl-acetonitrile

Nitrile hydratase and amidase are obtained from *Alcaligenes faecalis* grown on 30 mM 2-cyanobutane or 2-phenylacetonitrile as the sole carbon and nitrogen source in a minimal media. Fifty milliliters of Media A containing 30 mM 2-cyanobutane is inoculated with *Alcaligenes faecalis*. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of Media A with 30 mM 2-cyanobutane or 2-phenylacetonitrile. After 40 hours of incubation at 30° C., the cells are concentrated a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer pH 7.5 and again concentrated to a paste by centrifugation at 10,000 G. The washed paste then is passed through a French Press at 17,000 psi to rupture the cells and produce cell extract. Cell debris is removed by centrifugation for one half hour at 100,000 G and the enzyme-containing supernatant collected.

Racemic threo-2-(piperid-2-yl)-2-phenyl-2-acetonitrile (0.5 g) is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH 8 and 1 ml cell extract of *Alcaligenes faecalis* with nitrile hydratase and amidase activity. The reaction is maintained at 30° C. until the enantiomer excess as determined by chiral chromatography is no less than 98% of D-ritalinic acid, generally about 5 hours under these conditions.

Example 5

The Use of an Esterase/lipase for the Stereoselective Enrichment of DL-threo-α-phenyl-α-piperidyl-acetic acid methyl ester

A microbial source of a stereoselective esterase or lipase may be obtained from commercial sources such as Novo Nordisk's "Humicola lipolase" or an ATCC Pseudomonas strain 31809 or 31808. Esterase/lipase is obtained from Pseudomonas sp. ATCC strain 31809 grown on 1% olive oil in media A supplemented with 8 g/l nutrient broth. Fifty ml of media A containing the 1% olive oil and 8 g/l nutrient broth is inoculated with Pseudomonas sp. ATCC strain 31809. After the mixture is incubated at 30° C. for 48 hours, 10 ml of the mixture are subcultured into 250 ml of media with 1% olive oil supplemented with 8 g/l nutrient broth. After 24 hours of incubation at 30° C., the cells are concentrated to a paste by centrifugation at 10,000 G and washed with 50 ml phosphate buffer, pH 7.5 and again concentrated to a paste. Cells are ruptured as above.

DL-threo-α-phenyl-α-piperidylacetic acid methyl ester (0.5 g) prepared by the method of Hartmann is added to a mixture of 20 ml of 50 mM potassium phosphate buffer pH and 1 ml cell extract. The reaction is maintained at 30° C. until the enantiomeric excess, as determined by chiral chromatography, is no less than 98% D-threo-methylphenidate, generally in about 25 hours under these conditions.

Preparation of Exemplary Dosage Forms

Example 6

Tablets for chewing, each containing 5 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 tablets)

D-threo-methylphenidate	5.00 grams
mannitol	15.33 grams
lactose	10.00 grams
talc	1.40 grams
glycine	0.83 grams
stearic acid	0.66 grams
saccharin	0.10 grams
5% gelatin solution q.s.	

The solid ingredients are each forced through a 0.25 mm mesh sieve. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a 2 mm mesh sieve, dried at 50° C. and forced through a 1.7 mm mesh sieve. The D-threo-methylphenidate, glycine and saccharin are carefully mixed, the granulated mannitol and lactose, stearic acid and talc added and the whole mixed thoroughly. The mass is compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking groove on the one side.

Example 7

Tablets, each containing 10 milligrams of D-threo-methylphenidate, can be prepared in the following manner: composition (for 1000 tablets)

D-threo-methylphenidate	10.0 grams
lactose	328.5 grams
corn starch	17.5 grams
polyethylene glycol 6000	5.0 grams
talc	25.0 grams
magnesium stearate	4.0 grams
demineralized water q.s.	

The solid ingredients are first forced through a 0.6 mm mesh sieve. Then the d-threo-methylphenidate, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35° C., forced through a sieve of 1.2 mm mesh and compressed to form tablets of approximately 5 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 8

Gelatin dry-filled capsules, each containing 20 milligrams of D-threo-methylphenidate, can be prepared in the following manner:

Composition (for 1000 capsules)

D-threo-methylphenidate	20.0 grams
microcrystalline cellulose	6.0 grams
sodium lauryl sulfate	0.4 grams
magnesium stearate	1.6 grams

The sodium lauryl sulfate is sieved into the D-threo-methylphenidate through a 0.2 mm mesh sieve and the two components intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a 0.9 mm mesh sieve and the whole again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a 0.8 mm mesh sieve and, after mixing for a further 3 minutes, the mixture is introduced in portions of 28 milligrams each into gelatin dry-fill capsules.

Example 9

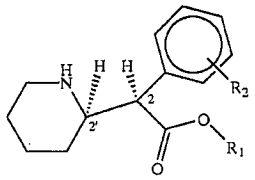
A 0.2% injectable or infusible solution can be prepared, in the following exemplary manner:

D-threo-methylphenidate	5.0 grams
sodium chloride	22.5 grams
phosphate buffer pH 7.4	300.0 grams
demineralized water to 2500 ml.	

The D-threo-methylphenidate is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 ml of H_2O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare unit dosage forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules such that each contains, respectively 2.0 or 5.0 milligrams of D-threo-methylphenidate.

What is claimed is:

1. A pharmaceutical unit dosage comprising from about 1 to about 50 milligrams of compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein R_1 is C_1–C_4 alkyl, and R_2 is hydrogen or C_1–C_4 alkyl, in a pharmaceutically acceptable carrier or diluent, said dosage form having less than 10% by weight of other stereoisomers of the compound or salt.

2. The unit dosage of claim 1 comprising from about 2 to about 20 milligrams of said compound.

3. The unit dosage of claim 1 comprising from about 2½ to about 12 milligrams of said compound.

4. The unit dosage of claim 1 in a form suitable for oral administration.

* * * * *

EXHIBIT D

US005837284A

United States Patent [19]

Mehta et al.

[11] Patent Number: 5,837,284

[45] Date of Patent: Nov. 17, 1998

[54] **DELIVERY OF MULTIPLE DOSES OF MEDICATIONS**

[76] Inventors: **Atul M. Mehta**, 252 E. Cresent Ave., Ramsey, N.J. 07446; **Andrew L. Zeitlin**, 1500 Whitebridge Rd., Millington, N.J. 07946; **Maghsoud M. Dariani**, 11 Byron La., Fanwood, N.J. 07023

[21] Appl. No.: **892,190**

[22] Filed: **Jul. 14, 1997**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 567,131, Dec. 4, 1995, abandoned, and a continuation-in-part of Ser. No. 583,317, Jan. 5, 1996, and a continuation-in-part of Ser. No. 647,642, May 15, 1996.

[51] **Int. Cl.**[6] **A61K 9/56**; A61K 9/54; A61K 9/58; A61K 9/22; A61K 31/21

[52] **U.S. Cl.** **424/459**; 424/458; 424/462; 424/468; 514/317

[58] **Field of Search** 424/458, 459, 424/462, 468; 514/317

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,794,001	12/1988	Mehta et al.	424/458
5,326,570	7/1994	Rudnic et al.	424/458
5,478,573	12/1995	Eichel et al.	424/480
5,500,227	3/1996	Oshlack et al.	424/476
5,639,476	6/1997	Oshlack et al.	424/658
5,672,360	9/1997	Sackler et al.	424/490

OTHER PUBLICATIONS

PDR, 46th ed. "Ritalin SR" pp. 880–881, 1992.

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Woodcock Washburn Kurtz Mackiewicz & Norris LLP

[57] **ABSTRACT**

Dosage forms for oral administration of a methylphenidate drug are provided. The dosage forms provide a substantially immediate dose of methylphenidate upon ingestion, followed by one or more additional doses at predetermined times. By providing such a drug release profile, the dosage forms eliminate the need for a patient to carry an additional dose for ingestion during the day. The dosage forms and methods provided are useful in administering methylphenidate and pharmaceutically acceptable salts thereof, which generally require one or more doses throughout the day.

30 Claims, 2 Drawing Sheets

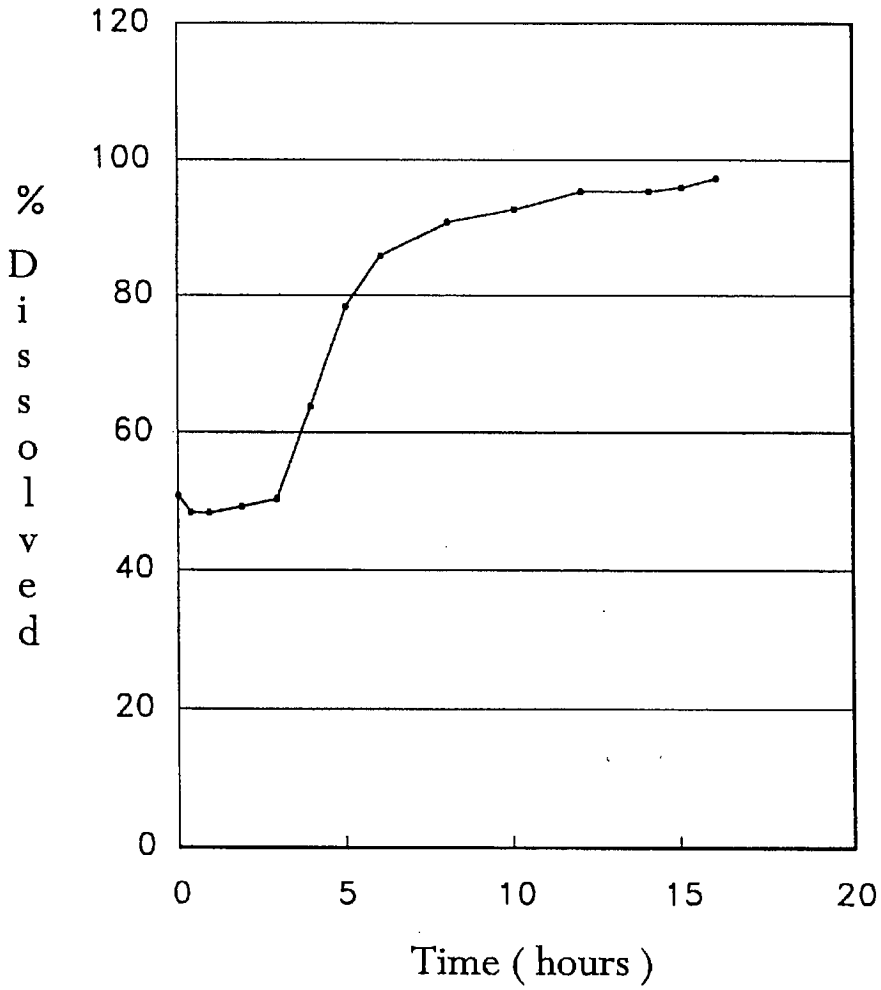


FIG. 1

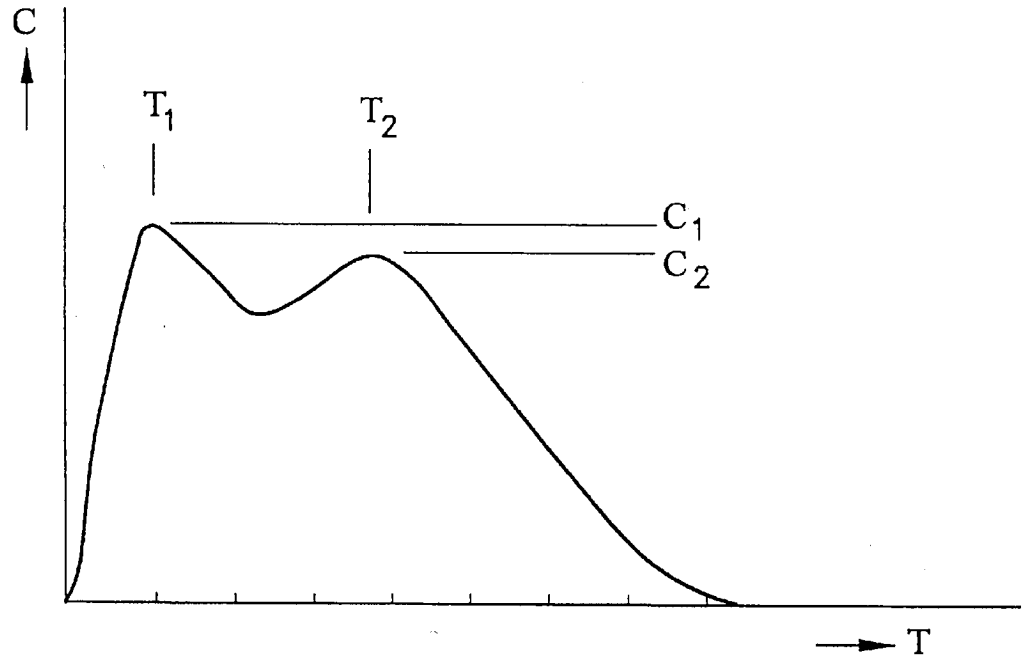


FIG. 2

DELIVERY OF MULTIPLE DOSES OF MEDICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation in part of application Ser. No. 08/567,131, filed Dec. 4, 1995, now abandoned; application Ser. No. 08/583,317, filed Jan. 5, 1996; and application Ser. No. 08/647,642, filed May 15, 1996.

FIELD OF THE INVENTION

The present invention relates to improved dosing of medications. In particular, the present invention relates to improved dosing of a medication whereby two or more effective, time-separated doses may be provided by administration of a single dosage unit. The second, and any later, dose is time-delayed following administration. Based on predictable in vitro release times, the dosage forms can be formulated to deliver delayed doses in vivo at desired times.

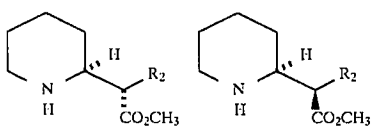
The dosage forms and methods of the present invention are particularly suitable for the administration of methylphenidate hydrochloride, and especially for the administration of a single isomer, d-threo-methylphenidate hydrochloride.

The administration of dosage forms which contain an immediate dosage and a delayed second dosage provides for reduced abuse potential, improved convenience of administration, and better patient compliance, especially when methylphenidate is used to treat certain central nervous system disorders.

BACKGROUND OF THE INVENTION

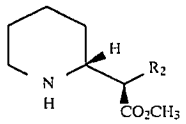
Attention Deficit Disorder (ADD), a commonly diagnosed nervous system illness in children, is generally treated with methylphenidate hydrochloride (available commercially as, e.g., Ritalin®). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by symptoms of hyperactivity, and is also treated with methylphenidate hydrochloride. Methylphenidate drugs have also been used to treat cognitive decline in patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS related conditions. See, e.g., Brown, G., *Intl. J. Psych. Med.* 25(1): 21–37 (1995); Holmes et al., *J. Clin. Psychiatry* 50:5–8 (1989).

Methylphenidate exists as four separate optical isomers as follows:

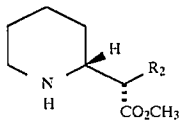


l-threo

d-erythro



d-threo



l-erythro

wherein R_2 is phenyl. Pharmaceutically acceptable salts are generally administered clinically. Other phenidate drugs, which also can be administered according to the invention, include those in which the methyl group in the above structures is replaced by C_2–C_4 alkyl and R_2 is optionally substituted with C_1–C_4 alkyl.

Clinically, the threo pair of enantiomers of methylphenidate hydrochloride is generally administered for the treatment of ADD and ADHD. The hydrochloride salt is commonly referred to simply as "methylphenidate". Unless indicated otherwise, the term "methylphenidate" is used broadly herein to include methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride.

The threo racemate (pair of enantiomers) of methylphenidate is a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines. Undesirable side effects associated with the use of the dl-threo racemate of methylphenidate include anorexia, weight loss, insomnia, dizziness and dysphoria. Furthermore, the racemate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation or ingestion, and thus carries a high potential for abuse.

Srinivas et al. studied the administration of dl-threo-, d-threo, and l-threo-methylphenidate to children suffering from ADHD, and reported that the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer (*Clin. Pharmacol. Ther.,* 52:561–568 (1992)). Therefore, while dl-threo-methylphenidate is generally used therapeutically, this racemate includes the l isomer which apparently makes no significant contribution to the pharmacological effectiveness of the drug, but likely contributes to the associated side effects. It is thus desirable to administer only the active d-threo form of the drug.

An additional problem is that children being treated with dl-threo methylphenidate must generally take one or more doses during the day. This creates a problem for school administrators who must store a controlled substance on school premises, with the associated risk that it may be stolen for illicit use. Furthermore, children may be traumatized by ridicule from peers when they must take medication at school.

Sustained release formulations of dl-threo methylphenidate have been developed, which provide for slow release of the drug over the course of the day. However, it has been observed that peak plasma concentrations of the drug are lower when sustained release formulations are used. In some studies, sustained release formulations of methylphenidate have been shown to have lower efficacy than conventional dosage forms.

There remains a need for methods for delivering methylphenidate with maximum effectiveness and minimal potential for abuse. Furthermore, it has been determined that there is a need for a dosage form which provides, in one administration, an initial release followed, at a predictable delay, by a second release, of maximally effective methylphenidate. This will eliminate the risk of theft or loss of the second dose, while minimizing undesirable side effects and maximizing ease of administration. The present invention is directed to these, as well as other, important ends.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts an in vitro time-concentration relationship (release profile) for certain preferred dosage forms in accordance with the invention.

FIG. 2 depicts a schematic representation of in vivo plasma concentration of a drug released according to the release profile shown in FIG. 1.

SUMMARY OF THE INVENTION

The present invention provides, in one embodiment, a therapeutic composition for the oral administration of a methylphenidate drug comprising a dosage form containing two groups of particles, each containing the methylphenidate drug. The term "particles", as used herein, includes pellets, granules, and the like. The first group of particles provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles can also comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, of the methylphenidate drug, in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. If desired, one or more additional doses may be delivered by additional particles, coated in a similar manner, but with a sufficient amount of ammonio methacrylate copolymer coating to provide the dosage after an additional delay. Methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride, can be prepared into the dosage forms of the invention.

In one embodiment of the present invention, the first group of particles comprises a methylphenidate drug and provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles may comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the particles of the methylphenidate drug in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion.

For example, the first group of particles can comprise a pharmaceutically acceptable salt of methylphenidate, such as methylphenidate hydrochloride, in powder form, or coated or uncoated particles containing the methylphenidate salt. The amount of methylphenidate salt in each group of particles can vary, depending upon the dosage requirements of the patient to whom the drug is to be administered. Generally, the daily dosage requirement for methylphenidate drugs is from about 1 mg to about 50 mg per day, preferably from about 2 mg to about 20 mg, and more preferably from about 2.5 to about 12 mg per day. The actual dosage to be administered will be determined by the attending physician as a matter of routine. Thus, depending upon the amounts of coating and/or and optional excipients and other additives, the amount of methylphenidate drug can be, for example, from about 2% to about 99% by weight of the first group of particles. In addition to the methylphenidate drug, the second group of particles comprises a filler, such as a hydrophobic filler, one or more ammonio methacrylate copolymers, and optional excipients and other additives. The filler can be present in an amount of, for example, from about 35% to about 45%, by weight, based on the total weight of the second group of particles.

Another embodiment of the present invention provides a method for treating disease, such as, for example, ADD, ADHD, or AIDS-related dementia, in a patient in need of treatment. This treatment comprises administering to the patient a dosage form providing once-daily oral administration of a methylphenidate drug such as methylphenidate hydrochloride. The dosage form comprises at least two groups of particles, each containing the methylphenidate drug. The first group of particles comprises from about 2% to about 99% by weight of the methylphenidate drug, depending upon desired the daily dosage, and provides a substantially immediate dose of methylphenidate upon ingestion by a mammal. The first group may comprise a coating and/or sealant. The second group of particles comprises coated particles. The coated particles comprise the methylphenidate drug in admixture with one or more binders, wherein the amount of methylphenidate drug is from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, and a coating comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion. The components of the two groups of particles can vary as described hereinabove. The initial dose can be administered separately from the delayed dose, if desired.

A further embodiment of the present invention provides dosage forms for the oral administration, in a single dosage form, of two doses of a pharmaceutically acceptable salt of d-threo-methylphenidate. The dosage forms comprise particles containing within their interiors from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, of the d-threo-methylphenidate salt, in admixture with one or more binders. The particles have a coating exterior to the methylphenidate salt, which comprises an ammonio methacrylate copolymer in a quantity sufficient to delay release of the d-threo-methylphenidate salt contained within by from about 2 hours to about 7 hours following administration. The dosage forms also comprise, exterior to the coating, an outer layer comprising from about 2% to about 99% by weight of the d-threo-methylphenidate salt, based on the weight of all components in the outer layer, to provide a substantially immediate dose of the d-threo-methylphenidate salt upon administration. The layer comprising the immediate dose of the d-threo-methylphenidate salt can, if desired, further comprise an outer sealant layer. If desired, the two doses of the d-threo-methylphenidate salt can be approximately equal.

The present invention also provides dosage forms providing plasma concentration profiles for methylphenidate having two maxima, temporally separated from each other by from about 2 hours to about 7 hours. Preferably, the magnitude of said maxima differs by no more than about 30 percent, more preferably by no more than about 20 percent, and most preferably by no more than about 10 percent.

"Methylphenidate" as used herein, includes all four optical isomers of the compound and all pharmaceutically acceptable salts thereof. When one or more particular isomers is contemplated, the isomer is indicated, as in d-threo, l-threo, etc. The combined threo isomers may be indicated simply as "threo" and the erythro isomers as "erythro". For therapeutic use in treating conditions treatable by methylphenidate drugs, dl-threo methylphenidate hydrochloride is generally used, while d-threo methylphenidate hydrochloride is preferred according to the present invention.

As discussed, the four isomers have exhibited varying levels of therapeutic activity, and have been shown to differ generally in producing unwanted side effects. The present invention provides dosage forms which maximize therapeu-

tic effectiveness and minimize undesirable side effects. In certain preferred embodiments, the dosage forms of the present invention provide administration of the two threo forms of methylphenidate. In particularly preferred embodiments, the dosage forms of the present invention provide administration of a single isomer, d-threo-methylphenidate, albeit in two or more doses.

The dosage forms of the present invention are intended for oral ingestion by a mammal, particularly a human. The dosage forms of the present invention are particularly suitable for the administration of methylphenidate drugs, in at least two doses. Most preferably, the dosage forms provide two doses of a d-threo methylphenidate drug such as d-threo methylphenidate hydrochloride. The second dose can be delayed by from about 2 hours to about 7 hours, preferably from about 3 hours to about 6 hours, and most preferably from about 4 hours to about 5 hours, following ingestion of the dosage form by a mammal. This eliminates the need for a patient, for example a child being treated for ADD, to carry a second dose for ingestion several hours after ingestion of a first dose. The exclusion of the l isomers and the d-erythro isomer eliminates the concurrent ingestion of forms of methylphenidate principally believed to be associated with adverse side effects and/or reduced effectiveness.

The temporal separation of the two doses provided according to the present invention can be represented graphically as in FIG. 1. FIG. 1 is an in vitro drug release profile of a dosage form of the present invention. The data were obtained by measuring the rate of dissolution of drug as a function of time. In this embodiment two doses are provided. The release of the first dose preferably occurs substantially immediately; for example, within about 30 minutes following administration. Following a period of little or substantially no drug release, the second dose is released. The two releases can be referred to as "pulses", and such a release profile can be referred to as "pulsatile".

FIG. 2 is a schematic representation of the plasma concentration of drug resulting from a release profile according to FIG. 1. The maximum concentration due to the first dose, C_1, occurs at t_1, preferably from about 1 hour to about 3 hours after ingestion, most preferably about 2 hours after ingestion. The release of the first dose is followed by a period during which substantially no drug is released, which lasts approximately 2–6 hours, preferably 3–5 hours, post ingestion. The second dose is then released, with the maximum concentration, C_2, at t_2, which is preferably about 6 hours post-ingestion. Preferably at least about 80% of the total drug has been released by about 6 hours following administration. In the embodiment represented by FIG. 2, the levels of drug released at the two maxima are nearly equal. Preferably, if two approximately equal doses are released, the release of the two doses provides a plasma concentration profile having two maxima, which differ from each other by no more than about 40 percent in magnitude, preferably by no more than about 30 percent, and more preferably by no more than about 25 percent. This is determined by the relationship:

$$|C_1-C_2|/C_1$$

In such embodiments is most preferred that the maxima differ by no more than 20%. However, embodiments in which the maxima of the two releases differ by more than 40 percent are within the scope of the invention. The appropriate relative amounts of drug in each release can be readily determined by one skilled in the art.

Dosage forms of the present invention provide controlled release of a methylphenidate drug, including pharmaceutically acceptable salts of methylphenidate, whereby an initial dose for immediate release can be combined with a delayed release of one or more additional doses. Such dosage forms may alternatively be referred to as "pulsatile" dosage forms.

"Immediate release", as used herein, means release within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following ingestion. "Delayed release", as used herein, refers to a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released. The terms "medication" and "drug" are used interchangeably herein.

According to the present invention, delayed release dosage forms can be combined with forms which provide immediate release of a drug. Thus, two or more dosage forms can be combined, one dosage form providing a portion of a patient's daily dosage needs of a drug and subsequent dosage forms providing additional portions of a patient's daily dosage needs. For example, a drug can be administered to a patient in two dosage forms simultaneously, one providing, e.g., about 30–50 percent of the patient's daily requirement of the drug and the second providing the remainder of the patient's daily requirement. Alternatively, and preferably, a single dosage form can be administered which includes an immediate dose of some portion of a patient's daily requirement and one or more delayed doses to provide the remaining portion or portions of the patient's daily requirement.

Dosage forms of the present invention provide an initial dose of a drug such as, for example, a pharmaceutically acceptable salt of d-threo-methylphenidate (also referred to herein as d-MPD), followed by an interval wherein substantially no additional drug is released, followed in turn by release of a second dose. If desired, a second substantially release-free interval may be provided following the second release, followed in turn by a third dose. Thus, dosage forms providing 3 or more doses are contemplated by the present invention. However, dosage forms providing 2 or 3 doses are generally preferred for therapeutic use, with 2 doses being more preferred. For example, the first dose can provide from about 30 percent to about 70 percent of a patient's daily prescribed intake of the drug and the second dose provides from about 70 percent to about 30 percent. If two approximately equal doses are desired, the initial dose preferably provides from about 40 percent to about 60 percent, and the second dose preferably provides from about 60 percent to about 40 percent, of a patient's prescribed daily intake of the drug. If desired, the first dose and the second dose can each provide about 50 percent of a patient's prescribed daily intake of drug. However, as will be apparent to one skilled in the art, the effect of drug metabolism in the body may require adjustment of the relative amounts of each dose, so that, for example, the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism. This can be observed in FIG. 2, which, as discussed above, represents the blood plasma level of a drug, such as a methylphenidate drug, delivered in a dosage form which provides a release profile as illustrated in FIG. 1.

The initial dose of methylphenidate drug in the dosage forms of the present invention can be provided by incorporating the methylphenidate drug into a form which allows

for substantially immediate release of the drug once the dosage form is ingested by a patient. Such forms include, for example, powders, coated and uncoated pellets, and coated and uncoated tablets. The dose for immediate release can be administered in a tablet or capsule form which may also include the delayed dose. For example, two or more groups of pellets may be combined within a hard gelatin capsule or compressed into a tablet. Powders can be granulated and can be combined with pellets and excipients and/or other additives, and contained within a capsule or compressed into a tablet. These and other dosage forms will be familiar to those skilled in the art.

The delayed dose of a methylphenidate drug in the dosage forms of the present invention is provided in part by the use of certain copolymers referred to as "ammonio methacrylate copolymers". Ammonio methacrylate copolymers comprise acrylic and/or methacrylic ester groups together with quaternary ammonium groups. According to the present invention, the copolymers are incorporated into a formulation which is used to coat particles containing a medication.

The "acrylic and/or methacrylic ester groups" in the copolymers used in the compositions and methods of the present invention are referred to herein collectively as "acrylic groups". The acrylic groups are preferably derived from monomers selected from C_1–C_6 alkyl esters of acrylic acid and C_1–C_6 alkyl esters of methacrylic acid. Preferred are C_1–C_4 alkyl esters of acrylic acid and methacrylic acid. Suitable monomers include, for example, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate. Ethyl acrylate and methyl methacrylate are preferred, and copolymers containing ethyl acrylate and methyl methacrylate are highly preferred. Also preferably, the copolymers have a molecular weight of about 150,000.

Quaternary ammonium groups in copolymers useful in forming coatings for use in the dosage forms of the present invention can be derived from monomers comprising quaternary ammonium groups. Preferably, the monomers are alkyl esters of acrylic or methacrylic acid, comprising alkyl groups having from 1 to 6 carbon atoms and a quaternary ammonium group in the alkyl portion. Monomers comprising quaternary ammonium groups can be prepared, for example, by reaction of monomers containing amino groups with alkylating agents such as, for example, alkyl halides, especially methyl chloride. Suitable monomers containing amino groups include 2-(N,N-dibutylamino)ethyl acrylate, 2-(N,N-dibutylamino)ethyl methacrylate, 4-diethylamino-1-methyl-butyl acrylamide, and 4-diethylamino-1-methyl-butyl methacrylamide. Other useful monomers containing amino groups are disclosed in U.S. Pat. No. 5,422,121, the disclosure of which is incorporated herein by reference. Particularly preferred as a monomer comprising a quaternary ammonium group is trimethylammonioethyl methacrylate chloride (TAMCl).

While ammonio methacrylate copolymers such as those described herein have been used for sustained delivery of certain medicaments, i.e., for the relatively constant administration of a drug, it has been surprisingly and unexpectedly found that dosage forms comprising a methylphenidate drug and a coating prepared from one or more ammonio methacrylate copolymers and certain fillers, can provide delayed or pulsatile release of the drug, a very distinct phenomenon. Methylphenidate drugs are amine-containing, rely upon body or membrane loading for efficacy, and are psychotropic. The ability to provide delayed release of a methylphenidate drugs using ammonio methacrylate copolymers is due to a combination of factors, including the composition of the ammonio methacrylate copolymers used, and the amount and composition of filler.

The ratio of acrylic groups to quaternary ammonium groups in the ammonio methacrylate copolymers influences the properties of the copolymers utilized in forming the coatings of the present invention. For use in the dosage forms and methods of the present invention, the ratio of acrylic groups to quaternary ammonium groups in the copolymers is preferably from about 10:1 to about 50:1, more preferably from about 15:1 to about 45:1. Preferably, in preparing a dosage form according to the present invention, two or more copolymers are used in combination. Also preferably, one of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 25:1 to about 45:1, more preferably from about 30:1 to about 40:1, and another of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 10:1 to about 25:1, more preferably from about 15:1 to about 20:1. Even more preferably, two ammonio methacrylate copolymers are used: a first copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 30:1 to about 40:1 and the second copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 15:1 to about 20:1. Most preferably, the copolymers are copolymers of methyl methacrylate, ethyl acrylate, and TAMCl, in ratios of 2:1:0.1 for the first copolymer and 2:1:0.2 for the second copolymer.

When two such ammonio methacrylate copolymers are used to form the coatings, the relative amounts of the two polymers is partly determinative of the delay and release properties of the dosage forms of the present invention. It is preferred that the ratio between the first polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 30:1 to about 40:1, and the second polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 15:1 to about 20:1, be from about 93:7 to about 97:3. More preferably, the ratio of the first polymer to the second polymer is from about 96:4 to about 94:6, and most preferably about 95:5.

Ammonio methacrylate copolymers used in the coatings of the dosage forms of the present invention can be prepared by methods known to those skilled in the art. Exemplary methods include emulsion polymerization, bulk polymerization and suspension polymerization. A suitable procedure is described in U.S. Pat. No. 3,979,349, the disclosure of which is incorporated herein by reference. Suitable ammonio methacrylate copolymers are known per se, and can be purchased from commercial providers. For example, suitable ammonio methacrylate polymers are available from Hüls America under the Eudragit® trademarks. The Eudragit® polymers and similar polymers, including methods for preparation, are described in Klaus O. R. Lehman, "Chemistry and Application Properties of Polymethacrylate Coating Systems", *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms*, 2nd. Ed., pp. 101–174, James Mc Ginity, Ed., Marcel Dekker, Inc., New York (1996), the disclosure of which is incorporated herein by reference.

The coatings of the present invention also preferably include a filler. The filler is preferably in powder form and is preferably hydrophobic. Exemplary fillers include talc, colloidal silica, fumed silica, gypsum, and glycerine monostearate. Talc is a particularly preferred filler.

The quantity of filler used in preparing coatings for the dosage forms of the present invention should be sufficient to minimize agglomeration of the particles. Agglomeration is highly undesirable because the agglomerates, rather than discrete particles, will become coated. Agglomerates are

susceptible to breaking into discrete particles, which will be partially uncoated, resulting in unwanted variability in release rates. Preferably, the amount of filler is from about 30 percent to about 50 percent by weight, based on the total weight of the dry polymer, commonly referred to as "total solids". More preferably the amount of filler is from about 35 percent to about 45 percent of total solids, and most preferably about 40 percent.

Coatings used in the dosage forms of the present invention also preferably include a material which improves the processing of the copolymers. Such materials are generally referred to as "plasticizers" and include, for example, citric acid esters, adipates, azelates, benzoates, citrates, stearates, isoebucates, sebacates, propanetriol acetate, polyethylene glycols, diethyl phthalate, dibutyl sebacate, propylene glycol and ethylene glycol. Citric acid esters are preferred, and triethyl citrate is particularly preferred. The amount of plasticizer to be used in the coating is preferably from about 10 percent to about 30 percent, more preferably from about 15 percent to about 25 percent, and most preferably about 20 percent, based on the weight of the dry polymer, i.e., total solids.

Dosage forms of the present invention preferably comprise particles containing d-MPD. In one embodiment, the dosage form comprises two groups of particles. A first group of particles provides the initial dose of d-MPD. As stated hereinabove, the initial dose can be in powder, pellet or other particulate form and can be uncoated. If the initial dose is in the form of a powder or sufficiently small particles, it can, if desired, be pressed into a solid form such as a tablet or caplet. In this embodiment, the delayed dose is provided by a second group of particles. The second group of particles is preferably in the form of pellets. The pellets can be of any shape, such as, for example, spheroids or ellipsoids, or may be irregularly shaped.

Suitable pellets for the initial dose and/or the second dose can be formed by, for example, depositing a layer of drug, and optional excipients, carriers, and other optional materials, onto small, pharmaceutically acceptable particles such as nonpareils. Such a layer can be deposited by methods known to those skilled in the art, such as, for example, spraying, using methods and equipment known to those skilled in the art. For example, a Wurster air suspension coater can be used. Spraying can also be accomplished using a pan coating system, wherein the drug is deposited by successive spraying accompanied by tumbling in a rotating pan. Alternatively, pellets can be formed, for either or both of the initial and delayed dose, by extrusion of the drug with suitable plasticizers and other processing aids as necessary.

Tablets or caplets, or other solid dose forms, comprising the initial dose and/or delayed dose or doses, can conveniently be administered. A solid dose form can be prepared by methods known to those skilled in the art. For example, the d-MPD, filler and other optional components may be compressed into tablets or inserted into capsules. If desired, the drug and other components of the dose form can be granulated, using processing aids, fillers, aqueous or non-aqueous solvents, and binders known to those skilled in the art. Granules can be filled into capsules, if desired. Alternatively, the d-MPD can be blended with a solvent and processed by known methods such as ball-milling, calendering, stirring, or roll-milling, then pressed into a desired shape. Suitable solvents useful in forming the particles comprising d-MPD, and other components of the dosage forms of the invention, include inert organic and inorganic solvents which do not adversely affect the components of the dosage forms. While water can be used for many drugs, including methylphenidate, useful solvents can be selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatic heterocyclic solvents, and mixtures thereof. Other solvents include acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, diglyme, and aqueous and non-aqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, and ethylene dichloride and methanol.

Following the formation of suitable particles, those particles to be used to deliver the delayed dose are then coated with a polymer-containing coating as described herein. The amount of coating to be used in forming the dosage forms, particularly the delayed dose, of the present invention, will be determined by the desired delivery properties, including the amount of drug to be delivered, the delay time required, and the size of the particles. Preferably, the coating on the particles providing the delayed dose, including all solid components of the coating such as copolymer, filler, plasticizer and optional additives and processing aids, is from about 10 percent to about 60 percent, more preferably from about 20 percent to about 50 percent, most preferably from about 30 percent to about 40 percent, of the total final weight of the particles. The appropriate amount of coating can advantageously be determined using in vitro measurements of drug release rates obtained with selected amounts of coating. The coating can be deposited by any method known to those skilled in the art, such as spray application. Spraying can be carried out by pan coating or by use of a fluid bed, such as the Wurster fluid bed described for use in depositing a drug.

After deposition of the drug, a sealant can be applied to any and/or all of the particles, prior to application of the polymeric coating. A sealant provides a physical barrier between the drug and the coating, to minimize or prevent interaction between the drug and the coating. Suitable sealants can be prepared from materials such as biologically inert, permeable, pharmaceutically acceptable polymers, such as, for example, hydroxypropylalkylcelluloses, wherein "alkyl" refers to C_1–C_6 hydrocarbon chains. Exemplary materials include hydroxypropyl methylcellulose, hydroxypropylethylcellulose, hydroxypropyl propylcellulose, and hydroxypropylbutylcellulose. Hydroxypropylmethylcellulose is preferred. While other materials are known to those skilled in the art for use as sealants, such as, for example, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, semipermeable cross-linked polymers such as poly (vinylbenzyltrimethyl)ammonium chloride, these are not preferred as they may affect the release rate of certain drugs including d-MPD. A sealant can be prepared by adding the material to water, and agitating for a time and at a rate sufficient to form a solution. The formation of a solution will be indicated, for example, by transparency and the absence of visually observable suspended material. The amount of material added to the water is not critical but is determined by viscosity. A solution which is too viscous will present difficulties in spraying. Generally, the amount of material should not exceed about 20 weight/volume percent, i.e., 20 g sealant material per 100 ml of water. Preferably, the

amount of material in the water is from about 5 percent to about 15 weight/ volume percent, and more preferably about 10 weight/volume percent.

Following deposition of the optional sealant and the coating, the coated particles are cured. "Curing" means that the particles are held at a controlled temperature for a time sufficient to provide stable release rates. Stability in release rate is indicated when further curing does not affect the release rate. In contrast, instability of release rate means that as the cure time is increased, the release rate continues to vary. Curing for a sufficient time ensures that substantially the same release rate is obtained with all particles of a particular size coated with a given amount of a given coating composition. A suitable curing time can be determined by one of skill in the art without undue experimentation, by noting the variability in in vitro release times as curing time is varied. As a general guideline, many formulations can be cured in about 24 hours.

Curing can be accomplished, for example, in a forced air oven. Curing can be carried out at any temperature above room temperature, "room temperature" being defined as from about 18° C. to about 25° C. Preferably, curing is carried out at a temperature of from about 30° C. to about 50° C., more preferably from about 35° C. to about 45° C., and most preferably about 40° C. Curing time can range from several hours to several days. Preferably, the coated particles are cured for at least about 24 hours, more preferably at least about 2 days, even more preferably at least about 3 days, still more preferably at least about 4 days, still even more preferably at least about 5 days, even more preferably at least about 6 days, and most preferably for about 7 days. While no significant adverse effects or advantages have been observed when the particles are cured for longer than about 7 days, it has been found that curing for less than about 24 hours may result in relatively poorer storage stability as compared to particles cured for longer periods of time.

The amount of methylphenidate drug contained in the first and second groups of particles depends upon the prescribed dosage to be delivered to a patient. The first group of particles can consist substantially entirely of a methylphenidate drug. "Substantially entirely" means that about 95 percent or more of the weight of the first group of particles can consist of a methylphenidate drug. If desired, the first group of particles can also contain pharmaceutically acceptable carriers, excipients, and other components which do not interfere with the substantially immediate release of the medication. "Substantially immediate" release, as used herein, means that at least about 90 percent of the medication is released within about 30 minutes from the time the drug is ingested. The second group of particles can contain from about 2 percent to about 75 percent, preferably from about 4 percent to about 50 percent, medication, based on the total weight of the particles including the coating to be deposited thereon.

According to the invention, a first and a second group of particles can be administered simultaneously as part of one dosage form. Any dosage form can be used. For example, the two groups of particles can be combined within a capsule. Alternatively, the two groups of particles can be pressed into a solid form such as a tablet. In pressing the particles into a solid form, suitable processing aids known to those skilled in the art can be used. Alternatively, particles coated to provide a delayed dose of a medication can be dispersed within or blended with, the medication in powder form.

As discussed, the dosage form can comprise a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose of methylphenidate drug. The particles comprise, in admixture with one or more binders, from about 2% to about 75% by weight of a methylphenidate drug for delayed release, and a coating comprising the pharmaceutically acceptable, substantially neutral copolymers described herein. The particles further comprise, exterior to the coating, an outer layer comprising methylphenidate drug, to provide an initial, substantially immediate, dose. The substantially immediate dose is preferably released within about 30 minutes, more preferably about 15 minutes, and most preferably within about 5 minutes following ingestion. The outer layer can optionally comprise additives such as, for example, binders, excipients, and lubricants known to those skilled in the art.

The dosage forms provided by the invention can be of any shape suitable for oral administration of a drug, such as spheroidal, cube-shaped, oval, bean shaped, or ellipsoidal. The dosage form may be in the form of granules, which may be irregularly shaped. In any of the embodiments of the present invention, although the size of the particles is generally not critical, a certain particle size or sizes can be preferred depending upon the characteristics of the dosage form. For example, the dosage form can comprise a capsule containing a first and/or second group of particles. The particles should then be of a size which allows for ease in handling, and which allows for the particles comprising a desired quantity of drug to be readily measured and inserted into the capsule. If the dosage form comprises a single group of particles providing a substantially immediate dose and a delayed dose, the particles are preferably of a size and shape which facilitate oral administration. For example, the particles can be in the form of tablets, caplets, etc. Alternatively, the particles can be contained within a capsule of suitable size and shape for oral administration. If desired, various fillers and/or binders known to those skilled in the art can be included in the particles to provide the desired size and shape.

It will be recognized by one skilled in the art that the dosage forms of the present invention may include, in either or both of the first dose and any delayed dose, pharmaceutically acceptable carriers, extenders, fillers, processing aids, and excipients known to those skilled in the art.

The following examples are merely illustrative of the present invention and should not be considered limiting of the scope of the invention in any way. These examples and equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure and the accompanying claims.

EXAMPLE 1

Preparation of layered pellets containing d-MPD hydrochloride

A solution of d-MPD hydrochloride was prepared as follows. To 300 grams (g) of deionized water were added 100 g of d-MPD hydrochloride, followed by moderate mixing, using a stirring paddle, for 5 minutes. A 10 percent (weight) solution of hydroxypropyl methylcellulose (HPMC E-6 from Dow Chemicals, Midland, Mich.; 250 g) was added, followed by homogenization for 5 minutes using an emulsifier head (Silverson, Chesham, UK; Model L4R). After addition of another 150 g of deionized water, the solution was sonicated for 15 minutes (Sonicor Model SC-150T; Instruments Corporation, Copiague, N.Y.), at which time the solution was clear.

A second solution was prepared by combining 300 g of deionized water and 300 g of a 10% (wt) HPMC E-6 solution and mixing for 5 minutes.

The first solution was sprayed onto 25/30 mesh non-pareil seeds (Ozone Co., Elmwood Park, N.J.) in a fluid bed apparatus (GPCG-1, Glatt Air Techniques, Inc., Ramsey, N.J.) using a Wurster head. The second solution was then sprayed to form a sealant. For both solutions, the spray rate was 8–9 g/minute. Inlet temperature was 50°–55° C. and the non-pareil seeds were maintained at 35°–40° C. Air volume was 6–7 meters per second (m/s).

EXAMPLE 2

Preparation of Coated Pellets containing d-MPD hydrochloride

A dispersion of 844 g of Eudragit® RS30D (ammoniomethacrylate copolymer from Hüls America, Somerset, N.J.; EA/MMA/TAMCl 1:2:0.1), was screened through a 60 mesh screen, then stirred for 15 minutes. A dispersion of 44 g of Eudragit® RL30D (EA/MMA/TAMCl 1:2:0.2) was similarly screened and stirred. The two dispersions were combined and stirred for 15 minutes, forming a combined dispersion. Triethyl citrate (TEC; from Moreflex, Greensboro, N.C.; 54 g) was added, followed by an additional 15 minutes of stirring. Deionized water (664 g) was added, followed by 15 minutes of stirring. Talc (108 g; from Luzenac, Englewood, Colo.) was added, followed by further stirring for 15 minutes.

The resulting combined dispersion was sprayed onto layered pellets prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 9–10 g/minute, inlet temperature 40°–45° C., and air volume 5–6 m/s. The non-pareils were maintained at 30°–35° C. during spraying. A total of 960 g of dispersion was sprayed onto the pellets, representing a 30% weight increase due to the applied coating.

EXAMPLE 3

Evaluation of drug release profile for coated pellets prepared according to Example 2

Pellets were prepared according to Example 2, varying the ratios of the polymers between 90:10 and 93:7.

Dissolution measurements

Dissolution was carried out in order to determine rate of release of d-MPD from the pellets. USP Apparatus I (United States Pharmacoepia Convention, Rockville, Md.) was used. The dissolution medium was 900 ml of deionized water (unless otherwise specified) and the temperature was maintained at 37° C. The sample cell size was 1 cm (a flow through cell), and the samples were stirred continuously at 100 rpm. The apparatus was equipped with a diode array spectrophotometer, and absorption at 220 nanometers (nanometers (run)) was measured to determine the concentration of d-MPD. Samples were measured at 60, 120, 180, 240, 360, 480, 600, 720, 840, 900, 960, 1080, 1200, 1320 and 1440 minutes.

Results of the dissolution measurements are presented in Table 1. The results indicate that the amount of drug released is influenced by: amount of coating, ratio of the two polymers, amount of talc, and curing time.

EXAMPLE 4

Comparative Example

A dispersion of 911.25 g of Eudragit® RS30D was passed through a 60 mesh screen and mixed with a similarly screened dispersion of 101.25 g of Eudragit® RL30D for 15 minutes at moderate speed. Triethyl citrate (61 g) was added, followed by an additional 15 minutes of mixing. After mixing, 991.5 g of deionized water, then 61 g of talc were added with 15 additional minutes of mixing following each addition. The resulting dispersion (1600 g) was sprayed onto 800 g of layered sealed pellets prepared according to Example 1.

No delay was observed; substantially all of the drug was released within approximately one hour. Result is shown in Table 1 (Trial 1).

EXAMPLE 5

Comparative Example

A dispersion of 600 g of Eudragit® NE30D was screened through a 60 mesh screen and mixed with a 600 g dispersion of magnesium stearate for 15 minutes at moderate speed. The resulting dispersion (750 g) was sprayed onto 750 g of layered and sealed pellets prepared according to Example 1.

After a delay of 2 hours, release of the drug was observed. About 85% of the drug was released after 14 total hours.

TABLE 1

RELEASE TIMES

Trial No.	% coat	Ratio	Delay	Talc, %	Cure time	Time for 85% release
1	40	90:10	none	20.0	24 hrs	1.0
2	30	95:5	4.0	20.0	"	8.0
3	30	95:5	4.0	20.0	"	8.0
4	30	93:7	1.0	20.0	"	3.0
5	40	93:7	1.0	20.0	"	4.0
6	30	93.5:6.5	2.0	20.0	"	5.0
7	40	"	2.0	20.0	"	5.0
8	30	94.5:5.5	2.0	20.0	"	8.0
9	40	"	1.0	20.0	"	5.0
10	30	94:6	2.0	20.0	"	5.0
11	40	"	2.0	20.0	"	5.0
12	30	95:5	2.0	40.0	"	5.0
13	40	"	3.0	40.0	"	8.0
14	30	96:4	4.0	40.0	"	10.0
15	40	"	5.0	40.0	"	10.0
16	30	"	4.0	40.0	7 days	10.0
17	20	95:5	2.0	40.0	"	5.0
18	30	"	3.0	40.0	"	6.0
19	30	"	3.0	40.0	"	6.0
20	30	"	2.0	40.0	"	6.0
21	40	"	3.0	40.0	"	8.0

What is claimed is:

1. A dosage form for the oral administration of a methylphenidate drug, comprising two groups of particles, each containing said drug, wherein:

a) said first group of particles provides a substantially immediate dose of said drug upon ingestion by a mammal, and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of said drug in admixture with one or more binders, said coating comprising a pharmaceutically acceptable ammonio methacrylate in a quantity sufficient to provide a dose of said medication delayed by from about 2 hours to about 7 hours following said ingestion.

2. The dosage form of claim 1 wherein said first group of particles comprises a pharmaceutically acceptable salt of methylphenidate in powder form.

3. The dosage form of claim 1 wherein said second group of particles comprises coated particles comprising a pharmaceutically acceptable salt of methylphenidate.

4. The dosage form of claim 2 wherein the amount of said pharmaceutically acceptable salt of methylphenidate in said first group of particles is from about 2% to about 99% by weight, based on the weight of said particles.

5. The dosage form of claim 4 wherein said pharmaceutically acceptable salt of methylphenidate comprises dl-threo methylphenidate hydrochloride.

6. The dosage form of claim 3 wherein said pharmaceutically acceptable salt of methylphenidate comprises dl-threo methylphenidate hydrochloride.

7. The dosage form of claim 1 wherein said second group of particles comprises from about 20% by weight to about 50% by weight of filler, based on the total weight of the copolymer.

8. The dosage form of claim 7 wherein said filler is selected from the group consisting of talc, colloidal silica, fumed silica, gypsum, and glycerine monostearate.

9. The dosage form of claim 8 wherein said filler is talc.

10. The dosage form of claim 9 wherein the amount of talc is from about 35% to about 45% by weight, based on the total weight of the copolymer.

11. The dosage form of claim 10 wherein the amount of talc is from about 38% to about 42% by weight, based on the total weight of the copolymer.

12. The dosage form of claim 11 wherein the amount of talc is about 40% by weight, based on the total weight of the copolymer.

13. The dosage form of claim 1 wherein the ammonio methacrylate copolymer comprises acrylic groups and quaternary ammonium groups in a ratio of from about 10:1 to about 50:1.

14. The dosage form of claim 13 wherein said ratio is from about 15:1 to about 45:1.

15. The dosage form of claim 14 wherein said ratio is from about 15:1 to about 20:1.

16. The dosage form of claim 15 wherein said ratio is from about 30:1 to about 40:1.

17. The dosage form of claim 1 comprising a first ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 30:1 to about 40:1, and a second ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 15:1 to about 20:1.

18. The dosage form of claim 17 wherein the ratio of said first copolymer to said second copolymer is from about 90:10 to about 99:1.

19. The dosage form of claim 18 wherein the ratio of said first copolymer to said second copolymer is from about 93:7 to about 97:3.

20. The dosage form of claim 19 wherein the ratio of said first copolymer to said second copolymer is about 95:5.

21. The dosage form of claim 1 wherein said delay is from about 3 hours to about 6 hours.

22. The dosage form of claim 1 wherein said delay is from about 4 hours to about 5 hours.

23. A dosage form for once-daily oral administration of a methylphenidate drug comprising:

a) particles comprising from about 2% by weight to about 99% by weight of said methylphenidate drug, in admixture with one or more binders,

b) a coating exterior to said methylphenidate drug, comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of said methylphenidate delayed by from about 2 hours to about 7 hours following administration, and

c) on the exterior surface of said coating, a layer comprising said methylphenidate drug, to provide a substantially immediate dose of said methylphenidate upon administration.

24. The dosage form of claim 23 wherein said methylphenidate is dl-threo-methylphenidate hydrochloride.

25. The dosage form of claim 23 wherein said methylphenidate is d-threo-methylphenidate hydrochloride.

26. The dosage form of claim 23 wherein said coating comprises a first ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 30:1 to about 40:1, and a second ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 15:1 to about 20:1.

27. A dosage form for the oral administration of d-threo-methylphenidate hydrochloride comprising two groups of particles, each containing d-threo-methylphenidate, wherein:

a) said first group of particles comprises d-threo-methylphenidate hydrochloride and provides a substantially immediate dose of said d-threo methylphenidate upon ingestion by a mammal, and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of d-threo-methylphenidate hydrochloride in admixture with one or more binders, said coating comprising a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a dose of said d-threo-methylphenidate delayed by from about 2 hours to about 7 hours following said ingestion.

28. A dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate providing an in vitro release profile comprising two pulses of drug release, wherein said pulses are temporally separated by from about 2 hours to about 7 hours.

29. A dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate providing an in vivo plasma concentration of said d-threo-methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about 2 hours to about 7 hours, and wherein the magnitude of said maxima differ by no more than about 30 percent.

30. A dosage form according to claim 23 wherein said ammonio methacrylate copolymer comprises a first copolymer of methyl methacrylate, ethyl acrylate and TAMCl in a ratio of 2:1:0.1 and a second copolymer of methyl methacrylate, ethyl acrylate, and TAMCl in a ratio of 2:1:0.2.

* * * * *

EXHIBIT E

US006635284B2

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

(10) **Patent No.: US 6,635,284 B2**
(45) **Date of Patent: *Oct. 21, 2003**

(54) **DELIVERY OF MULTIPLE DOSES OF MEDICATIONS**

(75) Inventors: **Atul M. Mehta**, Ramsey, NJ (US); **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

(73) Assignee: **Celegene Corporation**, Warren, NJ (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 45 days.

(21) Appl. No.: **09/038,470**

(22) Filed: **Mar. 11, 1998**

(65) **Prior Publication Data**

US 2003/0113373 A1 Jun. 19, 2003

Related U.S. Application Data

(60) Division of application No. 08/892,190, filed on Jul. 14, 1997, now Pat. No. 5,837,284, which is a continuation-in-part of application No. 08/567,131, filed on Dec. 4, 1995, now abandoned, and a continuation-in-part of application No. 08/583,317, filed on Jan. 5, 1996, now Pat. No. 5,733,756, and a continuation-in-part of application No. 08/647,642, filed on May 15, 1996, now abandoned.

(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/16; A61K 9/50; A61K 9/54; A61K 9/20

(52) **U.S. Cl.** **424/497**; 424/458; 424/474; 424/468; 424/464; 424/490; 424/462; 424/494; 424/489; 424/480

(58) **Field of Search** 424/489, 497, 424/464, 462, 480, 494, 468, 474, 490, 458

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,507,631	A	5/1950	Hartmann et al.	260/294
2,957,880	A	10/1960	Rometsch	546/233
4,137,300	A	1/1979	Sheth et al.	424/21
4,794,001	A	12/1988	Mehta et al.	424/458

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

CA	1297368	3/1992
FR	2 635 460	9/1994
WO	WO 93/05769	4/1993
WO	WO 97/03671	2/1997

(List continued on next page.)

OTHER PUBLICATIONS

Angrist et al., *J. Clin. Psychopharm.*, 1992, 12(4), 268–272.
Barkley et al., *Pediatrics*, 1990, 86(2), 184–192.
Barkley et al., *Pediatrics*, 1991, 87(4), 519–531.
Golinko, *Prog. Neuro–Psychopharm. Biol. Psychiat.*, 1984, 8, 1–8.

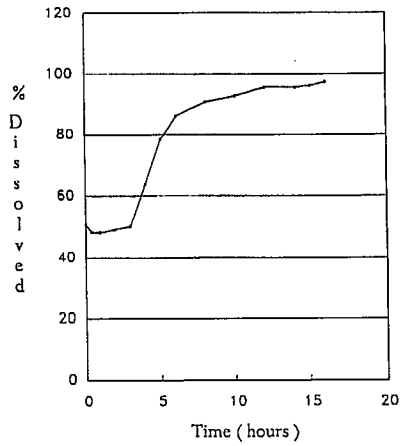
(List continued on next page.)

Primary Examiner—Thurman K. Page
Assistant Examiner—Humera N. Sheikh
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Dosage forms for oral administration of a methylphenidate drug are provided. The dosage forms provide a substantially immediate dose of methylphenidate upon ingestion, followed by one or more additional doses at predetermined times. By providing such a drug release profile, the dosage forms eliminate the need for a patient to carry an additional dose for ingestion during the day. The dosage forms and methods provided are useful in administering methylphenidate and pharmaceutically acceptable salts thereof, which generally require one or more doses throughout the day.

11 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

4,968,505	A	11/1990	Okada et al.	424/400
4,992,445	A	2/1991	Lawter et al.	514/279
5,104,899	A	4/1992	Young et al.	514/646
5,114,946	A	5/1992	Lawter et al.	514/279
5,133,974	A	7/1992	Paradissis et al.	424/480
5,156,850	A	10/1992	Wong et al.	424/473
5,202,128	A	4/1993	Morella et al.	424/469
5,217,718	A	6/1993	Colley et al.	424/449
5,223,265	A	6/1993	Wong	424/473
5,232,705	A	8/1993	Wong et al.	424/473
5,283,193	A	2/1994	Yamamoto et al.	435/280
5,284,769	A	2/1994	Evans et al.	435/280
5,308,348	A	5/1994	Balaban et al.	604/892.1
5,326,570	A	7/1994	Rudnic et al.	424/458
5,331,000	A	7/1994	Young et al.	514/570
5,362,755	A	11/1994	Barberich et al.	514/649
5,375,693	A	12/1994	Woosley et al.	514/317
5,449,743	A	9/1995	Kobayashi et al.	528/355
5,478,573	A	12/1995	Eichel et al.	424/480
5,500,227	A	3/1996	Oshlack et al.	424/476
5,512,293	A	4/1996	Landrau et al.	424/449
5,580,578	A	12/1996	Oshlack et al.	424/468
5,593,694	A	* 1/1997	Hayashida et al.	424/468
5,639,476	A	6/1997	Oshlack et al.	424/468
5,672,360	A	9/1997	Sackler et al.	424/490
5,874,090	A	2/1999	Baker et al.	424/400

FOREIGN PATENT DOCUMENTS

WO	WO 97/03672	2/1997
WO	WO 97/03673	2/1997
WO	WO 98/06380	2/1998
WO	WO 98/14168	4/1998
WO	WO 98/23263	6/1998
WO	WO 99/62496	9/1999

OTHER PUBLICATIONS

Holmes et al., "Psychostimulant Response in Aids–Related Complex Patients", *J. Clin. Psychiatry,* 1989, 50(1), 5–8 (Biosis Abstract No. 87129969).

Srinivas et al., "Enantioselective Pharmacolinetics and Pharmacodynamics of Racemic Threo–Methylphenidate in Children with Attention Deficit Hyperactivity Disorder", *Clin. Pharmacol.,* 1992, 52(5), 561–568 (Biosis Abstract No. 95066168).

Aoyama et al., "Pharmacolinetics and pharmacodynamics of (+)–threo–methylphenidate enantiomer in patients with hypersomnia", *Clin. Phamacol. Ther.,* 1994, 55(3), 270–276.

Bowden et al., "Reactions of Carbonyl Compounds in Basic Solutions the Alkaline Hydrolysis of N–Methyl, N–Phenyl, and Bicyclo Lactams Penicillins, and N–Aklyl–N–methylacetamides", *J. Chem. Soc. Perkin Trans.,* 1990, 12, 2111–2116.

Brown, "Pharmacological Action and Drug Development", *Chirality in Drug Design and Synthesis,* Academic Press Inc., 1990, 4–7.

Brown G., "The Use of Methylphenidate for Cognitive Decline Associated with HIV Disease", *Int'l J. Psychiatry Med.,* 1995, 25(1), 21–37.

Corey et al., "A New Synthetic Approach to the Penicillins", *J. Am. Chem. Soc.,* 1965, 87(11), 2518–2519.

Ding et al., "Cis– and trans–Axetidin–2–ones from Nitrones and Copper Acetylide", *J. Chem. Soc. Perkin,* 1976, 22, 2382–2386.

Douzenis et al., "Phychiatric Disorder in HIV Disease: Description of 200 Referrals to a Liaison psychiatry Service", *Proc 7th. Int'l Conf. AIDS,* 1991, 215 (M.B.2135—Summary).

Earle et al., "Synthesis and Hydrolysis of some Fused–ring β–Lactams", *J. Chem. Soc.,* 1969, 2093–2098.

Greenhill L., "Attention–Deficit Hyperactivity Disorder", *Child & Adol. Psych. Clin. N.A.,* 1995, 4(1), 123–168.

Greenhill, "Pharmacologic Treatment of Attention Deficit Hyperactivity Disorder", *Pediatric Psychopharmacology,* 1992, 15(1), 1–27.

Hou, J.P. et al., "Beta–Lactam Antibiotics: Their Physicochemical Properties and Biological Activities in Relation to Structure", *J. Pharm. Sci.,* 1971, 60(4), 503–532.

Klibanov, "Asymmetric Transformations Catalyzed by Enzymes in Organic Solvents", *Acc. Chem. Res.,* 1990, 23, 114–120.

Moll R., "Darstellung von 1–Aza–bicyclo[4.2.0] octan–2–on", *Naturforsch Teil B.,* 1966, 21, 297.

Navia et al., "The AIDS Dementia Complex: I. Clinical Features", *Annals of Neurology,* 1986, 19, 517–524.

Patrick et al., "Pharmacology of the Enantiomers of threo–Methylphenidate", *J. Pharmacol & Exp. Terhap.,* 1987, 241, 152–158.

Rieder et al., "Diagnosis of Sulfonamide Hypersensitivity Reactions by In–Vitro "Rechallenge" with Hydroxylamine Metabolites", *Ann. Intern Med.,* 1989, 110, 286–289.

Scott, "Stereoisomers and Drug Toxicity", *Drug Safety,* 1993, 8(2), 149–159.

Srinivas et al., "Enantiomeric Gas Chromatography Assay with Electron Capture Detection for d–Ritalinic Acid in Plasma", *J. Chromatagraph,* 1990, 530, 327–336.

Srinivas et al., "Enantioselective Pharmacokinetics of dl–threo–Methylphenidate in Humans", *Pharmacol Res.,* 1993, 10(1), 14–21.

Srinivas et al., "Sterioselective Disposition of Methylphenidate in Children with Attention Deficit Disorder", *J. Pharmacol. Exp. Ther.,* 1987, 241(1), 300–306.

Uetrecht et al., "Idiosyncratic Drug Reactions: Possible Role of Reactive Metabolites Generated by Leukocytes", *Pharmacol Res.,* 1989, 6(4), 265–273.

White et al., "Methylphenidate as a Treatment for Depression in Acquired Immunodeficiency Syndrome: An n–of–1 Trial", *J. Clin. Psychiatry,* 1992, 53(5), 153–156.

Staal et al., "Glutathione deficiency and human immunodeficiency virus infection", *Lancet,* 1992, 339, 909–912.

Physician's Desk Reference, 46th ed., "Ritalin SR", 1992, 880–881.

* cited by examiner

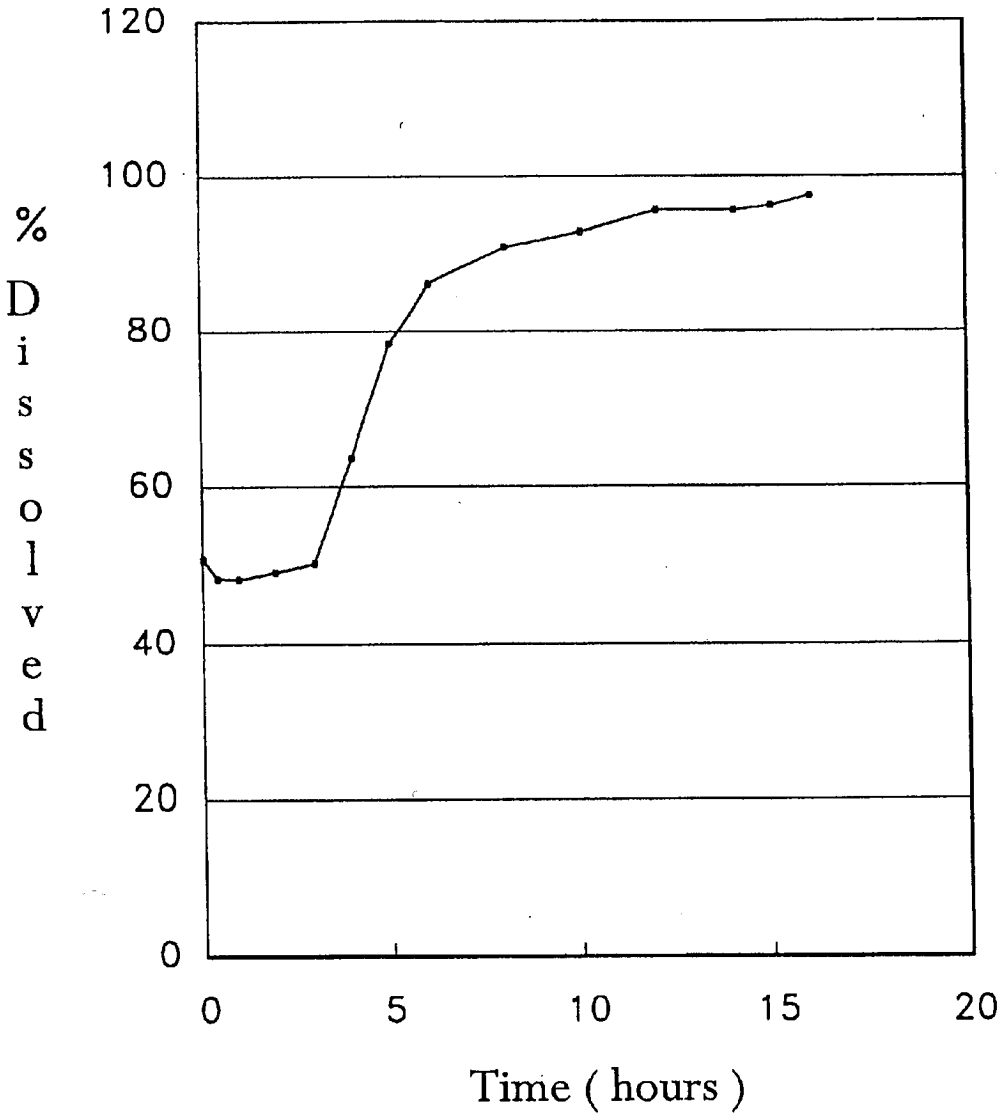


FIG. 1

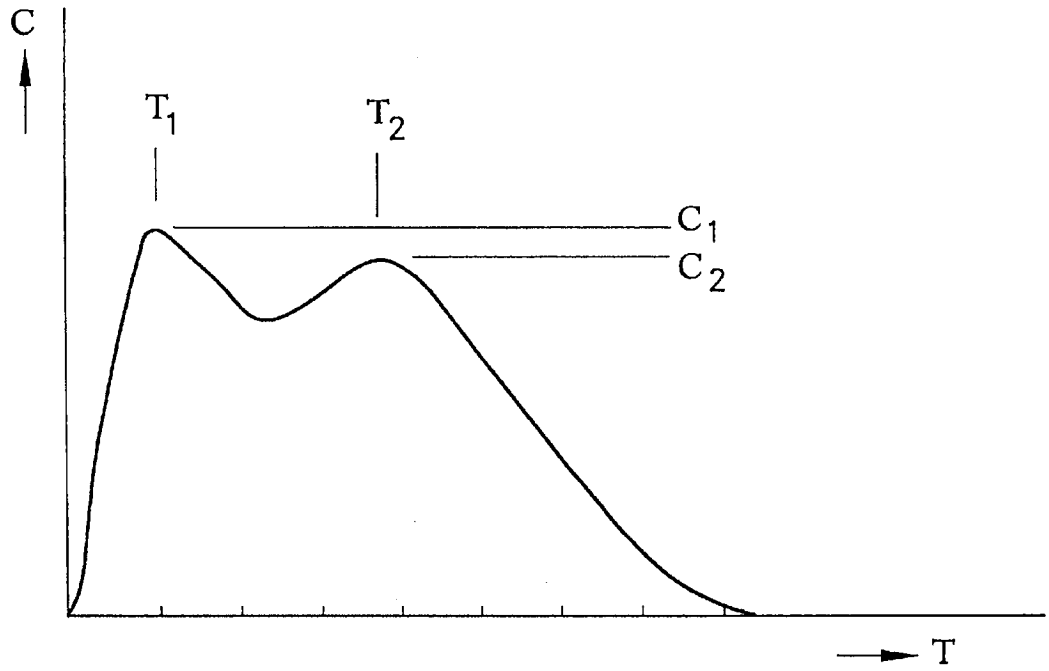


FIG. 2

DELIVERY OF MULTIPLE DOSES OF MEDICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional application of application Ser. No. 08/892,190, filed Jul, 14, 1997, now U.S. Pat. No. 5,837,284 which is a continuation in part of application Ser. No. 08/567,131, filed Dec. 4, 1995 now abandoned; application Ser. No. 08/583,317, filed Jan. 5, 1996 now U.S. Pat. No. 5,733,756; and application Ser. No. 08/647,642, filed May 15, 1996 now abandoned.

FIELD OF THE INVENTION

The present invention relates to improved dosing of medications. In particular, the present invention relates to improved dosing of a medication whereby two or more effective, time-separated doses may be provided by administration of a single dosage unit. The second, and any later, dose is time-delayed following administration. Based on predictable in vitro release times, the dosage forms can be formulated to deliver delayed doses in vivo at desired times.

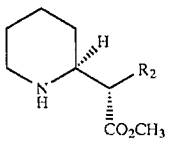
The dosage forms and methods of the present invention are particularly suitable for the administration of methylphenidate hydrochloride, and especially for the administration of a single isomer, d-threo-methylphenidate hydrochloride.

The administration of dosage forms which contain an immediate dosage and a delayed second dosage provides for reduced abuse potential, improved convenience of administration, and better patient compliance, especially when methylphenidate is used to treat certain central nervous system disorders.

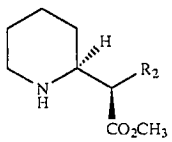
BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD), a commonly diagnosed nervous system illness in children, is generally treated with methylphenidate hydrochloride (available commercially as, e.g., Ritalin®). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by symptoms of hyperactivity, and is also treated with methylphenidate hydrochloride. Methylphenidate drugs have also been used to treat cognitive decline in patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS related conditions. See, e.g., Brown, G., *Intl. J. Psych. Med.* 25(1): 21–37 (1995); Holmes et al., *J. Clin. Psychiatry* 50: 5–8 (1989).

Methylphenidate exists as four separate optical isomers as follows:

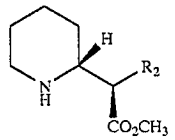


l-threo

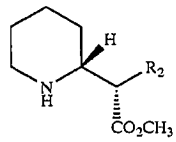


d-erythro

-continued



d-threo



l-erythro

wherein R_2, is phenyl. Pharmaceutically acceptable salts are generally administered clinically. Other phenidate drugs, which also can be administered according to the invention, include those in which the methyl group in the above structures is replaced by C_2–C_4 alkyl and R_2 is optionally substituted with C_1–C_4 alkyl.

Clinically, the threo pair of enantiomers of methylphenidate hydrochloride is generally administered for the treatment of ADD and ADHD. The hydrochloride salt is commonly referred to simply as "methylphenidate". Unless indicated otherwise, the term "methylphenidate" is used broadly herein to include methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride.

The threo racemate (pair of enantiomers) of methylphenidate is a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines. Undesirable side effects associated with the use of the dl-threo racemate of methylphenidate include anorexia, weight loss, insomnia, dizziness and dysphoria. Furthermore, the racemate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation or ingestion, and thus carries a high potential for abuse.

Srinivas et al. studied the administration of dl-threo-, d-threo, and l-threo-methylphenidate to children suffering from ADHD, and reported that the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer (*Clin. Pharmacol, Ther.*, 52: 561–568 (1992)). Therefore, while dl-threo-methylphenidate is generally used therapeutically, this racemate includes the l isomer which apparently makes no significant contribution to the pharmacological effectiveness of the drug, but likely contributes to the associated side effects. It is thus desirable to administer only the active d-threo form of the drug.

An additional problem is that children being treated with dl-threo methylphenidate must generally take one or more doses during the day. This creates a problem for school administrators who must store a controlled substance on school premises, with the associated risk that it may be stolen for illicit use. Furthermore, children may be traumatized by ridicule from peers when they must take medication at school.

Sustained release formulations of dl-threo methylphenidate have been developed, which provide for slow release of the drug over the course of the day. However, it has been observed that peak plasma concentrations of the drug are lower when sustained release formulations are used. In some studies, sustained release formulations of methylphenidate have been shown to have lower efficacy than conventional dosage forms.

There remains a need for methods for delivering methylphenidate with maximum effectiveness and minimal potential for abuse. Furthermore, it has been determined that there is a need for a dosage form which provides, in one administration, an initial release followed, at a predictable delay, by a second release, of maximally effective methylphenidate. This will eliminate the risk of theft or loss of the

second dose, while minimizing undesirable side effects and maximizing ease of administration. The present invention is directed to these, as well as other, important ends.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts an in vitro time-concentration relationship (release profile) for certain preferred dosage forms in accordance with the invention.

FIG. **2** depicts a schematic representation of in vivo plasma concentration of a drug released according to the release profile shown in FIG. **1**.

SUMMARY OF THE INVENTION

The present invention provides, in one embodiment, a therapeutic composition for the oral administration of a methylphenidate drug comprising a dosage form containing two groups of particles, each containing the methylphenidate drug. The term "particles", as used herein, includes pellets, granules, and the like. The first group of particles provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles can also comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, of the methylphenidate drug, in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. If desired, one or more additional doses may be delivered by additional particles, coated in a similar manner, but with a sufficient amount of ammonio methacrylate copolymer coating to provide the dosage after an additional delay. Methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride, can be prepared into the dosage forms of the invention.

In one embodiment of the present invention, the first group of particles comprises a methylphenidate drug and provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles may comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the particles of the methylphenidate drug in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion.

For example, the first group of particles can comprise a pharmaceutically acceptable salt of methylphenidate, such as methylphenidate hydrochloride, in powder form, or coated or uncoated particles containing the methylphenidate salt. The amount of methylphenidate salt in each group of particles can vary, depending upon the dosage requirements of the patient to whom the drug is to be administered. Generally, the daily dosage requirement for methylphenidate drugs is from about 1 mg to about 50 mg per day, preferably from about 2 mg to about 20 mg, and more preferably from about 2.5 to about 12 mg per day. The actual dosage to be administered will be determined by the attending physician as a matter of routine. Thus, depending upon the amounts of coating and/or and optional excipients and other additives, the amount of methylphenidate drug can be, for example, from about 2% to about 99% by weight of the first group of particles. In addition to the methylphenidate drug, the second group of particles comprises a filler, such as a hydrophobic filler, one or more ammonio methacrylate copolymers, and optional excipients and other additives. The filler can be present in an amount of, for example, from about 35% to about 45%, by weight, based on the total weight of the second group of particles.

Another embodiment of the present invention provides a method for treating disease, such as, for example, ADD, ADHD, or AIDS-related dementia, in a patient in need of treatment. This treatment comprises administering to the patient a dosage form providing once-daily oral administration of a methylphenidate drug such as methylphenidate hydrochloride. The dosage form comprises at least two groups of particles, each containing the methylphenidate drug. The first group of particles comprises from about 2% to about 99% by weight of the methylphenidate drug, depending upon desired the daily dosage, and provides a substantially immediate dose of methylphenidate upon ingestion by a mammal. The first group may comprise a coating and/or sealant. The second group of particles comprises coated particles. The coated particles comprise the methylphenidate drug in admixture with one or more binders, wherein the amount of methylphenidate drug is from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, and a coating comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion. The components of the two groups of particles can vary as described hereinabove. The initial dose can be administered separately from the delayed dose, if desired.

A further embodiment of the present invention provides dosage forms for the oral administration, in a single dosage form, of two doses of a pharmaceutically acceptable salt of d-threo-methylphenidate. The dosage forms comprise particles containing within their interiors from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, of the d-threo-methylphenidate salt, in admixture with one or more binders. The particles have a coating exterior to the methylphenidate salt, which comprises an ammonio methacrylate copolymer in a quantity sufficient to delay release of the d-threo-methylphenidate salt contained within by from about 2 hours to about 7 hours following administration. The dosage forms also comprise, exterior to the coating, an outer layer comprising from about 2% to about 99% by weight of the d-threo-methylphenidate salt, based on the weight of all components in the outer layer, to provide a substantially immediate dose of the d-threo-methylphenidate salt upon administration. The layer comprising the immediate dose of the d-threo-methylphenidate salt can, if desired, further comprise an outer sealant layer. If desired, the two doses of the d-threo-methylphenidate salt can be approximately equal.

The present invention also provides dosage forms providing plasma concentration profiles for methylphenidate having two maxima, temporally separated from each other by from about 2 hours to about 7 hours. Preferably, the magnitude of said maxima differs by no more than about 30 percent, more preferably by no more than about 20 percent, and most preferably by no more than about 10 percent.

"Methylphenidate" as used herein, includes all four optical isomers of the compound and all pharmaceutically

acceptable salts thereof. When one or more particular isomers is contemplated, the isomer is indicated, as in d-threo, l-threo, etc. The combined threo isomers may be indicated simply as "threo" and the erythro isomers as "erythro". For therapeutic use in treating conditions treatable by methylphenidate drugs, dl-threo methylphenidate hydrochloride is generally used, while d-threo methylphenidate hydrochloride is preferred according to the present invention.

As discussed, the four isomers have exhibited varying levels of therapeutic activity, and have been shown to differ generally in producing unwanted side effects. The present invention provides dosage forms which maximize therapeutic effectiveness and minimize undesirable side effects. In certain preferred embodiments, the dosage forms of the present invention provide administration of the two threo forms of methylphenidate. In particularly preferred embodiments, the dosage forms of the present invention provide administration of a single isomer, d-threo-methylphenidate, albeit in two or more doses.

The dosage forms of the present invention are intended for oral ingestion by a mammal, particularly a human. The dosage forms of the present invention are particularly suitable for the administration of methylphenidate drugs, in at least two doses. Most preferably, the dosage forms provide two doses of a d-threo methylphenidate drug such as d-threo methylphenidate hydrochloride. The second dose can be delayed by from about 2 hours to about 7 hours, preferably from about 3 hours to about 6 hours, and most preferably from about 4 hours to about 5 hours, following ingestion of the dosage form by a mammal. This eliminates the need for a patient, for example a child being treated for ADD, to carry a second dose for ingestion several hours after ingestion of a first dose. The exclusion of the l isomers and the d-erythro isomer eliminates the concurrent ingestion of forms of methylphenidate principally believed to be associated with adverse side effects and/or reduced effectiveness.

The temporal separation of the two doses provided according to the present invention can be represented graphically as in FIG. **1**. FIG. 1 is an in vitro drug release profile of a dosage form of the present invention. The data were obtained by measuring the rate of dissolution of drug as a function of time. In this embodiment two doses are provided. The release of the first dose preferably occurs substantially immediately; for example, within about 30 minutes following administration. Following a period of little or substantially no drug release, the second dose is released. The two releases can be referred to as "pulses", and such a release profile can be referred to as "pulsatile".

FIG. **2** is a schematic representation of the plasma concentration of drug resulting from a release profile according to FIG. 1. The maximum concentration due to the first dose, C_1, occurs at t_1, preferably from about 1 hour to about 3 hours after ingestion, most preferably about 2 hours after ingestion. The release of the first dose is followed by a period during which substantially no drug is released, which lasts approximately 2–6 hours, preferably 3–5 hours, post ingestion. The second dose is then released, with the maximum concentration, C_2, at t_2, which is preferably about 6 hours post-ingestion. Preferably at least about 80% of the total drug has been released by about 6 hours following administration. In the embodiment represented by FIG. 2, the levels of drug released at the two maxima are nearly equal. Preferably, if two approximately equal doses are released, the release of the two doses provides a plasma concentration profile having two maxima, which differ from each other by no more than about 40 percent in magnitude, preferably by no more than about 30 percent, and more preferably by no more than about 25 percent. This is determined by the relationship:

$$|C_1-C_2|/C_1$$

In such embodiments is most preferred that the maxima differ by no more than 20%. However, embodiments in which the maxima of the two releases differ by more than 40 percent are within the scope of the invention. The appropriate relative amounts of drug in each release can be readily determined by one skilled in the art.

Dosage forms of the present invention provide controlled release of a methylphenidate drug, including pharmaceutically acceptable salts of methylphenidate, whereby an initial dose for immediate release can be combined with a delayed release of one or more additional doses. Such dosage forms may alternatively be referred to as "pulsatile" dosage forms.

"Immediate release", as used herein, means release within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following ingestion. "Delayed release", as used herein, refers to a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released. The terms "medication" and "drug" are used interchangeably herein.

According to the present invention, delayed release dosage forms can be combined with forms which provide immediate release of a drug. Thus, two or more dosage forms can be combined, one dosage form providing a portion of a patient's daily dosage needs of a drug and subsequent dosage forms providing additional portions of a patient's daily dosage needs. For example, a drug can be administered to a patient in two dosage forms simultaneously, one providing, e.g., about 30–50 percent of the patient's daily requirement of the drug and the second providing the remainder of the patient's daily requirement. Alternatively, and preferably, a single dosage form can be administered which includes an immediate dose of some portion of a patient's daily requirement and one or more delayed doses to provide the remaining portion or portions of the patient's daily requirement.

Dosage forms of the present invention provide an initial dose of a drug such as, for example, a pharmaceutically acceptable salt of d-threo-methylphenidate (also referred to herein as d-MPD), followed by an interval wherein substantially no additional drug is released, followed in turn by release of a second dose. If desired, a second substantially release-free interval may be provided following the second release, followed in turn by a third dose. Thus, dosage forms providing 3 or more doses are contemplated by the present invention. However, dosage forms providing 2 or 3 doses are generally preferred for therapeutic use, with 2 doses being more preferred. For example, the first dose can provide from about 30 percent to about 70 percent of a patient's daily prescribed intake of the drug and the second dose provides from about 70 percent to about 30 percent. If two approximately equal doses are desired, the initial dose preferably provides from about 40 percent to about 60 percent, and the second dose preferably provides from about 60 percent to about 40 percent, of a patient's prescribed daily intake of the drug. If desired, the first dose and the second dose can each provide about 50 percent of a patient's prescribed daily intake of drug. However, as will be apparent to one skilled

in the art, the effect of drug metabolism in the body may require adjustment of the relative amounts of each dose, so that, for example, the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism. This can be observed in FIG. **2**, which, as discussed above, represents the blood plasma level of a drug, such as a methylphenidate drug, delivered in a dosage form which provides a release profile as illustrated in FIG. **1**.

The initial dose of methylphenidate drug in the dosage forms of the present invention can be provided by incorporating the methylphenidate drug into a form which allows for substantially immediate release of the drug once the dosage form is ingested by a patient. Such forms include, for example, powders, coated and uncoated pellets, and coated and uncoated tablets. The dose for immediate release can be administered in a tablet or capsule form which may also include the delayed dose. For example, two or more groups of pellets may be combined within a hard gelatin capsule or compressed into a tablet. Powders can be granulated and can be combined with pellets and excipients and/or other additives, and contained within a capsule or compressed into a tablet. These and other dosage forms will be familiar to those skilled in the art.

The delayed dose of a methylphenidate drug in the dosage forms of the present invention is provided in part by the use of certain copolymers referred to as "ammonio methacrylate copolymers". Ammonio methacrylate copolymers comprise acrylic and/or methacrylic ester groups together with quaternary ammonium groups. According to the present invention, the copolymers are incorporated into a formulation which is used to coat particles containing a medication.

The "acrylic and/or methacrylic ester groups" in the copolymers used in the compositions and methods of the present invention are referred to herein collectively as "acrylic groups". The acrylic groups are preferably derived from monomers selected from C_1–C_6 alkyl esters of acrylic acid and C_1–C_6 alkyl esters of methacrylic acid. Preferred are C_1–C_4 alkyl esters of acrylic acid and methacrylic acid. Suitable monomers include, for example, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate. Ethyl acrylate and methyl methacrylate are preferred, and copolymers containing ethyl acrylate and methyl methacrylate are highly preferred. Also preferably, the copolymers have a molecular weight of about 150,000.

Quaternary ammonium groups in copolymers useful in forming coatings for use in the dosage forms of the present invention can be derived from monomers comprising quaternary ammonium groups. Preferably, the monomers are alkyl esters of acrylic or methacrylic acid, comprising alkyl groups having from 1 to 6 carbon atoms and a quaternary ammonium group in the alkyl portion. Monomers comprising quaternary ammonium groups can be prepared, for example, by reaction of monomers containing amino groups with alkylating agents such as, for example, alkyl halides, especially methyl chloride. Suitable monomers containing amino groups include 2-(N,N-dibutylamino) ethyl acrylate, 2-(N,N-dibutylamino) ethyl methacrylate, 4-diethylamino-1-methyl-butyl acrylamide, and 4-diethylamino-1-methyl-butyl methacrylamide. Other useful monomers containing amino groups are disclosed in U.S. Pat. No. 5,422,121, the disclosure of which is incorporated herein by reference. Particularly preferred as a monomer comprising a quaternary ammonium group is trimethylammonioethyl methacrylate chloride (TAMCl).

While ammonio methacrylate copolymers such as those described herein have been used for sustained delivery of certain medicaments, i.e., for the relatively constant administration of a drug, it has been surprisingly and unexpectedly found that dosage forms comprising a methylphenidate drug and a coating prepared from one or more ammonio methacrylate copolymers and certain fillers, can provide delayed or pulsatile release of the drug, a very distinct phenomenon. Methylphenidate drugs are amine-containing, rely upon body or membrane loading for efficacy, and are psychotropic. The ability to provide delayed release of a methylphenidate drugs using ammonio methacrylate copolymers is due to a combination of factors, including the composition of the ammonio methacrylate copolymers used, and the amount and composition of filler.

The ratio of acrylic groups to quaternary ammonium groups in the ammonio methacrylate copolymers influences the properties of the copolymers utilized in forming the coatings of the present invention. For use in the dosage forms and methods of the present invention, the ratio of acrylic groups to quaternary ammonium groups in the copolymers is preferably from about 10:1 to about 50:1, more preferably from about 15:1 to about 45:1. Preferably, in preparing a dosage form according to the present invention, two or more copolymers are used in combination. Also preferably, one of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 25:1 to about 45:1, more preferably from about 30:1 to about 40:1, and another of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 10:1 to about 25:1, more preferably from about 15:1 to about 20:1. Even more preferably, two ammonio methacrylate copolymers are used: a first copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 30:1 to about 40:1 and the second copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 15:1 to about 20:1. Most preferably, the copolymers are copolymers of methyl methacrylate, ethyl acrylate, and TAMCl, in ratios of 2:1:0.1 for the first copolymer and 2:1:0.2 for the second copolymer.

When two such ammonio methacrylate copolymers are used to form the coatings, the relative amounts of the two polymers is partly determinative of the delay and release properties of the dosage forms of the present invention. It is preferred that the ratio between the first polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 30:1 to about 40:1, and the second polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 15:1 to about 20:1, be from about 93:7 to about 97:3. More preferably, the ratio of the first polymer to the second polymer is from about 96:4 to about 94:6, and most preferably about 95:5.

Ammonio methacrylate copolymers used in the coatings of the dosage forms of the present invention can be prepared by methods known to those skilled in the art. Exemplary methods include emulsion polymerization, bulk polymerization and suspension polymerization. A suitable procedure is described in U.S. Pat. No. 3,979,349, the disclosure of which is incorporated herein by reference. Suitable ammonio methacrylate copolymers are known per se, and can be purchased from commercial providers. For example, suitable ammonio methacrylate polymers are available from Hüils America under the Eudragit® trademarks. The Eudragit® polymers and similar polymers, including methods for preparation, are described in Klaus O. R. Lehman, "Chemistry and Application Properties of Polymethacrylate Coating Systems", *Aqueous Polymeric Coatings for Pharmaceutical Dosage*

Forms, 2nd. Ed., pp. 101–174, James Mc Ginity, Ed., Marcel Dekker, Inc., N.Y. (1996), the disclosure of which is incorporated herein by reference.

The coatings of the present invention also preferably include a filler. The filler is preferably in powder form and is preferably hydrophobic. Exemplary fillers include talc, colloidal silica, fumed silica, gypsum, and glycerine monostearate. Talc is a particularly preferred filler.

The quantity of filler used in preparing coatings for the dosage forms of the present invention should be sufficient to minimize agglomeration of the particles. Agglomeration is highly undesirable because the agglomerates, rather than discrete particles, will become coated. Agglomerates are susceptible to breaking into discrete particles, which will be partially uncoated, resulting in unwanted variability in release rates. Preferably, the amount of filler is from about 30 percent to about 50 percent by weight, based on the total weight of the dry polymer, commonly referred to as "total solids". More preferably the amount of filler is from about 35 percent to about 45 percent of total solids, and most preferably about 40 percent.

Coatings used in the dosage forms of the present invention also preferably include a material which improves the processing of the copolymers. Such materials are generally referred to as "plasticizers" and include, for example, citric acid esters, adipates, azelates, benzoates, citrates, stearates, isoebucates, sebacates, propanetriol acetate, polyethylene glycols, diethyl phthalate, dibutyl sebacate, propylene glycol and ethylene glycol. Citric acid esters are preferred, and triethyl citrate is particularly preferred. The amount of plasticizer to be used in the coating is preferably from about 10 percent to about 30 percent, more preferably from about 15 percent to about 25 percent, and most preferably about 20 percent, based on the weight of the dry polymer, i.e., total solids.

Dosage forms of the present invention preferably comprise particles containing d-MPD. In one embodiment, the dosage form comprises two groups of particles. A first group of particles provides the initial dose of d-MPD. As stated hereinabove, the initial dose can be in powder, pellet or other particulate form and can be uncoated. If the initial dose is in the form of a powder or sufficiently small particles, it can, if desired, be pressed into a solid form such as a tablet or caplet. In this embodiment, the delayed dose is provided by a second group of particles. The second group of particles is preferably in the form of pellets. The pellets can be of any shape, such as, for example, spheroids or ellipsoids, or may be irregularly shaped.

Suitable pellets for the initial dose and/or the second dose can be formed by, for example, depositing a layer of drug, and optional excipients, carriers, and other optional materials, onto small, pharmaceutically acceptable particles such as nonpareils. Such a layer can be deposited by methods known to those skilled in the art, such as, for example, spraying, using methods and equipment known to those skilled in the art. For example, a Wurster air suspension coater can be used. Spraying can also be accomplished using a pan coating system, wherein the drug is deposited by successive spraying accompanied by tumbling in a rotating pan. Alternatively, pellets can be formed, for either or both of the initial and delayed dose, by extrusion of the drug with suitable plasticizers and other processing aids as necessary.

Tablets or caplets, or other solid dose forms, comprising the initial dose and/or delayed dose or doses, can conveniently be administered. A solid dose form can be prepared by methods known to those skilled in the art. For example, the d-MPD, filler and other optional components may be compressed into tablets or inserted into capsules. If desired, the drug and other components of the dose form can be granulated, using processing aids, fillers, aqueous or non-aqueous solvents, and binders known to those skilled in the art. Granules can be filled into capsules, if desired. Alternatively, the d-MPD can be blended with a solvent and processed by known methods such as ball-milling, calendering, stirring, or roll-milling, then pressed into a desired shape. Suitable solvents useful in forming the particles comprising d-MPD, and other components of the dosage forms of the invention, include inert organic and inorganic solvents which do not adversely affect the components of the dosage forms. While water can be used for many drugs, including methylphenidate, useful solvents can be selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatic heterocyclic solvents, and mixtures thereof. Other solvents include acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, diglyme, and aqueous and non-aqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, and ethylene dichloride and methanol.

Following the formation of suitable particles, those particles to be used to deliver the delayed dose are then coated with a polymer-containing coating as described herein. The amount of coating to be used in forming the dosage forms, particularly the delayed dose, of the present invention, will be determined by the desired delivery properties, including the amount of drug to be delivered, the delay time required, and the size of the particles. Preferably, the coating on the particles providing the delayed dose, including all solid components of the coating such as copolymer, filler, plasticizer and optional additives and processing aids, is from about 10 percent to about 60 percent, more preferably from about 20 percent to about 50 percent, most preferably from about 30 percent to about 40 percent, of the total final weight of the particles. The appropriate amount of coating can advantageously be determined using in vitro measurements of drug release rates obtained with selected amounts of coating. The coating can be deposited by any method known to those skilled in the art, such as spray application. Spraying can be carried out by pan coating or by use of a fluid bed, such as the Wurster fluid bed described for use in depositing a drug.

After deposition of the drug, a sealant can be applied to any and/or all of the particles, prior to application of the polymeric coating. A sealant provides a physical barrier between the drug and the coating, to minimize or prevent interaction between the drug and the coating. Suitable sealants can be prepared from materials such as biologically inert, permeable, pharmaceutically acceptable polymers, such as, for example, hydroxypropylalkylcelluloses, wherein "alkyl" refers to C_1–C_6 hydrocarbon chains. Exemplary materials include hydroxypropyl methylcellulose, hydroxypropylethylcellulose, hydroxypropyl propylcellulose, and hydroxypropylbutylcellulose. Hydroxypropylmethylcellulose is preferred. While other materials are known to those skilled in the art for use as sealants, such as, for example, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyurethanes, semipermeable sulfonated polystyrenes,

semipermeable cross-linked polymers such as poly (vinylbenzyltrimethyl)ammonium chloride, these are not preferred as they may affect the release rate of certain drugs including d-MPD. A sealant can be prepared by adding the material to water, and agitating for a time and at a rate sufficient to form a solution. The formation of a solution will be indicated, for example, by transparency and the absence of visually observable suspended material. The amount of material added to the water is not critical but is determined by viscosity. A solution which is too viscous will present difficulties in spraying. Generally, the amount of material should not exceed about 20 weight/volume percent, i.e., 20 g sealant material per 100 ml of water. Preferably, the amount of material in the water is from about 5 percent to about 15 weight/volume percent, and more preferably about 10 weight/volume percent.

Following deposition of the optional sealant and the coating, the coated particles are cured. "Curing" means that the particles are held at a controlled temperature for a time sufficient to provide stable release rates. Stability in release rate is indicated when further curing does not affect the release rate. In contrast, instability of release rate means that as the cure time is increased, the release rate continues to vary. Curing for a sufficient time ensures that substantially the same release rate is obtained with all particles of a particular size coated with a given amount of a given coating composition. A suitable curing time can be determined by one of skill in the art without undue experimentation, by noting the variability in in vitro release times as curing time is varied. As a general guideline, many formulations can be cured in about 24 hours.

Curing can be accomplished, for example, in a forced air oven. Curing can be carried out at any temperature above room temperature, "room temperature" being defined as from about 18° C. to about 25° C. Preferably, curing is carried out at a temperature of from about 30° C. to about 50° C., more preferably from about 35° C. to about 45° C., and most preferably about 40° C. Curing time can range from several hours to several days. Preferably, the coated particles are cured for at least about 24 hours, more preferably at least about 2 days, even more preferably at least about 3 days, still more preferably at least about 4 days, still even more preferably at least about 5 days, even more preferably at least about 6 days, and most preferably for about 7 days. While no significant adverse effects or advantages have been observed when the particles are cured for longer than about 7 days, it has been found that curing for less than about 24 hours may result in relatively poorer storage stability as compared to particles cured for longer periods of time.

The amount of methylphenidate drug contained in the first and second groups of particles depends upon the prescribed dosage to be delivered to a patient. The first group of particles can consist substantially entirely of a methylphenidate drug. "Substantially entirely" means that about 95 percent or more of the weight of the first group of particles can consist of a methylphenidate drug. If desired, the first group of particles can also contain pharmaceutically acceptable carriers, excipients, and other components which do not interfere with the substantially immediate release of the medication. "Substantially immediate" release, as used herein, means that at least about 90 percent of the medication is released within about 30 minutes from the time the drug is ingested. The second group of particles can contain from about 2 percent to about 75 percent, preferably from about 4 percent to about 50 percent, medication, based on the total weight of the particles including the coating to be deposited thereon.

According to the invention, a first and a second group of particles can be administered simultaneously as part of one dosage form. Any dosage form can be used. For example, the two groups of particles can be combined within a capsule. Alternatively, the two groups of particles can be pressed into a solid form such as a tablet. In pressing the particles into a solid form, suitable processing aids known to those skilled in the art can be used. Alternatively, particles coated to provide a delayed dose of a medication can be dispersed within or blended with, the medication in powder form.

As discussed, the dosage form can comprise a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose of methylphenidate drug. The particles comprise, in admixture with one or more binders, from about 2% to about 75% by weight of a methylphenidate drug for delayed release, and a coating comprising the pharmaceutically acceptable, substantially neutral copolymers described herein. The particles further comprise, exterior to the coating, an outer layer comprising methylphenidate drug, to provide an initial, substantially immediate, dose. The substantially immediate dose is preferably released within about 30 minutes, more preferably about 15 minutes, and most preferably within about 5 minutes following ingestion. The outer layer can optionally comprise additives such as, for example, binders, excipients, and lubricants known to those skilled in the art.

The dosage forms provided by the invention can be of any shape suitable for oral administration of a drug, such as spheroidal, cube-shaped, oval, bean shaped, or ellipsoidal. The dosage form may be in the form of granules, which may be irregularly shaped. In any of the embodiments of the present invention, although the size of the particles is generally not critical, a certain particle size or sizes can be preferred depending upon the characteristics of the dosage form. For example, the dosage form can comprise a capsule containing a first and/or second group of particles. The particles should then be of a size which allows for ease in handling, and which allows for the particles comprising a desired quantity of drug to be readily measured and inserted into the capsule. If the dosage form comprises a single group of particles providing a substantially immediate dose and a delayed dose, the particles are preferably of a size and shape which facilitate oral administration. For example, the particles can be in the form of tablets, caplets, etc. Alternatively, the particles can be contained within a capsule of suitable size and shape for oral administration. If desired, various fillers and/or binders known to those skilled in the art can be included in the particles to provide the desired size and shape.

It will be recognized by one skilled in the art that the dosage forms of the present invention may include, in either or both of the first dose and any delayed dose, pharmaceutically acceptable carriers, extenders, fillers, processing aids, and excipients known to those skilled in the art.

The following examples are merely illustrative of the present invention and should not be considered limiting of the scope of the invention in any way. These examples and equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure and the accompanying claims.

EXAMPLE 1

Preparation of Layered Pellets Containing d-MPD Hydrochloride

A solution of d-MPD hydrochloride was prepared as follows. To 300 grams (g) of deionized water were added 100 g of d-MPD hydrochloride, followed by moderate

mixing, using a stirring paddle, for 5 minutes. A 10 percent (weight) solution of hydroxypropyl methylcellulose (HPMC E-6 from Dow Chemicals, Midland, Mich.; 250 g) was added, followed by homogenization for 5 minutes using an emulsifier head (Silverson, Chesham, UK; Model L4R). After addition of another 150 g of deionized water, the solution was sonicated for 15 minutes (Sonicor Model SC-150T; Instruments Corporation, Copiague, N.Y.), at which time the solution was clear.

A second solution was prepared by combining 300 g of deionized water and 300 g of a 10% (wt) HPMC E-6 solution and mixing for 5 minutes.

The first solution was sprayed onto 25/30 mesh non-pareil seeds (Ozone Co., Elmwood Park, N.J.) in a fluid bed apparatus (GPCG-1, Glatt Air Techniques, Inc., Ramsey, N.J.) using a Wurster head. The second solution was then sprayed to form a sealant. For both solutions, the spray rate was 8–9 g/minute. Inlet temperature was 50–55° C. and the non-pareil seeds were maintained at 35–40° C. Air volume was 6–7 meters per second (m/s).

EXAMPLE 2

Preparation of Coated Pellets Containing d-MPD Hydrochloride

A dispersion of 844 g of Eudragit® RS30D (ammoniomethacrylate copolymer from Hüils America, Somerset, N.J.; EA/MMA/TAMCI 1:2:0.1), was screened through a 60 mesh screen, then stirred for 15 minutes. A dispersion of 44 g of Eudragit® RL30D (EA/MMA/TAMCl 1:2:0.2) was similarly screened and stirred. The two dispersions were combined and stirred for 15 minutes, forming a combined dispersion. Triethyl citrate (TEC; from Morefiex, Greensboro, N.C.; 54 g) was added, followed by an additional 15 minutes of stirring. Deionized water (664 g) was added, followed by 15 minutes of stirring. Talc (108 g; from Luzenac, Englewood, Colo.) was added, followed by further stirring for 15 minutes.

The resulting combined dispersion was sprayed onto layered pellets prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 9–10 g/minute, inlet temperature 40–45° C., and air volume 5–6 m/s. The non-pareils were maintained at 30–35° C. during spraying. A total of 960 g of dispersion was sprayed onto the pellets, representing a 30% weight increase due to the applied coating.

EXAMPLE 3

Evaluation of Drug Release Profile for Coated Pellets Prepared According to Example 2

Pellets were prepared according to Example 2, varying the ratios of the polymers between 90:10 and 93:7.

Dissolution Measurements

Dissolution was carried out in order to determine rate of release of d-MPD from the pellets. USP Apparatus I (United States Pharmacoepia Convention, Rockville, Md.) was used. The dissolution medium was 900 ml of deionized water (unless otherwise specified) and the temperature was maintained at 37° C. The sample cell size was 1 cm (a flow through cell), and the samples were stirred continuously at 100 rpm. The apparatus was equipped with a diode array spectrophotometer, and absorption at 220 nanometers (nanometers (nm)) was measured to determine the concentration of d-MPD. Samples were measured at 60, 120, 180, 240, 360, 480, 600, 720, 840, 900, 960, 1080, 1200, 1320 and 1440 minutes.

Results of the dissolution measurements are presented in Table 1. The results indicate that the amount of drug released is influenced by: amount of coating, ratio of the two polymers, amount of talc, and curing time.

EXAMPLE 4: COMPARATIVE EXAMPLE

A dispersion of 911.25 g of Eudragit® RS30D was passed through a 60 mesh screen and mixed with a similarly screened dispersion of 101.25 g of Eudragit® RL30D for 15 minutes at moderate speed. Triethyl citrate (61 g) was added, followed by an additional 15 minutes of mixing. After mixing, 991.5 g of deionized water, then 61 g of talc were added with 15 additional minutes of mixing following each addition. The resulting dispersion (1600 g) was sprayed onto 800 g of layered sealed pellets prepared according to Example 1.

No delay was observed; substantially all of the drug was released within approximately one hour. Result is shown in Table 1 (Trial 1).

EXAMPLE 5: COMPARATIVE EXAMPLE

A dispersion of 600 g of Eudragit® NE30D was screened through a 60 mesh screen and mixed with a 600 g dispersion of magnesium stearate for 15 minutes at moderate speed. The resulting dispersion (750 g) was sprayed onto 750 g of layered and sealed pellets prepared according to Example 1.

After a delay of 2 hours, release of the drug was observed. About 85% of the drug was released after 14 total hours.

TABLE 1

RELEASE TIMES

Trial No.	% coat	Ratio	Delay	Talc, %	Cure time	Time for 85% release
1	40	90:10	none	20.0	24 hrs	1.0
2	30	95:5	4.0	20.0	"	8.0
3	30	95:5	4.0	20.0	"	8.0
4	30	93:7	1.0	20.0	"	3.0
5	40	93:7	1.0	20.0	"	4.0
6	30	93.5:6.5	2.0	20.0	"	5.0
7	40	"	2.0	20.0	"	5.0
8	30	94.5:5.5	2.0	20.0	"	8.0
9	40	"	1.0	20.0	"	5.0
10	30	94:6	2.0	20.0	"	5.0
11	40	"	2.0	20.0	"	5.0
12	30	95:5	2.0	40.0	"	5.0
13	40	"	3.0	40.0	"	8.0
14	30	96:4	4.0	40.0	"	10.0
15	40	"	5.0	40.0	"	10.0
16	30	"	4.0	40.0	7 days	10.0
17	20	95:5	2.0	40.0	"	5.0
18	30	"	3.0	40.0	"	6.0
19	30	"	3.0	40.0	"	6.0
20	30	"	2.0	40.0	"	6.0
21	40	"	3.0	40.0	"	8.0

What is claimed is:

1. A method for treating disease amenable to treatment with a phenidate drug in a patient in need of such treatment comprising administering to the patient a dosage form providing once-daily oral administration of d-threo-methylphenidate hydrochloride, said dosage form comprising two groups of particles, each containing d-threo-methylphenidate, wherein:

a) said first group of particles comprises from about 2% to about 99% by weight of d-threo-methylphenidate hydrochloride and provides a substantially immediate dose of said d-threo methylphenidate upon ingestion by a mammal; and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of d-threo-methylphenidate in admixture with one or more binders, and a coating

consisting of an ammonio methacrylate copolymer in an amount sufficient to provide a dose of said d-threo-methylphenidate hydrochloride delayed by from about 2 hours to about 7 hours following said ingestion.

2. A dosage form of a pharmaceutically acceptable salt of a methylphenidate providing an in vivo plasma concentration of said methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about two hours to about seven hours and wherein the magnitude of said maxima differ by no more than about 30%.

3. A method for treating disease amenable to treatment with a phenidate drug in a patient in need of such treatment comprising administering to the patient a dosage form providing once-daily oral administration of the phenidate drug, said dosage form comprising two groups of particles, each containing the drug wherein:

a) said first group of particles comprises from about 2% to about 99% by weight of the phenidate drug and provides a substantially immediate dose of said phenidate drug upon ingestion by a mammal; and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of the phenidate drug in admixture with one or more binders, and a coating consisting of an ammonio methacrylate copolymer in an amount sufficient to provide a dose of said phenidate drug delayed by from about 2 hours to about 7 hours following said ingestion.

4. The method of claim 3 wherein said delay is at least about 3 hours.

5. The method of claim 3 wherein said delay is at least about 4 hours.

6. The method of claim 1 wherein said delay is at least about 3 hours.

7. The method of claim 1 wherein said delay is at least about 4 hours.

8. The dosage form of claim 2 wherein the temporal separation is at least about 3 hours.

9. The dosage form of claim 2 wherein the temporal separation is at least about 4 hours.

10. A method for treating disease amenable to treatment with a phenidate drug in a patient in need of such treatment comprising administering to the patient a dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate, said dosage form providing an in vitro release profile comprising two pulses of drug release, wherein said pulses are temporally separated by from about 2 hours to about 7 hours.

11. A method for treating disease amenable to treatment with a phenidate, drug in a patient in need of such treatment comprising administering to the patient a dosage form of a pharmaceutically acceptable salt of d-threo-methylphenidate providing an in vivo plasma concentration of said d-threo-methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about 2 hours to about 7 hours, and wherein the magnitude of said maxima differ by no more than about 30 percent.

* * * * *

EXHIBIT F

US007431944B2

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

(10) **Patent No.: US 7,431,944 B2**
(45) **Date of Patent: *Oct. 7, 2008**

(54) **DELIVERY OF MULTIPLE DOSES OF MEDICATIONS**

(75) Inventors: **Atul M. Mehta**, Ramsey, NJ (US); **Andrew L. Zeitlin**, Millington, NJ (US); **Maghsoud M. Dariani**, Fanwood, NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 320 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/458,451**

(22) Filed: **Jun. 10, 2003**

(65) **Prior Publication Data**

US 2004/0091532 A1 May 13, 2004

Related U.S. Application Data

(60) Continuation of application No. 09/038,470, filed on Mar. 11, 1998, now Pat. No. 6,635,284, which is a division of application No. 09/892,190, filed on Jul. 14, 1997, now Pat. No. 5,837,284, which is a continuation-in-part of application No. 08/647,642, filed on May 15, 1996, now abandoned, and a continuation-in-part of application No. 08/583,317, filed on Jan. 5, 1996, now Pat. No. 5,733,756, and application No. 08/567,131, Dec. 4, 1995, now abandoned.

(51) **Int. Cl.**

A61K 9/50	(2006.01)
A61K 9/48	(2006.01)
A61K 9/54	(2006.01)
A61K 9/20	(2006.01)
A61K 9/22	(2006.01)
A61K 9/28	(2006.01)
A61K 9/36	(2006.01)
A61K 9/14	(2006.01)
A61K 9/16	(2006.01)

(52) **U.S. Cl.** **424/497**; 424/451; 424/458; 424/462; 424/464; 424/468; 424/474; 424/480; 424/489; 424/490

(58) **Field of Classification Search** 424/497, 424/458, 474, 468, 464, 490, 462, 494, 489, 424/480, 451

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,507,631 A 5/1950 Hartmann et al. 260/294

(Continued)

FOREIGN PATENT DOCUMENTS

CA 1297368 3/1992

(Continued)

OTHER PUBLICATIONS

Aoyama, T. et al., "Pharmacodynamic Modeling for Change of Locomotor Activity by Methyllphenidate in Rats," *Pharmaceutical Research,* 1997, 14(11), 1601-1606.

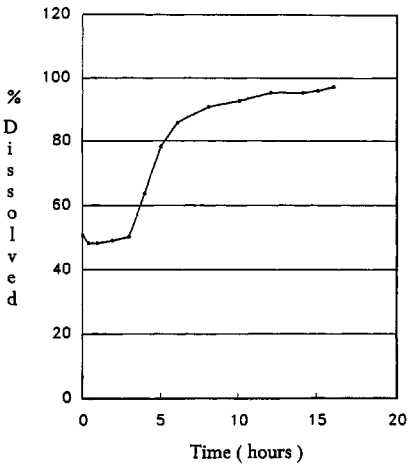
(Continued)

Primary Examiner—Humera N. Sheikh
(74) *Attorney, Agent, or Firm*—Woodcock Washburn LLP

(57) **ABSTRACT**

Dosage forms for oral administration of a methylphenidate drug are provided. The dosage forms provide a substantially immediate dose of methylphenidate upon ingestion, followed by one or more additional doses at predetermined times. By providing such a drug release profile, the dosage forms eliminate the need for a patient to carry an additional dose for ingestion during the day. The dosage forms and methods provided are useful in administering methylphenidate and pharmaceutically acceptable salts thereof, which generally require one or more doses throughout the day.

6 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

2,838,519	A	6/1958	Rometsch et al.	260/294.3
2,957,880	A	10/1960	Rometsch	546/233
4,137,300	A	1/1979	Sheth et al.	424/21
4,410,700	A	10/1983	Rice	546/149
4,794,001	A	12/1988	Mehta et al.	424/458
4,882,166	A	11/1989	Graham et al.	424/462
4,904,476	A	2/1990	Mehta et al.	424/456
4,968,505	A	11/1990	Okada et al.	424/400
4,986,987	A	1/1991	Ayer et al.	424/473
4,992,445	A	2/1991	Lawter et al.	514/279
5,104,899	A	4/1992	Young et al.	514/646
5,114,946	A	5/1992	Lawter et al.	514/279
5,133,974	A	7/1992	Paradissis et al.	424/480
5,137,733	A	8/1992	Noda et al.	424/497
5,156,850	A	10/1992	Wong et al.	424/473
5,158,777	A	10/1992	Abramowitz et al.	424/458
5,160,744	A	11/1992	Jao et al.	424/473
5,202,128	A	4/1993	Morella et al.	424/469
5,217,718	A	6/1993	Colley et al.	424/449
5,223,265	A	6/1993	Wong	424/473
5,229,131	A	7/1993	Amidon et al.	424/451
5,232,705	A	8/1993	Wong et al.	424/473
5,236,689	A	8/1993	Wong et al.	424/473
5,283,193	A	2/1994	Yamamoto et al.	435/280
5,284,769	A	2/1994	Evans et al.	
5,299,121	A	3/1994	Brill et al.	364/413.01
5,308,348	A	5/1994	Balaban et al.	604/892.1
5,326,570	A	7/1994	Rudnic et al.	424/458
5,331,000	A	7/1994	Young et al.	514/570
5,362,755	A	11/1994	Barberich et al.	514/649
5,375,693	A	12/1994	Woosley et al.	514/317
5,391,381	A	2/1995	Wong et al.	424/473
5,425,950	A	6/1995	Dandiker et al.	424/480
5,449,743	A	9/1995	Kobayashi et al.	528/355
5,478,573	A	12/1995	Eichel et al.	424/480
5,496,561	A	3/1996	Okada et al.	424/480
5,500,227	A	3/1996	Oshlack et al.	424/476
5,512,293	A	4/1996	Landrau et al.	424/449
5,567,441	A	10/1996	Chen	424/494
5,580,578	A	12/1996	Oshlack et al.	424/468
5,593,694	A	1/1997	Hayashida et al.	124/468
5,639,476	A	6/1997	Oshlack et al.	424/468
5,672,360	A	9/1997	Sackler et al.	424/490
5,733,756	A	3/1998	Zeitlin et al.	435/122
5,773,478	A	6/1998	Richards et al.	514/649
5,837,284	A	11/1998	Mehta et al.	424/459
5,874,090	A	2/1999	Baker et al.	424/400
5,908,850	A	6/1999	Zeitlin et al.	514/315
5,922,736	A *	7/1999	Dariani et al.	
5,936,091	A	8/1999	Khetani et al.	546/233
5,965,734	A	10/1999	Ramaswamy et al.	546/233
6,031,124	A	2/2000	Fox et al.	560/37
6,113,879	A	9/2000	Richards et al.	424/9.1
6,121,453	A	9/2000	Zavareh	546/238
6,127,385	A	10/2000	Midha et al.	514/317
6,217,904	B1	4/2001	Midha et al.	424/468
6,221,883	B1	4/2001	Baldessarini et al.	514/317
6,228,398	B1	5/2001	Devane et al.	424/484
6,242,464	B1	6/2001	Harris et al.	514/317
6,255,325	B1	7/2001	Dariani et al.	514/317
6,344,215	B1	2/2002	Bettman et al.	424/459
6,355,656	B1	3/2002	Zeitlin et al.	514/317
6,359,139	B1	3/2002	Khetani et al.	546/233
6,395,752	B1	5/2002	Midha et al.	514/317
6,441,178	B2	8/2002	Zavareh et al.	546/238
6,468,504	B1	10/2002	Richards et al.	424/9.1
6,486,177	B2	11/2002	Zeldis et al.	514/317
6,528,530	B2	3/2003	Zeitlin et al.	514/317
6,531,489	B2	3/2003	Harris et al.	514/317
6,602,887	B2	8/2003	Dariani et al.	517/317
6,635,284	B2 *	10/2003	Mehta et al.	
6,730,325	B2	5/2004	Devane et al.	424/489
6,962,997	B1	11/2005	Khetani et al.	546/233
7,115,631	B2	10/2006	Zeldis et al.	514/317
2002/0019535	A1	2/2002	Zavareh et al.	546/227
2002/0032335	A1	3/2002	Langston et al.	546/238
2002/0103162	A1	8/2002	Epstein et al.	
2002/0132793	A1	9/2002	Epstein et al.	514/79
2003/0049205	A1	3/2003	Richards et al.	424/9.1
2003/0105134	A1	6/2003	Harris et al.	514/317
2003/0170181	A1	9/2003	Midha	424/10.4

FOREIGN PATENT DOCUMENTS

CA	2 368 367		10/2000
CA	2 376 215	A1	12/2001
CA	2 223 643	C	12/2003
EP	0 636 366	A2	2/1995
EP	0 885 191	B1	1/2002
EP	0 889 874	B1	1/2002
EP	0 841 928	B1	9/2002
EP	0 879 228	B1	10/2002
EP	0 958 281	B1	3/2004
FR	2 635 460		9/1994
GB	589625		1/1945
GB	788226		12/1957
GB	878167		9/1961
RU	466229		4/1975
WO	WO93/05769		1/1993
WO	96/41617	A1	12/1996
WO	WO97/03671		2/1997
WO	WO97/03672		2/1997
WO	WO97/03673		2/1997
WO	WO97/27176		7/1997
WO	WO97/28124		8/1997
WO	WO97/32851		9/1997
WO	WO97/35836		10/1997
WO	WO98/06380		2/1998
WO	WO98/23263		4/1998
WO	WO98/25902		6/1998
WO	WO98/31668		7/1998
WO	WO98/14168		9/1998
WO	WO99/62496		12/1999
WO	WO 00/74680	A1	12/2000
WO	WO 01/43730	A3	6/2001
WO	2004/026258	A2	4/2004

OTHER PUBLICATIONS

Aoyama, T. et al., "Pharmacokinetics and pharmacodynamics of methylphenidate enantiomers in rats," *Psychopharmacology,* 1996, 127, 117-122.

Aoyama, T., et al., "Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers," *Eur. J. Clin. Pharmacol.,* 1993, 44, 79-84.

Barkley, R. A., et al., "The adolescent outcome of hyperactive children diagnosed by research criteria: I. An 8-year prospective follow-up study," *J. Am. Acad. Adolesc. Psychiatry.,* 1990, 29(4), 546-557.

Baughman, Jr., F. A., "Treatment of Attention-Deficit/Hyperactivity Disorder," *JAMA.,* Apr. 28, 1999, 218(16), 1490-1491.

Bruera, E., and Neumann, C. M., "The uses of psychotropics in symptom management in advanced cancer," *Pscyho-Oncology.,* 1998, 7, 346-358.

Carey, W. B., "What the multimodal treatment study of children with attention-deficit/hyperactivity disorder did and did not say about the use of methylphenidate for attention deficits," *Pediatrics,* 2000, 863-864.

Coyle, J. T., "Psychotic drug use in very young children," *J. Am. Med. Assn.,* 2000, 283(8), 1059-1060.

Davids, E. et al., "Stereoselective effects of methylphenidate on motor hyperactivity in juvenile rats induced by neonatal 6-hydroxydopamine lesioning," *Psychopharmacology,* 2002, 160, 92-98.

Ding, Y.-S. et al., "Chiral drugs: comparison of the pharmacokinetics of [11C]d-threo and *l-threo*-methylphenidate in the human and baboon brain," *Psychopharmacology,* 1997, 131, 71-78.

Ding, Y.-S. et al., "Is the L-threo Enantiomer of Methylphenidate (Ritalin) Inactive in the Brain when the Drug is Given Orally?" *ACNP 41st Annual Meeting,* Dec. 8-12, 2002, Scientific Abstract No. 119.

Garland, E. J., "Pharmacotherapy of adolescent attention deficit hyperactivity disorder: challenges, choices and caveats," *J. Psychopharmacology.,* 1998, 12(4), 385-395.

Golden, G. S., "Role of attention deficit hyperactivity disorder in learning disabilities," *Seminars in Neurology.,* 1991, 11(1), 35-41.

Goldman, L. S., et al., "Diagnosis and treatment of attention-deficit/hyperactivity disorder in children and adolescents," *J. Am. Med. Assn.,* 1998, 279(14), 1100-1107.

Jadad, A. R., et al., "Review: Pharmacologic interventions are more effective than non-pharmacologic for attention-deficit hyperactivity disorder," *Therapeutics, ACP Journal Club.,* Nov./Dec. 2000, 110.

Jensen, P. S., et al., "Are stimulants over-prescribed? Treatment of ADHD in four U.S. communities," *J. Am. Acad. Adolesc. Psychiatry.,* 1999, 37(7), 797-804.

Jonkman, L. M. et al., "Differences in plasma concentrations of the D- and L-*threo* methylphenidate enantiomers in responding and non-responding children with attention-deficit hyperactivity disorder," *Psychiatry Research,* 1998, 78, 115-118.

Kimko, H.C. et al., "Pharmacokinetics and Clinical Effectiveness of Methylphenidate," *Clin Pharmacokinet,* Dec. 1999, 37(6), 457-470.

LeFever, G. B., et al., "The extent of drug therapy for attention deficit-hyperactivity disorder among children in public schools," *American Journal of Public Health,* (Sep. 1999), (89)9, 1359-1364.

Lin, J. H., and Lu, A. H., "Role of pharmacokinetics and Metabolism in drug discovery and development," *Pharmacological Reviews,* 1997, 49(4), 403-449.

Llana, M. E. and Crismon, M. L., "Methylphenidate: increased abuse or appropriate use?" *J. Amer. Pharmaceut. Assn.,* 1999, 39(4), 526-530.

MacDougall, M. K., et al., "Symptom control in the pregnant cancer patient," *Seminars in Oncology.,* 2000, 27(6), 704-711.

McCarthy, M., "USA to improve care of children with ADHD," *The Lancet,* 2000, 355, 1161.

Mehta, M. A., et al., "Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain," *J. Neurosci.,* 2000, 20RC65: (1-6).

Modi, N. B. et al., "Dose-Proportional and Stereospecific Pharmacokinetics of Methylphenidate Delivered Using an Osmotic, Controlled-Release Oral Delivery System," *J Clin Pharmacol,* 2000, 40, 1141-1149.

Chapin, R. et al., "*Methylphenidate hydrochloride,*" Environmental Health Perspectives, 1997, 105 (supp 1), 319-320.

Patrick, K.S. et al., "Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention-Deficit Hyperactivity Disorder," *Human Psychopharmacology,* 1997, 12, 527-546.

Patrick K.S. et al, "The Absorption Of Sustained-Release Methylphenidate Formulations Compared To An Immediate-Release Formulation" Biopharmaceutics And Drug Disposition, Wiley, Chichester, US, vol. 10, No. 2, 1989, pp. 165-171.

Quinn, D.M.P., "Methylphenidate: The Role of the d-Isomer," undated, Department of Psychiatry, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, 369-373.

Rouhi, A.M, "Chirality at Work," *C&EN,* May 5, 2003, 56-61.

Schweitzer J. B., et al., "Attention deficit hyperactivity disorder," *Adv. Pathophysiol. And Treat. Psychiatric Disorders: Implications for Internal Med.,* 2001, 85(3), 757-777.

Shader R.I. et al., "Population Pharmacokinetics of Methylphenidate in Children with Attention-Deficit Hyperactivity Disorder," *J Clin Pharmacol,* 1999, 39, 775-785.

Spencer, T., et al., "Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle," *J. Am. Acad. Adolesc. Psychiatry.,* 1996, 35(4), 409-432.

Srinivas, N.R. "Role of Stereoselective Assays in Bioequivalence Studies of Racemic Drugs: Have We Reached a Consensus?" *J Clin Pharmacol,* Feb. 2004, 44, 115-119.

Srinivas, N.R., et al., "Enantiomeric Drug Development: Issues, Considerations, and Regulatory Requirements," *Journal of Pharmaceutical Sciences,* Sep. 2001, 90(9), 1205-1215.

Stein, M. A., et al., "Methylphenidate dosing: Twice daily versus three times daily," *Pediatrics.,* 1996, 98(4), 748-756.

Swanson, J. M., et al., "Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children," *Clin. Pharmacology and Therapeut.,* 1999, 66(3), 295-305.

Swanson, J. M., et al., "Analog classroom assessment of Adderall in children with ADHD," *J. Am. Acad. Adolesc. Psychiatry.,* 1998, 37(5), 519-525.

Taylor, M. A., "Attention-deficit hyperactivity disorder on the frontlines: Management in the primary care office," *Comp. Ther.,* 1999, 25(6/7), 313-325.

Teo, S. K., et al., "A 90-day oral gavage toxicity study of D-methylphenidate and D,L-methylphenidate in beagle dogs," *Internat. J. Toxicol.,* May/Jun. 2003, 22, 215-226.

Teo, S. K., et al., "D-Methylphenidate and D,L-methylphenidate are not developmental toxicants in rats and rabbits," *Birth Defects Research (Part B).,* Apr. 2003, 68, 162-171.

Teo, S. K., et al., "D-Methylphenidate is non-genotoxic in *in vitro* and *in vivo* assays," *Mutation Research.,* May 9, 2003, 537, 67-69.

Teo, S. K., et al., "Neurobehavioral effects of racemic *threo*-methylphenidate and its D and L enantiomers in rats," *Pharmacology, Biochemistry, and Behavior,* Feb. 2003, 74, 747-754.

Teo, S., et al., "A 90-day oral gavage toxicity study of D-methylphenidate and D,L-methylphenidate in Sprague-Dawley rats," *Toxicology.,* 2002, 179, 183-196.

Teo, S.K. et al., "The perinatal and postnatal toxicity of D-methylphenidate and D,L-methylphenidate in rats," *Reproductive Toxicology,* 2002, 16, 353-366.

Thai, D.L., et al., "Comparative Pharmacokinetics and Tissue Distribution of the *d*-enantiomers of Para-substituted Methylphenidate Analogs," *Drug Metabolism and Disposition,* 1999, 27(6),.

Thomson, M.R. et al., "Enantioselective Transesterification of Methylphenidate to Ethylphenidate After Coadministration with Ethanol," *Thirty-First Annual ACCP Meeting Abstracts,* 2002, Abstract No. 80.

Tripp, G. and Alsop, B., "Sensitivity to reward frequency in boys with attention deficit hyperactivity disorder," *J. Clin. Child Psychology.,* 1999, 28(3), 366-375.

Volkow, N. D. et al., "Mechanism of action of methylphenidate: Insights from PET imaging studies," *Journal of Attention Disorders,* 2002, 9(Suppl. Jan. 2002), S-31-S43.

Volkow, N.D. et al., "Effects of Methylphenidate on Regional Brain Glucose Metabolism in Humans: Relationship to Dopamine D_2 Receptors," *Am J Psychiatry,* Jan. 1997, 154(1), 50-55.

Volkow, N.D. et al., "Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects," *Psychopharmacology,* 1996, 123, 26-33.

Ward, M. F., et al., "The Wender Utah rating scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder," *Am. J. Psychiatry.,* 1993, 150(6), 885-890.

Weiler, M. D., et al., "Mother and Teacher Reports of ADHD Symptoms: DSM-IV Questionnaire Data," *J. Am. Acad.Child Adolesc. Psychiatry,* Sep. 1999, 38(9), 1139-1147.

Zametkin, A. J. and Ernst, M., "Problems in the management of attention-deficit/hyperactivity disorder," *New. Eng. Jour. Med.,* 1999, 340(1), 40-46.

Zito, J. M., et al., "Trends in the prescribing of psychotropic medications to preschoolers," *J. Am. Med. Assn.,* 2000, 283(8), 1025-1030.

Aoyama, T., et al., Gas chromatographic-mass spectrometric analysis of *threo*-methylphenidate enantiomers in plasma, *J. Chromatography,* 1989, 494, 420-423.

Axten, J.M., et al., "A stereoselective synthesis of *dl-threo*-methylphenidate: preparation and biological evaluation of novel analogues," *J. Org. Chem.,* 1998, 63, 9628-9629.

Axten, J.M., et al., "Enantioselective synthesis of $_D$-*threo*-methylphenidate," *J. Am. Chem. Soc.,* 1999, 121, 6511-6512.

Davies, H.M.L., et al., "Highly regio-, diastereo-, and enantioselective C—H insertions of methyl aryldiazoacetates into cyclic N-boc-

protected amines asymmetric synthesis of novel C_2-symmetric amines and *threo*-methylphenidate," *J. Am. Chem. Soc.,* 1999, 121, 6509-6510.

Deutsch, H.M., et al., "Synthesis and pharmacology of potential cocaine antagonists. 2. Structure-activity relationship studies of aromatic ring-substituted methylphenidate analogs," *J. Med. Chem.,* 1996, 39, 1201-1209.

Dirksen, SJ.H., et al., "A postmarketing clinical experience study of Metadate® CD," *Curr. Med. Res. and Opinion,* 2002, 18(7), 371-380.

Hubbard, J.W., et al., "Enantioselective aspects of the disposition of *dl-threo*-methylphenidate after the administration of a sustained-release formulation to children with attention deficit-hyperactivity disorder," *J. of Pharm. Sci.,* 1989, 78(11), 944-947.

Lim, H.K., "Enantiomeric resolution of *dl-threo*-methylphenidate, U.S.P. (Ritalin®), by high-performance liquid chromatography," *J. of Chromatography,* 1985, 328, 378-386.

Matsumura, Y., et al., "A convenient method for synthesis of enantiomerically enriched methylphenidate from *N*-methoxycarbonylpiperidine," *Organic Letters,* 1999, 1(2), 175-178.

Naito, T., et al., "Rearrangement of sulfonamide derivatives. V. Syntheses of methyl α-phenyl-2- and 4-piperidineacetate," *Chem. Pharm. Bull.,* 1964, 12(5), 588-590.

Panizzon, Leandro, "Preparation of pyridyl- and piperidylarylacetonitriles and some derivatives.", *Helvetica Chimica Acta,* 1944, 27, 1748-1756.

Prashad, M., et al., "Enzymatic resolution of (±)-*threo*-methylphenidate," *Tetrahedron: Asymmetry,* 1998, 9, 2133-2136.

Prashad, M., et al., "Enantioselective synthesis of (2S,2'*R*)-*erythro*-methylphenidate," *Tetrahedron: Asymmetry,* 1999, 10, 3479-3482.

Prashad, M., "The first enantioselective synthesis of (2,*R*,2',*R*)-threo(+)-methylphenidate hydrochloride," *J. Org. Chem.,* 1999, 64, 1750-1753.

Rochdi, M., et al., "Dose-proportional pharmacokinetics of a methylphenidate extended-release capsule," *Int. J. of Clin. Pharma. And Theraps.,* 2004, 42(5), 285-292.

Thai, D.I., et al., "Asymmetric synthesis and pharmacology of methylphenidate and its para-substituted derivatives," *J. Med. Chem.,* 1998, 41, 591-601.

Panizzon, L., Preparation of pyridyl and piperidyl arylacetonitriles and of a number of conversion products (Part 1), *Helvetica Chimica Acta,* 1944, 27, 1748-1756 (translation; previously cited with English abstract).

Eckerman, D.A., et al., "Enantioselective behavioral effects of *threo*-methylphenidate in rats," *Pharmacology Biochem. & Behav.,* 1991, 40, 875-880.

Srinivas, N.R., et al., "Enantioselective pharmacokinetics and pharmacodynamics of *dl-threo*- methylphenidate in children with attention deficit hyperactivity disorder," *Clin. Pharmacol. Ther.,* 1992, 52, 561-568.

Angrist, et al., *J. of Clin. Phsychopharmacol.,* 1992, 12, 268-272.

Aoyama, et al., "Pharmacolinetics and pharmacodynamics of (+)-threo-methylphenidate enantiomer in patients with hypersomnia," *Clin. Pharmacol. Ther.,* 1994, 55(3), 270-276.

Barkley, et al., *Pediatrics,* 1990, 86, 184-192.

Barkley, et al., *Pediatrics,* 1991, 87, 519-531.

Bowden, et al., "Reactions of carbonyl compounds in basic solutions the alkaline hydrolysis of N-alkyl-N-methylacetamides," *J. Chem. Soc. Perkin Trans.,* 1990, 12, 2111-2116.

Brown, C., "Pharmacological action and drug development," *Chirality in Drug Design and Synthesis, Academic Press, Inc.,* 1990, 4-7.

Brown, G., "The use of methylphenidate for cognitive decline associated with HIV disease," *Int'l J. Psychiatry Med.,* 1995, 25(1), 21-37.

Corey, et al., "A new synthetic approach to the penicillins," *J. Amer. Chem. Soc.,* 1965, 87(11), 2518-2519.

Ding, et al., "Cis- and trans-axetidin-2-ones from nitrones and copper acetylide," *J. Chem. Soc. Perkin,* 1976, 22, 2382-2386.

Douzenis, et al., "Phychiatric disorder in HIV disease: description of 200 referrals to a liaison psychiatry service," *Proc. 7th Int'l Conf. AIDS,* 1991, 215, M.B. 2135 Summary.

Earle, et al., "Synthesis and hydrolysis of some fused-ring β-lactams," *J. Chem. Soc.,* 1969, 2093-2098.

Golinko Prog. Neur-Psychopharmacol. & Biol. Phsychiat., 1984, 8, 1-8.

Greenhill, L., "Attention-deficit hyperactivity disorder," *Child & Adol. Psych. Clin. N.A.,* 1995, 4(1), 123-168.

Greenhill, "Pharmacologic treatment of attention deficit hyperactivity disorder," 1992, 15(1), 1-27.

Holmes, et al., "Psychostimulant response in aids-related complex patients," *J. Clin.* Psychiatry, Biosis Abstract No. 87129969, 50(1), 5-8.

Hou, J.P., et al., "Beta-lactam antibiotics: their physicochemical properties and biological activities in relation to structure," *J. Pharm. Sci.,* 1971, 60(4), 503-532.

Klibanov, A.M., "Asymmetric transformations catalyzed by enzymes in organic solvents," *Acc. Chem. Res.,* 1990, 23, 114-120.

Moll, F., "Darstellung von 1-Aza-bicyclo [4.2.0] octan-2-on," *Naturforsch Teil B.,* 1966, 21, 297.

Navia, et al., "The AIDS dementia complex: I. Clinical features," *Annals of Neurology,* 1986, 19, 517-524.

Patrick, et al., "Pharmacology of the enantiomers of threo-methylphenidate," *J. Pharmacol. & Exp. Terhap.,* 1987, 241, 152-158.

Rieder, et al., "Diagnosis of sulfonamide hypersensitivity reactions by in-vitro "rechallenge" with hydroxylamine metabolites," *Ann. Intern. Med.,* 1989, 110, 286-289.

Scott, "Stereoisomers and drug toxicity," *Drug Safety,* 1993, 8(2), 149-159.

Srinivas, et al., "Enantioselective pharmacolinetics and pharmacodynamics of racemic threo-methylphenidate in children with attention deficit hyperactivity disorder," *Clin. Pharmacol. Ther.,* Biosis Abstract No. 95066168, 52(2), 561-568, 1992.

Srinivas, et al., "Enantiomeric gas chromatography assay with electron capture detection for d-ritalinic acid in plasma," *J. Chromatagraph,* 1990, 530, 327-336.

Srinivas, et al., "Sterioselective disposition of methylphenidate in children with attention deficit disorder," *J. Pharmacol. Exp. Ther.,* 1987, 241, 300-306.

Srinivas, et al., "Enantioselective pharmacokinetics of dl-threo-methylphenidate in humans," *Pharmacol. Res.,* 1993, 10(1), 14-21.

Staal, et al., "Glutathione deficiency and human immunodeficiency virus infection," *Lancet,* 1992, 339, 909-912.

Uetrecht, et al., "Idiosyncratic drug reactions: possible role of reactive metabolites generated by leukocytes," *Pharmacol. Res.,* 1989, 6(4), 265-273.

White, et al., "Methylphenidate as a treatment for depression in acquired immunodeficiency syndrome: an n-of-1 trial," *J. Clin. Phsychiatry,* 1992, 53(5), 153-156.

Physicians's Desk Reference, 46th Ed., "Ritalin SR", 1992, 880-881.

Challman, T.D., et al., "Methylphenidate: its pharmacology and uses," *Mayo Clin Proc.,* 2000, 75, 711-721.

Sarhill, N., et al., "Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study," *Am. J. of Hospice & Palliative Care,* 2001, 18(3), 187-192.

Aoyama et al., Kinetic Analysis of Enantiomers of threo-Methylophenidate and Its Metabolite in two Healthy Subjects after Oral Administration as Determined by a Gas Chromatographic-Mass Spectrometric Method, 1990, vol. 79, No. 6, pp. 465-469.

Arnold, L. E. et al., "A Double-Blind, Placebo-Controlled Withdrawal Trial of Dexmethylphenidate Hydrochloride in Children with Attention Deficit Hyperactivity Disorder," 2004, *J. Am. Child Adolesc. Psychopharmacol.* 14(4):542-554.

Ding, Y-S. et al., "Brian Kinetics of Methylphenidate (Ritalin) Enantiomers After Oral Administration," *Synapse*, Sep. 2004, 53, 168-175.

Jaffe, P., "Will the real Ritalin please stand up?," *A Quarterly Newsletter by ad for Adults who have Attention Deficit Disorder*, 1992, *Issue* #10, 3 pages.

Jarvi et al., "Bioequivalence of Methylphenidate Tablets," Abstract PPDM 8169, *Pharmaceutical Research* vol. 7, No. 9, 1990, 2 pages.

Markowitz, J. S., et al., "Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: focus on methyl phenidate formulations," *Pharmacotherapy*, Oct. 2003, 23(10), 1281-1299.

Meyer, et al., "Bioequivalence of Methylphenidate Immediate-Release Tables Using a Replicated Study Design to Characterize Intrasubject variability," *Oharmaceutical Research*, vol. 17, No. 4, 2000, 381-384.

Patrick et al., "Distribution of Methylphenidate and P-Hydroxymethylphenidate in Rats," *Journal od Pharmacology and Experimental Therapeutics*, 1984, vol. 231, No. 1, 61-65.

Patrick, K. S. et al., "New methylphenidate formulations for the treatment of attention-deficit/hyperactivity disorder," *Expert Opin, Drug Deliv.*, 2005, 2(1), 121-143.

Patrick, K.S. et al., Poster Abstract 267, "Synthesis, Phamacology and Human Metabolic Formation of Ethylphenidate: the Transesterification Product of Methylphenidate and Ethanol," *The 56th Southwest Regional Meeting* 2004, Nov. 10-13, 2004, 2 pages.

Quinn, D. et al., "Comparative pharmacodynamics and plasma concentration of d-thero-methylphenidate hydrochloride after single doses of d-thero-methylphenidate hydrochloride and d,l-thero-methylphenidate hydrochrloride in a double-blinde, placebo-controlled, crossover laboratory school study in children with attention-deficit/hyperectivity disorder," Nov. 2004, *J. Am. Chil Adolesc. Psychiatry* 43(11):1422-1429.

Silva, R. et al., "Open -Label Study of Dexmethylphenidate Hydrochloride in Children and Adolescents with Attention Deficit Hyperactivity Disorder," 2004, *J. child Adolesc. Psychopharmacol.* 14(4):555-563.

Volkow, N.D. et al., "Evidence That Methylphenidate Enhances the Sliency of a Mathematical Task by Increasing Dopamine in the Human Brain," *Am. J. Psychiatry*, Jul. 2004, 161(7), 1173-1180.

Weiss, M., et al., "A post hoc analysis of d-thero-methylphenidate hydrochloride (Focalin) versus d,l-thero-methylphenidate hydrochloride (Ritalin)," *J. Am. Acad. Adolesc. Psychiatry*, Nov. 2004, 43(11), 1415-1421.

Wigal, S., et al., "A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder," *J. Am. Acad. Adolesc. Psychiatry*, Nov. 2004, 43(11), 1406-1414.

Amended Answer and Counterclaims of Defendant Teva Pharmaceuticals USA, Inc., filed Nov. 9, 2005, Civil Action No. 04-4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals corporation and Novartic Pharma AG v. Teva Pharmaceuticals USA, Inc.* Subject to Protective Order.

Study 97-M-01, Clinical Study Report, Mar. 10, 1998, Comparative Pharmacokinetics, Pharmacodynamics, and Safety of Single Doses of d-threo-Methy;phenidate Hydrochloride and dl-threo-Methylphenidate Hydrochloride in Children With Attention Deficit/Hyperactivity Disorder. Subject To Protective Order.

"Attention-deficit and disruptive behavior disorders: Attention-deficit/hyperactivity disorder," American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, *Fouth Ed.* (*DSM-IV*) Washington, DC, 1994, 78-85.

Al Abwal, H. et al., "The effects of methylphenidate (MP) on Narcotic-induced Cognitive Failure (MICF)," *Am. Soc. Clin. Oncology*, 27th Annual Meeting, May 19, 21, 1991, 1385, 1992, vol. 11, p. 397.

Avis, K.E., "Parental Preparations," *Remington's Pharmaceutical Sciences, 16th Ed.*, Osol, A. (Ed.), *Mack Publishing Co.*, 1980, 1463-1487.

Berrang, B. et al., "Enantiomeric alpha aminopropiophenones (cathinone): preparation and investigation," *J. Org Chem.*, 1982, 47(13), 2643-2647.

Brown, T.E., "Emerging understandings of attention-deficit disorders and comorbidities," *Attention-Deficit Disorders and Comorbidities in Children, Adolescents, and Adults*, American Psychiatric Press, Inc., 2000, Chapter1, 3-55.

Bruera, E., et al., "Methylphenidate associates with narcotics for the treatment of cancer pain," *Cancer Treat. Resp.*, 1987, 71(1), 67-70.

Bruera, E., et al., "Narcotics plus methylphenidate (ritalin) for advanced cancer pain," *Am. J. Nursing, Pain and Symptom Counsult*, Nov. 1988, 1665-1666.

Bruera, E., et al., "Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain," *Pain*, 1992, 48, 163-166.

Bruera, E., et al., "Overwhelming fatigue in advanced cancer," *Am. J. Nursing, Pain Consult*, Jan. 1988, 99-100.

Bruera, E., et al., "The use of methylphenidate in patients with incident cancer pain receiving regular opiates, A preliminary report," *Pain*, ISSN 0304-3959, Jul. 1992, 50(1), 75-77.

Bruera, E., et al., "Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer," *J. Pain and Symptom Management*, Mar. 1989, 4(1), 3-6.

Cella, D.F., et al., "The functional assessment of cancer therapy scale: development and validation of the general measure," *J. clin, Oncol.*, 1993, 11(3), 570-579.

Drimmer, E.J., et al., "Desipramine and methylphenidate combination treatment for depression: case report," *Am. J. pf Psychiatry*, 1983, 140(2), 241-242.

Faust, D., et al., "The development and initial validation of a sensitive bedside cognitive Screening test," *J. Nerv. Ment. Dis.*, 1989, 177(1), 25-31.

Feng, Z. et al., "Molecular determinants of the paltelet aggregation inhibitory activity of carbomaoylpiperidines," CA 117:111440, 1992.

Fernandez, F., et al., "Methylphenidate for depressive disorders in cancer patients," *Psychosomatics*, Sep. 1987, 28(9), 455-461.

Fernandez, F., et al., "Methylphenidate treatment for patients with head and neck cancer," *Head and Neck Surgery*, Mar./Apr. 1986, 8(4), 296-300.

Ferris, R.M., et al., "A comparison of the capacities of isomers of amphetamine, deoxypipradrol and methylphenidate to inhibit the uptake of tritiated catecholamines into rat cerebral cortex slices, synaptosomal preparations of rat cerebral cortex, hypothalamus and striatum and into adrenergic nerves of rabbit aorta," *J. of Pharmacology & Experimental therapeutics*, 1972, 181(3), 407-416.

Ferris, R.M., et al., "Comparison of the effects of the isomers of amphetamine, methylphenidate and deoxypipradrol on the uptake of l-[^{3}H]norepinephrine and [^{3}H]dopamine by synaptic cesicles from rat whole brain, striatum and hypothalamus," *J. of Pharmacology & Experimental Therapeutics*, 1979, 210(3), 422-428.

Folstein, S.E., et al., "Minimental state": a practical method for grading the cognitive state of patients for the clinician, *J. Psychiarty res.*, 1975, 12, 189-198.

Grob, C.S., et al., "Suspected adverse methylphenidate-imipramine interactions in children," *J. of Develop. & Behav. Pediatrics*, 1986, 7(4), 265-267.

Hales, R.E., et al., "Psychopharmacologic issues in the diagnosis and treatment of organic mental disorders," *Psychia. Clinics of North America*, Dec. 1984, 7(4), 817-829.

Jursic, B. S., et al., "Determination of enantomeric composition of 1-phenyl-2(2-piperidinyl-acetamide. A Routine Method for Evaluation of Enantiomeric purity of Primary Amides," *Tetrahedron: asymmetry*, 1994, 5(9), 1711-1716.

KAdouch, et al., *Neuropsychobiology*, 1977, 3(4), 250-255, HCAPLUS Abstract 88:115433.

Macleod, A.D., "Methylphenidate in terminal depression," *J. of Pain & Symptom Management*, 1998, 16(3), 193-198.

Meyers, C.A., et al., "Methylphenidate therapy improves cognition, mood, and function of brain tumor patients," *J. of Clinical Oncology*, 1998, 16(7), 2522-2527.

Ohashi, N. et al., "Acyl(amino)naphthalene derivatives," CA 104:186157, 1985.

Olin, J. et al., "Psychostimulants for depression in hospitalized cancer patients," *Psychosomatics*, Jan.-Feb. 1996, 37(1), 57-62.

Patrick, K. et al., "Synthesis of deuterium labelled methylphenidate, p-Hydroxymethylphenidate, Ritalinic Acid and p-Hydroxyritalinic Acid," Journal of Labelled Compuinds and Radiopharmaceuticals, 1982, 9(4), 485-490.

Physician's Desk Reference, 46th Ed., 1992, 880-881.

Radloff, L.S., "The CES-D scale: a self-report depression scale for research in the general population," *Applied Psychological Measurement*, Summer 1977, 1(3), 385-401.

Rapport, M.D., et al., "Methylphenidate and desipramine in hospitalized children: I. Separate and combined effects on cognitive function," *J. of the Am. Acad. Of Chils Adolescent Psychiatry*, 1993, 32(2), 333-342.

Reitan, R.M., "Validity of the trail making test as an indicator of organic brain damage," *Perceptual Motor Skills*, 1958, 8, 271-276.
Roehrs, T., et al., "Sleepiness and the reinforcing and subjective effects of methylphenidate," *Exp. Clin, Psychopharmacol.*, 1999, 7(2), 145-150 (Abstract only).
Srinivas, N.R., et al., "In vitro hydrolysis of RR,SS0threo-methylphenidate by blood esterases-differential and enantioselective interspecies variability," *Chirality*, 1991, 3, 99-103.
Stiebel, V., et al., "Long-term methylphenidate use in the medically ill patient with organic mood syndrome," *Psychosomatics*, 1990, 31(4), 454-456.
Sun, Z. et al., "Methylphenidate is Steroselectively Hydrolzyed by Human carboxylesterase CES1A1," *The Journal of Pharmacology and Experimental Therapeutics*, 2004, 310(2), 469-476.
Tyndale, R.F., et al., "Neuronal cytochrome P45oIID1 (Debrisoquine/sparteine-type): potent inhibition of activity by(-)-cocaine and nucleotide sequence identity to human hepatic P450 gene CYP2D6," *Molecular Pharmacology*, 1991, 40(1), 63-68.
Vanderplas, B. et al., "A convenient synthesis of cis-1R-N-benzyl-2S-hydroxymethyl cyclohexylamine," CA 118:101538, 1992.
Weitzner M.A., et al., "Methylphenidate in the treatment of neurobehavioral slowing associated with cancer and cancer treatment," *J. Neuropsychiatry*, Summer 1995, 7(3), 347-350.
Wilens, T. E., et al., "Pharmacotherapy of attention-deficit/hyperactivity disprder," *Attention-Deficit Disorders with Comorbidities*, Ch. 16, 509-535 (1995).
Wilwerding, M. B. et al., "A randomized crossover evaluation of methylphenidate in cancer patients receiving strong narcotics," *Soc. Clin. Oncology*, 29th Annual Meeting, May 16-18, 1993, 1615, 1993, vol. 12, p. 464.
Yellen, S.B., et al., "Measuring fatigue and other anemia-related symptoms with the functional assesment of cancer therapy (FACT) measurement system," *J. pain Symptom Manage.*, Feb. 1997, 13(2), 63-74.
Complaint, filed Aug. 19, 2004, Civil Action No. 04-4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. teva Pharmaceuticals USA, Inc.*
Answer and Counterclaim of Defendant teva Pharmaceuticals USA, Inc., filed Noc. 9, 2004, Civil Action No. 04-4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*
Plaintiffs' Reply to Defendant's Counterclaim, filed Nov. 29, 2004, Civil Action No. 04-4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*
Redacted Amended Answer and Counterclaims of Defendant Teva Pharmaceuticals USA, Inc., filed Nov. 9, 2005, Civil Action No. 04-4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*
Plaintiffs' Reply to Defendant's Amended Counterclaims, filed Dec. 5, 2005, Civil Action No. 04-4030(SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma AG v. Teva Pharmaceuticals USA, Inc.*
Beck, A.T., et al., "Assessment of depression: the depression inventory," *Mod. Probl. Pharmacopsychiatry*, 1974, 7, 155-169.
CAS RN6051-31-6 or RN 3019-58-7, May 22, 2001.
DeLong, R., et al., "Methylphenidate in neuropsychological Sequelae of radiotherapy and chemotherapy of childhood brain tumors and leukemia," *J. Child Neurology*, Oct. 1992, 7, 462-463.
Dobashi, A., et al., "Enantioselectivity of hydrogen-bond association in liquid-solid chromatography," *Journal of Liquid Chromotography*, 1986, 9(2 &3), 243-267.
Japan Chem. Soc., "Organic reaction," 1958, 1(18), 504-505 (translated attached).
Licamele, W.L., et al., "The Concurrent use of lithium and methylphenidate in a child," *J. of the Am. Acad. Of Child Adolescent Psychiatry*, 1989, 28(5), 785-787.
Massie, M. J. et al., "Diagnosis and treatment of depression in the cancer patient," *Clinical Psychiatry*, Mar. 1984, vol. 45, 3(2), 25-29.
Morrison, R. T. et al., *Organic Chemistry*, 3rd Rd., Allyn & Bacon, Inc. 1973, 32-34.
Nakano, T. et al., Algorithm for the treatment of major depression in patients with advanced cancer, *Psychiatry and Clinical Neurosciences*, Proceedings of the International Meeting on Japanese Psychopharmacology Algorithms, Yokohama, Apr. 23, 1998, ISSN1323-1316, 1999, Supplement 53, S61-S65.
O'Neill, W. M., "The cognitive and psychomotor effects of opioid drugs in cancer pain management," *Cancer Surveys*, Palliative Medicine Problem Areas in Pain and Symptom Management, 1994, 21, 67-84.
Pelham, W. E. et al., "Sustained Release and Standard Methylphenidate Effects on Cognitive and Social Behavior in Children with Attention Deficit Disorder," *Pediatrics*, Oct. 1987, 80(4), 491-501.
Plutchik, L., et al., "Methylphenidate in post liver transplant patients," *Psychosomatics*, Mar. -Apr. 1998, 39(2), 119-123.
Reich, M.G., "Amphetamines in oncology: review of the literature," *Cancer*, 1996, 83, 891-900 (English abstract).
Soares, J.R., "Sterochemical studies on potential cantral nervous system active agents and studies on the chemistry of some 3-benzoylpiperidines," *UMI Dissertation Services*, 1971, 1-180.
Srinivas, N. R., Thesis entitled "Enantioselective Pharmacokintics of dl-threo-Methylphenidate in Children with Attention-Deficit Hyperactivity Disorder and Healthy Adults," Thesis submission date: Apr. 1991.
Teo, S. K., et al., "A single-dose, two-way crossover, bioequivalence study of dexmethylphenidate HCl with and without food in healthy subjects," *J. Clin, Pharmacol.*, Feb. 2004, 44, 173-178.
Thai, D.L., et al., "Comparative Pharmacokinetics and Tissue Distribution of the d-enantiomers of Para-substituted Methylphenidate Analogs," *Drug Metabolism and disposition*, 1999, 27(6), 645-650.
Vigano, A. et al., "Methylphenidate for the management of somatization in terminal cancer patients," *J Pain and Symptom Mangement*, Feb. 1995, 10(2), 167-170.
Weitzner, M. A. et al., "The functional assessment of cancer therapy (FACT) scale: development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors," *Cancer*, Mar. 1, 1995, 75(5), 1151-1161.
Yee, J. D. et al., "Dextroamphetamine of methylphenidate as adjuvants to opioid analgesia for adolescents with cancer," *J Pain and Symptom Management*, Feb. 1994, 9(2), 122-125.
In the United States District Court For The District of New Jersey, Civil Action No. 04-CV-04030 (FLW), (consolidated with Civil Action No. 06-6154 (FLW)), District of New Jersey; *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Complaint for Patent Infringement with attached Exhibits A,B and C (Dec. 21, 2006).
In the United States District Court For The District of New Jersey, Civil Action No. 04/CV-04030 (FLW) and Civil Action No. 06-CV-6154 (FLW) , *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: First Amended Answer and Counterclaim of Defendant Teva Pharmaceuticals USA, Inc. in Civil Action No. 06-CV-6154 (FLW) (Mar. 23, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 04-cv-04030 (FLW) and Civil Action No. 06-CV-6154 (FLW) , *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Plaintiff's Reply to Defendant's Fisrt Amended Counterclaim in Civil Action No. 06-CV-6154 (FLW) (Apr. 12, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 06-CV-05818 (SDW), *Celgene Corporation, Novartis Pharmaveuticals Corporation and Novartis Pharma A.G.* v. *Abrika Pharmaceuticals, Inc. and Abrika Pharmaceuticals, LLLP*: Complaint For Patent infringement with attached Exhibits A and B (Dec. 4, 2006).
In the United States District Court For The District of New Jersey, Civil Action No. 2:06-CV-05818 (SDW)(MCA), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Abrika Pharmaceuticals, Inc. and Abrika Pharmaceuticals, LLLP* Answer and Counterclaim (Jun. 1, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 06-CV-05818 (SDW), *Celgene Corporation,*

Novartis Pharmaceuticals Corporation and Novartis Pharma A.G. v. *Abrika Pharmaceuticals, Inc. and Abrinks Pharmaceuticals, LLLP*: Plaintiff's Reply to the Counterclaim (Jun. 25, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-04459 (FLW)(JJH), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Complaint for Patent Infringement with attached Exhibits A-E (Sep. 14, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 2:06-CV-05818, *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Abrika Pharmaceuticals, Inc. and Abrika Pharmaceuticals, LLLP*: Dfendant's First Supplemental Response to Plaintiff Celgene Corporation's Interrogatories Nos. 6-10 (Sep. 28, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 2:07-cv-04819-SDW-MCA, *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *KV Pharmaceutical Company*: Complaint for Patent Infringement with attached Exhibits A and B (Oct. 4, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 3:07-cv-04854-FLW-JJH, *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Intellipharmaceutics Corp.*: Complaint For patent Infringement with attached Exhibits A-E (Oct. 5, 2007).
In the United States District Court For The District of New Jersey, *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Barr Laboratories, Inc. and Barr Pharmaceuticals, Inc.*: Complaint For Patent Infringement with attached Exhibits A & B (Oct. 3, 2007).
In the United States District Court For The District of New Jersey, Civil Action No. 04-CV-4030 (SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Defendant Teva Pharmaceuticals USA, Inc.'s Supplemental Responses to Plaintiff Celgene Corporation's First Set of Interrogatory Nos. 1-2, 4-7 and 10-15 (Jul. 14, 2005.
In the United States District Court For The District of New Jersey, Civil Action No. 04-CV-4030 (SRC), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Defendant Teva Pharmacceuticals USA, Inc.'s Second Supplemental Responses to Plaintill Celgene Corporation's First Set of Interrogatory Nos. 1, 5, 10-11, and 14.
Confidential, Trade Secret, and/or Proprietary Document, dated Jul. 8, 2004.
Confidential, Trade Secret, and/or Proprietary Document, dated Jul. 27, 2004.
Confidential, Trade Secret, and/or Proprietary Document, dated Oct. 23, 2006.
Confidential, Trade Secret, and/or Proprietary Document, dated Aug. 3, 2007.
Confidential, Trade Secret, and/or Proprietary Document, dated Aug. 21, 2007.
Confidential, Trade Secret, and/or Proprietary Document, dated Aug. 23, 2007.
Confidential, Trade Secret, and/or Proprietary Document, dated Sep. 17, 2007.
Confidential, Trade Secret, and/or Proprietary Document, dated Sep. 26, 2007.
Confidential, Trade Secret, and/or Proprietary Document, dated Oct. 5, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-4459 (FLW), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Teva's Answer and Counterclaims, Nov. 5, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-4459 (FLW), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Teva Pharmaceuticals USA, Inc.*: Plaintiffs' Reply to Defendant's Counterclaims, Nov. 28, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-4854 (FLW) (JJH), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Intellipharmaceuticals Corp.*: Answer and Counterclaims Demand For Jury Trial, Nov. 20, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-4854 (FLW) (JJH), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Intellipharmaceuticals Corp.*: Plaintiffs' Reply to Defendants's Counterclaims, Dec. 28, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-5367 (FLW) (TJB), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Actavis South Atlantic LLC and Abrika Pharmaceuticals, Inc.*: Complaint for Patent Infringement, Nov. 8, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-5367 (FLW) (TJB), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Actavis South atlantic LLC and Abrika Pharmaceuticals, Inc.*: Answer and Counterclaims, Dec. 18, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-5367, *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Actavis South Atlantic LLC Abrika Pharmaceuticals, Inc.*: Plaintiffs' Resply to Defendants' Answer and Counterclaims, Jan. 25, 2008.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-5552 (SDW) (MCA), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Barr Pharmaceuticals, Inc. and Barr Laboratories, Inc.*: Complaint for Patent Infringement, Nov. 16, 2007.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-5552 (SDW) (MCA), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Barr Pharmaceuticals, Inc. and Barr Laboratories, Inc.*: Defendants' Answer, Affirmative Defenses, Counterclaims and Jury Demand, Jan. 25, 2008.
In the United States District Court For The District of New Jersey, Civil Action No. 07-CV-5552 (SDW) (MCA), *Celgene Corporation, Novartis Pharmaceuticals Corporation and Novartis Pharma A.G.* v. *Barr Pharmaceuticals, Inc. and Barr Laboratories, Inc.*: Plaintiffs' Reply to Defendants' Counterclaims, Mar. 5, 2008.
In the United States Patent and Trademark Office, File History of Ex Parte Reexamination of Patent No. 6,355,656, Control. No. 90/007,177, Reexamination Certificate Issued on Mar. 27, 2007.

* cited by examiner

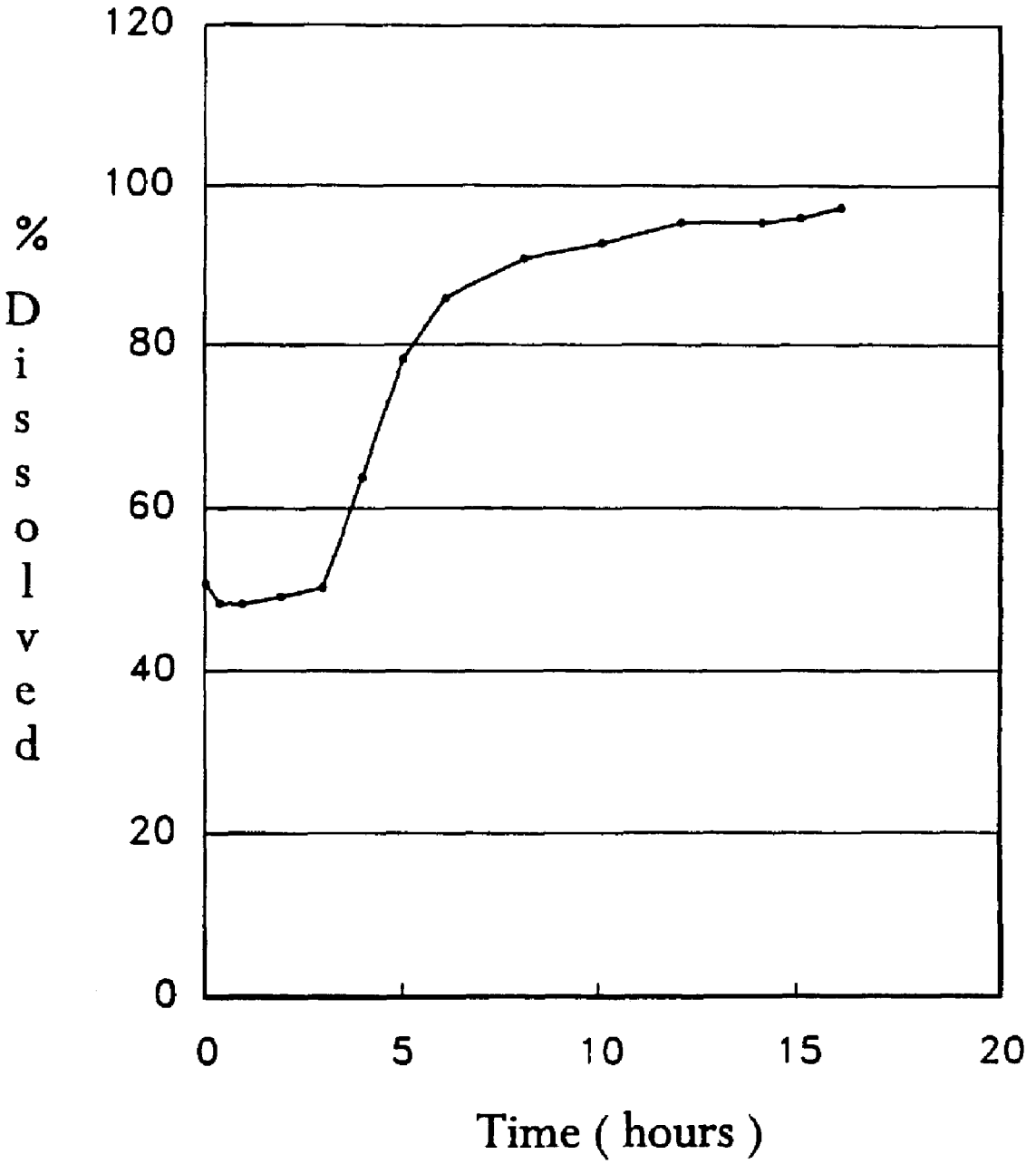


FIG. 1

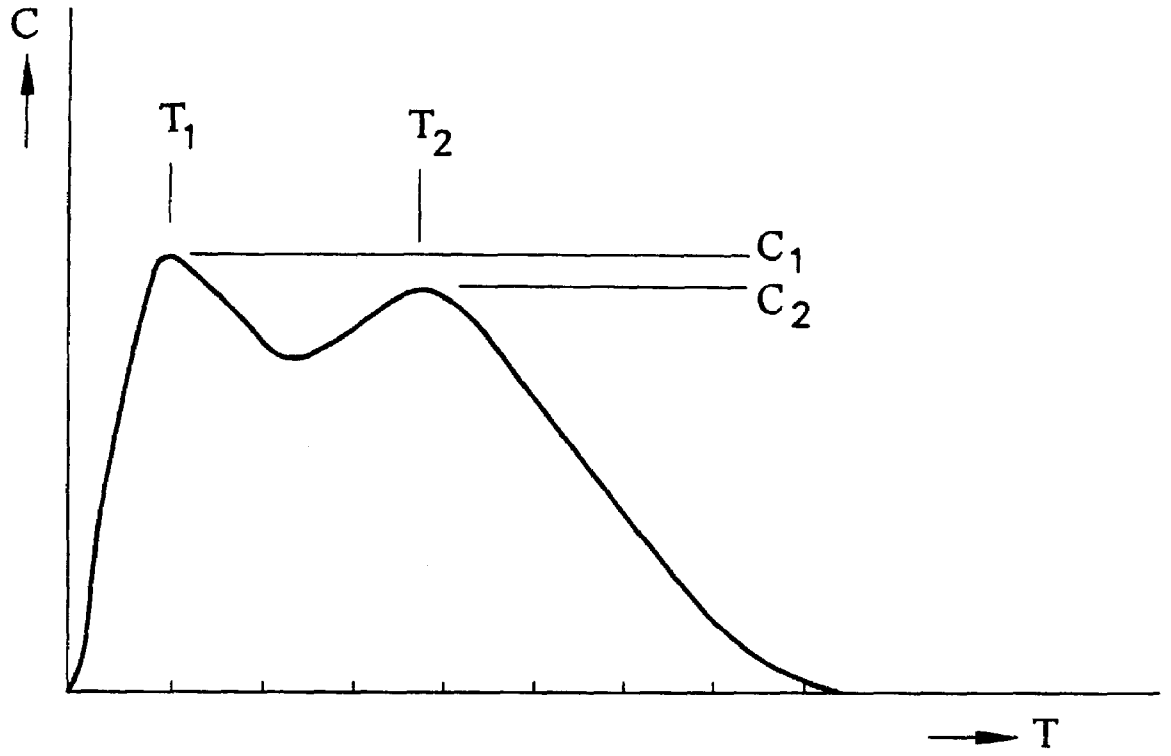


FIG. 2

DELIVERY OF MULTIPLE DOSES OF MEDICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of application Ser. No. 09/038,470, filed Mar. 11, 1998, now U.S. Pat. No. 6,635,284, which is a divisional application of application Ser. No. 09/892,190, filed Jul. 14, 1997, now U.S. Pat. No. 5,837,284, which is a continuation-in-part of application Ser. No. 08/647,642, filed May 15, 1996, now abandoned, and a continuation-in-part of application Ser. No. 08/583,317, filed Jan. 5, 1996, now U.S. Pat. No. 5,733,756, and application Ser. No. 08/567,131, filed Dec. 4, 1995, now abandoned, all of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved dosing of medications. In particular, the present invention relates to improved dosing of a medication whereby two or more effective, time-separated doses may be provided by administration of a single dosage unit. The second, and any later, dose is time-delayed following administration. Based on predictable in vitro release times, the dosage forms can be formulated to deliver delayed doses in vivo at desired times.

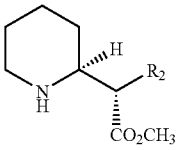
The dosage forms and methods of the present invention are particularly suitable for the administration of methylphenidate hydrochloride, and especially for the administration of a single isomer, d-threo-methylphenidate hydrochloride.

The administration of dosage forms which contain an immediate dosage and a delayed second dosage provides for reduced abuse potential, improved convenience of administration, and better patient compliance, especially when methylphenidate is used to treat certain central nervous system disorders.

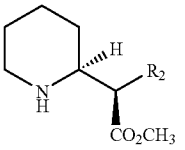
BACKGROUND OF THE INVENTION

Attention Deficit Disorder (ADD), a commonly diagnosed nervous system illness in children, is generally treated with methylphenidate hydrochloride (available commercially as, e.g., Ritalin®). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by symptoms of hyperactivity, and is also treated with methylphenidate hydrochloride. Methylphenidate drugs have also been used to treat cognitive decline in patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS related conditions. See, e.g., Brown, G., *Intl. J. Psych. Med.* 25(1): 21–37 (1995); Holmes et al., *J. Clin. Psychiatry* 50: 5–8 (1989).

Methylphenidate exists as four separate optical isomers as follows:

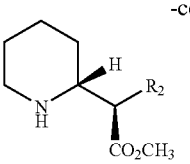


l-threo

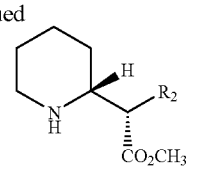


d-erythro

-continued



d-threo



l-erythro

wherein R_2 is phenyl. Pharmaceutically acceptable salts are generally administered clinically. Other phenidate drugs, which also can be administered according to the invention, include those in which the methyl group in the above structures is replaced by C_2–C_4 alkyl and R_2 is optionally substituted with C_1–C_4 alkyl.

Clinically, the threo pair of enantiomers of methylphenidate hydrochloride is generally administered for the treatment of ADD and ADHD. The hydrochloride salt is commonly referred to simply as "methylphenidate". Unless indicated otherwise, the term "methylphenidate" is used broadly herein to include methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride.

The threo racemate (pair of enantiomers) of methylphenidate is a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines. Undesirable side effects associated with the use of the dl-threo racemate of methylphenidate include anorexia, weight loss, insomnia, dizziness and dysphoria. Furthermore, the racemate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation or ingestion, and thus carries a high potential for abuse.

Srinivas et al. studied the administration of dl-threo-, d-threo, and l-threo-methylphenidate to children suffering from ADHD, and reported that the pharmacodynamic activity of dl-threo-methylphenidate resides in the d-threo isomer (*Clin. Pharmacol. Ther.*, 52: 561–568 (1992)). Therefore, while dl-threo-methylphenidate is generally used therapeutically, this racemate includes the l isomer which apparently makes no significant contribution to the pharmacological effectiveness of the drug, but likely contributes to the associated side effects. It is thus desirable to administer only the active d-threo form of the drug.

An additional problem is that children being treated with dl-threo methylphenidate must generally take one or more doses during the day. This creates a problem for school administrators who must store a controlled substance on school premises, with the associated risk that it may be stolen for illicit use. Furthermore, children may be traumatized by ridicule from peers when they must take medication at school.

Sustained release formulations of dl-threo methylphenidate have been developed, which provide for slow release of the drug over the course of the day. However, it has been observed that peak plasma concentrations of the drug are lower when sustained release formulations are used. In some studies, sustained release formulations of methylphenidate have been shown to have lower efficacy than conventional dosage forms.

There remains a need for methods for delivering methylphenidate with maximum effectiveness and minimal potential for abuse. Furthermore, it has been determined that there is a need for a dosage form which provides, in one administration, an initial release followed, at a predictable delay, by a second release, of maximally effective methylphenidate. This

will eliminate the risk of theft or loss of the second dose, while minimizing undesirable side effects and maximizing ease of administration. The present invention is directed to these, as well as other, important ends.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts an in vitro time-concentration relationship (release profile) for certain preferred dosage forms in accordance with the invention.

FIG. **2** depicts a schematic representation of in vivo plasma concentration of a drug released according to the release profile shown in FIG. **1**.

SUMMARY OF THE INVENTION

The present invention provides, in one embodiment, a therapeutic composition for the oral administration of a methylphenidate drug comprising a dosage form containing two groups of particles, each containing the methylphenidate drug. The term "particles", as used herein, includes pellets, granules, and the like. The first group of particles provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles can also comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, of the methylphenidate drug, in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. If desired, one or more additional doses may be delivered by additional particles, coated in a similar manner, but with a sufficient amount of ammonio methacrylate copolymer coating to provide the dosage after an additional delay. Methylphenidate and pharmaceutically acceptable salts thereof, including methylphenidate hydrochloride, can be prepared into the dosage forms of the invention.

In one embodiment of the present invention, the first group of particles comprises a methylphenidate drug and provides a substantially immediate dose of the methylphenidate drug upon ingestion by a mammal. The first group of particles may comprise a coating and/or sealant. The second group of particles comprises coated particles, which comprise from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the particles of the methylphenidate drug in admixture with one or more binders. The coating comprises a pharmaceutically acceptable ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion.

For example, the first group of particles can comprise a pharmaceutically acceptable salt of methylphenidate, such as methylphenidate hydrochloride, in powder form, or coated or uncoated particles containing the methylphenidate salt. The amount of methylphenidate salt in each group of particles can vary, depending upon the dosage requirements of the patient to whom the drug is to be administered. Generally, the daily dosage requirement for methylphenidate drugs is from about 1 mg to about 50 mg per day, preferably from about 2 mg to about 20 mg, and more preferably from about 2.5 to about 12 mg per day. The actual dosage to be administered will be determined by the attending physician as a matter of routine. Thus, depending upon the amounts of coating and/or and optional excipients and other additives, the amount of methylphenidate drug can be, for example, from about 2% to about 99% by weight of the first group of particles. In addition to the methylphenidate drug, the second group of particles comprises a filler, such as a hydrophobic filler, one or more ammonio methacrylate copolymers, and optional excipients and other additives. The filler can be present in an amount of, for example, from about 35% to about 45%, by weight, based on the total weight of the second group of particles.

Another embodiment of the present invention provides a method for treating disease, such as, for example, ADD, ADHD, or AIDS-related dementia, in a patient in need of treatment. This treatment comprises administering to the patient a dosage form providing once-daily oral administration of a methylphenidate drug such as methylphenidate hydrochloride. The dosage form comprises at least two groups of particles, each containing the methylphenidate drug. The first group of particles comprises from about 2% to about 99% by weight of the methylphenidate drug, depending upon desired the daily dosage, and provides a substantially immediate dose of methylphenidate upon ingestion by a mammal. The first group may comprise a coating and/or sealant. The second group of particles comprises coated particles. The coated particles comprise the methylphenidate drug in admixture with one or more binders, wherein the amount of methylphenidate drug is from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, by weight of the second group of particles, and a coating comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion. The components of the two groups of particles can vary as described hereinabove. The initial dose can be administered separately from the delayed dose, if desired.

A further embodiment of the present invention provides dosage forms for the oral administration, in a single dosage form, of two doses of a pharmaceutically acceptable salt of d-threo-methylphenidate. The dosage forms comprise particles containing within their interiors from about 2% to about 75%, preferably from about 2.5% to about 50%, and more preferably from about 5% to about 20%, of the d-threo-methylphenidate salt, in admixture with one or more binders. The particles have a coating exterior to the methylphenidate salt, which comprises an ammonio methacrylate copolymer in a quantity sufficient to delay release of the d-threo-methylphenidate salt contained within by from about 2 hours to about 7 hours following administration. The dosage forms also comprise, exterior to the coating, an outer layer comprising from about 2% to about 99% by weight of the d-threo-methylphenidate salt, based on the weight of all components in the outer layer, to provide a substantially immediate dose of the d-threo-methylphenidate salt upon administration. The layer comprising the immediate dose of the d-threo-methylphenidate salt can, if desired, further comprise an outer sealant layer. If desired, the two doses of the d-threo-methylphenidate salt can be approximately equal.

The present invention also provides dosage forms providing plasma concentration profiles for methylphenidate having two maxima, temporally separated from each other by from about 2 hours to about 7 hours. Preferably, the magnitude of said maxima differs by no more than about 30 percent, more preferably by no more than about 20 percent, and most preferably by no more than about 10 percent.

"Methylphenidate" as used herein, includes all four optical isomers of the compound and all pharmaceutically acceptable salts thereof. When one or more particular isomers is contemplated, the isomer is indicated, as in d-threo, l-threo, etc. The combined threo isomers may be indicated simply as "threo" and the erythro isomers as "erythro". For therapeutic use in treating conditions treatable by methylphenidate drugs, dl-

threo methylphenidate hydrochloride is generally used, while d-threo methylphenidate hydrochloride is preferred according to the present invention.

As discussed, the four isomers have exhibited varying levels of therapeutic activity, and have been shown to differ generally in producing unwanted side effects. The present invention provides dosage forms which maximize therapeutic effectiveness and minimize undesirable side effects. In certain preferred embodiments, the dosage forms of the present invention provide administration of the two threo forms of methylphenidate. In particularly preferred embodiments, the dosage forms of the present invention provide administration of a single isomer, d-threo-methylphenidate, albeit in two or more doses.

The dosage forms of the present invention are intended for oral ingestion by a mammal, particularly a human. The dosage forms of the present invention are particularly suitable for the administration of methylphenidate drugs, in at least two doses. Most preferably, the dosage forms provide two doses of a d-threo methylphenidate drug such as d-threo methylphenidate hydrochloride. The second dose can be delayed by from about 2 hours to about 7 hours, preferably from about 3 hours to about 6 hours, and most preferably from about 4 hours to about 5 hours, following ingestion of the dosage form by a mammal. This eliminates the need for a patient, for example a child being treated for ADD, to carry a second dose for ingestion several hours after ingestion of a first dose. The exclusion of the l isomers and the d-erythro isomer eliminates the concurrent ingestion of forms of methylphenidate principally believed to be associated with adverse side effects and/or reduced effectiveness.

The temporal separation of the two doses provided according to the present invention can be represented graphically as in FIG. **1**. FIG. **1** is an in vitro drug release profile of a dosage form of the present invention. The data were obtained by measuring the rate of dissolution of drug as a function of time. In this embodiment two doses are provided. The release of the first dose preferably occurs substantially immediately; for example, within about 30 minutes following administration. Following a period of little or substantially no drug release, the second dose is released. The two releases can be referred to as "pulses", and such a release profile can be referred to as "pulsatile".

FIG. **2** is a schematic representation of the plasma concentration of drug resulting from a release profile according to FIG. **1**. The maximum concentration due to the first dose, C_1, occurs at t_1, preferably from about 1 hour to about 3 hours after ingestion, most preferably about 2 hours after ingestion. The release of the first dose is followed by a period during which substantially no drug is released, which lasts approximately 2–6 hours, preferably 3–5 hours, post ingestion. The second dose is then released, with the maximum concentration, C_2, at t_2, which is preferably about 6 hours post-ingestion. Preferably at least about 80% of the total drug has been released by about 6 hours following administration. In the embodiment represented by FIG. **2**, the levels of drug released at the two maxima are nearly equal. Preferably, if two approximately equal doses are released, the release of the two doses provides a plasma concentration profile having two maxima, which differ from each other by no more than about 40 percent in magnitude, preferably by no more than about 30 percent, and more preferably by no more than about 25 percent. This is determined by the relationship:

$$|C_1-C_2|/C_1$$

In such embodiments is most preferred that the maxima differ by no more than 20%. However, embodiments in which the maxima of the two releases differ by more than 40 percent are within the scope of the invention. The appropriate relative amounts of drug in each release can be readily determined by one skilled in the art.

Dosage forms of the present invention provide controlled release of a methylphenidate drug, including pharmaceutically acceptable salts of methylphenidate, whereby an initial dose for immediate release can be combined with a delayed release of one or more additional doses. Such dosage forms may alternatively be referred to as "pulsatile" dosage forms.

"Immediate release", as used herein, means release within about a half hour following ingestion, preferably about 15 minutes, and more preferably within about 5 minutes following ingestion. "Delayed release", as used herein, refers to a drug release profile which includes a period during which no more than about 10 percent of the drug in a particular dosage form is released, followed by a period of from about 0.5 hour to about 2.5 hours, preferably about 1.5 hours, more preferably about 1 hour, in which no less than about 70 percent, preferably no less than about 80 percent, and more preferably no less than about 90 percent, of the drug is released. The terms "medication" and "drug" are used interchangeably herein.

According to the present invention, delayed release dosage forms can be combined with forms which provide immediate release of a drug. Thus, two or more dosage forms can be combined, one dosage form providing a portion of a patient's daily dosage needs of a drug and subsequent dosage forms providing additional portions of a patient's daily dosage needs. For example, a drug can be administered to a patient in two dosage forms simultaneously, one providing, e.g., about 30–50 percent of the patient's daily requirement of the drug and the second providing the remainder of the patient's daily requirement. Alternatively, and preferably, a single dosage form can be administered which includes an immediate dose of some portion of a patient's daily requirement and one or more delayed doses to provide the remaining portion or portions of the patient's daily requirement.

Dosage forms of the present invention provide an initial dose of a drug such as, for example, a pharmaceutically acceptable salt of d-threo-methylphenidate (also referred to herein as d-MPD), followed by an interval wherein substantially no additional drug is released, followed in turn by release of a second dose. If desired, a second substantially release-free interval may be provided following the second release, followed in turn by a third dose. Thus, dosage forms providing 3 or more doses are contemplated by the present invention. However, dosage forms providing 2 or 3 doses are generally preferred for therapeutic use, with 2 doses being more preferred. For example, the first dose can provide from about 30 percent to about 70 percent of a patient's daily prescribed intake of the drug and the second dose provides from about 70 percent to about 30 percent. If two approximately equal doses are desired, the initial dose preferably provides from about 40 percent to about 60 percent, and the second dose preferably provides from about 60 percent to about 40 percent, of a patient's prescribed daily intake of the drug. If desired, the first dose and the second dose can each provide about 50 percent of a patient's prescribed daily intake of drug. However, as will be apparent to one skilled in the art, the effect of drug metabolism in the body may require adjustment of the relative amounts of each dose, so that, for example, the second dose may have to be adjusted to provide more of the drug than the first dose, to compensate for any competition between drug release and drug metabolism. This can be observed in FIG. **2**, which, as discussed above, represents the blood plasma level of a drug, such as a methylphenidate drug, delivered in a dosage form which provides a release profile as illustrated in FIG. **1**.

The initial dose of methylphenidate drug in the dosage forms of the present invention can be provided by incorpo-

rating the methylphenidate drug into a form which allows for substantially immediate release of the drug once the dosage form is ingested by a patient. Such forms include, for example, powders, coated and uncoated pellets, and coated and uncoated tablets. The dose for immediate release can be administered in a tablet or capsule form which may also include the delayed dose. For example, two or more groups of pellets may be combined within a hard gelatin capsule or compressed into a tablet. Powders can be granulated and can be combined with pellets and excipients and/or other additives, and contained within a capsule or compressed into a tablet. These and other dosage forms will be familiar to those skilled in the art.

The delayed dose of a methylphenidate drug in the dosage forms of the present invention is provided in part by the use of certain copolymers referred to as "ammonio methacrylate copolymers". Ammonio methacrylate copolymers comprise acrylic and/or methacrylic ester groups together with quaternary ammonium groups. According to the present invention, the copolymers are incorporated into a formulation which is used to coat particles containing a medication.

The "acrylic and/or methacrylic ester groups" in the copolymers used in the compositions and methods of the present invention are referred to herein collectively as "acrylic groups". The acrylic groups are preferably derived from monomers selected from C_1–C_6 alkyl esters of acrylic acid and C_1–C_6 alkyl esters of methacrylic acid. Preferred are C_1–C_4 alkyl esters of acrylic acid and methacrylic acid. Suitable monomers include, for example, methyl acrylate, ethyl acrylate, methyl methacrylate, and ethyl methacrylate. Ethyl acrylate and methyl methacrylate are preferred, and copolymers containing ethyl acrylate and methyl methacrylate are highly preferred. Also preferably, the copolymers have a molecular weight of about 150,000.

Quaternary ammonium groups in copolymers useful in forming coatings for use in the dosage forms of the present invention can be derived from monomers comprising quaternary ammonium groups. Preferably, the monomers are alkyl esters of acrylic or methacrylic acid, comprising alkyl groups having from 1 to 6 carbon atoms and a quaternary ammonium group in the alkyl portion. Monomers comprising quaternary ammonium groups can be prepared, for example, by reaction of monomers containing amino groups with alkylating agents such as, for example, alkyl halides, especially methyl chloride. Suitable monomers containing amino groups include 2-(N,N-dibutylamino) ethyl acrylate, 2-(N,N-dibutylamino) ethyl methacrylate, 4-diethylamino-1-methyl-butyl acrylamide, and 4-diethylamino-1-methyl-butyl methacrylamide. Other useful monomers containing amino groups are disclosed in U.S. Pat. No. 5,422,121, the disclosure of which is incorporated herein by reference. Particularly preferred as a monomer comprising a quaternary ammonium group is trimethylammonioethyl methacrylate chloride (TAMCl).

While ammonio methacrylate copolymers such as those described herein have been used for sustained delivery of certain medicaments, i.e., for the relatively constant administration of a drug, it has been surprisingly and unexpectedly found that dosage forms comprising a methylphenidate drug and a coating prepared from one or more ammonio methacrylate copolymers and certain fillers, can provide delayed or pulsatile release of the drug, a very distinct phenomenon. Methylphenidate drugs are amine-containing, rely upon body or membrane loading for efficacy, and are psychotropic. The ability to provide delayed release of a methylphenidate drugs using ammonio methacrylate copolymers is due to a combination of factors, including the composition of the ammonio methacrylate copolymers used, and the amount and composition of filler.

The ratio of acrylic groups to quaternary ammonium groups in the ammonio methacrylate copolymers influences the properties of the copolymers utilized in forming the coatings of the present invention. For use in the dosage forms and methods of the present invention, the ratio of acrylic groups to quaternary ammonium groups in the copolymers is preferably from about 10:1 to about 50:1, more preferably from about 15:1 to about 45:1. Preferably, in preparing a dosage form according to the present invention, two or more copolymers are used in combination. Also preferably, one of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 25:1 to about 45:1, more preferably from about 30:1 to about 40:1, and another of the copolymers comprises acrylic groups and quaternary ammonium groups in a ratio of from about 10:1 to about 25:1, more preferably from about 15:1 to about 20:1. Even more preferably, two ammonio methacrylate copolymers are used: a first copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 30:1 to about 40:1 and the second copolymer comprising acrylic groups and quaternary ammonium groups in a ratio of from about 15:1 to about 20:1. Most preferably, the copolymers are copolymers of methyl methacrylate, ethyl acrylate, and TAMCl, in ratios of 2:1:0.1 for the first copolymer and 2:1:0.2 for the second copolymer.

When two such ammonio methacrylate copolymers are used to form the coatings, the relative amounts of the two polymers is partly determinative of the delay and release properties of the dosage forms of the present invention. It is preferred that the ratio between the first polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 30:1 to about 40:1, and the second polymer, most preferably having an acrylic group/quaternary ammonium group ratio of from about 15:1 to about 20:1, be from about 93:7 to about 97:3. More preferably, the ratio of the first polymer to the second polymer is from about 96:4 to about 94:6, and most preferably about 95:5.

Ammonio methacrylate copolymers used in the coatings of the dosage forms of the present invention can be prepared by methods known to those skilled in the art. Exemplary methods include emulsion polymerization, bulk polymerization and suspension polymerization. A suitable procedure is described in U.S. Pat. No. 3,979,349, the disclosure of which is incorporated herein by reference. Suitable ammonio methacrylate copolymers are known per se, and can be purchased from commercial providers. For example, suitable ammonio methacrylate polymers are available from Hüls America under the Eudragit® trademarks. The Eudragit® polymers and similar polymers, including methods for preparation, are described in Klaus O. R. Lehman, "Chemistry and Application Properties of Polymethacrylate Coating Systems", *Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms,* 2nd. Ed., pp. 101–174, James Mc Ginity, Ed., Marcel Dekker, Inc., NY (1996), the disclosure of which is incorporated herein by reference.

The coatings of the present invention also preferably include a filler. The filler is preferably in powder form and is preferably hydrophobic. Exemplary fillers include talc, colloidal silica, fumed silica, gypsum, and glycerine monostearate. Talc is a particularly preferred filler.

The quantity of filler used in preparing coatings for the dosage forms of the present invention should be sufficient to minimize agglomeration of the particles. Agglomeration is highly undesirable because the agglomerates, rather than discrete particles, will become coated. Agglomerates are suscep-

tible to breaking into discrete particles, which will be partially uncoated, resulting in unwanted variability in release rates. Preferably, the amount of filler is from about 30 percent to about 50 percent by weight, based on the total weight of the dry polymer, commonly referred to as "total solids". More preferably the amount of filler is from about 35 percent to about 45 percent of total solids, and most preferably about 40 percent.

Coatings used in the dosage forms of the present invention also preferably include a material which improves the processing of the copolymers. Such materials are generally referred to as "plasticizers" and include, for example, citric acid esters, adipates, azelates, benzoates, citrates, stearates, isoebucates, sebacates, propanetriol acetate, polyethylene glycols, diethyl phthalate, dibutyl sebacate, propylene glycol and ethylene glycol. Citric acid esters are preferred, and triethyl citrate is particularly preferred. The amount of plasticizer to be used in the coating is preferably from about 10 percent to about 30 percent, more preferably from about 15 percent to about 25 percent, and most preferably about 20 percent, based on the weight of the dry polymer, i.e., total solids.

Dosage forms of the present invention preferably comprise particles containing d-MPD. In one embodiment, the dosage form comprises two groups of particles. A first group of particles provides the initial dose of d-MPD. As stated hereinabove, the initial dose can be in powder, pellet or other particulate form and can be uncoated. If the initial dose is in the form of a powder or sufficiently small particles, it can, if desired, be pressed into a solid form such as a tablet or caplet. In this embodiment, the delayed dose is provided by a second group of particles. The second group of particles is preferably in the form of pellets. The pellets can be of any shape, such as, for example, spheroids or ellipsoids, or may be irregularly shaped.

Suitable pellets for the initial dose and/or the second dose can be formed by, for example, depositing a layer of drug, and optional excipients, carriers, and other optional materials, onto small, pharmaceutically acceptable particles such as nonpareils. Such a layer can be deposited by methods known to those skilled in the art, such as, for example, spraying, using methods and equipment known to those skilled in the art. For example, a Wurster air suspension coater can be used. Spraying can also be accomplished using a pan coating system, wherein the drug is deposited by successive spraying accompanied by tumbling in a rotating pan. Alternatively, pellets can be formed, for either or both of the initial and delayed dose, by extrusion of the drug with suitable plasticizers and other processing aids as necessary.

Tablets or caplets, or other solid dose forms, comprising the initial dose and/or delayed dose or doses, can conveniently be administered. A solid dose form can be prepared by methods known to those skilled in the art. For example, the d-MPD, filler and other optional components may be compressed into tablets or inserted into capsules. If desired, the drug and other components of the dose form can be granulated, using processing aids, fillers, aqueous or non-aqueous solvents, and binders known to those skilled in the art. Granules can be filled into capsules, if desired. Alternatively, the d-MPD can be blended with a solvent and processed by known methods such as ball-milling, calendering, stirring, or roll-milling, then pressed into a desired shape. Suitable solvents useful in forming the particles comprising d-MPD, and other components of the dosage forms of the invention, include inert organic and inorganic solvents which do not adversely affect the components of the dosage forms. While water can be used for many drugs, including methylphenidate, useful solvents can be selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatic heterocyclic solvents, and mixtures thereof. Other solvents include acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, diglyme, and aqueous and non-aqueous mixtures thereof, such as acetone and water, acetone and methanol, acetone and ethyl alcohol, and ethylene dichloride and methanol.

Following the formation of suitable particles, those particles to be used to deliver the delayed dose are then coated with a polymer-containing coating as described herein. The amount of coating to be used in forming the dosage forms, particularly the delayed dose, of the present invention, will be determined by the desired delivery properties, including the amount of drug to be delivered, the delay time required, and the size of the particles. Preferably, the coating on the particles providing the delayed dose, including all solid components of the coating such as copolymer, filler, plasticizer and optional additives and processing aids, is from about 10 percent to about 60 percent, more preferably from about 20 percent to about 50 percent, most preferably from about 30 percent to about 40 percent, of the total final weight of the particles. The appropriate amount of coating can advantageously be determined using in vitro measurements of drug release rates obtained with selected amounts of coating. The coating can be deposited by any method known to those skilled in the art, such as spray application. Spraying can be carried out by pan coating or by use of a fluid bed, such as the Wurster fluid bed described for use in depositing a drug.

After deposition of the drug, a sealant can be applied to any and/or all of the particles, prior to application of the polymeric coating. A sealant provides a physical barrier between the drug and the coating, to minimize or prevent interaction between the drug and the coating. Suitable sealants can be prepared from materials such as biologically inert, permeable, pharmaceutically acceptable polymers, such as, for example, hydroxypropylalkylcelluloses, wherein "alkyl" refers to C_1–C_6 hydrocarbon chains. Exemplary materials include hydroxypropyl methylcellulose, hydroxypropylethylcellulose, hydroxypropyl propylcellulose, and hydroxypropylbutylcellulose. Hydroxypropylmethylcellulose is preferred. While other materials are known to those skilled in the art for use as sealants, such as, for example, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, semipermeable cross-linked polymers such as poly(vinylbenzyltrimethyl)ammonium chloride, these are not preferred as they may affect the release rate of certain drugs including d-MPD. A sealant can be prepared by adding the material to water, and agitating for a time and at a rate sufficient to form a solution. The formation of a solution will be indicated, for example, by transparency and the absence of visually observable suspended material. The amount of material added to the water is not critical but is determined by viscosity. A solution which is too viscous will present difficulties in spraying. Generally, the amount of material should not exceed about 20 weight/volume percent, i.e., 20 g sealant material per 100 ml of water. Preferably, the amount of material in the water is from about 5 percent to about 15 weight/volume percent, and more preferably about 10 weight/volume percent.

Following deposition of the optional sealant and the coating, the coated particles are cured. "Curing" means that the particles are held at a controlled temperature for a time sufficient to provide stable release rates. Stability in release rate is indicated when further curing does not affect the release rate. In contrast, instability of release rate means that as the cure time is increased, the release rate continues to vary. Curing for a sufficient time ensures that substantially the same release rate is obtained with all particles of a particular size coated with a given amount of a given coating composition. A suitable curing time can be determined by one of skill in the art without undue experimentation, by noting the variability in in vitro release times as curing time is varied. As a general guideline, many formulations can be cured in about 24 hours.

Curing can be accomplished, for example, in a forced air oven. Curing can be carried out at any temperature above room temperature, "room temperature" being defined as from about 18° C. to about 25° C. Preferably, curing is carried out at a temperature of from about 30° C. to about 50° C., more preferably from about 35° C. to about 45° C., and most preferably about 40° C. Curing time can range from several hours to several days. Preferably, the coated particles are cured for at least about 24 hours, more preferably at least about 2 days, even more preferably at least about 3 days, still more preferably at least about 4 days, still even more preferably at least about 5 days, even more preferably at least about 6 days, and most preferably for about 7 days. While no significant adverse effects or advantages have been observed when the particles are cured for longer than about 7 days, it has been found that curing for less than about 24 hours may result in relatively poorer storage stability as compared to particles cured for longer periods of time.

The amount of methylphenidate drug contained in the first and second groups of particles depends upon the prescribed dosage to be delivered to a patient. The first group of particles can consist substantially entirely of a methylphenidate drug. "Substantially entirely" means that about 95 percent or more of the weight of the first group of particles can consist of a methylphenidate drug. If desired, the first group of particles can also contain pharmaceutically acceptable carriers, excipients, and other components which do not interfere with the substantially immediate release of the medication. "Substantially immediate" release, as used herein, means that at least about 90 percent of the medication is released within about 30 minutes from the time the drug is ingested. The second group of particles can contain from about 2 percent to about 75 percent, preferably from about 4 percent to about 50 percent, medication, based on the total weight of the particles including the coating to be deposited thereon.

According to the invention, a first and a second group of particles can be administered simultaneously as part of one dosage form. Any dosage form can be used. For example, the two groups of particles can be combined within a capsule. Alternatively, the two groups of particles can be pressed into a solid form such as a tablet. In pressing the particles into a solid form, suitable processing aids known to those skilled in the art can be used. Alternatively, particles coated to provide a delayed dose of a medication can be dispersed within or blended with, the medication in powder form.

As discussed, the dosage form can comprise a single group of particles providing both a substantially immediate dose of a methylphenidate drug, and a delayed dose of methylphenidate drug. The particles comprise, in admixture with one or more binders, from about 2% to about 75% by weight of a methylphenidate drug for delayed release, and a coating comprising the pharmaceutically acceptable, substantially neutral copolymers described herein. The particles further comprise, exterior to the coating, an outer layer comprising methylphenidate drug, to provide an initial, substantially immediate, dose. The substantially immediate dose is preferably released within about 30 minutes, more preferably about 15 minutes, and most preferably within about 5 minutes following ingestion. The outer layer can optionally comprise additives such as, for example, binders, excipients, and lubricants known to those skilled in the art.

The dosage forms provided by the invention can be of any shape suitable for oral administration of a drug, such as spheroidal, cube-shaped, oval, bean shaped, or ellipsoidal. The dosage form may be in the form of granules, which may be irregularly shaped. In any of the embodiments of the present invention, although the size of the particles is generally not critical, a certain particle size or sizes can be preferred depending upon the characteristics of the dosage form. For example, the dosage form can comprise a capsule containing a first and/or second group of particles. The particles should then be of a size which allows for ease in handling, and which allows for the particles comprising a desired quantity of drug to be readily measured and inserted into the capsule. If the dosage form comprises a single group of particles providing a substantially immediate dose and a delayed dose, the particles are preferably of a size and shape which facilitate oral administration. For example, the particles can be in the form of tablets, caplets, etc. Alternatively, the particles can be contained within a capsule of suitable size and shape for oral administration. If desired, various fillers and/or binders known to those skilled in the art can be included in the particles to provide the desired size and shape.

It will be recognized by one skilled in the art that the dosage forms of the present invention may include, in either or both of the first dose and any delayed dose, pharmaceutically acceptable carriers, extenders, fillers, processing aids, and excipients known to those skilled in the art.

The following examples are merely illustrative of the present invention and should not be considered limiting of the scope of the invention in any way. These examples and equivalents thereof will become more apparent to those skilled in the art in light of the present disclosure and the accompanying claims.

EXAMPLE 1

Preparation of Layered Pellets Containing d-MPD Hydrochloride

A solution of d-MPD hydrochloride was prepared as follows. To 300 grams (g) of deionized water were added 100 g of d-MPD hydrochloride, followed by moderate mixing, using a stirring paddle, for 5 minutes. A 10 percent (weight) solution of hydroxypropyl methylcellulose (HPMC E-6 from Dow Chemicals, Midland, Mich.; 250 g) was added, followed by homogenization for 5 minutes using an emulsifier head (Silverson, Chesham, UK; Model L4R). After addition of another 150 g of deionized water, the solution was sonicated for 15 minutes (Sonicor Model SC-150T; Instruments Corporation, Copiague, N.Y.), at which time the solution was clear.

A second solution was prepared by combining 300 g of deionized water and 300 g of a 10% (wt) HPMC E-6 solution and mixing for 5 minutes.

The first solution was sprayed onto 25/30 mesh non-pareil seeds (Ozone Co., Elmwood Park, N.J.) in a fluid bed apparatus (GPCG-1, Glatt Air Techniques, Inc., Ramsey, N.J.) using a Wurster head. The second solution was then sprayed to form a sealant. For both solutions, the spray rate was 8–9 g/minute. Inlet temperature was 50–55° C. and the non-pareil seeds were maintained at 35–40° C. Air volume was 6–7 meters per second (m/s).

EXAMPLE 2

Preparation of Coated Pellets Containing d-MPD Hydrochloride

A dispersion of 844 g of Eudragit® RS30D (ammoniomethacrylate copolymer from Hüls America, Somerset, N.J.; EA/MMA/TAMCl 1:2:0.1), was screened through a 60 mesh screen, then stirred for 15 minutes. A dispersion of 44 g of Eudragit® RL30D (EA/MMA/TAMCl 1:2:0.2) was similarly screened and stirred. The two dispersions were combined and stirred for 15 minutes, forming a combined dispersion. Triethyl citrate (TEC; from Moreflex, Greensboro, N.C.; 54 g) was added, followed by an additional 15 minutes of stirring. Deionized water (664 g) was added, followed by 15 minutes of stirring. Talc (108 g; from Luzenac, Englewood, Colo.) was added, followed by further stirring for 15 minutes.

The resulting combined dispersion was sprayed onto layered pellets prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 9–10 g/minute, inlet temperature 40–45° C., and air volume 5–6 m/s. The non-pareils were maintained at 30–35° C. during spraying. A total of 960 g of dispersion was sprayed onto the pellets, representing a 30% weight increase due to the applied coating.

EXAMPLE 3

Evaluation of Drug Release Profile for Coated Pellets Prepared According to Example 2

Pellets were prepared according to Example 2, varying the ratios of the polymers between 90:10 and 93:7.

Dissolution Measurements

Dissolution was carried out in order to determine rate of release of d-MPD from the pellets. USP Apparatus I (United States Pharmacoepia Convention, Rockville, Md.) was used. The dissolution medium was 900 ml of deionized water (unless otherwise specified) and the temperature was maintained at 37° C. The sample cell size was 1 cm (a flow through cell), and the samples were stirred continuously at 100 rpm. The apparatus was equipped with a diode array spectrophotometer, and absorption at 220 nanometers (nanometers (nm)) was measured to determine the concentration of d-MPD. Samples were measured at 60, 120, 180, 240, 360, 480, 600, 720, 840, 900, 960, 1080, 1200, 1320 and 1440 minutes.

Results of the dissolution measurements are presented in Table 1. The results indicate that the amount of drug released is influenced by: amount of coating, ratio of the two polymers, amount of talc, and curing time.

EXAMPLE 4

Comparative Example

A dispersion of 911.25 g of Eudragit® RS30D was passed through a 60 mesh screen and mixed with a similarly screened dispersion of 101.25 g of Eudragit® RL30D for 15 minutes at moderate speed. Triethyl citrate (61 g) was added, followed by an additional 15 minutes of mixing. After mixing, 991.5 g of deionized water, then 61 g of talc were added with 15 additional minutes of mixing following each addition. The resulting dispersion (1600 g) was sprayed onto 800 g of layered sealed pellets prepared according to Example 1.

No delay was observed; substantially all of the drug was released within approximately one hour. Result is shown in Table 1 (Trial 1).

EXAMPLE 5

Comparative Example

A dispersion of 600 g of Eudragit® NE30D was screened through a 60 mesh screen and mixed with a 600 g dispersion of magnesium stearate for 15 minutes at moderate speed. The resulting dispersion (750 g) was sprayed onto 750 g of layered and sealed pellets prepared according to Example 1.

After a delay of 2 hours, release of the drug was observed. About 85% of the drug was released after 14 total hours.

TABLE 1

		RELEASE TIMES				
Trial No.	% coat	Ratio	Delay	Talc, %	Cure time	Time for 85% release
1	40	90:10	none	20.0	24 hrs	1.0
2	30	95:5	4.0	20.0	"	8.0
3	30	95:5	4.0	20.0	"	8.0
4	30	93:7	1.0	20.0	"	3.0
5	40	93:7	1.0	20.0	"	4.0
6	30	93.5:6.5	2.0	20.0	"	5.0
7	40	"	2.0	20.0	"	5.0
8	30	94.5:5.5	2.0	20.0	"	8.0
9	40	"	1.0	20.0	"	5.0
10	30	94:6	2.0	20.0	"	5.0
11	40	"	2.0	20.0	"	5.0
12	30	95:5	2.0	40.0	"	5.0
13	40	"	3.0	40.0	"	8.0
14	30	96:4	4.0	40.0	"	10.0
15	40	"	5.0	40.0	"	10.0
16	30	"	4.0	40.0	7 days	10.0
17	20	95:5	2.0	40.0	"	5.0
18	30	"	3.0	40.0	"	6.0
19	30	"	3.0	40.0	"	6.0
20	30	"	2.0	40.0	"	6.0
21	40	"	3.0	40.0	"	8.0

What is claimed:

1. A solid dosage form comprising d-threo methylphenidate or salt thereof providing a plasma concentration profile of said d-threo methylphenidate or salt thereof comprising two maxima temporally separated by from about two hours to about seven hours, said solid dosage form comprising:

(a) a first group of particles comprising from about 2% to about 99% by weight of d-threo methylphenidate or salt thereof; and

(b) a second group of particles comprising coated particles, said coated particles comprising from about 2% to about 75% by weight of d-threo methylphenidate or salt thereof in admixture with one or more binders and a coating comprising an ammonio methacrylate copolymer.

2. The solid dosage form of claim **1**, wherein said solid dosage form is a tablet.

3. The solid dosage form of claim **1**, wherein said solid dosage form is a capsule.

4. The solid dosage form of claim **1**, wherein the d-threo methylphenidate or salt thereof is d-threo methylphenidate hydrochloride.

5. The solid dosage form of claim **1**, wherein the first group of particles provides a substantially immediate dose of said d-threo methylphenidate upon ingestion by a mammal.

6. The solid dosage form of claim **1**, wherein the magnitude of said plasma concentration profile maxima differ by no more than about 30%.

* * * * *