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Attorneys for Plaintiffs
Shire Laboratories, Inc. and Shire LLC

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SHIRE LABORATORIES, INC., AND SHIRE LLC, Plaintiffs, v. ANDRX PHARMACEUTICALS, LLC, ANDRX CORPORATION, AND WATSON PHARMACEUTICALS, INC., Defendants.	Civil Action No. 2:06-CV-05394 (KSH)(PS) **DOCUMENT ELECTRONICALLY-FILED**

AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND DECLARATORY RELIEF

Plaintiffs Shire Laboratories, Inc. and Shire LLC (collectively "Shire"), by their attorneys, for their Complaint, alleges as follows:

Nature of the Action

1. This action arises under the patent laws of the United States, 35 U.S.C. § 1 *et seq.*, and the Declaratory Judgment Act 28 U.S.C. §§ 2201 and 2202. Shire seeks declaratory relief, i.e., declarations that the patents in suit are infringed, injunctive relief precluding infringement, and attorneys' fees.

The Parties

2. Shire Laboratories, Inc. ("Shire Labs") is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at 1550 East Gude Drive, Rockville, Maryland 20850.

3. Shire LLC is a limited liability company organized and existing under the laws of the State of Kentucky and has its principal place of business at 9200 Brookfield Ct., Suite 108, Florence, KY 41042. On or about December 15, 2006, Shire Labs merged with and into Shire LLC.

4. Upon information and belief, defendant Andrx Pharmaceuticals, LLC ("Andrx LLC") is a limited liability company organized and existing under the laws of the State of Delaware and has its principal place of business at 4955 Orange Drive, Davie, Florida 33314. Upon information and belief, Andrx LLC operates, conducts, and transacts business in New Jersey and contracts to supply goods and services in New Jersey. Upon information and belief, Andrx LLC is a wholly-owned subsidiary of Andrx Corporation ("Andrx Corp.").

5. Upon information and belief, defendant Andrx Corp. is a corporation organized and existing under the laws of the State of Delaware, and has its principal place of business at 4955 Orange Drive, Davie, Florida 33314. Upon information and belief, Andrx Corp. operates, conducts, and transacts business in New Jersey and contracts to supply goods and services in New Jersey. Upon information and belief, Andrx Corp. operates and transacts

business in New Jersey by and through its subsidiaries which are registered to do business in New Jersey. Upon information and belief, Andrx Corp. is a wholly-owned subsidiary of Watson Pharmaceuticals, Inc. Upon information and belief, Andrx Corp. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, alone or through its subsidiaries.

6. Upon information and belief, defendant Watson Pharmaceuticals, Inc. ("Watson") is a corporation organized and existing under the laws of the State of Nevada and has its principal place of business at 311 Bonnie Circle, Corona, California 92880. Upon information and belief, Watson operates, conducts, and transacts business in New Jersey and contracts to supply goods and services in New Jersey. Upon information and belief, Watson operates and transacts business in New Jersey by and through its subsidiaries which are registered to do business in New Jersey. Upon information and belief, Watson manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, alone or through its subsidiaries.

Jurisdiction and Venue

7. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, for infringement of United States Patent Nos. 6,322,819 B1 ("the '819 patent"), and 6,605,300 B1 ("the '300 patent"). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

8. Andrx LLC, Andrx Corp. and Watson are subject to personal jurisdiction in this judicial district by virtue of, *inter alia,* their conducting of business in the state.

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

Regulatory Requirements for Approval of New and Generic Drugs

10. Any person wishing to market a pioneering drug – that is, a new drug that has not previously been approved by the Food and Drug Administration ("FDA") – must first file a new drug application ("NDA") with FDA demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b). To secure approval of an NDA, the NDA applicant must, among other things, collect and submit to FDA extensive animal and human clinical trial data at a substantial cost of time and money.

11. A person wishing to market a generic copy of a pioneering drug that has previously been approved by FDA may follow a truncated approval process by filing an abbreviated new drug application ("ANDA") for the generic version of the drug. In the ANDA, the applicant must demonstrate, among other things, bioequivalence of the generic copy of the pioneering drug. 21 U.S.C. § 355(j)(2)(A)(iv). To demonstrate bioequivalence, the ANDA applicant must show that the rate and extent of absorption of the therapeutic ingredient in the generic drug does not significantly differ from that in the pioneering drug, or, if the rate of absorption differs, that such difference is intentional, is reflected in the proposed labeling, is not essential to attain effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. 21 U.S.C. § 355(j)(7)(B).

12. However, unlike an NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. The ANDA applicant is not required, for example, to conduct well controlled clinical trials concerning the safety and effectiveness of the proposed drug. Instead, the ANDA applicant is permitted to piggy-back on the safety and effectiveness data developed and submitted by the NDA holder. 21 U.S.C. § 355(j).

13. Nor does an ANDA applicant establish any new conditions of use for the proposed drug product. Instead, an ANDA applicant may only seek approval for conditions of

use that have previously been approved in connection with an approved NDA. 21 U.S.C. § 355(j)(2)(A)(i).

14. No person may market a new drug in the United States without an approved NDA or a generic version of a drug without an approved ANDA. 21 U.S.C. § 355(a).

Plaintiff's Approved Adderall XR® Drug

15. Shire LLC is the assignee of the '819 and '300 patents, which are the subject of this civil action, having acquired the patents on or about December 15, 2006, following a merger with Shire Labs. Shire Development Inc. is currently the holder of approved New Drug Application ("NDA") No. 21-303, which was approved by FDA for the manufacture and sale of a pharmaceutical composition containing mixed amphetamine salts for treatment of Attention Deficit Hyperactivity Disorder ("ADHD"), having acquired the NDA on or about December 1, 2006, from Shire Labs. Shire US Inc. markets and sells this composition in the United States under the trade name Adderall XR®.

16. FDA has listed the '819 and '300 patents in the Orange Book -- formally known as Approved Drug Products With Therapeutic Equivalence Evaluations -- in connection with NDA 21-303.

17. The '819 patent qualifies for listing in the Orange Book in connection with NDA No. 21-303 because it claims a drug product that is the subject of the NDA.

18. The '300 patent qualifies for listing in the Orange Book in connection with NDA No. 21-303 because it claims a pharmaceutical preparation that is the subject of the NDA.

The Andrx ANDA

19. Upon information and belief, Andrx LLC submitted, and Andrx Corp. caused to be submitted, an abbreviated new drug application, Abbreviated New Drug Application ("ANDA") No. 78-436 ("Andrx ANDA"), to FDA under § 505(j) of the Federal

Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j), seeking approval to engage in commercial manufacture and sale of capsules containing mixed amphetamine salts at the 5 mg, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg strengths.

20. Upon information and belief, Andrx Corp. and Andrx LLC sent Shire Labs (the former NDA holder) a "Patent Certification Under 21 C.F.R. § 319.94 and Notice of Certification or Noninfringement of a Patent Under 21 C.F.R. § 314.95" ("the Notice Letter"). The Notice Letter represented that Andrx LLC had submitted to FDA the Andrx ANDA and purported paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for capsules containing mixed amphetamine salts at the 5 mg, 10 mg, 15 mg, 20 mg, 25 mg and 30 mg strengths that are purportedly bioequivalent to Shire's Adderall XR® products. The purpose of the Andrx ANDA and purported paragraph IV certifications was to obtain approval under section 505(j) of the FDCA to engage in the commercial manufacture and sale of its capsules containing mixed amphetamine salts before the expiration of the patents listed in the Orange Book for NDA No. 21-303. Hence, Andrx's purpose in submitting the Andrx ANDA is to market its products described therein before expiration of the '819 and '300 patents.

21. The Andrx Notice Letter offered to grant Shire Labs access to certain confidential information in the Andrx ANDA. Shire Labs requested that Andrx LLC and Andrx Corp. provide certain product information on a confidential basis. Although Andrx LLC and Andrx Corp. indicated to Shire Labs that the requested information would be forthcoming, they failed to provide that information before the expiration of the statutory period under 21 U.S.C. § 355(j)(5)(B)(iii).

22. Upon information and belief, Andrx LLC, Andrx Corp and Watson have assisted with, participated in, provided material support to the preparation and submission of, and/or intend to support the further prosecution of the Andrx ANDA.

23. Upon information and belief, if the Andrx ANDA is approved by FDA, Andrx LLC, Andrx Corp. and Watson will manufacture, offer for sale, or sell the products for which approval is sought in ANDA No. 78-436.

24. Upon information and belief, if the Andrx ANDA is approved by FDA, Andrx LLC, Andrx Corp. and Watson will induce or contribute to the manufacture, offer for sale, or sell the products for which approval is sought in ANDA No. 78-436.

COUNT I

(Patent Infringement of the '819 Patent)

25. Shire re-alleges paragraphs 1 through 24 above as fully set forth therein.

26. On November 27, 2001, the United States Patent and Trademark Office duly and legally issued the '819 patent, entitled "Oral Pulsed Drug Delivery System." A true and correct copy of the '819 patent is attached hereto as Exhibit A.

27. The '819 patent discloses and claims, *inter alia,* a pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts.

28. Upon information and belief, the submission of the Andrx ANDA to FDA with a paragraph IV certification for the '819 patent for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of a drug product before the expiration of the '819 is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

29. Upon information and belief, Andrx LLC's, Andrx Corp.'s, and Watson's commercial manufacture, use, sale, offer for sale, or importation into the United States of the proposed drug products that are the subject of the Andrx ANDA would infringe one or more

claims of the '819 patent, and Andrx LLC, Andrx Corp., and Watson would be liable jointly and severally as infringers under 35 U.S.C. §§ 271(a) and/or (g).

30. Upon information and belief, Andrx LLC's, Andrx Corp.'s, and Watson's commercial manufacture, use, sale, offer for sale, or importation into the United States of the proposed drug products that are the subject of the Andrx ANDA would actively induce and contribute to infringement of the '819 patent, and Andrx LLC, Andrx Corp., and Watson jointly and severally would be liable as infringers under 35 U.S.C. §§ 271(b) and/or (c).

31. Andrx LLC, Andrx Corp., and Watson had actual and constructive notice of the '819 patent prior to filing the Andrx ANDA and filed the Andrx ANDA with a baseless paragraph IV certification without adequate justification for claiming the patent to be invalid and non-infringed. In addition, those entities sent a baseless notice of paragraph IV certification to Shire Labs that included a confidential offer of access in support of their claim of non-infringement, but failed to provide the requested information before the expiration of the statutory period under 21 U.S.C. § 355(j)(5)(B)(iii). Andrx LLC's, Andrx Corp.'s, and Watson's conduct in filing the Andrx ANDA and certifying non-infringement has been, and continues to be, willful.

32. Shire will be irreparably harmed if Andrx LLC, Andrx Corp., and Watson are not enjoined from infringing or actively inducing or contributing to infringement of the '819 patent. Shire does not have an adequate remedy at law and, considering the balance of hardships between Shire and Defendants, a remedy at equity is warranted. Further, the public interest would not be disserved by a permanent injunction.

COUNT II

(Patent Infringement of the '300 Patent)

33. Shire re-alleges paragraphs 1 through 24 above as fully set forth therein.

34. On August 12, 2003, the United States Patent and Trademark Office duly and legally issued the '300 patent, entitled "Oral Pulsed Drug Delivery System." A true and correct copy of the '300 patent is attached hereto as Exhibit B.

35. The '300 patent discloses and claims, *inter alia,* a pharmaceutical preparation for the delivery of mixed amphetamine salts.

36. Upon information and belief, the submission of the Andrx ANDA to FDA with a paragraph IV certification for the '300 patent for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of a drug product before the expiration of the '300 patent is an act of infringement under 35 U.S.C. § 271(e)(2)(A).

37. Upon information and belief, Andrx LLC's, Andrx Corp.'s, and Watson's commercial manufacture, use, sale, offer for sale, or importation into the United States of the proposed drug products that are the subject of the Andrx ANDA would infringe one or more claims of the '300 patent, and Andrx LLC, Andrx Corp., and Watson would be liable jointly and severally as infringers under 35 U.S.C. §§ 271(a) and/or (g).

38. Upon information and belief, Andrx LLC's, Andrx Corp.'s, and Watson's commercial manufacture, use, sale, offer for sale, or importation into the United States of the proposed drug products that are the subject of the Andrx ANDA would actively induce and contribute to infringement of the '300 patent, and Andrx LLC, Andrx Corp., and Watson jointly and severally would be liable as infringers under 35 U.S.C. §§ 271(b) and/or (c).

39. Andrx LLC, Andrx Corp., and Watson had actual and constructive notice of the '300 patent prior to filing the Andrx ANDA and filed the Andrx ANDA with a baseless paragraph IV certification without adequate justification for claiming the patent to be invalid and non-infringed. In addition, those entities sent a baseless notice of paragraph IV certification to

Shire Labs that included a confidential offer of access in support of their claim of non-infringement, but failed to provide the requested information before the expiration of the statutory period under 21 U.S.C. § 355(j)(5)(B)(iii). Andrx LLC's, Andrx Corp.'s, and Watson's conduct in filing the Andrx ANDA and certifying non-infringement has been, and continues to be, willful.

40. Shire will be irreparably harmed if Andrx LLC, Andrx Corp., and Watson are not enjoined from infringing or actively inducing or contributing to infringement of the '300 patent. Shire does not have an adequate remedy at law and, considering the balance of hardships between Shire and Defendants, a remedy at equity is warranted. Further, the public interest would not be disserved by a permanent injunction.

Prayer for Relief

WHEREFORE, Shire seeks the following relief:

A. A judgment that Andrx LLC, Andrx Corp., and Watson have infringed the '819 and '300 patents under 35 U.S.C. § 271(e)(2)(A);

B. A judgment providing that the effective date of any FDA approval of the Andrx ANDA be not earlier than the expiration date of the '819 and '300 patents, including any extensions or regulatory exclusivities appended thereto;

C. A judgment declaring that the making, using, selling, offering to sell, or importing of the products for which approval is sought in the Andrx ANDA would constitute infringement of the '819 and '300 patents, or inducing or contributing to such conduct, by Andrx LLC, Andrx Corp., and Watson pursuant to 35 U.S.C. § 271(a), (b), (c) and/or (g);

D. A judgment permanently enjoining Andrx LLC, Andrx Corp., Watson, and their officers, agents, servants and employees, and those persons in active concert or participation with any of them, from making, using selling, or offering to sell in the United States, or importing into the United States, the products for which approval is sought in the Andrx ANDA, or any product that infringes or induces or contributes to the infringement of the '819 and '300 patents, until the expiration of those patents, including any extensions or regulatory exclusivities appended thereto;

E. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court determines to be just and proper.

Respectfully submitted,

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Dated: December 19, 2006

LOCAL CIVIL RULE 11.2 CERTIFICATION

I HEREBY CERTIFY that this matter is not the subject of any other action asserted by plaintiff herein, except for a matter captioned Shire LLC v. Andrx Pharmaceuticals, LLC, Andrx Corporation and Watson Pharmaceuticals, Inc., filed contemporaneously herewith in the United States District Court for the Southern District of Florida, and a matter captioned Shire Laboratories Inc. v. TEVA Pharmaceutical Industries LTD. and TEVA Pharmaceuticals USA, Inc., concerning the same patents and now pending before the United States District Court for the Eastern District of Pennsylvania.

Respectfully submitted,

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LOCAL CIVIL RULE 201.1 CERTIFICATION

Pursuant to L. Civ. R. 201.1, the undersigned counsel for plaintiff hereby certifies that the amount in controversy, excluding interest, cost and punitive damages exceeds $150,000, and that this action is not appropriate for compulsory arbitration.

Respectfully submitted,

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Dated: December 19, 2006

EXHIBIT A

US006322819B1

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

(10) **Patent No.: US 6,322,819 B1**
(45) **Date of Patent: *Nov. 27, 2001**

(54) **ORAL PULSED DOSE DRUG DELIVERY SYSTEM**

(75) Inventors: **Beth A. Burnside**, Bethesda; **Xiaodi Guo**, Derwood; **Kimberly Fiske**, Bethesda; **Richard A. Couch**, Chevy Chase; **Donald J. Treacy**, Annapolis, all of MD (US); **Rong-Kun Chang**, Hockessin, DE (US); **Charlotte McGuinness**, Bethesda; **Edward M. Rudnic**, North Potomac, both of MD (US)

(73) Assignee: **Shire Laboratories, Inc.**, Rockville, MD (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 0 days.

(21) Appl. No.: **09/176,542**

(22) Filed: **Oct. 21, 1998**

(51) **Int. Cl.**[7] **A61K 9/16**

(52) **U.S. Cl.** **424/494**; 424/472; 424/480

(58) **Field of Search** 424/494, 457, 424/471, 472, 480, 497, 461, 462, 470, 458, 459, 460, 468, 482

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Primary Examiner—Diana Dudash
Assistant Examiner—Alysia Berman
(74) *Attorney, Agent, or Firm*—Elliot M. Olstein; Raymond J. Lillie

(57) **ABSTRACT**

A multiple pulsed dose drug delivery system for pharmaceutically active amphetamine salts, comprising an immediate-release component and an enteric delayed-release component wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating. The product can be composed of either one or a number of beads in a dosage form, including either capsule, tablet, or sachet method for administering the beads.

24 Claims, 8 Drawing Sheets

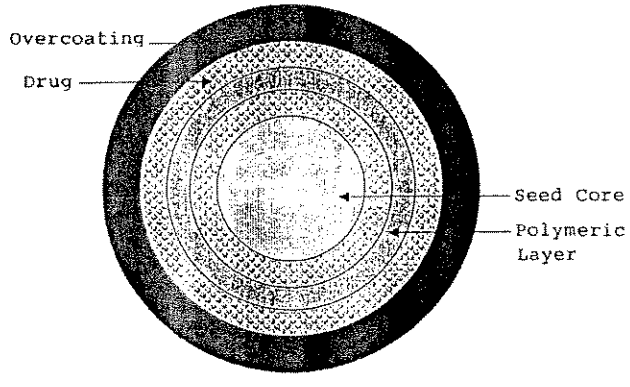

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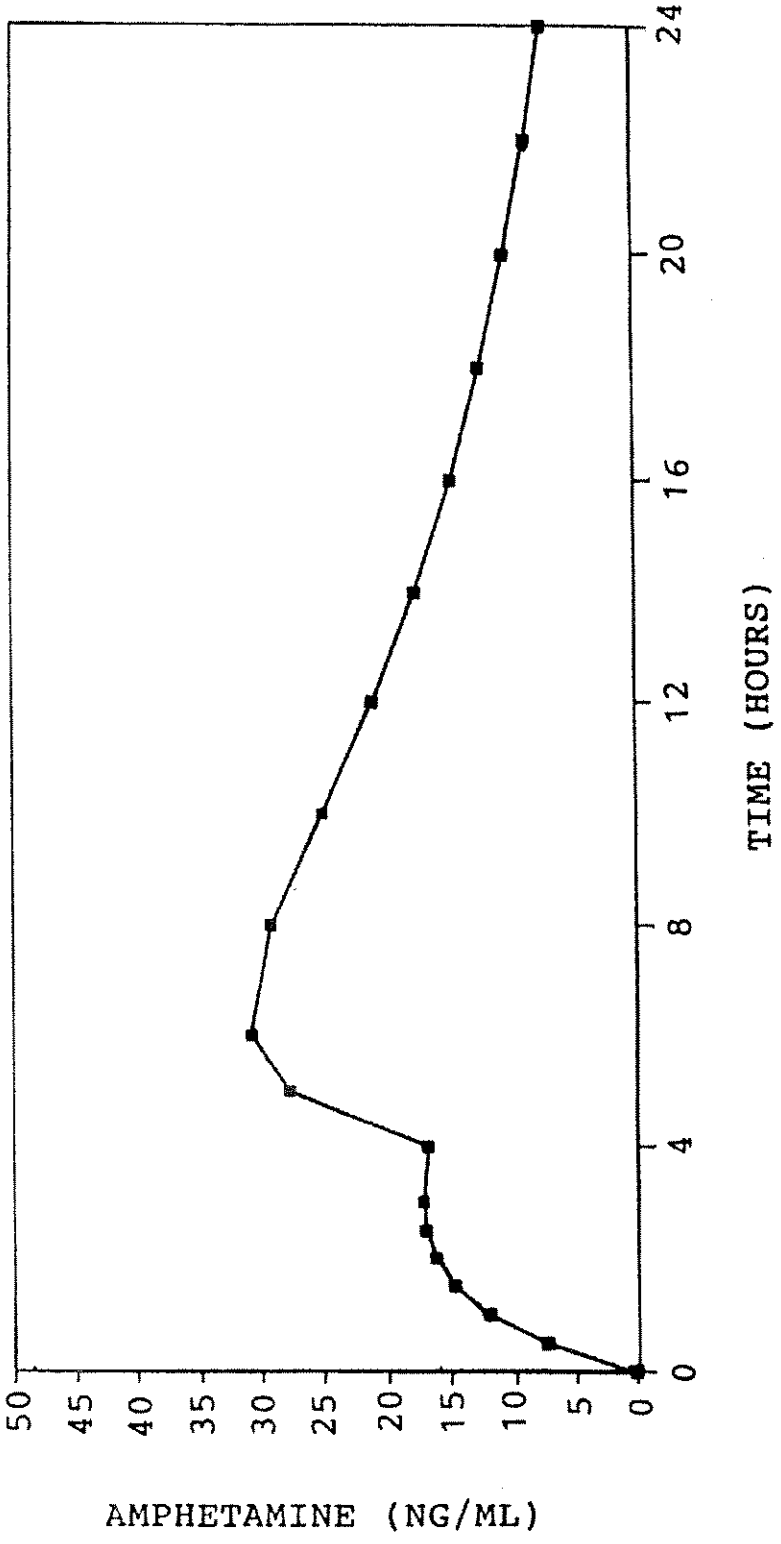
FIG. 1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45
40
35
30
25
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15
10
5
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4
8
12
16
20
24

FIG. 2A

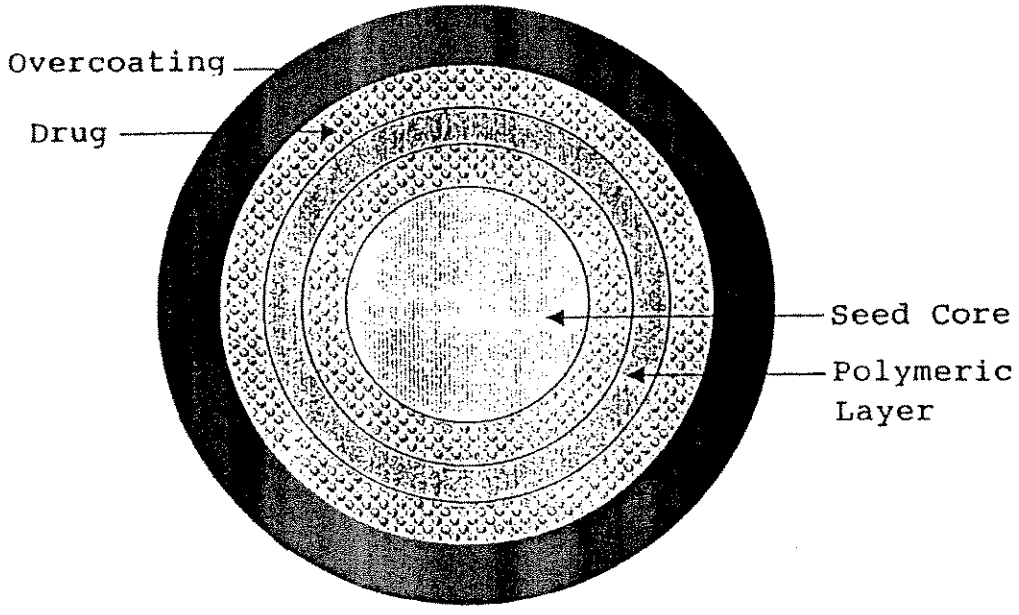
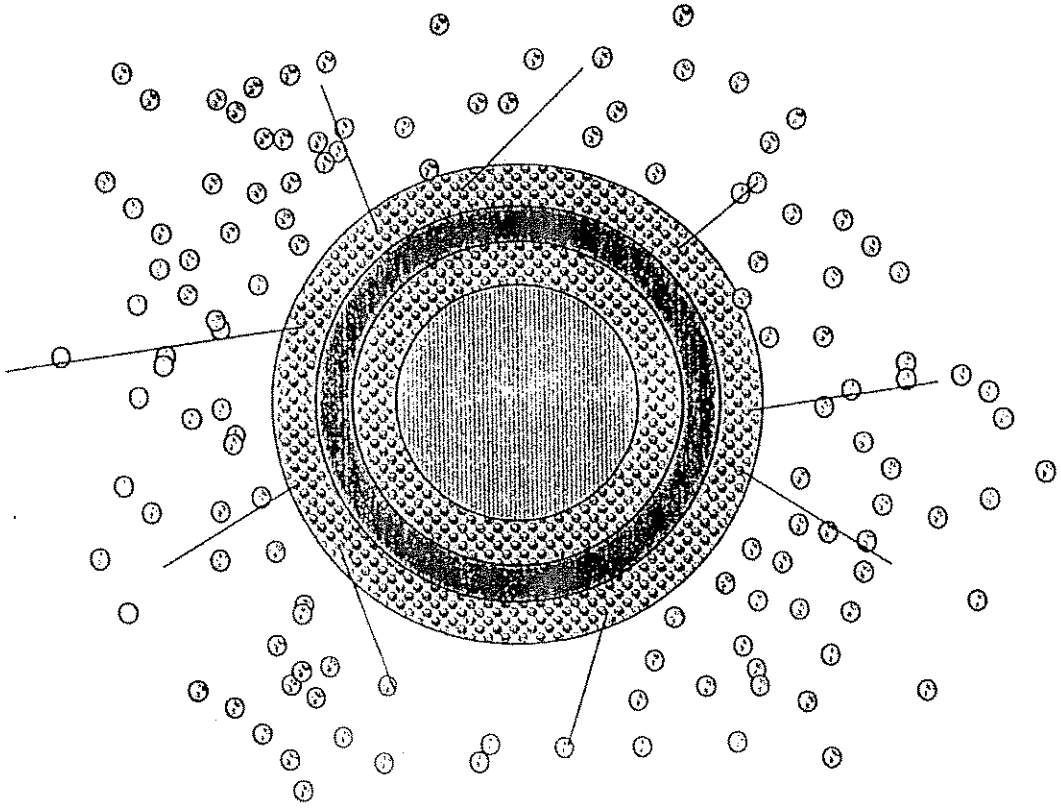


FIG. 2B



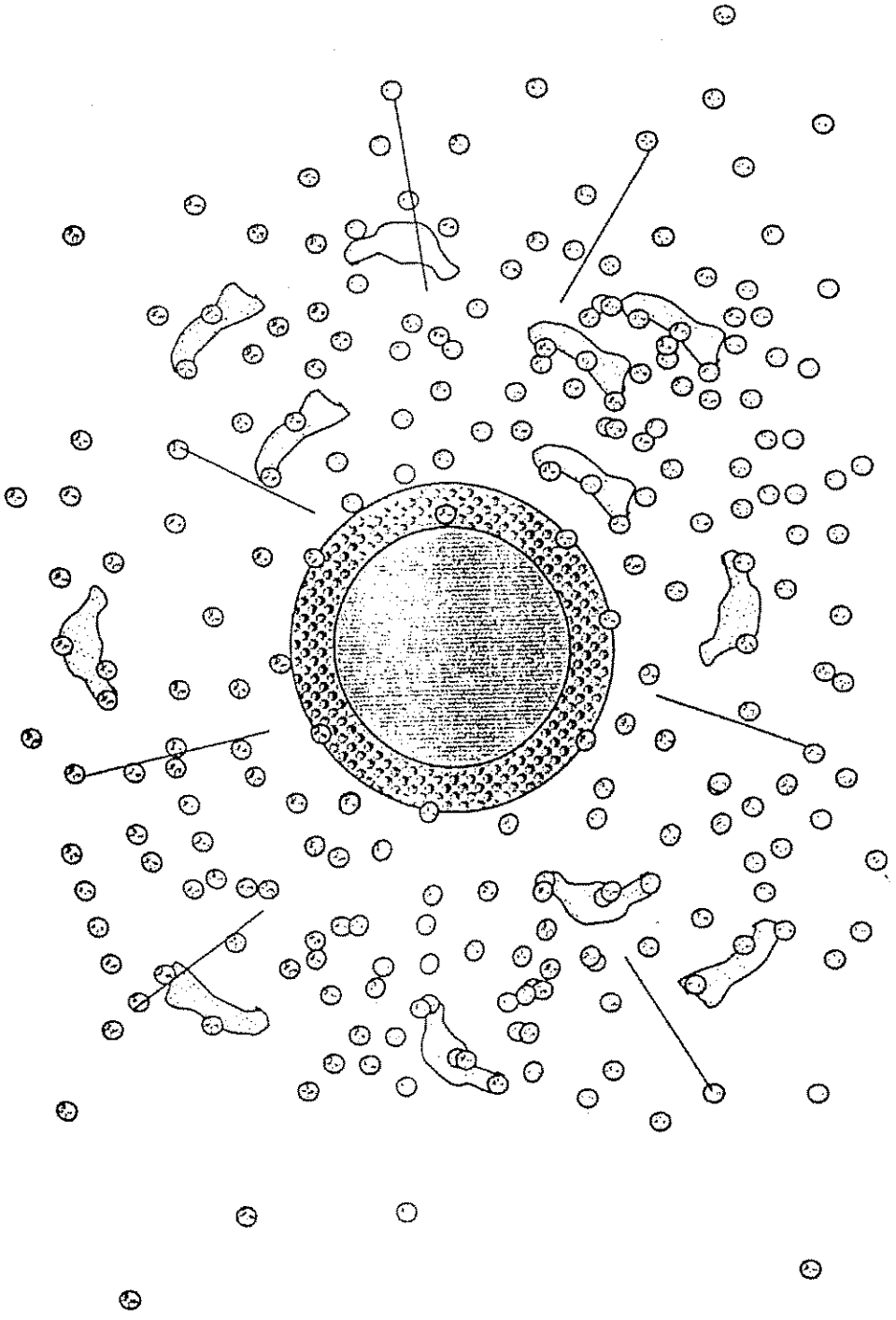


FIG. 2C

FIG. 3

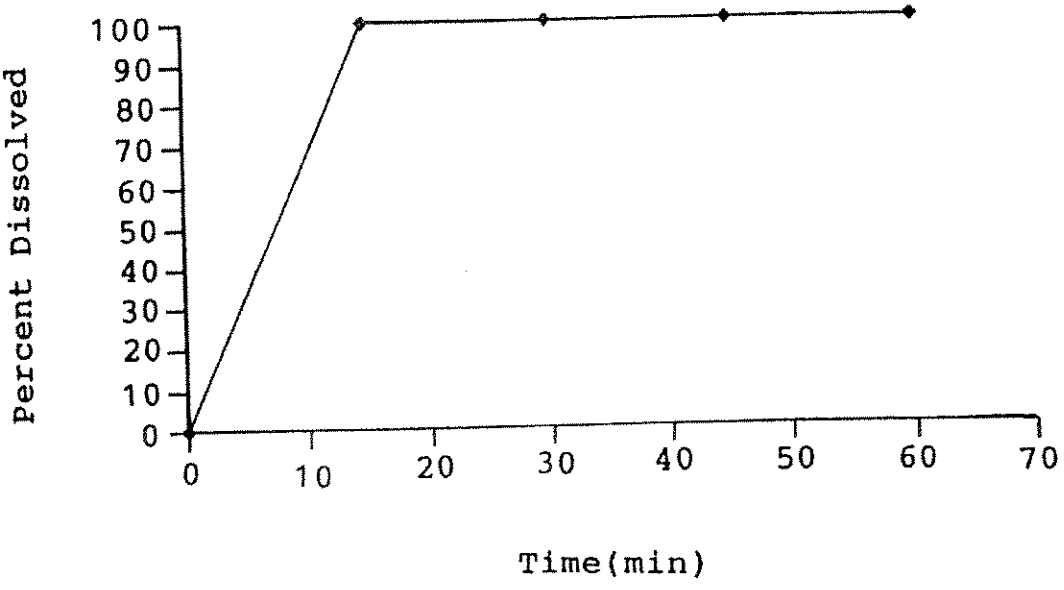
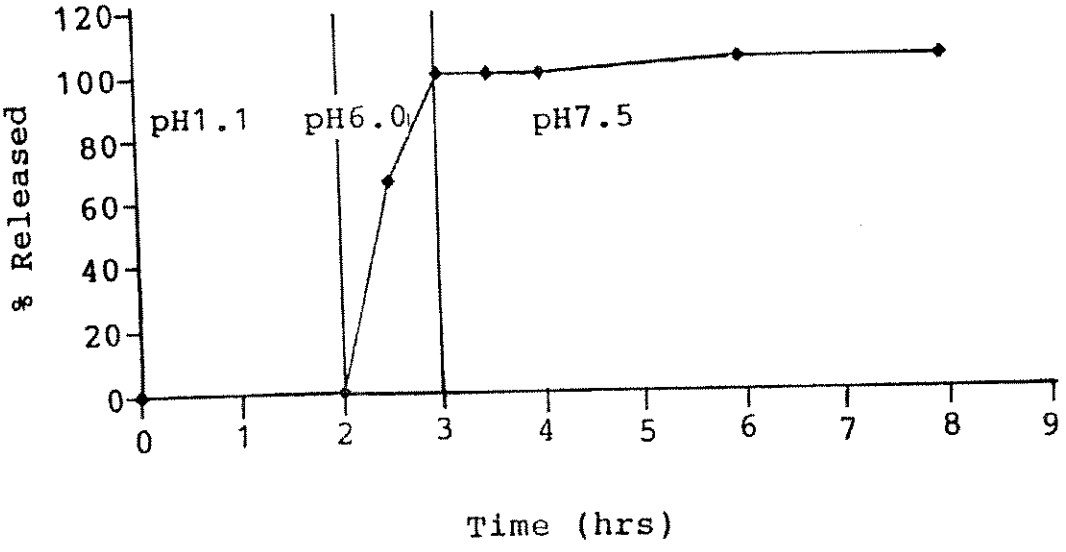

Percent Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
Time(min)

FIG. 4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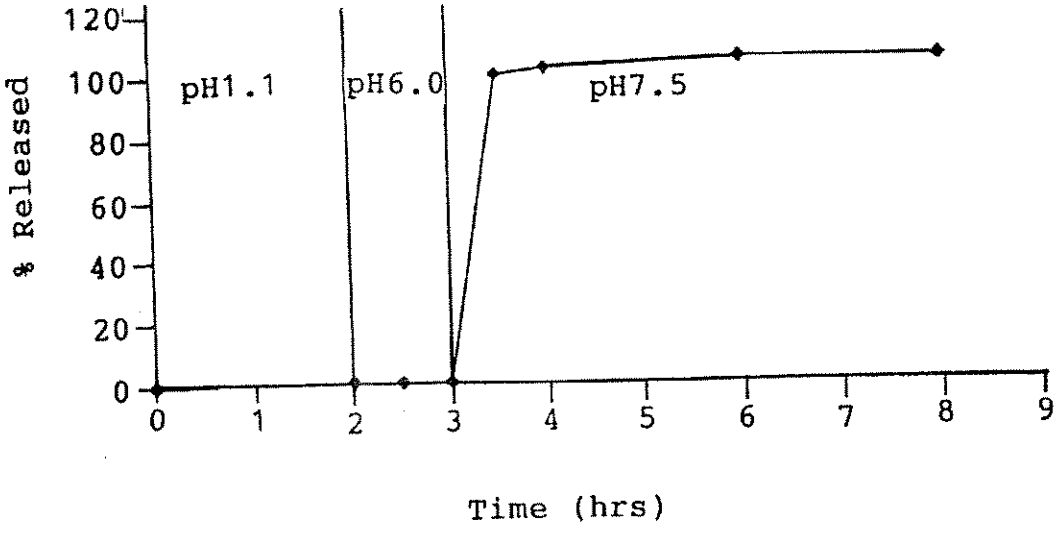
100
80
60
40
20
0
% Released
pH1.1
pH6.0
pH7.5
0
1
2
3
4
5
6
7
8
9
Time (hrs)

FIG. 5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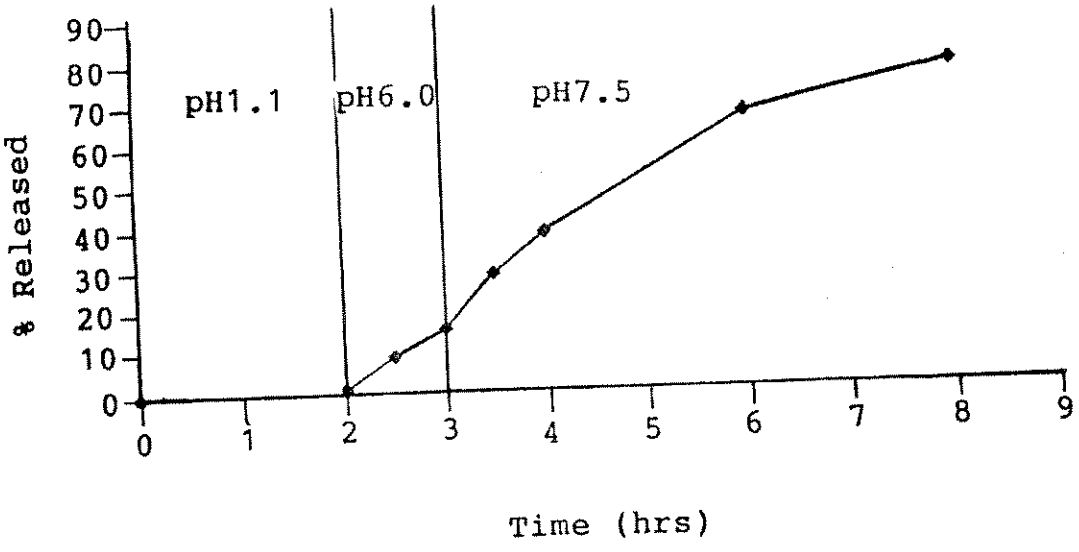
100
80
60
40
20
0
% Released
pH1.1
pH6.0
pH7.5
0
1
2
3
4
5
6
7
8
9
Time (hrs)

FIG. 6


% Released
90
80
70
60
50
40
30
20
10
0
pH1.1
pH6.0
pH7.5
0
1
2
3
4
5
6
7
8
9
Time (hrs)

ORAL PULSED DOSE DRUG DELIVERY SYSTEM

This invention pertains to a multiple dosage form delivery system comprising one or more amphetamine salts for administering the amphetamine salts to a recipient.

BACKGROUND OF THE INVENTION

Traditionally, drug delivery systems have focused on constant/sustained drug ouput with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems, compared to immediate release preparations. However, for certain drugs, sustained release delivery is not suitable and is affected by the following factors:

First pass metabolism: Some drugs, such as β blockers, β-estradiol, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

Biological tolerance: Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.

Chronopharmacology and circadian rhythms: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours (1,2).

Local therapeutic need: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

Gastric irritation or drug instability in gastric fluid: For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

Drug absorption differences in various gastrointestinal segments: In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feces.

Pulsed dose delivery systems, prepared as either single unit or multiple unit formulations, and which are capable of releasing the drug after a predetermined time, have been studied to address the aforementioned problematic areas for sustained release preparations. These same factors are also problematic in pulsed dose formulation development. For example, gastrointestinal transit times vary not only from patient to patient but also within patients as a result of food intake, stress, and illness; thus a single-unit pulsed-release system may give higher variability compared to a multiple unit system. Additionally, drug layering or core making for multiple unit systems is a time-consuming and hard-to-

optimize process. Particularly challenging for formulation scientists has been overcoming two conflicting hurdles for pulsatile formulation development, i.e., lag time and rapid release.

Various enteric materials, e.g., cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and the EUDRAGIT® acrylic polymers, have been used as gastroresistant, enterosoluble coatings for single drug pulse release in the intestine (3). The enteric materials, which are soluble at higher pH values, are frequently used for colon-specific delivery systems. Due to their pH-dependent attributes and the uncertainty of gastric retention time, in-vivo performance as well as inter- and intra-subject variability are major issues for using enteric coated systems as a time-controlled release of drugs.

A retarding swellable hydrophilic coating has been used for oral delayed release systems (4,5). It was demonstrated that lag time was linearly correlated with coating weight gain and drug release was pH independent.

Hydroxypropyl methylcellulose barriers with erodible and/or gellable characteristics formed using press coating technology for tablet dosage forms have been described to achieve time-programmed release of drugs (6). Barrier formulation variables, such as grade of hydroxypropyl methylcellulose, water-soluble and water-insoluble excipients, significantly altered the lag time and the release rate from the center cores.

Special grades of hydroxypropyl methylcellulose, e.g., METOLOSE® 60SH, 90SH (Shin-Etsu Ltd., Japan), and METHOCEL® F4M (Dow Chemical Company, USA), as a hydrophilic matrix material have been used to achieve bimodal drug release for several drugs, i.e., aspirin, ibuprofen, and adinazolam (7). Bimodal release is characterized by a rapid initial release, followed by a period of constant release, and finalized by a second rapid drug release.

Tablets or capsules coated with a hydrophobic wax-surfactant layer, made from an aqueous dispersion of carnauba wax, beeswax, polyoxyethylene sorbitan monooleate, and hydroxypropyl methylcellulose have been used for rapid drug release after a predetermined lag time. For example,. However, even though a two-hour lag time was achieved for the model drug theophylline at a higher coating level (60%), three hours were required for a complete release of theophylline after the lag time. (8)

A sustained-release drug delivery system is described in U.S. Pat. No. 4,871,549. When this system is placed into dissolution medium or the gastrointestinal tract, water influx and the volume expansion of the swelling agent cause the explosion of the water permeable membrane. The drug thus releases after a predetermined time period.

The OROS® push-pull system (Alza Company) has been developed for pulsatile delivery of water-soluble and water-insoluble drugs (a specific site (e.g., colon) in the gastrointestinal tract (11). The drug formulation is contained within a water-insoluble capsule body and is sealed with a hydrogel plug. Upon oral administration, the capsule cap dissolves in the gastric juice and the hydrogel plug swells. At a controlled and predetermined time point, the swollen plug is ejected from the PULSINCAP® dosage form and the encapsulated drug is released. A pulsatile capsule system containing captopril with release after a nominal 5-hr period was found to perform reproducibly in dissolution and gamma scintigraphy studies. However, in the majority of subjects, no measurable amounts of the drug were observed in the blood, possibly due to instability of the drug in the distal intestine. (12)

ADDERAL® comprises a mixture of four amphetamine sulfate salts which, in combination is indicated for treatment of Attention Deficit of age. One disadvantage of current treatment is that a tablet form is commonly used which many young children have difficulty in swallowing. Another disadvantage of current treatment is that two separate doses are administered, one in the morning and one approximately 4–6 hours later, commonly away from home under other than parental supervision. This current form of treatment, therefore, requires a second treatment which is time-consuming, inconvenient and may be problematic for those children having difficulties in swallowing table t formulations.

SUMMARY OF THE INVENTION

Accordingly, in view of a need for successfully administering a multiple pulsed dose of amphetamine salts and mixtures thereof, the present invention provides an oral multiple pulsed dose delivery system for amphetamine salts and mixtures thereof. FIG. 1 illustrates the desired target plasma level profile of the pharmaceutical active contained within the delivery system.

In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts that includes:

(a) one or more pharmaceutically active amphetamine salts that are covered with an immediate release coating, and

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

In one embodiment, the immediate release and enteric release portions of the composition are present on the same core.

In another embodiment, the immediate release and enteric release components are present on different cores.

It is also contemplated that the composition may include a combination of the hereinabove referred to cores (one or more cores that include both components on the same core and one or more cores that include only one of the two components on the core).

The present invention provides a composition in which there is immediate release of drug and enteric release of drug wherein the enteric release is a pulsed release and wherein the drug includes one or more amphetamine salts and mixtures thereof.

The immediate release component releases the pharmaceutical agent in a pulsed dose upon oral administration of the delivery system.

The enteric release coating layer retards or delays the release of the pharmaceutical active or drug for a specified time period ("lag time") until a predetermined time, at which time the release of the drug is rapid and complete, i.e., the entire dose is released within about 30–60 minutes under predetermined environmental conditions, i.e. a particular location within the gastrointestinal tract.

The delay or lag time will take into consideration factors such as transit times, food effects, inflammatory bowel disease, use of antacids or other medicaments which alter the pH of the GI tract.

In a preferred embodiment, the lag time period is only time-dependent, i.e., pH independent. The lag time is preferably within 4 to 6 hours after oral administration of the delivery system.

In one aspect, the present invention is directed to a composition that provides for enteric release of at least one pharmaceutically active amphetamine salt, including at least one pharmaceutically active amphetamine salt that is coated with an enteric coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

In attempting to provide for enteric release of an amphetamine salt, applicants found that use of an enteric release coating as generally practiced in the art did not provide effective enteric release.

Typical enteric coating levels did not meet the above requirements for the desired dosage profile of amphetamine salts. Using the typical amount of enteric coating (10–20 μ) resulted in undesired premature leakage of the drug from the delivery system into the upper gastrointestinal tract and thus no drug delivery at the desired location in the gastrointestinal tract after the appropriate lag time. Thus this coating did not meet the requirements for the drug release profile to provide full beneficial therapeutic activity at the desired time.

Surprisingly, applicants found that using a thicker application of enteric coating on the formulation allowed for the second pulsed dose to be released only and completely at the appropriate time in the desired predetermined area of the gastrointestinal tract, i.e., in the intestine.

Th is was surprising because an increase in thickness of about 5–10 $\mu$of enteric coatings above a minimum thickness of about 10–20 μtypically does not have a significant effect on release of d rug from within such coatings. Enteric coatings typically are pH dependent and will only dissolve/disperse when exposed to the appropriate environment. Typically, application of a thicker coating (greater than 20 μ) will only marginally increase the time for complete release at the appropriate environmental condition i.e., for a brief period of time (20 minutes). Using the typical coating, applicants could not achieve the desired result—rather, the coating leaked before the predetermined time in an inappropriate environment resulting in significant loss of the therapeutic agent.

Accordingly, in one aspect, the pulsed enteric release of the amphetamine salts is accomplished by employing a certain minimum thickness of the enteric coating .

In one embodiment of the invention, the pulsed dose delivery comprises a composition which comprises one or more pharmaceutically active amphetamine salts; an enteric coating over the one or more pharmaceutically active amphetamine salts, wherein the thickness of the enteric coating layer is at least 25 μ; a further layer of one or more pharmaceutically active amphetamine salts over the enteric coating layer; and an immediate release layer coating. The thicker enteric coating surprisingly provides the required delayed i m mediate release of the pharmaceutically active amphetamine salt at the desire d time in the desired area of the gastrointestinal tract. FIG. 2 illustrates a model of this delivery system.

In this aspect, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed around which the enteric coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

It has further been discovered that a delayed immediate release drug delivery can also be accomplished by coating the drug first with a protective layer prior to applying the enteric coating.

Thus, in another embodiment, the pulsed enteric release is accomplished by employing a protective layer between the drug and the enteric coating. When using a protective coating, the enteric coating may be of an increased thickness or may be of lower thickness.

Thus, in another aspect, the object of the invention is met by providing a composition comprising one or more pharmaceutically active amphetamine salts; a protective layer coating over the one or more pharmaceutically active amphetamine salt layer(s), and an enteric coating layer over the protective coating layer; a further pharmaceutically active amphetamine salt layer and an immediate release layer coating. In a preferred embodiment of this aspect, the thickness of the enteric coating is at least 25 μ, and the protective layer comprises an immediate release coating.

With respect to this embodiment of the invention, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed, during the core seed manufacturing process, around which the protective coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

In another embodiment, the pulsed enteric release is accomplished by employing a protective layer over the enteric coating.

Accordingly, in this embodiment of the present invention, there is provided a pulsed dose release drug delivery system comprising one or more pharmaceutically active amphetamine salts; an enteric coating layer over the pharmaceutically active amphetamine salt layer(s); and a protective layer over the enteric coating; a second pharmaceutically active amphetamine salt layer; and an immediate release layer coating.

In one aspect of this embodiment, the protective layer is comprised of one or more components, which includes an immediate release layer and a modifying layer. The modifying layer is preferably comprised of a semi water-permeable polymer. Applicants have surprisingly found that a semi-permeable polymer coating used in combination with an immediate release layer coating provided a delayed pulsed release drug delivery profile when layered over the enteric coating.

Thus, in this embodiment, the protective layer comprises a semi-permeable polymer and an immediate release coating layer. In a preferred embodiment, the modifying layer comprises a first layer of a semi-permeable polymer which is adjacent to the enteric coating layer and a second coating layer over the semi-permeable polymer coating layer comprising an immediate release polymer coating layer.

In one aspect of this embodiment, a semi-permeable polymer, which may comprise a low water-permeable pH-insensitive polymer, is layered onto the outer surface of the enteric layer, in order to obtain prolonged delayed release time. This semi-permeable polymer coating controls the erosion of the pH-sensitive enteric polymer in an alkaline pH environment in which a pH-sensitive polymer will dissolve rapidly. Another pH-sensitive layer may be applied onto the surface of a low water-permeability layer to further delay the release time.

In a still further aspect of the invention, in addition to a protective layer, the composition comprises an acid which is incorporated into the pharmaceutical active layer or coated onto the surface of the active layer to reduce the pH value of the environment around the enteric polymer layer. The acid layer may also be applied on the outer layer of the pH-sensitive enteric polymer layer, followed by a layer of low water-permeability polymer. The release of the active thus may be delayed and the dissolution rate may be increased in an alkaline environment.

In a further embodiment, the protective coating may be used both over the drug and over the enteric coating.

With respect to this embodiment of the invention, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed, during the core seed manufacturing process, around which the enteric coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

The drug delivery system of the present invention as described herein preferably comprises one or a number of beads or beadlets in a dosage form, either capsule, tablet, sachet or other method of orally administering the beads.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** illustrates a multiple pulse drug delivery system target plasma profile of the drug delivery system of the present invention. The profile reflects an immediate-release component followed by a delayed-release component.

FIG. **2** schematically illustrates the delayed-release system of the present invention.

FIG. **2***a* graphically illustrates a pulsed dose delivery system.

FIGS. **2***b* and c graphically illustrate the drug release mechanism from the proposed delivery system.

FIG. **3** is a plot of the percent drug released versus time from the drug-loaded pellets described in Example 1 which exemplifies the immediate release component of the present invention.

FIG. **4** is a plot of the percent drug released versus time from the coated pellets described in Example 2 which exemplifies the immediate release component and the delayed release components of the present invention.

FIG. **5** is a plot of the percent drug released versus time from the coated pellets of Example 3 which exemplifies the immediate release component and the delayed release components of the present invention.

FIG. **6** illustrates the drug release profile of coated pellets described in Example 4 which exemplifies the immediate release component and the delayed release components of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises a core or starting seed, either prepared or commercially available product. The cores or starting seeds can be sugar spheres; spheres made from microcrystalline cellulose and any suitable drug crystals.

The materials that can be employed in making drug-containing pellets are any of those commonly used in pharmaceutics and should be selected on the basis of compatibility with the active drug and the physicochemical properties of the pellets. The additives except active drugs are chosen below as examples:

Binders such as cellulose derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer and the like.

Disintegration agents such as corn starch, pregelatinized starch, cross-linked carboxymethylcellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®), cross-linked polyvinylpyrrolidone (PLASDONE® XL), and any disintegration agents used in tablet preparations.

Filling agents such as lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

Surfactants such as sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, bile salts, glyceryl monostearate, PLURONIC® line (BASF), and the like.

Solubilizer such as citric acid, succinic acid, fumaric acid, malic acid, tartaric acid, maleic acid, glutaric acid sodium bicarbonate and sodium carbonate and the like.

Stabilizers such as any antioxidation agents, buffers, acids, and the like, can also be utilized.

Methods of manufacturing the core include

a. Extrusion-Spheronization—Drug(s) and other additives are granulated by addition of a binder solution. The wet mass is passed through an extruder equipped with a certain size screen. The extrudates are spheronized in a marumerizer. The resulting pellets are dried and sieved for further applications.

b. High-Shear Granulation—Drug(s) and other additives are dry-mixed and then the mixture is wetted by addition of a binder solution in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

c. Solution or Suspension Layering—A drug solution or dispersion with or without a binder is sprayed onto starting seeds with a certain particle size in a fluid bed processor or other suitable equipment. The drug thus is coated on the surface of the starting seeds. The drug-loaded pellets are dried for further applications.

For purposes of the present invention, the core particles have a diameter in the range of about 500–1500 microns; preferably 100–800 microns.

These particles can then be coated in a fluidized bed apparatus with an alternating sequence of coating layers.

The core may be coated directly with a layer or layers of at least one pharmaceutically active amphetamine salts and/or the pharmaceutically active amphetamine salt may be incorporated into the core material. Pharmaceutical active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base, all chemical and chiral derivatives and salts thereof; methylphenidate, all chemical and chiral derivatives and salts thereof; phenylpropanolamine and its salts; and all other compounds indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

A protective layer may be added on top of t he pharmaceutical active containing layer and also may be provided between active layers. A separation or protective layer may be added onto the surface of the active-loaded core, and then the enteric layer is coated thereupon. Another active layer may also be added to the enteric layer to deliver an initial dose.

A protective coating layer may be applied immediately outside the core, either a drug-containing core or a drug-layered core, by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. Suitable materials for the protective layer include cellulose derivatives such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, ethyl cellulose aqueous dispersions (AQUACOAT®, SURELEASE®), EUDRAGIT® RL 30D, OPADRY® and the like. The suggested coating levels are from 1 to 6%, preferably 2–4% (w/w).

The enteric coating layer is applied onto the cores with or without seal coating by conventional coating techniques, such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. All commercially available pH-sensitive polymers are included. The pharmaceutical active is not released in the acidic stomach environment of approximately below pH 4.5, but not limited to this value. The pharmaceutical active should become available when the pH-sensitive layer dissolves at the greater pH; after a certain delayed time; or after the unit passes through the stomach. The preferred delay time is in the range of two to six hours.

Enteric polymers include cellulose acetate phthalate, Cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, materials known under the trade name EUDRAGIT® L12.5, L100, or EUDRAGIT® S12.5, S100 or similar compounds used to obtain enteric coatings. Aqueous colloidal polymer dispersions or re-dispersions can be also applied, e.g. EUDRAGIT® L 30D-55, EUDRAGIT® L100–55, EUDRAGIT® S100, EUDRAGIT® preparation 4110D (Rohm Pharma); AQUATERIC®, AQUACOAT® CPD 30 (FMC); KOLLICOAT MAE® 30D and 30DP (BASF); EASTACRYL® 30D (Eastman Chemical).

The enteric polymers used in this invention can be modified by mixing with other known coating products that are not pH sensitive. Examples of such coating products include the neutral methacrylic acid esters with a small portion of trimethylammonioethyl methacrylate chloride, sold currently under the trade names EUDRAGIT® and EUDRAGIT® RL; a neutral ester dispersion without any functional groups, sold under the trade names EUDRAGIT® NE30D and EUDRAGIT® NE30; and other pH independent coating products.

The modifying component of the protective layer used over the enteric coating can include a water penetration barrier layer (semipermeable polymer) which can be successively coated after the enteric coating to reduce the water penetration rate through the enteric coating layer and thus increase the lag time of the drug release. Sustained-release coatings commonly known to one skilled in the art can be used for this purpose by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. For example, the following materials can be used, but not limited to: Cellulose acetate, Cellulose acetate butyrate, Cellulose acetate propionate, Ethyl cellulose, Fatty acids and their esters, Waxes, zein, and aqueous polymer dispersions such as EUDRAGIT® RS and RL 30D, EUDRAGIT® NE 30D, AQUACOAT®, SURELEASE®, cellulose acetate latex. The combination of above polymers and hydrophilic polymers such as Hydroxyethyl cellulose, Hydroxypropyl cellulose (KLUCEL®, Hercules Corp.), Hydroxypropyl methylcellulose (METHOCEL®, Dow Chemical Corp.), Polyvinylpyrrolidone can also be used.

An overcoating layer can further optionally be applied to the composition of the present invention. OPADRY®, OPADRY II® (Colorcon) and corresponding color and colorless grades from Colorcon can be used to protect the pellets from being tacky and provide colors to the product. The suggested levels of protective or color coating are from 1 to 6%, preferably 2–3% (w/w).

Many ingredients can be incorporated into the overcoating formula, for example to provide a quicker immediate release, such as plasticizers: acetyltriethyl citrate, triethyl citrate, acetyltributyl citrate, dibutylsebacate, triacetin, polyethylene glycols, propylene glycol and the others; lubricants: talc, colloidal silica dioxide, magnesium stearate, calcium stearate, titanium dioxide, magnesium silicate, and the like.

The composition, preferably in beadlet form, can be incorporated into hard gelatin capsules, either with additional excipients, or alone. Typical excipients to be added to a capsule formulation include, but are not limited to: fillers such as microcrystalline cellulose, soy polysaccharides, calcium phosphate dihydrate, calcium sulfate, lactose, sucrose, sorbitol, or any other inert filler. In addition, there can be flow aids such as fumed silicon dioxide, silica gel, magnesium stearate, calcium stearate or any other material imparting flow to powders. A lubricant can further be added if necessary by using polyethylene glycol, leucine, glyceryl behenate, magnesium stearate or calcium stearate.

The composition may also be incorporated into a tablet, in particular by incorporation into a tablet matrix, which rapidly disperses the particles after ingestion. In order to incorporate these particles into such a tablet, a filler/binder must be added to a table that can accept the particles, but will not allow their destruction during the tableting process. Materials that are suitable for this purpose include, but are not limited to, microcrystalline cellulose (A VICEL®), soy polysaccharide (EMCOSOY®), pre-gelatinized starches (STARCH® 1500, NATIONAL® 1551), and polyethylene glycols (CARBOWAX®). The materials should be present in the range of 5–75% (w/w), with a preferred range of 25–50% (w/w).

In addition, disintegrants are added in order to disperse the beads once the tablet is ingested. Suitable disintegrants include, but are not limited to: cross-linked sodium carboxymethyl cellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®, PRIMOJEL®), and cross-linked polyvinylpolypyrrolidone (Plasone-XL). These materials should be present in the rate of 3–15% (w/w), with a preferred range of 5–10% (w/w).

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behanate, and hydrogenated vegetable oil. These lubricants should be present in amounts from 0.1–10% (w/w), with a preferred range of 0.3–3.0% (w/w).

Tablets are formed, for example, as follows. The particles are introduced into a blender along with AVICEL®, disintegrants and lubricant, mixed for a set number of minutes to provide a homogeneous blend which is then put in the hopper of a tablet press with which tablets are compressed. The compression force used is adequate to form a tablet; however, not sufficient to fracture the beads or coatings.

It will be appreciated that the multiple dosage form of the present invention can deliver rapid and complete dosages of pharmaceutically active amphetamine salts to achieve the desired levels of the drug in a recipient over the course of about 8 hours with a single oral administration.

In so doing, the levels of drug in blood plasma of the pharmaceutically active amphetamine salts will reach a peak fairly rapidly after about 2 hours, and after about 4 hours a second pulse dose is released, wherein a second fairly rapid additive increase of plasma drug levels occurs which slowly decreases over the course of the next 12 hours.

The following examples are presented to illustrate and do not limit the invention.

EXAMPLES

Example 1

Immediate release formulation

The following formulation was used to layer the drug onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg were put into a FLM-15 fluid bed processor with a 9" Wurster column and fluidized at 60° C. The suspension of mixed amphetamine salts (MAS) with 1% HPMC E5 Premium (Dow Chemical) as a binder was sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines were observed with a yield of at least 98%. The drug-loaded cores were used to test enteric coatings and sustained release coatings.

TABLE 1

Ingredients	Amount (%)
Nonpareil seed	88.00
mixed amphetamine salts	11.40
METHOCEL ® ES Premium	0.60
Water	*

*removed during processing

The drug release profile of the drug-loaded pellets of this example is shown in FIG. 3.

Example 2

The following formulation was used to coat the mixed amphetamine salts loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55 (Rohm Pharma, Germany) coating dispersion. 2 kg of MASL pellets were loaded into a fluid bed processor with a reduced Wurster column equipped with a precision coater (MP 2/3, Niro Inc.). The coating dispersion was prepared by dispersing Triethyl citrate, Talc and EUDRAGIT® L 30D-55 into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized MASL pellets. The spraying was continued until the targeted coating level was achieved (20 μ). The coated pellets were dried at 30–35° C. for 5 minutes before stopping the process. The enteric coated PPA pellets were tested at different pH buffers by a USP paddle method. The drug content was analyzed using HPLC. The results showed that the enteric coating delayed the drug release from the coated pellets until after exposure to pH 6 or higher. (Reference # AR98I25-4)

TABLE 2

Ingredients	Amount (%)
MASL pellets	40.00
EUDRAGIT ® L 30D-55	24.88
Triethyl citrate	2.52
Talc	2.60
Water	*

*removed during processing

The drug release profile of the coated pellets of this example is shown in FIG. 4.

Example 3

The following formulation was used to coat the MASL pellets from Example 1 with the EUDRAGIT® 4110D

(Rohm Pharma, Germany) coating dispersion. MASL pellets (2 kg) were loaded in a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by dispersing Triethyl citrate, Talc and EUDRAGIT® 4110D into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized MASL pellets. The spraying was continued until the targeted coating level was achieved. The coated pellets were dried at 30–35° C. for 5 minutes before stopping the process. The enteric coated MASL pellets were tested u sing a USP paddle method at different pH buffers. The drug content was analyzed using HPLC. The enteric coating delayed the drug release for several hours from the coated pellets until the pH value reached 6.8 or higher. (Reference # AR98125-3)

TABLE 3

Ingredients	Amount (%)
MASL pellets	70.00
EUDRAGIT ® 4110D	26.24
Triethyl citrate	0.76
Talc	3.00
Water	*

*removed during processing

The drug release profile of coated pellets of this example is shown in FIG. 5.

Example 4

The following formulation was selected to coat the enteric coated MASL pellets. Coated MASL pellets from Example 2 or coated MASL pellets from Example 3 (2 kg of either) were loaded into a fluid bed processor with a reduced Wurster column (GPGC- 1 5, Glatt). The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water for at least 15 minutes prior to spraying. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized pellets. The spraying was continued until the targeted coating level was achieved. The coated pellets were coated with a thin layer of OPADRY® white (Colorcon) (2%) to prevent the tackiness of the coated pellets during storage. The coated pellets were then dried at 35–40° C. for 10 minutes before discharging from the bed. The drug dissolution from both coated pellets was performed using a USP paddle method at different pH buffers. The drug content was analyzed using HPLC. The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release up to 2 hours after the buffer switched from pH 1 to pH 7.5. (Reference ## AR98125-1)

TABLE 4

Ingredients	Amount, kg
Enteric coated MASL pellets	90.00
SURLEASE ®	8.00
OPADRY ® white	2.00
Water	*

*removed during processing

The drug release profile of the coated pellets from this example is shown in FIG. 6.

CITED LITERATURE

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What is claimed is:

1. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts, comprising:

(a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating; and

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release.

2. The composition of claim 1 wherein said enteric release coating has a thickness of at least 25μ.

3. The pharmaceutical composition of claim 1 wherein the one or more pharmaceutically active amphetamine salts are coated onto a core.

4. The pharmaceutical composition of claim 1 wherein the one or more pharmaceutically active amphetamine salts are incorporated into a core.

5. The pharmaceutical composition of claim 1 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on a single core.

6. The pharmaceutical composition of claim 1 wherein the one or more pharmaceutically active amphetamine salts

covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on different cores.

7. The composition of claim 1 wherein said enteric release coating is a non-pH dependent enteric release coating.

8. A pharmaceutical composition for delivery of at least one amphetamine salt, comprising:

(a) at least one pharmaceutically active amphetamine salt covered with an immediate release coating; and

(b) at least one pharmaceutically active amphetamine salt covered with an enteric release coating, said component (a) providing for an immediate release of amphetamine salt to provide a first blood level of amphetamine salt and component (b) providing a delayed pulse enteric release of amphetamine salt that increases the blood level of amphetamine salt to a second level that is greater than the first level provided by component (a), wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release.

9. The pharmaceutical composition of claim 8 wherein the one or more pharmaceutically active amphetamine salts are coated onto a core.

10. The pharmaceutical composition of claim 8 wherein the one or more pharmaceutically active amphetamine salts are incorporated into a core.

11. The pharmaceutical composition of claim 8 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on a single core.

12. The pharmaceutical composition of claim 8 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on different cores.

13. A pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts comprising:

(a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating;

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases essentially all of said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and

(c) a protective layer over the enteric release coating.

14. The pharmaceutical composition of claim 13 wherein the one or more pharmaceutically active amphetamine salts are coated onto a core.

15. The pharmaceutical composition of claim 13 wherein the one or more pharmaceutically active amphetamine salts are incorporated into a core.

16. The pharmaceutical composition of claim 13 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on a single core.

17. The pharmaceutical composition of claim 13 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present On different cores.

18. A pharmaceutical composition for delivery of one or more pharmaceutically active amphetamine salts comprising:

(a) one or more pharmaceutically active amphetamine salts covered with an immediate release coating;

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating that provides for delayed pulsed enteric release, wherein said enteric release coating releases said one or more pharmaceutically active amphetamine salts coated with said enteric coating within about 60 minutes after initiation of said delayed pulsed enteric release; and

(c) a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating.

19. The pharmaceutical composition of claim 18 wherein The delayed pulsed release is from 4 to 6 hours after administration of the pharmaceutical composition.

20. The pharmaceutical composition of claim 18 wherein the delayed pulse enteric release, releases the amphetamine salt in about 30 to 60 minutes after initiation of the release.

21. The pharmaceutical composition of claim 18 wherein the one or more pharmaceutically active amphetamine salts are coated onto a core.

22. The pharmaceutical composition of claim 18 wherein the one or more pharmaceutically active amphetamine salts are incorporated into a core.

23. The pharmaceutical composition of claim 18 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on a single core.

24. The pharmaceutical composition of claim 18 wherein the one or more pharmaceutically active amphetamine salts covered with an immediate release coating and the one or more pharmaceutically active amphetamine salts covered with an enteric release coating are present on different cores.

* * * * *

EXHIBIT B

US006605300B1

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

(10) **Patent No.: US 6,605,300 B1**
(45) **Date of Patent: Aug. 12, 2003**

(54) **ORAL PULSED DOSE DRUG DELIVERY SYSTEM**

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(73) Assignee: **Shire Laboratories, Inc.**, Rockville, MD (US)

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

(21) Appl. No.: **09/807,462**

(22) PCT Filed: **Oct. 20, 1999**

(86) PCT No.: **PCT/US99/24554**

§ 371 (c)(1),
(2), (4) Date: **Jul. 19, 2001**

(87) PCT Pub. No.: **WO00/23055**

PCT Pub. Date: **Apr. 27, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/176,542, filed on Oct. 21, 1998, now Pat. No. 6,322,819.

(51) **Int. Cl.**[7] **A61K 33/22**; A61K 33/24; A61K 33/36; A61K 31/135

(52) **U.S. Cl.** **424/452**; 424/458; 424/468; 424/469; 424/470; 424/471; 424/472; 424/514; 424/649

(58) **Field of Search** 424/457, 458, 424/468, 469, 470, 471, 472; 514/649

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Primary Examiner—Russell Travers
(74) *Attorney, Agent, or Firm*—Millen, White, Zelano & Branigan, P.C.

(57) **ABSTRACT**

A multiple pulsed dose drug delivery system for pharmaceutically active amphetamine salts, comprising an immediate-release component and an enteric delayed-release component wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating. The product can be composed of either one or a number of beads in a dosage form, including either capsule, tablet, or sachet method for administering the beads.

18 Claims, 7 Drawing Sheets

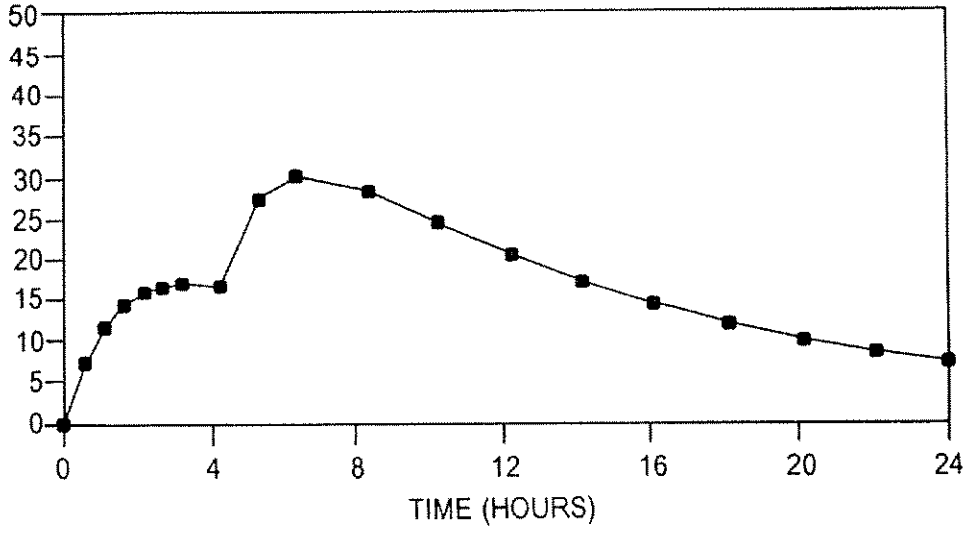


FIG. 1

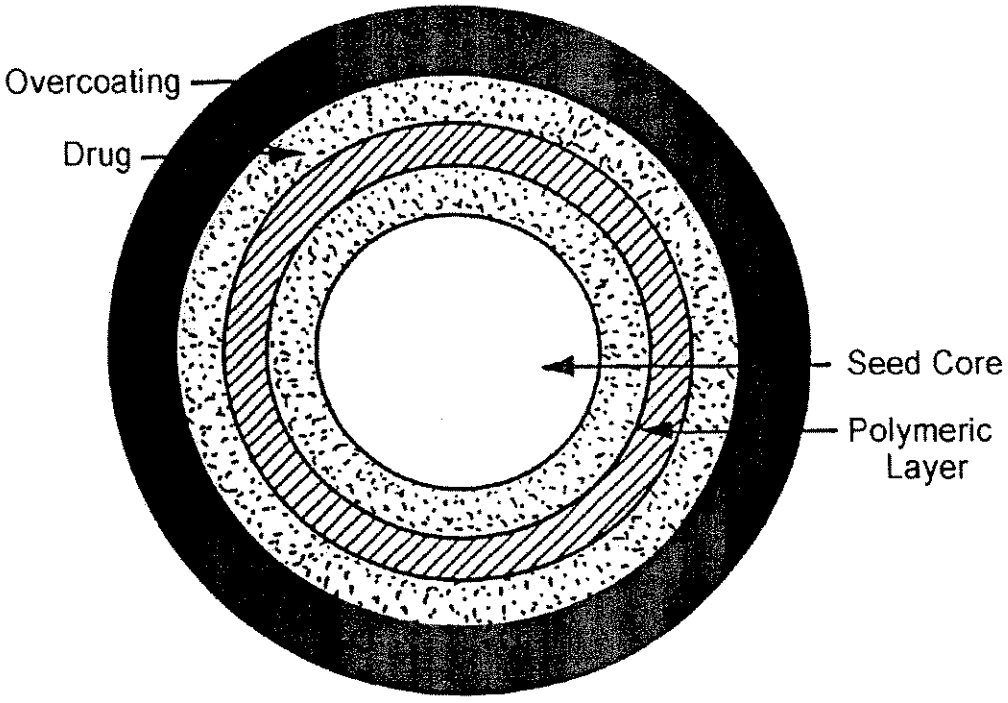


FIG. 2A

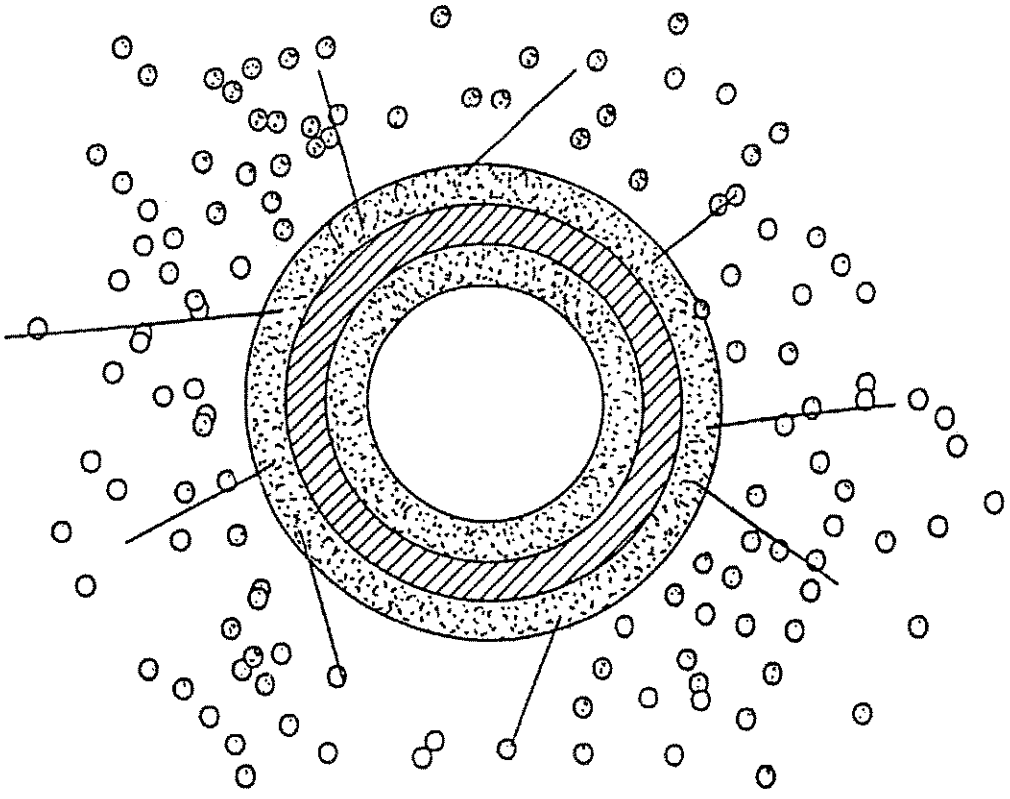


FIG. 2B

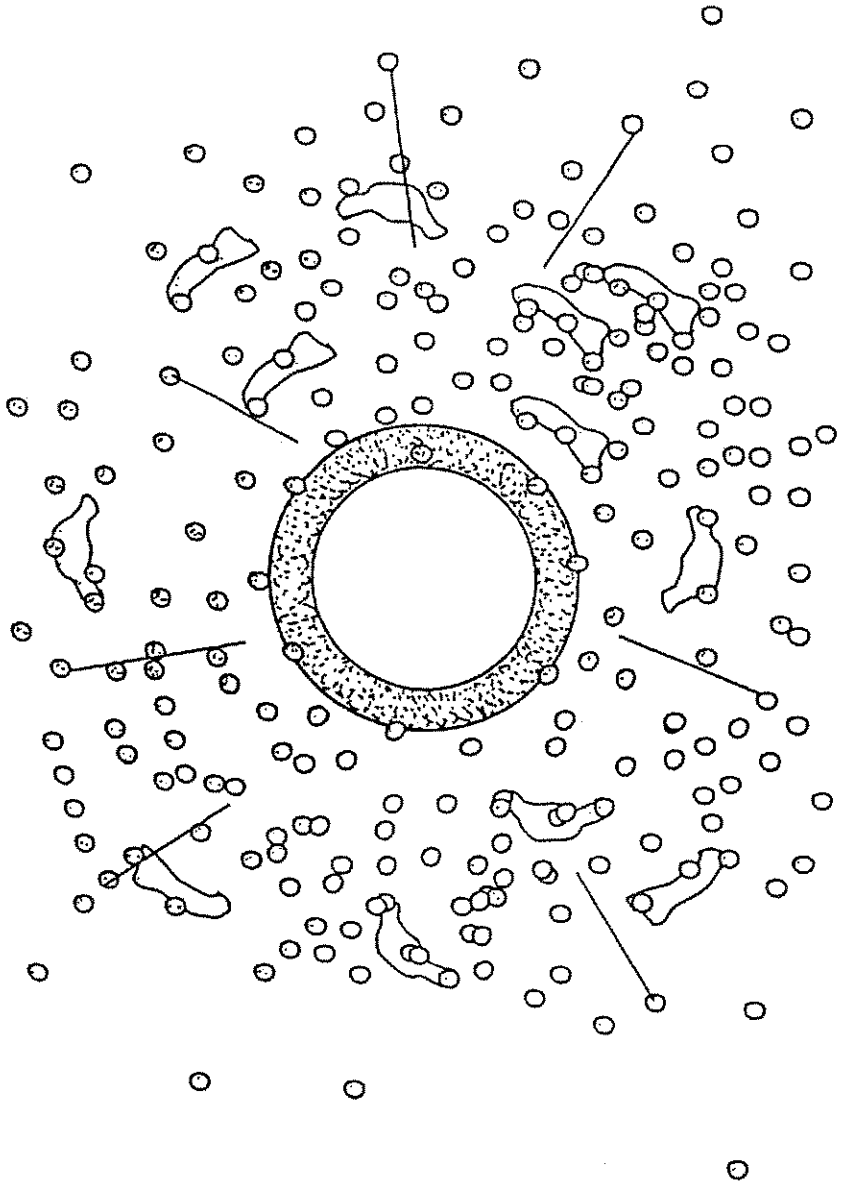


FIG. 2C

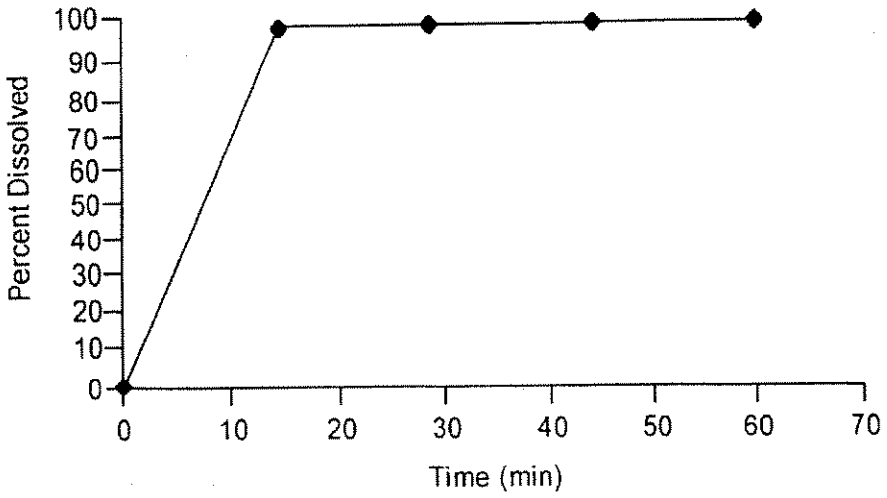
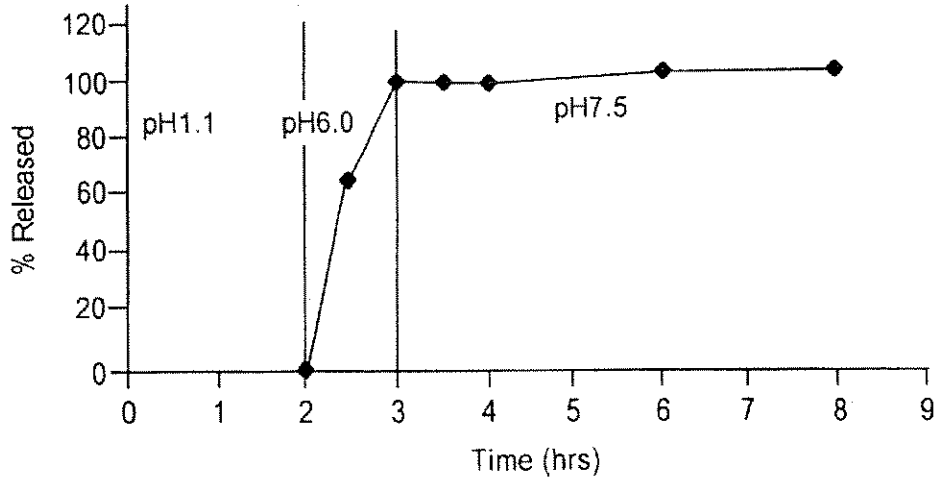

Percent Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
Time (min)

FIG. 3


% Released
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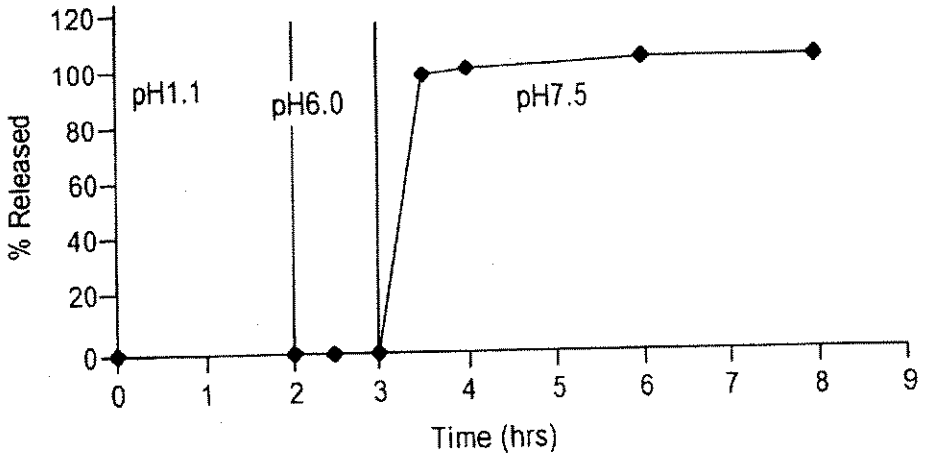
100
80
60
40
20
0
pH1.1
pH6.0
pH7.5
0
1
2
3
4
5
6
7
8
9
Time (hrs)

FIG. 4


120
100
80
60
40
20
0
% Released
pH1.1
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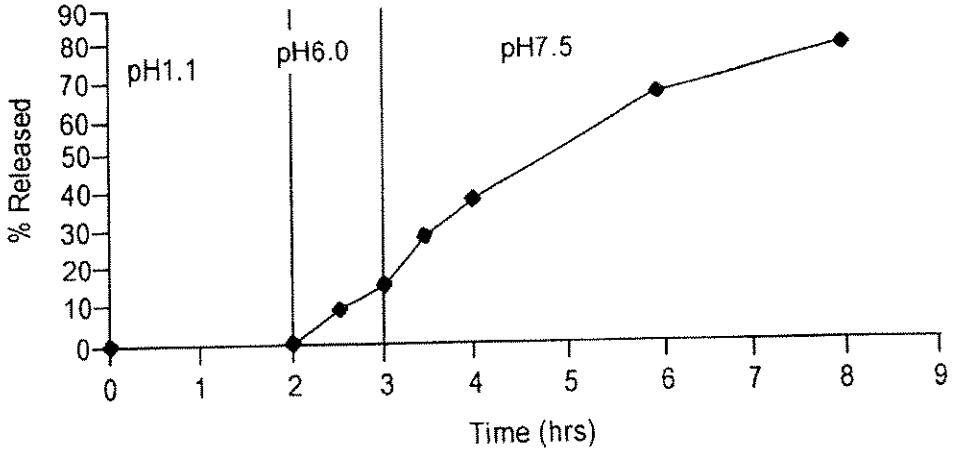
pH7.5
0
1
2
3
4
5
6
7
8
9
Time (hrs)

FIG. 5


90
80
70
60
50
40
30
20
10
0
% Released
pH1.1
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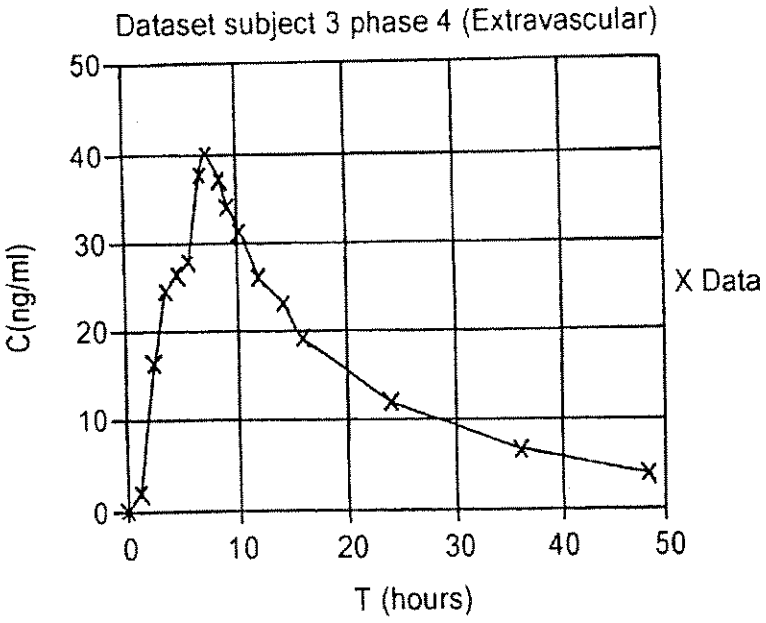
pH7.5
0
1
2
3
4
5
6
7
8
9
Time (hrs)

FIG. 6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C(ng/ml)
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40
30
20
10
0
0
10
20
30
40
50
T (hours)
X Data

FIG. 7

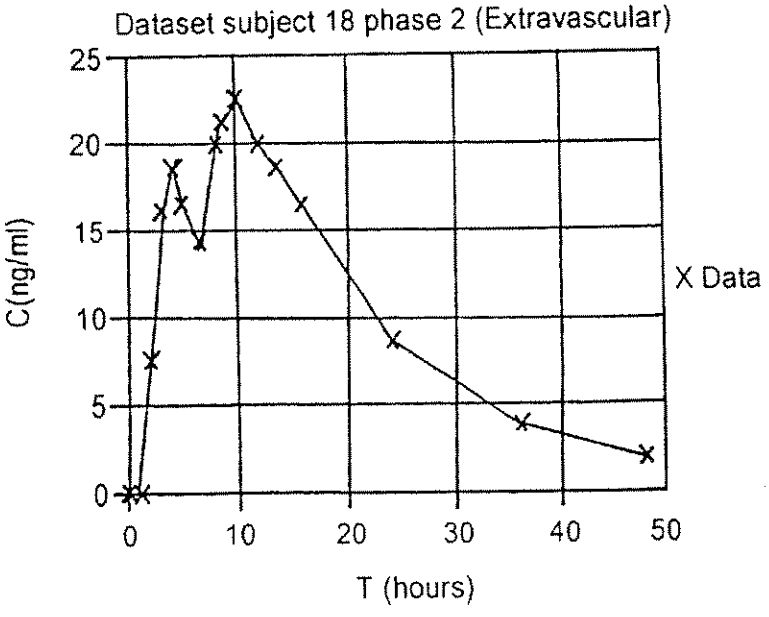
Dataset subject 18 phase 2 (Extravascular)
C(ng/ml)
25
20
15
10
5
0
0
10
20
30
40
50
T (hours)
X Data

FIG. 8

ORAL PULSED DOSE DRUG DELIVERY SYSTEM

This application is a 371 of PCT/US99/24554 filed Oct. 20, 1999, which is continuation-in-part of application Ser. No. 09/176,542, filed Oct. 21, 1998, now U.S. Pat. No. 6,322,819 the contents of which are incorporated herein by reference.

This invention pertains to a multiple unit dosage form delivery system comprising one or more amphetamine salts for administering the amphetamine salts to a recipient.

BACKGROUND OF THE INVENTION

Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems, compared to immediate release preparations. However, for certain drugs, sustained release delivery is not suitable and is affected by the following factors:

- First pass metabolism: Some drugs, such as β blockers, β-estradiol, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize presystemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.
- Biological tolerance: Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.
- Chronopharmacology and circadian rhythms: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours (1,2).
- Local therapeutic need: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.
- Gastric irritation or drug instability in gastric fluid: For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.
- Drug absorption differences in various gastrointestinal segments: In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feces.

Pulsed dose delivery systems, prepared as either single unit or multiple unit formulations, and which are capable of releasing the drug after a predetermined time, have been studied to address the aforementioned problematic areas for

sustained release preparations. These same factors are also problematic in pulsed dose formulation development. For example, gastrointestinal transit times vary not only from patient to patient but also within patients as a result of food intake, stress, and illness; thus a single-unit pulsed-release system may give higher variability compared to a multiple unit system. Additionally, drug layering or core making for multiple unit systems is a time-consuming and hard-to-optimize process. Particularly challenging for formulation scientists has been overcoming two conflicting hurdles for pulsatile formulation development, i.e., lag time and rapid release.

Various enteric materials, e.g., cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, and the EUDRAGIT® acrylic polymers, have been used as gastroresistant, enterosoluble coatings for single drug pulse release in the intestine (3). The enteric materials, which are soluble at higher pH values, are frequently used for colon-specific delivery systems. Due to their pH-dependent attributes and the uncertainty of gastric retention time, in-vivo performance as well as inter- and intra-subject variability are major issues for using enteric, coated systems as a time-controlled release of drugs.

A retarding swellable hydrophilic coating has been used for oral delayed release systems (4,5). It was demonstrated that lag time was linearly correlated with coating weight gain and drug release was pH independent.

Hydroxypropyl methylcellulose barriers with erodible and/or gellable characteristics formed using press coating technology for tablet dosage forms have been described to achieve time-programmed release of drugs (6). Barrier formulation variables, such as grade of hydroxypropyl methylcellulose, water-soluble and water-insoluble excipients, significantly altered the lag time and the release rate from the center cores.

Special grades of hydroxypropyl methylcellulose, e.g., METOLOSE® 60SH, 90SH (Shin-Etsu Ltd., Japan), and METHOCEL® F4M (Dow Chemical Company, USA), as a hydrophilic matrix material have been used to achieve bimodal drug release for several drugs, i.e., aspirin, ibuprofen, and adinazolam (7). Bimodal release is characterized by a rapid initial release, followed by a period of constant release, and finalized by a second rapid drug release.

Tablets or capsules coated with a hydrophobic wax-surfactant layer, made from an aqueous dispersion of carnauba wax, beeswax, polyoxyethylene sorbitan monooleate, and hydroxypropyl methylcellulose have been used for rapid drug release after a predetermined lag time. However, even though a two-hour lag time was achieved for the model drug theophylline at a higher coating level (60%), three hours were required for a complete release of theophylline after the lag time. (8)

A sustained-release drug delivery system is described in U.S. Pat. No. 4,871,549. When this system is placed into dissolution medium or the gastrointestinal tract, water influx and the volume expansion of the swelling agent cause the explosion of the water permeable membrane. The drug thus releases after a predetermined time period. The OROS® push-pull system (Alza Company) has been developed for pulsatile delivery of water-soluble and water-insoluble drugs (9,10), e.g. the OROS-CT® system and is based on the swelling properties of an osmotic core compartment which provides a pH-independent, time-controlled drug release.

The PULSINCAP® dosage form releases its drug content at either a predetermined time or at a specific site (e.g., colon) in the gastrointestinal tract (11). The drug formula-

tion is contained within a water-insoluble capsule body and is sealed with a hydrogel plug. Upon oral administration, the capsule cap dissolves in the gastric juice and the hydrogel plug swells. At a controlled and predetermined time point, the swollen plug is ejected from the PULSINCAP® dosage form and the encapsulated drug is released. A pulsatile capsule system containing captopril with release after a nominal 5-hr period was found to perform reproducibly in dissolution and gamma scintigraphy studies. However, in the majority of subjects, no measurable amounts of the drug were observed in the blood, possibly due to instability of the drug in the distal intestine. (12)

ADDERALL® comprises a mixture of four amphetamine salts, dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, which in combination, are indicated for treatment of Attention Deficit Hyperactivity Disorder in children from 3–10 years of age. One disadvantage of current treatment is that a tablet form is commonly used which many young children have difficulty in swallowing. Another disadvantage of current treatment is that two separate dose are administered, one in the morning and one approximately 4–6 hours later, commonly away from home under other than parental supervision. This current form of treatment, therefore, requires a second treatment which is time-consuming, inconvenient and may be problematic for those children having difficulty in swallowing table formulations.

SUMMARY OF THE INVENTION

Accordingly, in view of a need for successfully administering a multiple unit pulsed dose of amphetamine salts and mixtures thereof, the present invention provides an oral multiple unit pulsed dose delivery system for amphetamine salts and mixtures thereof. FIG. 1 illustrates the desired target plasma level profile of the pharmaceutical active contained within the delivery system.

In accordance with a preferred embodiment of the present invention, there is provided a pharmaceutical composition for delivering one or more pharmaceutically active amphetamine salts that includes:

(a) one or more pharmaceutically active amphetamine salts that are covered with an immediate release coating, and

(b) one or more pharmaceutically active amphetamine salts that are covered with an enteric release coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

In one embodiment, the immediate release and enteric release portions of the composition are present on the same core.

In another embodiment, the immediate release and enteric release components are present on different cores.

It is also contemplated that the composition may include a combination of the hereinabove referred to cores (one or more cores that include both components on the same core and one or more cores that include only one of the two components on the core).

The present invention provides a composition in which there is immediate release of drug and enteric release of drug wherein the enteric release is a pulsed release and wherein the drug includes one or more amphetamine salts and mixtures thereof.

The immediate release component releases the pharmaceutical agent in a pulsed dose upon oral administration of the delivery system.

The enteric release coating layer retards or delays the release of the pharmaceutical active or drug for a specified time period ("lag time") until a predetermined time, at which time the release of the drug is rapid and complete, i.e., the entire dose is released within about 30–60 minutes under predetermined environmental conditions, i.e. a particular location within the gastrointestinal tract.

The delay or lag time will take into consideration factors such as transit times, food effects, inflammatory bowel disease, use of antacids or other medicaments which alter the pH of the GI tract.

In a preferred embodiment, the lag time period is only time-dependent, i.e., pH independent. The lag time is preferably within 4 to 6 hours after oral administration of the delivery system.

In one aspect, the present invention is directed to a composition that provides for enteric release of at least one pharmaceutically active amphetamine salt, including at least one pharmaceutically active amphetamine salt that is coated with an enteric coating wherein (1) the enteric release coating has a defined minimum thickness and/or (2) there is a protective layer between the at least one pharmaceutically active amphetamine salt and the enteric release coating and/or (3) there is a protective layer over the enteric release coating.

In attempting to provide for enteric release of an amphetamine salt, applicants found that use of an enteric release coating as generally practiced in the art did not provide effective enteric release.

Typical enteric coating levels did not meet the above requirements for the desired dosage profile of amphetamine salts. Using the typical amount of enteric coating (10–20μ) resulted in undesired premature leakage of the drug from the delivery system into the upper gastrointestinal tract and thus no drug delivery at the desired location in the gastrointestinal tract after the appropriate lag time. Thus this coating did not meet the requirements for the drug release profile to provide full beneficial therapeutic activity at the desired time.

Surprisingly, applicants found that using a thicker application of enteric coating on the formulation allowed for the second pulsed dose to be released only and completely at the appropriate time in the desired predetermined area of the gastrointestinal tract, i.e., in the intestine.

This was surprising because an increase in thickness of about 5–10μ of enteric coatings above a minimum thickness of about 10–20μ typically does not have a significant effect on release of drug from within such coatings. Enteric coatings typically are pH dependent and will only dissolve/disperse when exposed to the appropriate environment. Typically, application of a thicker coating (greater than 20μ) will only marginally increase the time for complete release at the appropriate environmental condition i.e., for a brief period of time (20 minutes). Using the typical coating, applicants could not achieve the desired result—rather, the coating leaked before the predetermined time in an inappropriate environment resulting in significant loss of the therapeutic agent.

Accordingly, in one aspect, the pulsed enteric release of the amphetamine salts is accomplished by employing a certain minimum thickness of the enteric coating.

In one embodiment of the invention, the pulsed dose delivery comprises a composition which comprises one or more pharmaceutically active amphetamine salts; an enteric

coating over the one or more pharmaceutically active amphetamine salts, wherein the thickness of the enteric coating layer is at least 25μ; a further layer of one or more pharmaceutically active amphetamine salts over the enteric coating layer; and an immediate release layer coating. The thicker enteric coating surprisingly provides the required delayed immediate release of the pharmaceutically active amphetamine salt at the desired time in the desired area of the gastrointestinal tract. FIG. 2 illustrates a model of this delivery system.

In this aspect, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed around which the enteric coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

It has further been discovered that a delayed immediate release drug delivery can also be accomplished by coating the drug first with a protective layer prior to applying the enteric coating.

Thus, in another embodiment, the pulsed enteric release is accomplished by employing a protective layer between the drug and the enteric coating. When using a protective coating, the enteric coating may be of an increased thickness or may be of lower thickness.

Thus, in another aspect, the object of the invention is met by providing a composition comprising one or more pharmaceutically active amphetamine salts; a protective layer coating over the one or more pharmaceutically active amphetamine salt layer(s), and an enteric coating layer over the protective coating layer; a further pharmaceutically active amphetamine salt layer and an immediate release layer coating. In a preferred embodiment of this aspect, the thickness of the enteric coating is at least 25μ, and the protective layer comprises an immediate release coating.

With respect to this embodiment of the invention, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed, during the core seed manufacturing process, around which the protective coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

In another embodiment, the pulsed enteric release is accomplished by employing a protective layer over the enteric coating.

Accordingly, in this embodiment of the present invention, there is provided a pulsed dose release drug delivery system comprising one or more pharmaceutically active amphetamine salts; an enteric coating layer over the pharmaceutically active amphetamine salt layer(s); and a protective layer over the enteric coating; a second pharmaceutically active amphetamine salt layer; and an immediate release layer coating.

In one aspect of this embodiment, the protective layer is comprised of one or more components, which includes an immediate release layer and a modifying layer. The modifying layer is preferably comprised of a semi water-permeable polymer. Applicants have surprisingly found that a semi-permeable polymer coating used in combination with an immediate release layer coating provided a delayed pulsed release drug delivery profile when layered over the enteric coating.

Thus, in this embodiment, the protective layer comprises a semi-permeable polymer and an immediate release coating layer. In a preferred embodiment, the modifying layer comprises a first layer of a semi-permeable polymer which is adjacent to the enteric coating layer and a second coating layer over the semi-permeable polymer coating layer comprising an immediate release polymer coating layer.

In one aspect of this embodiment, a semi-permeable polymer, which may comprise a low water-permeable pH-insensitive polymer, is layered onto the outer surface of the enteric layer, in order to obtain prolonged delayed release time. This semi-permeable polymer coating controls the erosion of the pH-sensitive enteric polymer in an alkaline pH environment in which a pH-sensitive polymer will dissolve rapidly. Another pH-sensitive layer may be applied onto the surface of a low water-permeability layer to further delay the release time.

In a still further aspect of the invention, in addition to a protective layer, the composition comprises an acid which is incorporated into the pharmaceutical active layer or coated onto the surface of the active layer to reduce the pH value of the environment around the enteric polymer layer. The acid layer may also be applied on the outer layer of the pH-sensitive enteric polymer layer, followed by a layer of low water-permeability polymer. The release of the active thus may be delayed and the dissolution rate may be increased in an alkaline environment.

In a further embodiment, the protective coating may be used both over the drug and over the enteric coating.

With respect to this embodiment of the invention, the one or more pharmaceutically active amphetamine salts can be provided within or as a part of a core seed, during the core seed manufacturing process, around which the enteric coating is applied. Alternatively, a core seed can be coated with one or more layers of one or more pharmaceutically active amphetamine salts.

The drug delivery system of the present invention as described herein preferably comprises one or a number of beads or beadlets in a dosage form, either capsule, tablet, sachet or other method of orally administering the beads.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a multiple pulse drug delivery system target plasma profile of the drug delivery system of the present invention. The profile reflects an immediate-release component followed by a delayed-release component.

FIG. 2*a* graphically illustrates a pulsed dose delivery system.

FIGS. 2*b* and *c* graphically illustrate the drug release mechanism from the proposed delivery system.

FIG. 3 is a plot of the percent drug released versus time from the drug-loaded pellets described in Example 1 which exemplifies the immediate release component of the present invention.

FIG. 4 is a plot of the percent drug released versus time from the coated pellets described in Example 2 which exemplifies the immediate release component and the delayed release components of the present invention.

FIG. 5 is a plot of the percent drug released versus time from the coated pellets of Example 3 which exemplifies the immediate release component and the delayed release components of the present invention.

FIG. 6 illustrates the drug release profile of coated pellets described in Example 4 which exemplifies the immediate release component and the delayed release components of the present invention.

FIG. 7 is a plot of a profile of plasma amphetamine concentration after administration of a composite capsule containing the immediate release pellets and delayed release pellets from Examples 1 and 2, respectively.

FIG. 8 is a plot of a profile of plasma amphetamine concentration after administration of a composite capsule

containing the immediate release pellets and delayed release pellets from Examples 1 and 3, respectively.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises a core or starting seed, either prepared or commercially available product. The cores or starting seeds can be sugar spheres; spheres made from microcrystalline cellulose and any suitable drug crystals.

The materials that can be employed in making drug-containing pellets are any of those commonly used in pharmaceutics and should be selected on the basis of compatibility with the active drug and the physicochemical properties of the pellets. The additives except active drugs are chosen below as examples:

Binders such as cellulose derivatives such as methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer and the like.

Disintegration agents such as corn starch, pregelatinized starch, cross-linked carboxymethylcellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®), cross-linked polyvinylpyrrolidone (PLASDONE XL®), and any disintegration agents used in tablet preparations.

Filling agents such as lactose, calcium carbonate, calcium phosphate, calcium sulfate, microcrystalline cellulose, dextran, starches, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

Surfactants such as sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, bile salts, glyceryl monostearate, PLURONIC® line (BASF), and the like.

Solubilizers such as citric acid, succinic acid, fumaric acid, malic acid, tartaric acid, maleic acid, glutaric acid sodium bicarbonate and sodium carbonate and the like.

Stabilizers such as any antioxidation agents, buffers, acids, and the like, can also be utilized.

Methods of manufacturing the core include

a. Extrusion-Spheronization—Drug(s) and other additives are granulated by addition of a binder solution. The wet mass is passed through an extruder equipped with a certain size screen. The extrudates are spheronized in a marumerizer. The resulting pellets are dried and sieved for further applications.

b. High-Shear Granulation—Drug(s) and other additives are dry-mixed and then the mixture is wetted by addition of a binder solution in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

c. Solution or Suspension Layering—A drug solution or dispersion with or without a binder is sprayed onto starting seeds with a certain particle size in a fluid bed processor or other suitable equipment. The drug thus is coated on the surface of the starting seeds. The drug-loaded pellets are dried for further applications.

For purposes of the present invention, the core particles have a diameter in the range of about 50–1500 microns; preferably 100–800 microns.

These particles can then be coated in a fluidized bed apparatus with an alternating sequence of coating layers.

The core may be coated directly with a layer or layers of at least one pharmaceutically active amphetamine salts and/or the pharmaceutically active amphetamine salt may be incorporated into the core material. Pharmaceutical active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base, all chemical and chiral derivatives and salts thereof; methylphenidate, all chemical and chiral derivatives and salts thereof; phenylpropanolamine and its salts; and all other compounds indicated for the treatment of attention deficit hyperactivity disorder (ADHD).

A protective layer may be added on top of the pharmaceutical active containing layer and also may be provided between active layers. A separation or protective layer may be added onto the surface of the active-loaded core, and then the enteric layer is coated thereupon. Another active layer may also be added to the enteric layer to deliver an initial dose.

A protective coating layer may be applied immediately outside the core, either a drug-containing core or a drug-layered core, by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. Suitable materials for the protective layer include cellulose derivatives such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinylpyrrolidone/vinyl acetate copolymer, ethyl cellulose aqueous dispersions (AQUACOAT®, SURELEASE®), EUDRAGIT® RL 30D, OPADRY® and the like. The suggested coating levels are from 1 to 6%, preferably 2–4% (w/w).

The enteric coating layer is applied onto the cores with or without seal coating by conventional coating techniques, such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. All commercially available pH-sensitive polymers are included. The pharmaceutical active is not released in the acidic stomach environment of approximately below pH 4.5, but not limited to this value. The pharmaceutical active should become available when the pH-sensitive layer dissolves at the greater pH; after a certain delayed time; or after the unit passes through the stomach. The preferred delay time is in the range of two to six hours.

Enteric polymers include cellulose acetate phthalate, Cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, carboxymethylethylcellulose, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, materials known under the trade name EUDRAGIT® L12.5, L100, or EUDRAGIT® S12.5, S100 or similar compounds used to obtain enteric coatings. Aqueous colloidal polymer dispersions or re-dispersions can be also applied, e.g. EUDRAGIT® L 30D-55, EUDRAGIT® L100-55, EUDRAGIT® S100, EUDRAGIT® preparation 4110D (Rohm Pharma); AQUATERIC®, AQUACOAT® CPD 30 (FMC); KOLLICOAT MAE® 30D and 30DP (BASF); EASTACRYL® 30D (Eastman Chemical).

The enteric polymers used in this invention can be modified by mixing with other known coating products that are not pH sensitive. Examples of such coating products include the neutral methacrylic acid esters with a small portion of trimethylammonioethyl methacrylate chloride, sold currently under the trade names EUDRAGIT® RS and EUDRAGIT® RL; a neutral ester dispersion without any functional groups, sold under the trade names EUDRAGIT® NE30D; and other pH independent coating products.

The modifying component of the protective layer used over the enteric coating can include a water penetration barrier layer (semipermeable polymer) which can be successively coated after the enteric coating to reduce the water penetration rate through the enteric coating layer and thus increase the lag time of the drug release. Sustained-release coatings commonly known to one skilled in the art can be used for this purpose by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water or suitable organic solvents or by using aqueous polymer dispersions. For example, the following materials can be used, but not limited to: Cellulose acetate, Cellulose acetate butyrate, Cellulose acetate propionate, Ethyl cellulose, Fatty acids and their esters, Waxes, zein, and aqueous polymer dispersions such as EUDRAGIT® RS and RL 30D, EUDRAGIT® NE 30D, AQUACOAT®, SURELEASE®, cellulose acetate latex. The combination of above polymers and hydrophilic polymers such as Hydroxyethyl cellulose, Hydroxypropyl cellulose (KLUCEL®, Hercules Corp.), Hydroxypropyl methylcellulose (METHOCEL®, Dow Chemical Corp.), Polyvinylpyrrolidone can also be used.

An overcoating layer can further optionally be applied to the composition of the present invention. OPADRY®, OPADRY II® (Colorcon) and corresponding color and colorless grades from Colorcon can be used to protect the pellets from being tacky and provide colors to the product. The suggested levels of protective or color coating are from 1 to 6%, preferably 2–3% (w/w).

Many ingredients can be incorporated into the overcoating formula, for example to provide a quicker immediate release, such as plasticizers: acetyltriethyl citrate, triethyl citrate, acetyltributyl citrate; dibutylsebacate, triacetin, polyethylene glycols, propylene glycol and the others; lubricants: talc, colloidal silica dioxide, magnesium stearate, calcium stearate, titanium dioxide, magnesium silicate, and the like.

The composition, preferably in beadlet form, can be incorporated into hard gelatin capsules, either with additional excipients, or alone. Typical excipients to be added to a capsule formulation include, but are not limited to: fillers such as microcrystalline cellulose, soy polysaccharides, calcium phosphate dihydrate, calcium sulfate, lactose, sucrose, sorbitol, or any other inert filler. In addition, there can be flow aids such as fumed silicon dioxide, silica gel, magnesium stearate, calcium stearate or any other material imparting flow to powders. A lubricant can further be added if necessary by using polyethylene glycol, leucine, glyceryl behenate, magnesium stearate or calcium stearate.

The composition may also be incorporated into a tablet, in particular by incorporation into a tablet matrix, which rapidly disperses the particles after ingestion. In order to incorporate these particles into such a tablet, a filler/binder must be added to a table that can accept the particles, but will not allow their destruction during the tableting process. Materials that are suitable for this purpose include, but are not limited to, microcrystalline cellulose (AVICEL®), soy polysaccharide (EMCOSOY®), pre-gelatinized starches (STARCH® 1500, NATIONAL® 1551), and polyethylene glycols (CARBOWAX®). The materials should be present in the range of 5–75% (w/w), with a preferred range of 25–50% (w/w).

In addition, disintegrants are added in order to disperse the beads once the tablet is ingested. Suitable disintegrants include, but are not limited to: cross-linked sodium carboxymethyl cellulose (AC-DI-SOL®), sodium starch glycolate (EXPLOTAB®, PRIMOJEL®), and cross-linked polyvinylpolypyrrolidone (Plasone-XL). These materials should be present in the rate of 3–15% (w/w), with a preferred range of 5–10% (w/w).

Lubricants are also added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behanate, and hydrogenated vegetable oil. These lubricants should be present in amounts from 0.1–10% (w/w), with a preferred range of 0.3–3.0% (w/w).

Tablets are formed, for example, as follows. The particles are introduced into a blender along with AVICEL®, disintegrants and lubricant, mixed for a set number of minutes to provide a homogeneous blend which is then put in the hopper of a tablet press with which tablets are compressed. The compression force used is adequate to form a tablet; however, not sufficient to fracture the beads or coatings.

It will be appreciated that the multiple dosage form of the present invention can deliver rapid and complete dosages of pharmaceutically active amphetamine salts to achieve the desired levels of the drug in a recipient over the course of about 8 hours with a single oral administration.

In so doing, the levels of drug in blood plasma of the pharmaceutically active amphetamine salts will reach a peak fairly rapidly after about 2 hours, and after about 4 hours a second pulse dose is released, wherein a second fairly rapid additive increase of plasma drug levels occurs which slowly decreases over the course of the next 12 hours.

The following examples are presented to illustrate and do not limit the invention.

EXAMPLES

Example 1

Immediate Release Formulation

The following formulation was used to layer the drug onto sugar spheres. Nonpareil seeds (30/35 mesh, Paulaur Corp., NJ), 6.8 kg were put into a FLM-15 fluid bed processor with a 9" Wurster column and fluidized at 60° C. The suspension of mixed amphetamine salts (MAS) with 1% HPMC E5 Premium (Dow Chemical) as a binder was sprayed onto the seed under suitable conditions. Almost no agglomeration and no fines were observed with a yield of at least 98%. The drug-loaded cores were used to test enteric coatings and sustained release coatings.

TABLE 1

Ingredients	Amount (%)
Nonpareil seed	88.00
mixed amphetamine salts	11.40
METHOCEL® E5 Premium	0.60
Water	*

*removed during processing

The drug release profile of the drug-loaded pellets of this example is shown in FIG. 3.

Example 2

The following formulation was used to coat the mixed amphetamine salts loaded (MASL) pellets from Example 1 with the EUDRAGIT® L 30D-55 (Rohm Pharma, Germany) coating dispersion. 2 kg of MASL pellets were loaded into a fluid bed processor with a reduced Wurster column equipped with a precision coater (MP 2/3, Niro Inc.). The coating dispersion was prepared by dispersing Triethyl citrate, Talc and EUDRAGIT® L 30D-55 into water and

mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized MASL pellets. The spraying was continued until the targeted coating level was achieved (20μ). The coated pellets were dried at 30–35° C. for 5 minutes before stopping the process. The enteric coated PPA pellets were tested at different pH buffers by a USP paddle method. The drug content was analyzed using HPLC. The results showed that the enteric coating delayed the drug release from the coated pellets until after exposure to pH 6 or higher (see Table 2 below). (Reference #AR98125-4)

TABLE 2

Ingredients	Amount (%)
MASL pellets	40.00
EUDRAGIT ® L 30D-55	24.88
Triethyl citrate	2.52
Talc	2.60
Water	*

*removed during processing

The drug release profile of the coated pellets of this example is shown in FIG. 4.

Example 3

The following formulation was used to coat the MASL pellets from Example 1 with the EUDRAGIT® 4110D (Rohm Pharma, Germany) coating dispersion. MASL pellets (2 kg) were loaded in a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by dispersing Triethyl citrate, Talc and EUDRAGIT® 4110D into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized MASL pellets. The spraying was continued until the targeted coating level was achieved. The coated pellets were dried at 30–35° C. for 5 minutes before stopping the process. The enteric coated MASL pellets were tested using a USP paddle method at different pH buffers. The drug content was analyzed using HPLC. The enteric coating delayed the drug release for several hours from the coated pellets until the pH value reached 6.8 or higher, as shown below in Table 3. (Reference #AR98125-3)

TABLE 3

Ingredients	Amount (%)
MASL pellets	70.00
Eudragit ® 4110D	26.24
Triethyl citrate	0.76
Talc	3.00
Water	*

*removed during processing

The drug release profile of coated pellets of this example is shown in FIG. 5.

Example 4

The following formulation was selected to coat the enteric coated MASL pellets. Coated MASL pellets from Example 2 or coated MASL pellets from Example 3 (2 kg of either) were loaded into a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by mixing SURELEASE® (Colorcon) and water for at least 15 minutes prior to spraying. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized pellets. The spraying was continued until the targeted coating level was achieved. The coated pellets were coated with a thin layer of OPADRY® white (Colorcon) (2%) to prevent the tackiness of the coated pellets during storage. The coated pellets were then dried at 35–40° C. for 10 minutes before discharging from the bed. The drug dissolution from both coated pellets was performed using a USP paddle method at different pH buffers. The drug content was analyzed using HPLC. The 8% SURELEASE® coating slightly sustained the drug release from EUDRAGIT® L 30D-55 coated pellets at pH 7.5 buffer, while the SURELEASE® coating delayed the drug release up to 2 hours after the buffer switched from pH 1 to pH 7.5. (Reference ##AR98125-1)

TABLE 4

Ingredients	Amount, (%)
Enteric coated MASL pellets	90.00
SURELEASE ®	8.00
OPADRY ® white	2.00
Water	*

*removed during processing

The drug release profile of the coated pellets from this example is shown in FIG. 6.

Example 5

A pulsatile delivery system can be achieved by combining the immediate release pellets (Example 1) with delayed release pellets (Example 2 or Example 3). The immediate-release pellets equivalent to half the dose and the delayed-release pellets equivalent to half the dose are filled into a hard gelatin capsule to produce the oral pulsed dose delivery system. The delayed-release portion releases the amphetamine salts rapidly and completely, after a specified lag time. The capsule products containing immediate-release pellets and delayed-release pellets (Example 1 plus Example 2 and Example 1 plus Example 3) were tested in a crossover human study. FIGS. 7 and 8 show the typical profiles of plasma amphetamine concentration after administration of a composite capsule containing the immediate-release pellets and delayed-release pellets from Examples 1 and 2 (10 mg dose each pellet type) and a capsule containing the pellets from immediate-release pellets and delayed-release pellets from Examples 1 and 3 (10 mg dose each pellet type), respectively. The general plasma profiles are similar to the desired target plasma level profile shown in FIG. 1.

It is to be understood, however, that the scope of the present invention is not to be limited to the specific embodiments described above. The invention may be practiced other than as particularly described and still be within the scope of the accompanying claims.

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What is claimed is:

1. A pharmaceutical formulation for delivery of a mixture of amphetamine base salts effective to treat ADHD in a human patient comprising:

an immediate release dosage form that provides immediate release upon oral administration to said patient;

a delayed enteric release dosage form that provides delayed release upon oral administration to said patient; and

a pharmaceutically acceptable carrier;

wherein said amphetamine base salts comprise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate;

wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt, and the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration previously reached after release of said immediate release dosage form; and

wherein said pharmaceutical formulation, when containing about a total dose of 20 mg, will produce in a human individual a plasma concentration versus time curve (ng/ml versus hours) having an area under the curve (AUC) of about 467 to about 714 ng hr/ml.

2. A formulation of claim **1** wherein said plasma concentration curve has a maximum concentration (C_{max}) of about 22.5 to about 40 ng/ml for about a total dose of 20 mg.

3. A formulation of claim **2** wherein the time after said oral administration to reach said C_{max} value is about 7 to about 10 hours.

4. A formulation of claim **1** wherein the time after said oral administration to reach maximum concentration of said plasma concentration curve is about 7 to about 10 hours.

5. A formulation of claim **2**, **3** or **4** wherein said AUC is about 714 ng hr/ml.

6. A formulation of claim **3** wherein said AUC is about 714 ng hr/ml, the time after said oral administration to reach said C_{max} value is about 7 hours and C_{max} is about 40 ng/ml.

7. A formulation of claim **2** wherein C_{max} is about 40 ng/ml.

8. A formulation of claim **3** or **4** wherein said time is about 7 hours.

9. A formulation of one of claims **1–4**, **6** or **7** wherein said salts are contained in about equal amounts within each of said dosage forms.

10. A formulation of one of claims **1–4**, **6** or **7** wherein said delayed enteric release dosage form comprises a coating of a thickness of at least 20 μm which comprises dried about 30% (dry substance) aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards.

11. A formulation of claim **10** wherein said thickness is at least 25 μm.

12. A pharmaceutical formulation for delivery of a mixture of amphetamine base salts effective to treat ADHD in a human patient comprising:

an immediate release dosage form that provides immediate release upon oral administration to said patient;

a delayed enteric release dosage form that provides delayed release upon oral administration to said patient, wherein said enteric release dosage form comprises a coating of a thickness of at least 20 μm which comprises dried aqueous dispersion of an anionic copolymer based on methacrylic acid and acrylic acid ethyl ester, said coating being soluble at a pH of about 5.5 upwards; and

a pharmaceutically acceptable carrier;

wherein said amphetamine base salts comprise dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate;

wherein said pharmaceutical formulation is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt, and the peak plasma concentration of amphetamine base salts reached after release of said delayed enteric release dosage form exceeds the peak plasma concentration of said salts previously reached after release of said immediate release dosage form.

13. A formulation of claim **12** wherein said thickness is at least 25 μm.

14. A formulation of claim **12**, wherein said dried aqueous dispersion of an anionic copolymer is a dried about 30% (dry substance) aqueous dispersion of an anionic copolymer.

15. A formulation of claim **1** formulated for a total dose of 20 mg.

16. A formulation of claim **2** formulated for a total dose of 20 mg.

17. A formulation of claim **1** formulated for a total dose different from about 20 mg and having an AUC proportional to said 20 mg AUC.

18. A formulation of claim **2** formulated for a total dose different from about 20 mg and having a C_{max} proportional to said 20 mg C_{max}.

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