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UTILITY PATENT APPLICATION TRANSMITTAL

(ONLY FOR NEW NONPROVISIONAL APPLICATIONS UNDER 37 CFR 1.53(B))

Attorney Docket No.	20342/1202653-US8
First Inventor	Amir Shojaei
Title	CONTROLLED DOSE DRUG DELIVERY SYSTEM
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. [ ] **Fee Transmittal Form** (e.g., PTO/SB/17) *(Submit an original and a duplicate for fee processing)*
2. [ ] **Applicant claims small entity status.** See 37 CFR 1.27.
3. [X] **Specification** [*Total Pages* 56] Both the claims and abstract must start on a new page *(For information on the preferred arrangement, see MPEP 608.01(a))*
4. [X] **Drawing(s)** *(35 U.S.C. 113)* [*Total Sheets* 10]
5. **Oath or Declaration** [*Total Sheets*]
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 18 completed)*
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).
6. [X] **Application Data Sheet.** See 37 CFR 1.76
7. [ ] **CD-ROM or CD-R** in duplicate, large table or Computer Program *(Appendix)*
   [ ] Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. Computer Readable Form (CRF)
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ACCOMPANYING APPLICATION PARTS

9. [ ] **Assignment Papers** (cover sheet & document(s))
   Name of Assignee:
10. [ ] **37 CFR 3.73(b) Statement** *(when there is an assignee)* [ ] **Power of Attorney**
11. [ ] **English Translation Document** *(if applicable)*
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16. [ ] **Nonpublication Request** under 35 U.S.C.122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
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18. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:*
    [ ] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No.:
    Prior application information: Examiner *Art Unit:*

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Application Data Sheet

Application Information

Application Type::	Regular
Subject Matter::	Utility
Suggested Group Art Unit::	1615
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	CONTROLLED DOSE DRUG DELIVERY SYSTEM
Attorney Docket Number::	20342/1202653-US8
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	10
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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CONTROLLED DOSE DRUG DELIVERY SYSTEM

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 reduce adverse effects. Reduced dosing frequency and improved patient compliance can also be expected for constant/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 ß-blockers, ß-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 a symptom or disease onset can occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours (Lemmer, B, J Controlled Release. 1991; 16:63-74; Lemmer B, Pulsatile Drug Delivery: Current Applications and Future Trends (R Gurney, HE Junginger, NA Peppeas, eds.) 1993; 11-24).

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 exhibit 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 (Xu X and Lee P, Pharm Res. 1993; 10(8):1144-1152). 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 (Gazzaniga et al., Eur J Pharm Biopharm. 1994; 40(4):246-250; Gazzaniga et al., S.T.P. Pharma Sciences. 1996; 5(1):83-88). 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 (Conte et al., Biomaterials. 1993; 14(13):1017-1023). 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) have been used as a hydrophilic matrix material to achieve bimodal drug release for several drugs, i.e., aspirin, ibuprofen, and adinazolam (WO 87/00044). Bimodal release is characterized by a rapid initial release, followed by a period of constant release, and then 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. (Walia et al., Pharm Dev Tech. 1998; 3(1):103-113)

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 (Theeuwes, Drug Dev Ind Pharm. 1983; 9(7):1331-1357; Theeuwes F, Novel Drug Delivery and Its Therapeutic Application (LF Prescott and WS Nimmos eds.) 1989; 323-340), 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 (WO 90/09168). 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, reproducible 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. (Wilding et al., Pharm Res. 1992;9(5):654-657)

ADDERALL® is an immediate release composition, which includes a mixture of four amphetamine salts: dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate. This combination of amphetamines is indicated for the treatment of Attention Deficit Hyperactivity Disorder in children from 3-10 years of age.

One disadvantage of immediate release-only treatments for children 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 requires a second treatment, which is time-consuming, inconvenient and may be problematic for those children having difficulties in swallowing tablet formulations. ADDERALL XR® met the need for a dosage form, which can be administered once, in place of the two oral doses which are needed using the conventional drug delivery formulations of the prior art. See U.S. Patent Nos. 6,322,819 and 6,605,300; co-pending Reissue Application Nos. 11/091,010 and 11/091,011.

There are currently two medications (ADDERALL XR® and STRATTERA™) approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD in adults. ADDERALL XR® is a mixed amphetamine salts medication. STRATTERA™ is an atomoxetine (a norepinephrine reuptake inhibitor) medication. Long acting stimulant preparations, such as ADDERALL XR® and CONCERTA® (methylphenidate), are designed to provide a duration of effect up to 12 hours. However, clinicians have noted that a proportion of patients treated with these formulations require additional treatment with a short-acting stimulant to extend the daily therapeutic effect. For patients taking long-acting stimulant formulations who require duration of clinical benefit beyond 10-12 hours, clinicians have augmented the morning long-acting formulation, typically at 8-10 hours post-dose, with a dose of the same immediate-release (IR) medication. Typically, the dose of the IR medication is smaller than the long-acting dose. This augmentation strategy is most relevant to the "longer day demands" of adult and adolescents, rather than school age, pediatric patients.

Thus, a need exists for a once-daily, long-acting oral composition that provides effective treatment of ADHD, without supplementation, for patients with longer day demands (e.g., 14-16 awake hours).

SUMMARY OF THE INVENTION

The present invention provides a long-acting amphetamine pharmaceutical composition, which includes an immediate release component, a delayed pulsed release component and a sustained release component, to meet the therapeutic needs for ADHD patients with longer-day demands. The present invention fills the need for once-daily longer-day treatment of ADHD by providing an amphetamine pharmaceutical composition that is bioequivalent to an equal dosage of ADDERALL XR® followed by an IR amphetamine composition 8 hours later.

The addition of a second delayed pulsed release formulation, having a lag time of about 8 hours, to ADDERALL XR® cannot, as one might expect, meet the recognized need for a once-daily long-acting amphetamine composition that meets a patient's longer day requirements (i.e., a once-daily amphetamine composition that is bioequivalent to ADDERALL XR® plus an immediate release amphetamine composition administered 8 hours later). A delayed pulsed formulation having a lag time of about 8 hours would be unsuitable because it would release the active agent in the distal gastrointestinal tract (the colon), resulting in decreased absorption of the active agent.

Unexpectedly, it has been discovered that a sustained release formulation administered in combination with immediate release and delayed pulsed release components similar to those present in ADDERALL XR® can mimic the bioavailability of an equivalent total amphetamine dosage provided by ADDERALL XR® followed by an immediate release amphetamine composition 8 hours later. However, the "usual" or "typical" construction for a sustained release formulation is not suitable. Typically, a sustained release formulation is constructed with a delayed release coating overlaying a sustained release coating. Such a usual or typical sustained release construction results in a Tmax that is too early after administration to a patient to result in a composition that meets the longer-day requirements for the treatment of ADHD. For example, the dissolution profiles for a typical sustained release formulation (PD0149-124) and a sustained release formulation of the present invention (PD0149-120) are illustrated in **FIG. 1**. PD0149-124 has a typical sustained release formulation construction, wherein the immediate release bead

of Example 1 (*see* Examples 1 and 2, *infra*) is coated with a sustained release coating (SURELEASE®), the sustained release coating is coated with a delayed release coating (EUDRAGIT® FS30 D), and the delayed release coating is coated with a protective layer (OPADRY®). PD0149-120 is an embodiment of a sustained release formulation of the present invention. PD0149-120 has a construction wherein the immediate release bead of Example 1 is coated with a delayed release coating (EUDRAGIT® FS30 D), the delayed release coating is coated with a protective coating (OPADRY®), and the protective coating is coated with a sustained release coating (SURELEASE®). As illustrated in **FIG. 1**, PD0149-120 provides a later Tmax relative to a typically-constructed sustained release formulation, PD0149-124.

According to the present invention, an atypical, counter-intuitive construction for a sustained release amphetamine formulation, when administered in combination with an immediate release formulation and a delayed pulsed release formulation, is bioequivalent to ADDERALL XR® followed by an immediate release amphetamine formulation administered 8 hours later. A sustained release formulation of the present invention comprises at least one amphetamine salt layered onto, or incorporated into, a core; a delayed release coating layered onto the amphetamine core; a sustained release coating layered onto the delayed release coating; and, optionally, a protective coating. See **FIG. 2.** In a preferred embodiment, the delayed release component is pH dependent.

A sustained release pharmaceutical formulation of the present invention can comprise about 10% to about 150% of the amphetamine dosage of the immediate release mixed amphetamine salt composition and/or an extended release mixed amphetamine salt composition. For example, the sustained release formulation can be administered, in the same or different dosage forms, with the IR and delayed pulsed release components of ADDERALL XR® in an amphetamine dosage ratio of 1:1:1 (e.g., 10 mg immediate release amphetamine, 10 mg delayed pulsed release amphetamine, 10 mg sustained release amphetamine). Thus, in this example, the sustained release composition comprises about 33% of the total amphetamine dose. In another example, a patient with ADHD and insomnia can be administered a reduced amount of the sustained release composition, e.g., 10 mg immediate release amphetamine, 10 mg delayed pulsed release amphetamine, and 5 mg sustained release amphetamine (the sustained release composition comprises 20% of the total amphetamine dose). Thus, according to the present

invention, a clinician can adjust the sustained release formulation dosage to meet the needs of an individual patient suffering from ADHD.

The pharmaceutical composition of the present invention, comprising an immediate release amphetamine component, a delayed pulsed release amphetamine component and a sustained release amphetamine component, delivers, in a single dose, mixed amphetamine salts to a patient with a pharmacokinetic profile similar to a 2-dose treatment with a currently available commercial extended release composition (i.e., ADDERALL XR®) plus an immediate release composition administered about eight hours after the ADDERALL XR®. See, for example, **FIG. 9**. This similarity in bioequivalence is surprising because it would be expected that some part of the drug delivered by the delayed release components of compositions of the present invention (i.e., the delayed pulsed release and/or the sustained release components) would be lost (i.e., not absorbed) in the colon. The FDA package insert and labeling for ADDERALL XR® (Shire US, Inc.) are hereby incorporated by reference in their entirety.

Preferred amphetamine salts are those in ADDERALL XR®, i.e., dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate. However, the invention is not limited to these salts. Other amphetamines and amphetamine salts can be used in the pharmaceutical compositions of the present invention including, for example, amphetamine base, chemical and chiral derivatives thereof; other amphetamine salts; and mixtures of the foregoing.

The three components comprising the extended release amphetamine composition of the invention release doses of the active ingredients at varying, pre-determined times to provide for full day treatment (i.e., about 14 hours to about 16 hours) of conditions such as ADHD. A treatment for ADHD, which can be delivered in a single dosage is especially beneficial to adolescents and adults who typically have longer daily waking hours compared to children.

The compositions of the present invention comprise an immediate release component, a delayed pulsed release component, and a sustained release component. In embodiments of the invention, delayed pulsed release and/or sustained release can be provided by an enteric coating.

In a particular embodiment, the immediate release component, delayed pulsed release component and sustained release component each contain equal amounts of active ingredient.

In one embodiment, the immediate release, delayed pulsed release and sustained release components of the composition are present on the same core. In another embodiment, the immediate release and delayed pulsed release components are present on different cores. In a further embodiment, the delayed pulsed release and sustained release components are present on different cores. In a preferred embodiment, the immediate release, delayed pulsed release and sustained release components are present on different cores. See **FIG. 3**.

In yet another embodiment, the amphetamine salt is coated onto a core. In a further embodiment, the amphetamine salt is incorporated into a core.

It is contemplated that compositions of the present invention can include a combination of the hereinabove referred to cores (one or more cores that include three components on the same core, one or more cores that include two of the three components on the core, and one or more cores that include one of the three components on the core).

In an embodiment of the present invention, a pharmaceutical composition is provided in which there is immediate release of drug, a delayed pulsed release of drug, and a sustained release of drug, and wherein the drug includes one or more amphetamine salts and mixtures thereof. In a preferred embodiment, the delayed pulsed release of drug begins about one hour after oral administration of the composition to a patient in the fasted state and the sustained release of drug begins about four hours to about six hours after oral administration to a patient in the fasted state.

Surprisingly, amphetamine salt pharmaceutical compositions of the present invention deliver about bioequivalent drug levels to a patient in either a fasted state or fed state. Thus, an amphetamine salt composition according to the present invention does not exhibit a food effect. This is surprising because it would be expected that some of the drug delivered by delayed release would be released earlier in the presence of food (especially fatty food) due to the increase in gastric pH that accompanies the ingestion of food.

A pharmaceutical composition according to the present invention includes:

(a) an immediate release bead comprising an amphetamine salt;

(b) a first delayed release bead comprising an amphetamine salt; and

(c) a second delayed release bead comprising an amphetamine salt;

wherein the first delayed release bead provides pulsed release of the mixed amphetamine salt and the second delayed release bead provides sustained release of the mixed amphetamine salt.

A pharmaceutical composition of the present invention provides a patient with at least about 14 hours to about 16 hours of effective therapy for Attention Deficit Hyperactivity Disorder (ADHD).

In an embodiment of the invention, the *d*-amphetamine C_{max} after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient is about 50 ng/ml.

In another embodiment, the *d*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient is about 1058 ng·hr/ml.

Further, according to an embodiment of the present invention, the *d*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient is about 1085 ng·hr/ml.

In an embodiment, the present invention provides a pharmaceutical composition, wherein the *d*-amphetamine T_{max} is about 8.2 hours after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient.

In a particular embodiment, the *l*-amphetamine C_{max} after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient is about 15 ng/ml.

In a further embodiment, the *l*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient is about 354 ng·hr/ml.

In another embodiment, the *l*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient is about 373 ng·hr/ml.

Further, in an embodiment of the present invention, the *l*-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg amphetamine pharmaceutical composition to a human patient.

In a further embodiment, a protective layer is provided over at least one enteric coating. In another embodiment, a protective layer is provided between the amphetamine salt and at least

one enteric coating. A protective layer can also be provided over the sustained release coating according to the present invention.

In a particular embodiment, the amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

In a more particular embodiment, the amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

In an aspect of the present invention, the pharmaceutical composition does not exhibit a food effect.

The present invention encompasses methods for treating ADHD, which comprise administering the amphetamine salt pharmaceutical composition of the present invention to a patient suffering from ADHD.

The delayed pulsed release and sustained release components retard or delay the release of the pharmaceutically active ingredient(s) for a specified time period ("lag time") until a predetermined time. For example, a delayed pulsed release component having an enteric coating layer retards or delays the release of the pharmaceutical active or drug for a lag time, then releases the drug rapidly and completely, i.e., a pulsed release. In one embodiment of a delayed pulsed release, the entire dose is released within about 30-60 minutes following a lag time after administration of the composition. In another example, a sustained release component having an enteric release coating retards or delays the release of the pharmaceutical active or drug for a lag time and then the release of the drug is sustained (i.e., release of the entire dose takes greater than about 60 minutes).

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 can alter the pH of the GI tract.

According to the present invention, the lag time for the delayed pulsed release component can be pH dependent or pH independent. In an embodiment of the invention, the lag time for the delayed pulsed release component is only time-dependent, i.e., pH independent. In a preferred embodiment, the lag time is pH dependent.

According to the present invention, a lag time can be about 1 hour to about 14 hours. Multiple dose formulations can have more than one lag time. In a preferred embodiment, the delayed pulsed release component has a lag time of about 60 minutes and the sustained release component has a lag time of about 4 to about 6 hours.

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 delayed pulsed release of an amphetamine salt, applicants found that use of an enteric release coating as generally practiced in the art did not provide the desired release profile. Using the typical amount of enteric coating (10 to 15 wt %) for the delayed pulsed release component resulted in undesired premature leakage of the drug from the delivery system into the upper gastrointestinal tract, and drug delivery at the desired, more distal location in the gastrointestinal tract was reduced. Thus, this coating did not meet the requirements for a drug release profile, which provides full beneficial therapeutic activity at the desired time.

Applicants found that using a thicker application of enteric coating on the delayed pulsed release component allowed for the delayed release 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 enteric coating thickness above a minimum thickness of about 5 to 10 wt % typically does not have a significant effect on release of drug from within such coatings. Typically, application of a thicker coating (greater than 15 wt %) will only marginally increase the time i.e., for a brief period of time (about 20 minutes) for complete release at the appropriate environmental condition (e.g., the appropriate pH for a pH dependent coating) or appropriate time after ingestion (e.g., when a pH independent coating is used). Using the typical coating, applicants could not achieve the desired delayed pulsed release -- 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, i.e., a coating weight percent of about 24 to about 30 wt %.

In one embodiment of the invention, the pulsed dose delivery comprises a multi-layered composition which comprises (1) one or more amphetamine salts; (2) an enteric coating over the one or more amphetamine salts; (3) a sustained release coating over the enteric coating; (4) a second application (e.g., a layer) of amphetamine salts over the sustained release coating; (5) a second enteric coating over the one or more pharmaceutically active amphetamine salts; (6) a third application (e.g., layer) of one or more amphetamine salts over the second enteric coating layer; and an immediate release layer coating.

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

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

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

In one aspect of the invention, 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 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 further 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 ingrdient 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 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 amphetamine salts.

Compositions of the present invention encompass mixed amphetamine salt dosages of about 10 mg to about 100 mg. In an embodiment of the present invention, the pharmaceutical composition comprises a mixed amphetamine salt dosage of about 12.5 mg. In further embodiments of the present invention, the pharmaceutical composition comprises a mixed amphetamine salt dosage of about 18.75 mg, about 25 mg, about 31.25 mg, about 37.5 mg, about 43.75 mg, about 50 mg, about 62.5 mg, and about 75 mg. Dissolution profiles for 12.5 mg, 25 mg, 37.5 mg and 50 mg compositions of the invention are provided in **FIGS. 4-7**, respectively.

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. In a specific embodiment of the present invention, the drug delivery system comprises three beads or beadlets in a dosage form, either capsule, tablet, sachet or other method of orally administering the beads. In a preferred embodiment, the immediate release beads, the delayed pulsed release beads, and the sustained release beads are present in the composition in an about 1:1:1 ratio.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 , is a graph showing the dissolution profiles for a typical sustained release formulation (PD0149-124) and a sustained release formulation of the present invention (PD0149-120). HFS is the formulation exemplified in Example 2, *infra*; HIR is the formulation exemplified in Example 1, *infra;* and FS is EUDRAGIT® FS30 D.

FIGURE 2 illustrates the construction of the sustained release bead.

FIGURE 3 illustrates a 3-bead controlled dose drug delivery system of the present invention, including an immediate release component (IR bead), a delayed pulsed release component (DR1 bead) and a sustained release component (DR2 bead).

FIGURE 4 is a graph showing the dissolution profile of a 12.5 mg mixed amphetamine salt 3-bead composition according to the invention.

FIGURE 5 is a graph showing the dissolution profile of a 25 mg mixed amphetamine salt 3-bead composition according to the invention. The following pH conditions were used: at 0-2 hours, pH 1.1; at 2-3 hours, pH 6.0; at three hours and greater, pH 7.5.

FIGURE 6 is a graph showing the dissolution profile of a 37.5 mg mixed amphetamine salt 3-bead composition according to the invention. The following pH conditions were used: at 0-2 hours, pH 1.1; at 2-3 hours, pH 6.0; at three hours and greater, pH 7.5.

FIGURE 7 is a graph showing the dissolution profile of a 50 mg mixed amphetamine salt 3-bead composition according to the invention. The following pH conditions were used: at 0-2 hours, pH 1.1; at 2-3 hours, pH 6.0; at three hours and greater, pH 7.5.

FIGURE 8 is a graph showing the dissolution profile of a SPD465 sustained release bead (HDR2). The following pH conditions were used: at 0-2 hours, pH 1.1; at 2-3 hours, pH 6.0; at three hours and greater, pH 7.5.

FIGURE 9 graphically illustrates the mean d-amphetamine plasma concentration of SPD465 37.5 mg compared to ADDERALL XR® 25 mg followed by immediate release mixed amphetamine salts 12.5 mg 8 hours later.

FIGURE 10 graphically illustrates the mean l-amphetamine plasma concentration of SPD465 37.5 mg compared to ADDERALL XR® 25 mg followed by immediate release mixed amphetamine salts 12.5 mg 8 hours later.

FIGURE 11 graphically illustrates mean d-amphetamine plasma concentrations over time following administration of a single dose and seven once-daily doses of 12.5 mg SPD465 to healthy subjects.

FIGURE 12 graphically illustrates mean d-amphetamine plasma concentrations over time following administration of seven once-daily doses of SPD465 to healthy subjects.

FIGURE 13 graphically illustrates the power model analysis of mean and individual Day 7 Cmax values for d-amphetamine by dose.

FIGURE 14 graphically illustrates the power model analysis of mean and individual Day 7 AUC_{0-24} values for d-amphetamine by dose.

FIGURE 15 graphically illustrates mean l-amphetamine plasma concentrations over time following administration of a single dose and seven once-daily doses of 12.5 mg SPD465 to healthy subjects.

FIGURE 16 graphically illustrates mean d-amphetamine plasma concentrations over time following administration of seven once-daily doses of SPD465 to healthy subjects.

FIGURE 17 graphically illustrates the power model analysis of mean and individual Day 7 Cmax values for l-amphetamine by dose.

FIGURE 18 graphically illustrates the power model analysis of mean and individual Day 7 AUC_{0-24} values for l-amphetamine by dose.

DETAILED DESCRIPTION OF THE INVENTION

Various types of controlled drug release and release profiles are contemplated by the present invention.

The terms "bead" and "pellet" refer to a discrete component of a dosage form. For example, a capsule shell is filled with a plurality of beads or pellets. As used herein, bead and pellet encompass any discrete component of a dosage form.

"Immediate" and "delayed" release" refer to the onset of release in relationship to administration of the drug. "Immediate" means that the release of drug begins very soon, within a relatively short time after administration, e.g. a few minutes or less. "Delayed" means that the release of drug is postponed, and begins or is triggered some period of time after administration (e.g., the lag time), typically a relatively long period of time, e.g. more than one hour.

"Rapid" and "slow" release refer to the rate of release after onset. Once delivery of the drug begins, it may be released relatively quickly or relatively slowly. A rapid release indicates that, after onset, a maximum or peak dose is reached in a relatively short period of time. A slow release indicates that, after onset, a maximum or peak dose is reached in a relatively long period of time. Once reached, the maximum dose may fall off at any pace (e.g. fast, slow, or constant).

"Sustained" or "continuous" refers to the period of on-going release, and means that the delivery of drug goes on (it continues or is sustained) for an extended period of time after initial onset, typically more than one hour, whatever the shape of the dose release profile. For example, the drug release is sustained between a maximum and minimum value (more than zero) for some relatively long period of time. This release may be at a constant dose, or at a dose which diminishes over time.

"Constant" release refers to the dose that is being released, and means that a drug is delivered at a relatively constant dose over a moderate or extended period of time. This can be represented by a dose release profile that is relatively flat or only gently sloped after initial onset, i.e. without highly distinct peaks and valleys. Thus, a constant release will typically be sustained or continuous, but a sustained or continuous release may not be constant.

"Pulsed" release means that a drug is delivered in one or more doses that fluctuate between a maximum and minimum dose over a period of time. This can be represented by a dose release profile having one or more distinct peaks or valleys. However, two or more pulsed

releases may produce an overlapping, overall, or composite release profile that appears or effectively is constant. When two or more pulsed releases occur, there may or may not be a period of no release between pulses. Typically, pulsed release results in release of essentially all of a drug within about 60 minutes or less.

"Extended" release refers to a formulation which provides either a release of drug within a targeted dose range for a relatively long period, or a plasma level of drug within a targeted dose range for a relatively long period, without regard for the particular mechanism or character of release, e.g. as sustained, pulsed, or constant.

"Effective therapy" or "effective treatment," as used herein, means to prevent, alleviate, arrest, or inhibit at least one symptom or sign of ADHD. Symptoms and signs of ADHD include, for example, inattention, hyperactivity and impulsivity.

"Food effect," as used herein, means a significant difference in the bioavailability of a drug in a patient when the drug is administered in a fasted state compared to a fed state. "No food effect" means that there is no significant difference in the bioavailability of a drug in a patient when the drug is administered in a fasted state compared to a fed state.

The term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system, *i.e.*, the degree of precision required for a particular purpose, such as a pharmaceutical formulation. For example, "about" can mean within 1 or more than 1 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

Drug release and drug release profiles are measures or representations of the manner and timing by which a formulation releases or delivers active ingredients (drug) to a receiving environment (e.g. the stomach, intestines, etc.) upon administration. Various methods are known for evaluating drug release and producing release profiles, including *in vitro* tests which model the *in vivo* behavior of a formulation. These include USP dissolution testing for immediate release and controlled release solid dosage forms.

Drug release profiles are distinct from plasma profiles. A plasma profile is a measure or representation of the dose or level of active ingredient (drug) in the bloodstream of a mammal, e.g. a patient receiving a drug formulation. Upon release of a drug from a formulation, e.g. into the gut of a mammal, the amount of drug that is present in the bloodstream over time can be determined.

A drug release profile may be designed to produce a desired or targeted plasma profile. Often, but not necessarily, a plasma profile will mimic a release profile. For example, it might be expected that a sustained release of drug would more likely produce a sustained dose in the plasma, or that a pulsed release would produce a pulsed (peak and valley) plasma profile. This is not necessarily so, however. For example, the half-life of the drug in the blood stream (its rate of decay) may be such that a sustained or continuous plasma profile could result from a pulsed delivery profile. Other factors may also play a role, such as bio-absorption, bioavailability, and first pass effect. The plasma profile produced by a particular release profile may also vary from patient to patient.

Measures of bioavailability well known in the art include the area under the plasma concentration-time curve (AUC), the concentration maximum (C_{max}), and the time to C_{max} (T_{max}).

AUC is a measurement of the area under the plasma concentration-time curve, and is representative of the amount of drug absorbed following administration of a single dose of a drug (Remington: The Science and Practice of Pharmacy, (Alfonso R. Gennaro ed. 2000), page 999).

C_{max} is the maximum plasma concentration achieved after oral drug administration (Remington, page 999). An oral drug administration results in one C_{max}, but may result in greater than one "peak plasma concentration" or "plasma concentration peak" (for example, following the administration of a pulsed dose formulation).

T_{max} is the amount of time necessary to achieve the C_{max} after oral drug administration, and is related to the rate of absorption of a drug (Remington, page 999).

Bioequivalence is the absence of a significantly different rate and extent of absorption in the availability of the active ingredient when administered at the same dose under similar conditions. Bioequivalence can be measured by pharmacokinetic parameters such as, for example, AUC and Cmax.

A drug delivery system of the invention typically may comprise a core seed or matrix, which may or may not be loaded with drug, and one or more coating layers comprising drug, and/or comprising a layer have release characteristics which control the onset and release characteristics of the drug. An exemplary core is a sugar core. Exemplary matrixes include hydrophilic matrixes. Polymers useful for forming a hydrophilic matrix include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), poly(ethylene oxide), poly(vinyl alcohol), xanthan gum, carbomer, carrageenan, and zooglan. Other similar hydrophilic polymers may also be employed.

Coating layers can provide immediate release, delayed pulsed release or sustained release. Immediate release of the drug from the immediate-release layer can be achieved by any of various methods known in the art. One example is the use of a very thin layer or coating which by virtue of its thinness is quickly penetrated by gastric fluid allowing rapid leaching of the drug. Another example is by incorporating the drug in a mixture that includes a supporting binder or other inert material that dissolves readily in gastric fluid, releasing the drug as the material dissolves. A third is the use of a supporting binder or other inert material that rapidly disintegrates upon contact with gastric fluid, with both the material and the drug quickly dispersing into the fluid as small particles. Examples of materials that rapidly disintegrate and disperse are lactose and microcrystalline cellulose. An example of a suspending agent and binder is hydroxypropyl methylcellulose.

Enteric coatings for the delayed pulsed release component can be pH-dependent or pH-independent. Enteric coatings for the sustained release component are pH dependent. A pH dependent coating is activated to release drug within a known pH range, which typically is matched to the local pH of the environment where delayed release is desired. Exemplary pH dependent coatings 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).

A pH independent coating includes materials susceptible to enzymatic activation by azo-reductases in intestinal bacteria (i.e., azo-polymers) or materials susceptible to degradation by polysaccaridases in the colon (natural polysaccarides). Non-limiting examples of azo-polymers include co-polymers of 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA). Non-limiting examples of natural polysaccharides include amylose, chitosan, chrondoitin, dextran, and xylan.

The sustained release component can include sustained release coatings, sustained release matrices, and sustained release osmotic systems. Sustained release coatings can be prepared using a water-insoluble polymer, a combination of water-insoluble polymers, or a combination water-insoluble and water-soluble polymers. Conventional sustained release polymers well known to those of ordinary skill in the formulary arts can be used for the sustained release matrix.

Exemplary sustained release coatings can include polyvinyl acetate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, fatty acids and esters thereof, alkyl alcohols, waxes, zein (prolamine from corn), and aqueous polymeric dispersions such as EUDRAGIT® RS and RL30D, EUDRAGIT® NE30D, AQUACOAT®, SURELEASE®, KOLLICOAT® SR30D, and cellulose acetate latex.

Principles of sustained release formulation technology applicable to this invention, include those disclosed in R.K. Chang and J.R. Robinson, chapter 4: "Sustained Drug Release from Tablets and Particles Through Coating," in Pharmaceutical Dosage Forms: Tablets, volume 3, edited by H.A. Lieberman, L. Lachman, and J.B. Schwartz, Marcel Dekker, Inc., 1991; R.J. Campbell and G.L. Sackett, chapter 3: "Film coating," in Pharmaceutical Unit Operations: Coating, edited by K.E. Avis, A.J. Shukla, and R.K. Chang, Interpharm Press, Inc., 1999.

The present invention comprises a core or starting seed, either a 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. Pharmaceutically active amphetamine salts contemplated to be within the scope of the present invention include amphetamine base and salts thereof. Preferred pharmaceutically active amphetamine salts include dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.

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 delayed pulsed or sustained release layer is coated thereupon. Another active layer may also be added to the enteric delayed pulsed or sustained 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 delayed pulsed release or sustained release 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. Suitable coaters are well known in the art. For example, any commercially available pH-sensitive polymer can be used. With such a polymer, the

pharmaceutical active is not released in the acidic stomach environment of approximately below pH 4.5, but is 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.

Suitable enteric polymers for the delayed pulsed release component and sustained release component include, for example, 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 delayed pulsed release and sustained release 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 delayed pulsed release or sustained release 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. Coatings commonly known to one skilled in the art can be used for this purpose and applied by conventional 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). Talc can also be used for this purpose, e.g., a 2% w/w talc treatment can be applied.

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 can 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 can be added to assure proper tableting, and these can include, but are not limited to: magnesium stearate, calcium stearate, stearic acid, polyethylene glycol, leucine, glyceryl behenate, 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.

A tablet according to the present invention can be constructed in three layers, wherein the immediate release component is dry blended, and the delayed pulsed release and the sustained release components are wet granulated. The tablet is then formed in a one layer or a three layer compression. Upon dissolution of the layers in the one layer or three layer tablet, each component is released and acts in its own way (i.e., the immediate release particles provide immediate release, the delayed pulsed release particles provide delayed pulsed release, and the sustained release particles provide sustained release after a lag time).

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 14 hours to about 16 hours with a single oral administration.

This invention also encompasses the use of a longer-day amphetamine composition to treat conditions other than ADHD. These conditions include, but are not limited to, Alzheimer's disease and other memory disorders, fibromyalgia, chronic fatigue, depression, obsessive

compulsive disorder, alone or in combination with a SSRI; oppositional defiant disorder (ODD), with or without ADHD and with or without any compositions or formulations of guanfacine or buproprion; anxiety, with or without ADHD and alone or in combination with an anxiolytic or SSRI; resistant depression; stroke rehabilitation; Parkinson's disease; mood disorder; schizophrenia; Huntington's disorder; dementia, e.g. AIDS dementia and frontal lobe dementia; movement dysfunction; apathy; fatigue; Pick's disease; sleep disorders, e.g., narcolepsy, cataplexy, sleep paralysis and hypnagogic hallucinations; etc.

The invention also contemplates combinations of the longer-day amphetamine compositions of this invention with other therapeutic agents. The drugs can be formulated in the same dosage form as the longer-day amphetamine composition dose of the invention or can be formulated separately, in which case, the drugs can be administered sequentially in any order or simultaneously. Typically, dosages can be in the same ranges as for each drug used separately or, where synergistic effects occur, one or more of the combined drugs can be used in lower dosages.

The other therapeutic agents can include e.g., for Alzheimer's: galanthamine, tacrine, donepezil, rivastigmine, memantine, human growth hormone, selegiline hydrochoride, estrogen, clioquinol, ibuprofen, and Gingko bilboa; for ADHD: methylphenidate (e.g., RITALIN®, CONCERTA®), amphetamine, pemoline, clonidine, guanfacine, etc; for depression: fluoxetine hydrochloride, sertraline HCL, paroxetine HCL, reboxetine, bupropion HCL, olanzapine, fluoxetine hydrochloride, amitriptyline, imipramine, nortriptyline, phenelzine, tranylcypromine sulfate, trazodone, and venlafaxine; for mood disorder: thorazine, haloperidol, thiothixene, thioridazine, risperadone, clozapine, risperidone, and olanzapine; for fatigue: benzodiazepines, naproxen, fluoxetine hydrochloride, sertraline HCL, paroxetine HCL, venlafaxine, and trazodone; for fibromyalgia: phenytoin, carbamazepine, valproate, divalproex, desipramine, nortriptyline, amitryptiline, doxepin, and non-steroidal inflammatory drugs; for oppositional defiant disorder (ODD): clonidine, risperidone, and olanzepine; for apathy: amisulpride, olanzapine, visperidone, quetiapine, clozapine, and zotepine; for Parkinson's disease: levodopa, bromocriptine, pergolide, and pramipexole; for schizophrenia: clozapine, olanzepine, quetiapine fumarate, and risperidone; for Huntington's disorder: haloperidol and clonzepam; for dementia: thioridazine, haloperidol, risperidone, tacrine, donepezil, and rivastigmine; for narcolepsy:

modafinil, amphetamine, modafinil and RITALIN®; for cataplexy: sodium oxybate; for hallucinations: clozapine, risperidone, olanzepine, and quetiapine fumarate; for sleep paralysis: PEROCET®, VICODIN®, and LORCET®; for obsessive compulsive disorder: clomipramine, fluoxetine hydrochloride, sertraline HCL, paroxetine HCL, fluvoxamine; and for anxiety: amitryptiline, amoxepine, bupropion HCL, carbamazepine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, VENTYL®, trimipramine etc; selective serotonin reuptake inhibitors (SSRIs) including fluoxetine hydrochloride, fluvoxamine, nefazodone, paroxetine HCL, sertraline HCL venlafaxine, etc., benzodiazepines, including alprazolam, chlordiazepoxide, clonazepam, diazepam, flurazepam, lorazepam, oxazepam, triazolam, etc., monamine oxidase inhibitors including moclobemide, phenelzine, tranylcypromine sulfate, etc.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

The following examples are presented for illustration and do not limit the invention.

EXAMPLES

Example 1

Immediate Release Formulation (HIR)

Sugar sphere seeds (30/35 Mesh, NF) were put into a FLM-15 fluid bed processor with a 9-Wurster column and fluidized at 60°C. A suspension of a mixture containing amphetamine aspartate; amphetamine sulfate, USP; dextroamphetamine saccharate; and dextroamphetamine sulfate, USP with Hypromellose 2910, USP/NF as a binder was sprayed onto the seeds under suitable conditions. After drying, an OPADRY® Beige, YS-1-17274-A seal coating was applied. The ingredients are listed by weight percent in Table 1.

TABLE 1

Ingredient	Weight %
Amphetamine aspartate	4.75

Amphetamine sulfate, USP	4.75
Dextroamphetamine saccharate	4.75
Dextroamphetamine sulfate, USP/NF	4.75
Sugar sphere 30/35 mesh, USP/NF	78.00
OPADRY® Beige, YS-1-17274-A	2.00
Hypromellose 2910, USP/NF	1.00
Purified water, USP	*
	Total 100.00

* removed during processing

Example 2

Intermediate Formulation (HFS)

The following formulation was used to coat the immediate release mixed amphetamine salt pellets from Example 1 with EUDRAGIT® FS30D (also referred to herein as EUDRAGIT® 4110D) (Rohm Pharma, Germany) coating dispersion. The immediate release pellets of Example 1 were loaded in a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by dispersing triethyl citrate, USP/NF; talc, USP/NF and EUDRAGIT® FS30D into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized mixed amphetamine salt pellets. The spraying was continued until the targeted coating level of 25-30 weight percent (wt %) was achieved. The coated pellets were dried at 30-35° C. for 5 minutes before stopping the process. After drying, the pellets were coated with OPADRY® Beige, YS-1-17274-A. The ingredients are listed by weight percent in Table 2.

TABLE 2

Ingredients	Weight (%)
Immediate release pellets (Example 1)	65.50
MAA/MA/MMA Copolymer Suspension (EUDRAGIT® FS30 D)*	27.77

Triethyl citrate, USP/NF	1.35
Talc, USP/NF	3.38
OPADRY® Beige, YS-1-17274-A	2.00
Water	**
	Total 100.00

*MAA/MA/MMA Copolymer Suspension is Methyl Acrylate, MethylMethacrylate, and Methacrylic Acid Copolymer (EUDRAGIT® FS30D)

** removed during processing

Example 3

Delayed Release Formulation (HDR)

The following formulation was used to coat the immediate release mixed amphetamine salt pellets from Example 1 with EUDRAGIT® L30 D-55 coating dispersion. The immediate release pellets of Example 1 were loaded in a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by dispersing Triethyl citrate, USP/NF; Talc, USP/NF and EUDRAGIT® L30D-55 into water and mixing for at least 30 minutes. Under suitable fluidization conditions, the coating dispersion was sprayed onto the fluidized mixed amphetamine salt pellets. The spraying was continued until the targeted coating level of 27-32 weight percent was achieved. The coated pellets were dried at 30-35° C. for 5 minutes before stopping the process. After drying, the pellets were coated with OPADRY® Beige, YS-1-17274-A. The ingredients are listed by weight percent in Table 3.

TABLE 3

Ingredients	Weight (%)
Immediate release pellets (Example 1)	63.00
Methacrylic Acid Copolymer Dispersion, USP/NF (EUDRAGIT® L30 D-55)*	29.03
Triethyl citrate, USP/NF	2.94

Talc, USP/NF	3.04
OPADRY® Beige, YS-1-17274-A	2.00
Water	**
	Total 100.01

*Methacrylic Acid Copolymer Dispersion, USP/NF (EUDRAGIT® L30 D-55) is supplied as a 30% aqueous dispersion.

** removed during processing

Example 4

Sustained Release Formulation (HDR2)

Intermediate formulation pellets from Example 2 were loaded into a fluid bed processor with a reduced Wurster column (GPGC-15, Glatt). The coating dispersion was prepared by mixing SURELEASE®, talc, USP/NF 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 of 7-9 weight percent of SURELEASE® solids was achieved. The coated pellets were then dried at 35-40° C. for 10 minutes before discharging from the bed. The ingredients are listed by weight percent in **Table 4**. The dissolution profile for the HDR2 sustained release bead is shown in **FIG. 8**.

TABLE 4

Ingredients	Weight (%)
Intermediate formulation (Example 2)	90.00
Talc, USP/NF	2.00
SURELEASE® Clear E-7-19010*	8.00
Water	**
	Total 100.00

*SURELEASE® Clear E-7-19010 is supplied as a 24.5% solids aqueous dispersion

** removed during processing

A 12.5 mg mixed amphetamine salt sustained release bead (lot no. B02013) produced according to this Example was administered to 12 subjects aged 18-55 years old and compared to ADDERALL® 10 mg in a crossover study (Clinical Study 101). Two other prototype beads were also tested. A parametric (normal theory) general linear model was applied to the calculation of AUC, Cmax, Tmax and $t_{1/2}$ for each of the formulations. AUC and Cmax were also analyzed on a log scale to assess bioequivalence between test treatments. The results for the sustained release bead and the reference ADDERALL® are shown in Table 5.

TABLE 5

d-amphetamine				
	AUC (0-inf) (ng.hr/mL)	AUC (0-t) (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)
12.5 mg mixed amphetamine salt sustained release bead	367.19*	353.64*	18.67	8.83*
10 mg ADDERALL® (reference)	280.59	266.70	18.62	2.17
ratio of test to reference (90% CI)	1.03 (0.97-1.11)**	1.05 (0.98-1.12)**	0.80 (0.76-0.84)	
l-amphetamine				
12.5 mg mixed amphetamine salt sustained release bead	125.23*	112.44*	5.64	9.33*
10 mg ADDERALL® (reference)	100.64	87.93	5.53	2.50
ratio of test to reference (90% CI)	0.99 (0.91-1.08)**	1.02 (0.93-1.11)**	0.81 (0.76-0.87)	

*$p<0.05$ compared to 10 mg ADDERALL®
**90% confidence interval fell within recommended 0.80-1.25 limits of bioequivalence when analyzed on logarithmic scale.

The results of this pharmacokinetic study showed that a single dose of the sustained release formulation had a Tmax significantly longer than a single dose of ADDERALL®.

Additionally, the AUCs of the sustained release formulation were equivalent to that of dose-adjusted ADDERALL® for both d- and l- amphetamine.

Example 5

Controlled Release Capsules (SPD465 25 mg/capsule)

A controlled release capsule was produced by combining the immediate release pellets of Example 1, and delayed release pellets of Example 3 and Example 4. The theoretical milligram/capsule of components for controlled release capsules, 25 mg/capsule are listed in Table 5. The theoretical potency of each pellet type was derived based on the starting ingredients for manufacture. Based on the actual manufacturing process, along with observation of process losses, the target potency value was: 170 mg/gram for Example 1 immediate release pellets, 107.1 mg/gram for Example 3 delayed release pellets, and 100.2 mg/gram for Example 4 delayed release pellets. The components are listed by theoretical milligrams/capsule in Table 6.

TABLE 6

Components	Theoretical milligram/capsule
Immediate release pellets of Example 1*	43.86
Delayed release pellets of Example 3**	69.62
Delayed release pellets of Example 4***	74.40
Capsule shell	61.00
Total	248.88

*The theoretical fill weight was calculated based on the theoretical potency of Example 1 immediate release pellets, 190 mg/gram.

** The theoretical fill weight was calculated based on the theoretical potency of Example 3 delayed release pellets, 119.7 mg/gram.

*** The theoretical fill weight was calculated based on the theoretical potency of Example 4 delayed release pellets, 112.0 mg/gram.

The dissolution profile for SPD465 25 mg (lot no. A03547A) is shown in **FIG. 5**.

Example 6

Controlled Release Capsules (SPD465 37.5 mg/capsule)

A controlled release capsule was produced by combining the immediate release pellets of Example 1, and the delayed release pellets of Example 3 and Example 4. The theoretical milligram/capsule of components for controlled release capsules, 37.5 mg/capsule are listed in Table 7. The theoretical potency of each pellet type was derived based on the starting ingredients for manufacture. Based on the actual manufacturing process, along with observation of process losses, the target potency value was: 170 mg/gram for Example 1 immediate release pellets, 107.1 mg/gram for Example 3 delayed release pellets, and 100.2 mg/gram for Example 4 delayed release pellets. The components are listed by theoretical milligrams/capsule in Table 7.

TABLE 7

Components	Theoretical milligram/capsule
Immediate release pellets of Example 1*	65.79
Delayed release pellets of Example 3**	104.43
Delayed release pellets of Example 4***	111.6
Capsule shell	81.00
Total	362.82

*The theoretical fill weight was calculated based on the theoretical potency of Example 1 immediate release pellets, 190 mg/gram.

** The theoretical fill weight was calculated based on the theoretical potency of Example 3 delayed release pellets, 119.7 mg/gram.

*** The theoretical fill weight was calculated based on the theoretical potency of Example 4 delayed release pellets, 112.0 mg/gram.

The dissolution profile for SPD465 37.5 mg (lot no. A03549B) is shown in **FIG. 6**.

Example 7

Controlled Release Capsules (SPD465 50 mg/capsule)

A controlled release capsule was produced by combining the immediate release pellets of Example 1, and delayed release pellets of Example 3 and Example 4. The theoretical

milligram/capsule of components for controlled release capsules, 50 mg/capsule are listed in Table 8. The theoretical potency of each pellet type was derived based on the starting ingredients for manufacture. Based on the actual manufacturing process, along with observation of process losses, the target potency value was: 170 mg/gram for Example 1 immediate release pellets, 107.1 mg/gram for Example 3 delayed release pellets, and 100.2 mg/gram for Example 4 delayed release pellets. The components are listed by theoretical milligrams/capsule in Table 8.

TABLE 8

Components	Theoretical milligram/capsule
Immediate release pellets of Example 1*	87.72
Delayed release pellets of Example 3**	139.24
Delayed release pellets of Example 4***	148.80
Capsule shell	96.00
Total	471.76

*The theoretical fill weight was calculated based on the theoretical potency of Example 1 immediate release pellets, 190 mg/gram.

** The theoretical fill weight was calculated based on the theoretical potency of Example 3 delayed release pellets, 119.7 mg/gram.

*** The theoretical fill weight was calculated based on the theoretical potency of Example 4 delayed release pellets, 112.0 mg/gram.

The dissolution profile for SPD465 50 mg (lot no. A03536B) is shown in **FIG. 7**.

Example 8

A Phase I Pharmacokinetic Study in Healthy Adult Volunteers to Evaluate the Pharmacokinetic Profile of the 37.5 mg Controlled Release Composition of Example 6 Relative to 25 mg ADDERALL XR® + 12.5 mg Mixed Amphetamine Salts IR (Clinical Study 103)

The objective of this study was to assess the pharmacokinetics (PK) of the 37.5 mg controlled release composition of Example 6 compared to a reference treatment of ADDERALL XR® 25 mg followed by a 12.5 mg dose of the mixed amphetamine salts immediate-release (IR) formulation disclosed in Example 1 administered 8 hours later.

This was an open-label, randomized, single-dose, 2-way crossover, 2-period, phase I study with at least a 7-day washout between each period. In period 1, subjects were randomized to receive a single morning dose of one of the two study formulations. Each subject was crossed over to receive the alternate treatment in the subsequent period. In Treatment A, subjects received a single 37.5 mg dose of the controlled release composition of Example 6. In Treatment B, subjects received a single 25 mg dose of ADDERALL XR® followed by a 12.5 mg dose of the mixed amphetamine salts immediate release formulation of Example 1 administered 8 hours later. See **Table 9**.

TABLE 9

Treatment	Composition	Dose	Route of Administration
A	Composition of Example 6 (Batch no. A03383-002L)	1 x 37.5 mg	Oral
B	ADDERALL XR® and the immediate release bead of Example 1	1 x 25 mg ADDERALL XR® (Batch no. A02936B) followed 8 hours later by 1 x 12.5 mg bead of Example 1 (Batch no. A03383-003L)	Oral

At screening, each subject provided a medical and medication history. A 12-lead electrocardiogram (ECG), vital signs, height, and weight were obtained. Blood and urine samples were collected for routine clinical laboratory analysis, antibody screening for Human Immunodeficiency Virus (HIV), Hepatitis B and C, and urine alcohol and drug screen. A serum pregnancy test was conducted on all women of child-bearing potential (WOCP) during screening.

For each treatment period, subjects reported to the clinic the morning prior to dosing at which time continued eligibility was confirmed by urine alcohol and drug screen, urine pregnancy test for WOCP, weight, routine clinical laboratory analysis, 12-lead ECGs, and vital signs. Subjects also underwent a physical examination, and a brief medical and medication history was completed.

Blood samples for the determination of plasma *d*- and *l*-amphetamine concentrations were collected at specified times in each treatment period. Vital sign measurements were obtained prior to dosing and at 2, 4, 8, 12, 24, and 60 hours post-dose. Adverse events (AEs) and concomitant medications were reported throughout each treatment period. Twelve-lead ECG measurements were collected prior to dosing and at 2, 4, 8, 12, 24, and 60 hours post-dose.

Exit assessments at the end of each treatment period included a physical examination, 12-lead ECG, routine clinical laboratory measurements, vital signs, and AE assessment. A serum pregnancy test for WOCP was performed at study exit/withdrawal. A follow-up telephone call to assess AEs was made to all subjects 30±2 days after last exposure to study medication.

Duration of study: 11 days (two treatment periods, each with four days of confinement and a 7-day washout period between study medication dosing).

Pharmacokinetics: *d*- and *l*-amphetamine concentrations were determined in plasma samples collected at the following times: 30 minutes prior to dosing (Time 0) on Day 1, and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours post-dose for each treatment. Plasma *d*- and *l*-amphetamine concentrations were measured with a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method.

Statistical methods:

Pharmacokinetic parameters were compared between treatment groups using an analysis of variance (ANOVA) with sequence, period, and treatment as fixed effects, and subject nested within sequence as a random effect. This analysis was performed for the natural log transformations of maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to time infinity ($AUC_{(0\text{-inf})}$), and area under the plasma concentration-time curve from time 0 to last measured time ($AUC_{(0\text{-last})}$) using SAS PROC MIXED.

For C_{max}, $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-last})}$, exponentiated least squares (LS) means for each treatment were obtained by taking the antilog of the LS means on the log scale. Ratios of the exponentiated LS means for the test treatment (SPD465 37.5mg) relative to the reference treatment (25mg ADDERALL XR® followed by 12.5mg mixed amphetamine salts IR 8 hours later) and 90% confidence intervals (CIs) of the ratios were provided. The 90% CIs were

obtained by taking the antilog of the 90% CIs for the difference between the LS means on the log scale.

C_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, terminal half-life (t½), terminal phase rate constant (λ_Z), and time of maximum plasma concentration (t_{max}) were summarized descriptively for each treatment.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 7.1 adverse event dictionary. The frequency of treatment-emergent adverse events (TEAE) was tabulated by body system and preferred term for each treatment. AEs were further summarized by severity, relationship to study drug, gender, and ethnicity. AEs leading to study withdrawal were summarized separately by body system, preferred term, and treatment group.

Clinical laboratory evaluations were summarized by treatment and visit. Hematology and biochemistry were summarized using descriptive statistics; discrete urinalysis measurements were summarized using frequencies and percents and continuous urinalysis measurements were summarized using descriptive statistics. Laboratory data outside the normal range was flagged in the subject data listings.

Vital signs, including pulse, systolic and diastolic BP, and respiration rate, were summarized by treatment for each measured time point using descriptive statistics. Change from baseline was also calculated and summarized for each post baseline time point.

Results:

Subject demographics**:** The overall gender distribution was 60% (12/20) females and 40% (8/20) males. The overall racial distribution was 90% (18/20) White and 10% (2/20) Black/African-American. The age of the study subjects ranged from 21-50 years with an overall mean age (SD) of 30.0 years (8.83). Subjects weighed between 61 kg and 97 kg with a mean weight (SD) of 73.8 kg (10.15), and height ranged between 158 cm-188 cm with a mean height (SD) of 172.6 cm (8.05). Body Mass Index ranged between 20.1 kg/m^2-29.2 kg/m^2 with a mean BMI (SD) of 24.75 (2.267).

Pharmacokinetic results:

FIG. 9 shows the d-amphetamine plasma concentration profile of SPD465 37.5 mg compared to ADDERALL XR® (25 mg) followed by immediate release mixed amphetamine salts (12.5 mg) eight hours later. Exposure to *d*-amphetamine, as described by C_{max} and AUC values, was comparable following Treatment A and Treatment B. The 90% CI of the test-to-reference ratios were within the bioequivalence range of 80%-125%.

FIG. 10 shows the l-amphetamine plasma concentration profile of SPD465 37.5 mg compared to ADDERALL XR® (25 mg) followed by immediate release mixed amphetamine salts (12.5 mg) eight hours later. C_{max} and AUC values of *l*-amphetamine following a dose of Treatment A were similar to those following Treatment B; 90% CI of the test-to-reference ratios were within the bioequivalence range of 80%-125%.

The elimination half lives of *d*- and *l*-amphetamine were similar for both treatments. See Table 10.

TABLE 10

Plasma Pharmacokinetic Parameters for *d*- and *l*-Amphetamine After a Single Dose of 37.5 mg SPD465 (Treatment A) or 25 mg ADDERALL XR® + 12.5 mg Mixed Amphetamine Salts (Treatment B)

Parameters	Treatment A			Treatment B			Exponentiated LS Mean Ratio % (A)/(B)	90% CI
	n	Mean (±SD)	LS Mean	n	Mean (±SD)	LS Mean		
d-Amphetamine								
C_{max} (ng/mL)	20	50.3 (7.5)	49.7	19	49.3 (7.4)	49.2	101.0	(96.9, 105.3)
$AUC_{(0\text{-last})}$ (ng·hr/mL)	20	1058.0 (184.5)	1042.4	19	997.9 (172.9)	1000.8	104.2	(100.2, 108.3)
$AUC_{(0\text{-inf})}$ (ng·hr/mL)	20	1084.9 (196.2)	1067.8	19	1019.5 (181.3)	1022.5	104.4	(100.3, 108.7)
T_{max} (hr)	20	8.2 (2.0)		19	9.7(2.1)			
l-Amphetamine								
C_{max}	20	14.7	14.6	19	16.0	16.0	90.9	(87.5, 94.4)

(ng/mL)		(2.2)			(2.3)			
$AUC_{(0\text{-last})}$ (ng·hr/mL)	20	353.5 (66.0)	347.6	19	364.1 (66.5)	364.6	95.3	(91.0, 99.8)
$AUC_{(0\text{-inf})}$ (ng·hr/mL)	20	372.8 (73.5)	365.9	19	382.3 (69.0)	383.9	95.3	(91.2, 99.6)
T_{max} (hr)	20	8.4 (2.1)		19	10.7 (1.3)			

LS=Least squares

Conclusions:

Treatment A and Treatment B were bioequivalent with respect to C_{max} and AUC of *d*- and *l*-amphetamine. All treatments were well tolerated and all reported AEs were expected.

Example 9

A Phase I Study to Evaluate the Pharmacokinetic Profile of SPD 465 50 mg Under Fed, Fasted, and Sprinkled Conditions in Healthy Adult Volunteers (Clinical Study 105)

This was an open-label, randomized, single-dose, 3-way crossover, 3-period study with a minimum 7-day washout between each study drug dosing. Sixteen healthy male and female subjects between the ages of 18 and 55 participated in the study. This study was designed to evaluate (1) the effect of a high fat meal on the PK of SPD465 50 mg compared to a reference treatment and (2) the effect of a SPD465 50 mg capsule sprinkled on applesauce compared to a reference treatment. The reference treatment was a 50 mg dose of SPD465 following an at least 10-hour fast. See Table 11. The primary objective of this study was to assess the effect of a high fat meal on the bioavailability of SPD465 relative to the fasted state.

TABLE 11

Treatment	Study Drug	Dosage
Treatment A (reference)	SPD465 (batch no. A03445-001L)	1 x 50 mg capsule after an at least 10 hour fast
Treatment B	SPD465 (batch no. A03445-001L)	1 x 50 mg capsule following a high fat meal
Treatment C	SPD465 (batch no. A03445-	1 x 50 mg capsule sprinkled on 1

	001L)	tablespoon of applesauce

The study included three single-dose treatment periods separated by a minimum 7-day washout period between study drug dosing. On study day 1 of each period, according to the randomization schedule, the subjects were administered a single dose of SPD465 50 mg following an at least 10-hour fast, SPD465 50 mg following a standard high fat meal or the contents of a SPD465 50 mg capsule sprinkled on applesauce.

Blood samples for the determination of plasma *d*- and *l*- amphetamine concentrations were collected 30 minutes prior to drug administration (0 hour) and at 1 ,2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours after dosing in each treatment period.

Results:

d-amphetamine

d-Amphetamine plasma levels as described by C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were highest in fasted subjects, slightly lower in subjects receiving SPD465 sprinkled on applesauce, and lowest in subjects pretreated with a high-fat meal. See Tables 12 and 13. The 90% CI of the test-to-reference ratios, with fasted as the reference treatment, were within the typically acceptable bioequivalence range of 80% to 125%, which indicates that the there were no significant differences across the unfed/fed conditions. The CIs on the ratios between subjects receiving the high-fat meal and fasted subjects were less than 100%.

The median time to maximum d-amphetamine plasma concentrations (T_{max}) in fasted subjects and those who received SPD465 sprinkled on applesauce was 7 and 7.5 hours, respectively. The T_{max} in subjects who received SPD465 following a high-fat meal was delayed approximately 4 to 5 hours with a median value of 12 hours.

Table 12

d-Amphetamine Plasma Pharmacokinetic Parameters Following a Single Dose Administration of 50 mg SPD465

Parameter	Fasted (A) n = 14	High Fat Meal (B) n = 16	Sprinkled (C) n = 16
C_{max} (ng/ml) Mean (SD)	72.3 (13.72)	60.0 (7.09)	67.3 (7.69)
T_{max} (hr) Median (Min, Max)	7.0 (6.0, 10.0)	12.0 (8.0, 14.0)	7.5 (5.0, 9.0)

$AUC_{(0\text{-}last)}$ (hr*ng/ml) Mean (SD)	1531.9 (292.36)	1382.6 (289.85)	1450.8 (253.28)
$AUC_{(0\text{-}inf)}$ (hr*ng/ml) Mean (SD)	1589.5 (359.98)	1433.8 (339.50)	1497.9 (300.83)
λz (1/hr) Mean (SD)	0.07 (0.014)	0.07 (0.011)	0.07 (0.012)
$t_{1/2}$ (hr) Mean (SD)	10.9 (2.60)	10.5 (2.11)	10.6 (2.22)

Table 13

Statistical Analysis Results of Plasma d-Amphetamine Following a Single Dose Administration of 50 mg SPD465

Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A) n = 14	High-Fat Meal (B) n = 16	Sprinkled (C) n = 16	B/A	C/A	B/A	C/A
$AUC_{(0\text{-inf})}$ (hr*ng/mL)	1528.3	1392.5	1463.7	91.1	95.8	86.7, 95.8	91.1, 100.6
$AUC_{(0\text{-last})}$ (hr*ng/mL)	1484.2	1350.3	1424.5	91.0	96.0	86.7, 95.5	91.5, 100.7
C_{max} (ng/mL)	69.6	59.4	66.7	85.3	95.8	80.4, 90.5	90.3, 101.6

LS = Least squares

l-amphetamine

l-Amphetamine plasma levels as described by C_{max}, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-inf})}$ were highest in fasted subjects, slightly lower in subjects receiving SPD465 sprinkled on apple sauce, and lowest in subjects pretreated with a high-fat meal. See Tables 14 and 15. The 90% CI of the test-to-reference ratios, with fasted as the reference treatment, were within the typically acceptable bioequivalence range of 80% to 125%, which indicates that the there were no significant differences across the unfed/fed conditions. The CIs on the ratios between subjects receiving the high-fat meal and fasted subjects were less than 100%.

The median time to maximum l-amphetamine plasma concentrations (T_{max}) in fasted subjects and those who received SPD465 sprinkled on applesauce was 7.5 and 8 hours, respectively. The T_{max} in subjects who received SPD465 following a high-fat meal was delayed approximately 4.5 hours with a median value of 12 hours.

Table 14

l-Amphetamine Plasma Pharmacokinetic Parameters Following a Single Dose Administration of 50 mg SPD465

Parameter	Fasted (A) n = 14	High Fat Meal (B) n = 16	Sprinkled (C) n = 16
C_{max} (ng/ml) Mean (SD)	21.1 (3.74)	17.6 (2.21)	20.0 (2.50)
T_{max} (hr) Median (Min, Max)	7.5 (6.0, 12.0)	12.0 (8.0, 14.0)	8.0 (5.0, 12.0)
$AUC_{(0\text{-last})}$ (hr*ng/ml) Mean (SD)	506.9 (107.92)	448.3 (107.79)	479.2 (100.83)
$AUC_{(0\text{-inf})}$ (hr*ng/ml) Mean (SD)	545.2 (147.92)	481.7 (138.43)	511.4 (127.13)
λz (1/hr) Mean (SD)	0.05 (0.014)	0.06 (0.013)	0.06 (0.011)
$t_{1/2}$ (hr) Mean (SD)	13.6 (3.70)	12.8 (3.30)	13.0 (3.22)

Table 15

Statistical Analysis Results of Plasma l-Amphetamine Following a Single Dose Administration of 50 mg SPD465

Parameter	Exponentiated LS Means			Ratio of LS Means		90% CI	
	Fasted (A) n = 14	High-Fat Meal (B) n = 16	Sprinkled (C) n = 16	B/A	C/A	B/A	C/A
$AUC_{(0\text{-inf})}$ (hr*ng/mL)	522.3	463.4	495.0	88.7	94.8	83.9, 93.9	89.6, 100.3
$AUC_{(0\text{-last})}$ (hr*ng/mL)	492.2	436.1	468.1	88.6	95.1	83.8, 93.7	90.0, 100.5
C_{max} (ng/mL)	20.4	17.4	19.8	85.2	96.9	80.2, 90.6	91.2, 103.0

LS = Least squares

Conclusion

There were no statistically significant differences in plasma d- or l- amphetamine levels when SPD465 50 mg was administered to subjects in a fasted state, following a high-fat meal, or when the SPD465 was administered with applesauce. The pharmacokinetic findings indicate that in the presence of a high-fat meal, the rate of absorption of d- and l- amphetamines is

decreased but the extent of absorption is unaffected. Thus, these results show that SPD465 administered with food was bioequivalent to SPD465 administered without food.

Example 10

An open-label, incomplete block randomization, three-period, four treatment, dose escalating study of the pharmacokinetics of SPD 465 administered at steady state in healthy adult volunteers (Clinical Study 110)

The primary objective of this study was to determine the pharmacokinetics of SPD465 following repeat dose administration over a range of doses from 12.5 mg to 75 mg. All 18 subjects received SPD465 at a dose of 12.5 mg once daily for 7 days in Period 1. The dose was increased so that about half the subjects received 25 mg and the others received 50 mg once daily for the next 7 days (Period 2). In Period 3, all subjects were increased to 75 mg once daily for 7 days following Period 2.

Blood samples were collected from each subject on days 1, 5, 6 and 7 of each Period for the determination of d- and l- amphetamine concentrations. Blood and urine samples were collected on day 7 of Period 3 for metabolite identification.

Subjects were administered the SPD465 dosages described in Table 16.

Table 16

Dose level	Mode of administration	Batch Number
12.5 mg (Period 1)	1 x 12.5 mg capsule	A08763A
25 mg (Period 2)	1 x 25 mg capsule	A08767A
50 mg (Period 2)	1 x 50 mg capsule	A08762A
75 mg (Period 3)	2 x 37.5 mg capsules	A08761A

The calculated pharmacokinetic parameters included:

Cmax: maximum plasma concentration

Tmax: time of maximum plasma concentration

AUC_{0-24}: area under the plasma concentration-time curve from time 0 to time 24 hours

Cmin: minimum plasma concentration

CL/F: apparent oral clearance

CL/F/Wt: weight adjusted apparent oral clearance

R: accumulation ratio

AUC_{0-24}/AUC_{0-24}12.5mg: area under the plasma concentration-time curve from time 0 to time 24 hours on Day 7 at 25 mg, 50 mg, and 75 mg relative to the AUC_{0-24} on Day 7 at 12.5 mg.

Pharmacokinetic parameters were calculated by non-compartmental techniques using WinNonlin® Professional version 4.1. All calculations were based on actual sampling times. The pharmacokinetic parameters were determined from plasma concentration-time data measured using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method.

The pharmacokinetic results are graphically illustrated in **FIGS. 11-12** and **15-16** shown in Table 17.

TABLE 17

Parameter	Statistic	Single dose (Day 1)	Multiple dose (Day 7)			
		12.5 mg (N=18)*	12.5 mg (N=18)*	25 mg (N=9)	50 mg (N=8)	75 mg (N=17)*
d-amphetamine						
Cmax (ng/mL)	Mean (SD)	17.0 (2.9)	22.4 (5.8)	48.5 (4.6)	94.2 (32.1)	153.5 (24.6)
Tmax (hr)	Median (min., max.)	8.0 (6.0, 9.0)	6.0 (2.0, 10.1)	8.0 (6.0, 9.0)	6.0 (4.0, 12.1)	8.0 (6.0, 12.0)
AUC_{0-24} (hr*ng/mL)	Mean (SD)	248.5 (45.3)	351.3 (87.5)	742.0 (77.5)	1499.7 (504.9)	2526.2 (495.1)
Cmin (ng/mL)	Mean (SD)	--	7.6 (2.9)	17.2 (5.6)	38.2 (10.5)	66.8 (23.8)
CL/F (L/hr)	Mean (SD)	39.0 (7.2)	29.5 (13.5)	25.5 (2.8)	29.5 (16.6)	22.9 (3.7)
CL/F/Wt (L/hr/kg)	Mean (SD)	0.51 (0.09)	0.40 (0.18)	0.35 (0.05)	0.40 (0.23)	0.31 (0.06)
R	Mean (SD)	--	1.4 (0.30)	--	--	--
AUC_{0-24}/ AUC_{0-24}	Mean (SD)	--	--	2.2 (0.4)	4.2 (0.6)	8.0 (4.0)

12.5mg						
l-amphetamine						
Cmax (ng/ml)	Mean (SD)	5.2 (0.9)	7.6 (1.8)	15.9 (1.6)	30.2 (8.7)	52.0 (9.6)
Tmax (hr)	Median (min., max.)	8.0 (6.0, 10.0)	8.0 (2.0, 10.1)	8.0 (4.0, 9.0)	9.0 (4.0, 12.1)	8.0 (6.0, 12.0)
AUC_{0-24} (hr*ng/mL)	Mean (SD)	81.3 (14.8)	126.4 (29.9)	261.5 (31.8)	514.7 (148.5)	899.3 (205.9)
Cmin (ng/mL)	Mean (SD)	--	3.0 (1.0)	6.6 (2.1)	14.8 (4.3)	26.8 (10.1)
CL/F (L/hr)	Mean (SD)	39.7 (7.1)	26.8 (10.2)	24.2 (3.1)	26.6 (9.7)	21.6 (3.9)
CL/F/Wt (L/hr/kg)	Mean (SD)	0.52 (0.08)	0.36 (0.14)	0.34 (0.05)	0.36 (0.14)	0.30 (0.07)
R	Mean (SD)	--	1.6 (0.3)	--	--	--
AUC_{0-24}/ AUC_{0-24} 12.5 mg	Mean (SD)	--	--	2.2 (0.4)	4.1 (0.8)	7.8 (3.4)

*N indicates the number of subjects in the safety population who took drug. Due to early termination or missing data, some subjects may not be contributing to the results at all time points.

The dose proportionality of the Cmax and AUC_{0-24} of SPD465 d- and l- amphetamine were analyzed using the power model and graphically by plotting individual subject and mean Day 7 Cmax and AUC_{0-24} against dose with the estimated power model regression line. See **FIGS. 13-14** and **17-18**.

These results showed that repeated doses of SPD465 led to the accumulation of d- and l-amphetamine in plasma consistent with the half-life and dosing of the compound. Further, the Cmax and AUC_{0-24} increased linearly with increasing doses of SPD465. Because SPD465 includes an immediate release bead, a delayed pulsed release bead, and a sustained release bead in a 1:1:1 ratio, the Cmax and AUC_{0-24} for the sustained release bead alone also increases linearly with increasing doses of SPD465 (e.g., the Cmax for 25 mg of the sustained release bead is twice the Cmax for 12.5 mg of the sustained release bead, and the Cmax for 37.5 mg of the sustained release bead is 3x the Cmax for 12.5 mg of the sustained release bead).

The disclosures of patents, patent applications, publications, product descriptions, and

protocols cited throughout this application are incorporated by reference in their entireties.

It is to be understood 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.

CLAIMS:

1. A pharmaceutical composition comprising:

(a) an immediate release bead comprising at least one amphetamine salt;

(b) a first delayed release bead comprising at least one amphetamine salt; and

(c) a second delayed release bead comprising at least one amphetamine salt;

wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt and the second delayed release bead provides sustained release of the at least one amphetamine salt.

2. The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

3. The pharmaceutical composition of claim 2, wherein the enteric coating is pH dependent.

4. The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.

5. The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coating.

6. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is bioequivalent to ADDERALL® XR followed by an immediate release amphetamine formulation administered 8 hours after the ADDERALL® XR;

wherein the combined dosage of the ADDERALL® XR and the immediate release formulation is equal to the dosage of the pharmaceutical composition.

7. The pharmaceutical composition of claim 1, wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a *d*-amphetamine C_{max} of about 50 ng/ml.

8. The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1058 ng·hr/ml.

9. The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1085 ng·hr/ml.

10. The pharmaceutical composition of claim 1, wherein the *d*-amphetamine T_{max} is about 8.2 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

11. The pharmaceutical composition of claim 1, wherein the *l*-amphetamine C_{max} after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 15 ng/ml.

12. The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 354 ng·hr/ml.

13. The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 373 ng·hr/ml.

14. The pharmaceutical composition of claim 1, wherein the *l*-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

15. The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on a single core.

16. The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.

17. The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.

18. The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.

19. The pharmaceutical composition of claim 2, which further comprises a protective layer over at least one enteric coating.

20. The pharmaceutical composition of claim 2, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.

21. The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

22. The pharmaceutical composition of claim 21, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

23. The pharmaceutical composition of claim 1, wherein the composition does not exhibit a food effect.

24. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 12.5 mg.

25. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 18.75 mg.

26. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 25 mg.

27. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 31.25 mg.

28. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 37.5 mg.

29. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 43.75 mg.

30. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 50 mg.

31. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 62.5 mg.

32. The composition of claim 6, wherein the amount of at least one amphetamine salt is about 75 mg.

33. A pharmaceutical composition comprising:
at least one amphetamine salt and a pharmaceutically acceptable carrier;
wherein the composition provides an about bioequivalent plasma level of amphetamine in a patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL®.

34. The composition of claim 33, wherein the composition provides an about bioequivalent plasma level of d-amphetamine in the patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL®.

35. The composition of claim 33, wherein the composition provides an about bioequivalent plasma level of l-amphetamine in the patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® and an immediate

release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL®.

36. A method for treating ADHD, which comprises administering the pharmaceutical composition of claim 1 to a patient suffering from ADHD.

37. A sustained release pharmaceutical composition comprising:

(a) at least one amphetamine salt,

(b) a sustained release coating, and

(c) a delayed release coating,

wherein the at least one amphetamine salt is released about 4 to about 6 hours after oral administration to a patient.

38. The pharmaceutical composition of claim 37, wherein the sustained release coating is external to the delayed release coating.

39. The pharmaceutical composition of claim 37, wherein about 50% of the at least one amphetamine salt is released at about six hours at a pH of about 7.5.

40. The pharmaceutical composition of claim 37, comprising:

(a) at least one amphetamine salt layered onto a core,

(b) a delayed release coating layered onto the at least one amphetamine salt;

(c) a sustained release coating layered onto the delayed release coating, and

(d) a protective coating layered onto the sustained release coating.

41. The pharmaceutical composition of claim 37, wherein the at least one amphetamine salt comprises dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

42. The pharmaceutical composition of claim 37, wherein the delayed release coating is selected from the group consisting of: cellulose acetate phthalate; cellulose acetate trimellitate; hydroxypropyl methylcellulose phthalate; polyvinyl acetate phthalate;

carboxymethylethylcellulose; co-polymerized methacrylic acid/methacrylic acid methyl esters, EUDRAGIT® L12.5, L100; EUDRAGIT® S12.5, S100; and EUDRAGIT® FS30 D.

43. The pharmaceutical composition of claim 37, wherein the sustained release coating is selected from the group consisting of: polyvinyl acetate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, fatty acids and esters thereof, alkyl alcohols, waxes, zein (prolamine from corn), EUDRAGIT® RS and RL30D, EUDRAGIT® NE30D, AQUACOAT®, SURELEASE®, KOLLICOAT® SR30D, and cellulose acetate latex.

44. The pharmaceutical composition of claim 42, wherein the delayed release coating is EUDRAGIT® FS-30D.

45. The pharmaceutical composition of claim 43, wherein the sustained release coating is SURELEASE®.

46. The pharmaceutical composition of claim 37, comprising 12.5 mg of the at least one amphetamine salt; wherein the composition has an d-amphetamine AUC (0-inf) of about 367 ng.hr/mL.

47. The pharmaceutical composition of claim 37, comprising 12.5 mg of the at least one amphetamine salt; wherein the composition has an l-amphetamine AUC (0-inf) of about 125 ng.hr/mL.

48. The pharmaceutical composition of claim 37, wherein the composition comprises 18.75 mg, 25 mg, 31.25 mg, 37.5 mg, or 50 mg of at least one amphetamine salt and has an AUC (0-inf) that is linearly proportional to the AUC (0-inf) for a 12.5 mg at least one amphetamine salt composition.

49. The pharmaceutical composition of claim 37, comprising 12.5 mg of the at least one amphetamine salt; wherein the composition has an d-amphetamine Cmax of about 18.67 ng/mL.

50. The pharmaceutical composition of claim 37, comprising 12.5 mg of the at least one amphetamine salt; wherein the composition has an l-amphetamine Cmax of about 5.64 ng/mL.

51. The pharmaceutical composition of claim 37, wherein the composition comprises 18.75 mg, 25 mg, 37.5 mg, or 50 mg of at least one amphetamine salt and has a Cmax that is linearly proportional to the Cmax for a 12.5 mg at least one amphetamine salt composition.

52. The pharmaceutical composition of claim 37, comprising 12.5 mg of the at least one amphetamine salt; wherein the composition has an d-amphetamine Tmax of about 8.83 hours.

53. The pharmaceutical composition of claim 37, comprising 12.5 mg of the at least one amphetamine salt; wherein the composition has an l-amphetamine Tmax of about 9.33 hours.

54. The pharmaceutical composition of claim 37, wherein the composition comprises 18.75 mg, 25 mg, 37.5 mg, or 50 mg of at least one amphetamine salt and has a Tmax that is linearly proportional to the Tmax for a 12.5 mg at least one amphetamine salt composition.

55. A method of treating ADHD comprising administering the pharmaceutical composition of claim 37 in combination with an immediate release mixed amphetamine salt composition and/or an extended release mixed amphetamine salt composition to a patient in need of such treatment.

56. The method of claim 55, wherein the pharmaceutical composition of claim 37 and the immediate release mixed amphetamine salt composition and/or the extended release mixed amphetamine salt composition are administered simultaneously.

57. The method of claim 55, wherein the sustained release pharmaceutical composition comprises about 10% to about 150% of the amphetamine dosage of the immediate release mixed amphetamine salt composition and/or an extended release mixed amphetamine salt composition.

58. The method of claim 55, wherein the immediate release mixed amphetamine salt composition and/or an extended release mixed amphetamine salt composition is ADDERALL XR®.

Abstract

A multiple pulsed dose drug delivery system for pharmaceutically active amphetamine salts, comprising a pharmaceutically active amphetamine salt covered with an immediate-release coating and a pharmaceutically active amphetamine salt covered with an enteric coating wherein the immediate release coating and the enteric coating provide for multiple pulsed dose delivery of the pharmaceutically active amphetamine salt. 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.

FIG. 1

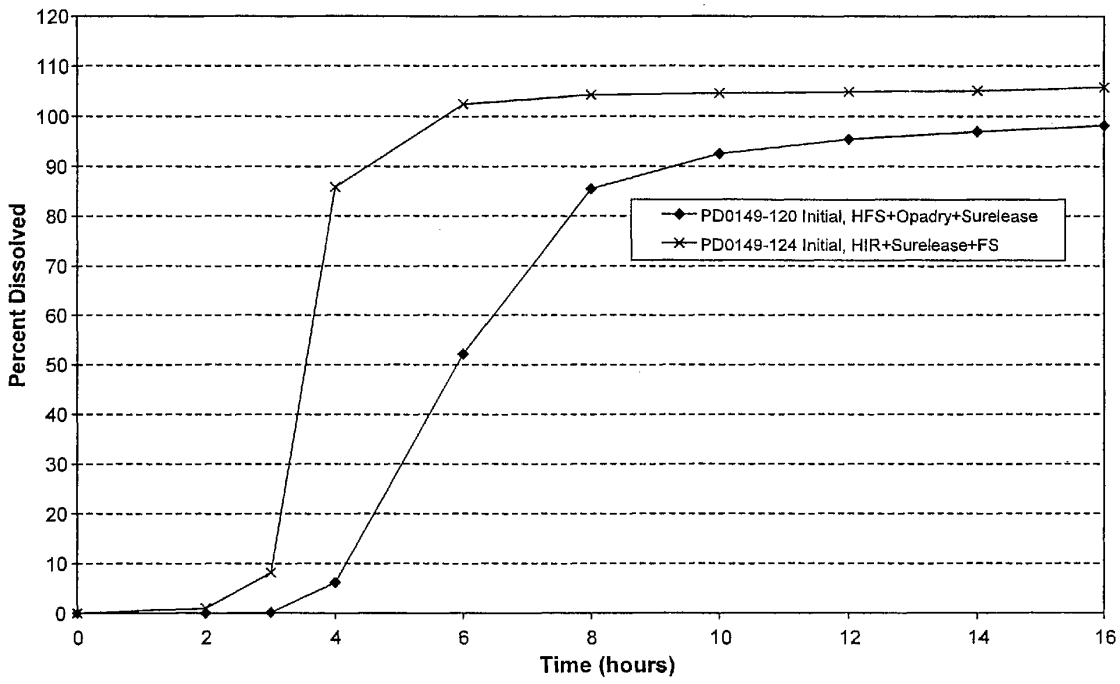

120
110
100
90
80
70
60
50
40
30
20
10
0
Percent Dissolved
0
2
4
6
8
10
12
14
16
Time (hours)
PD0149-120 Initial, HFS+Opadry+Surelease
PD0149-124 Initial, HIR+Surelease+FS

FIG. 2

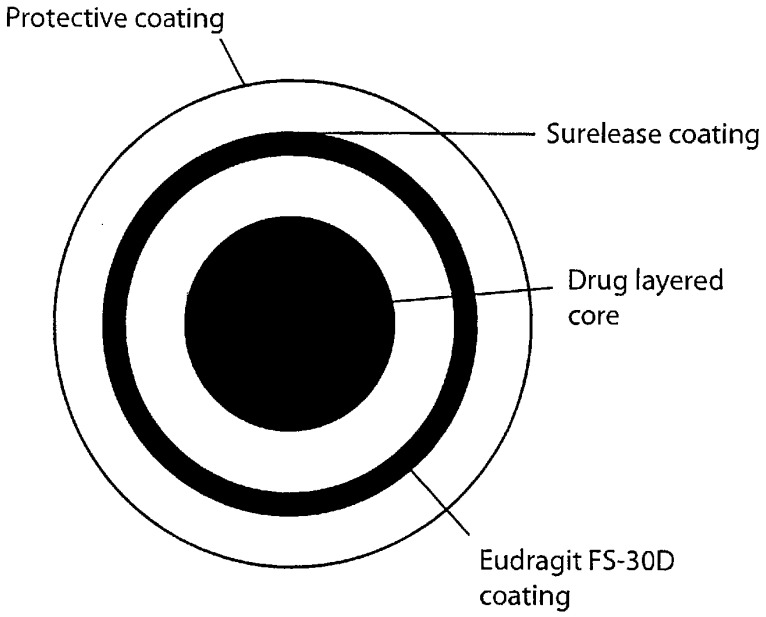


FIG. 3

SPD465 Sustained Release Capsule

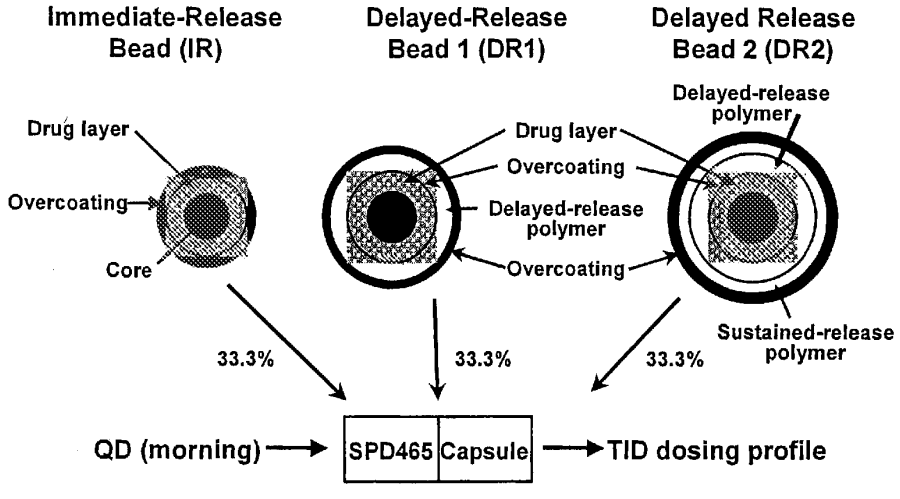


FIG. 4

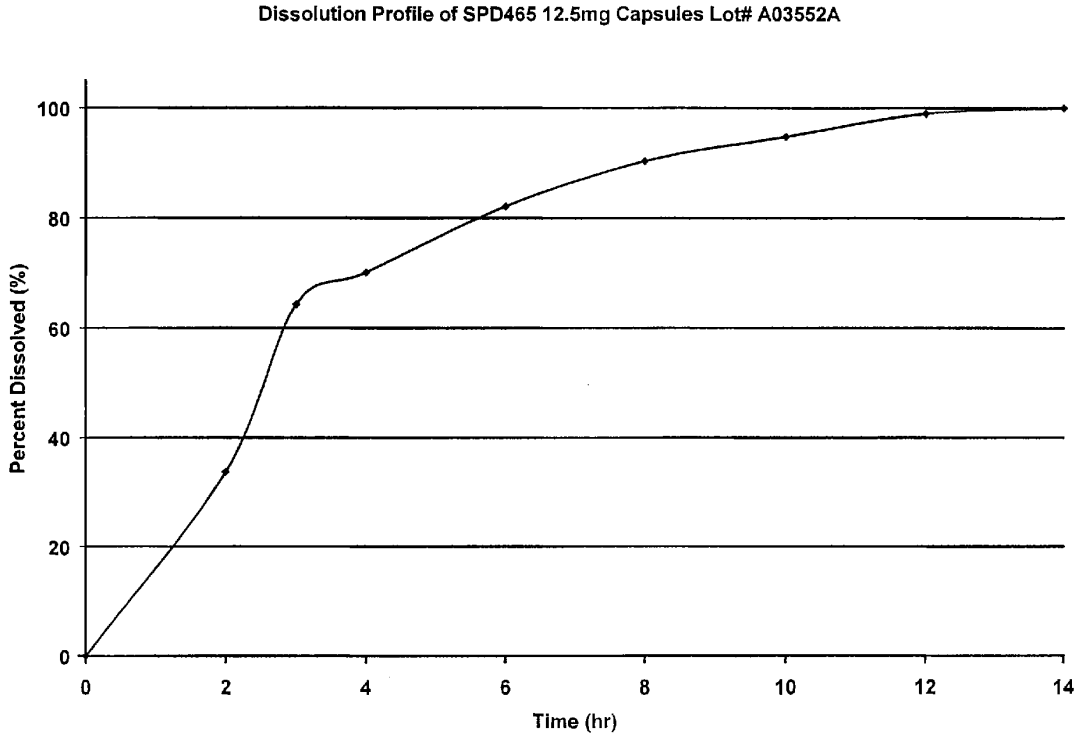

Dissolution Profile of SPD465 12.5mg Capsules Lot# A03552A
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 5

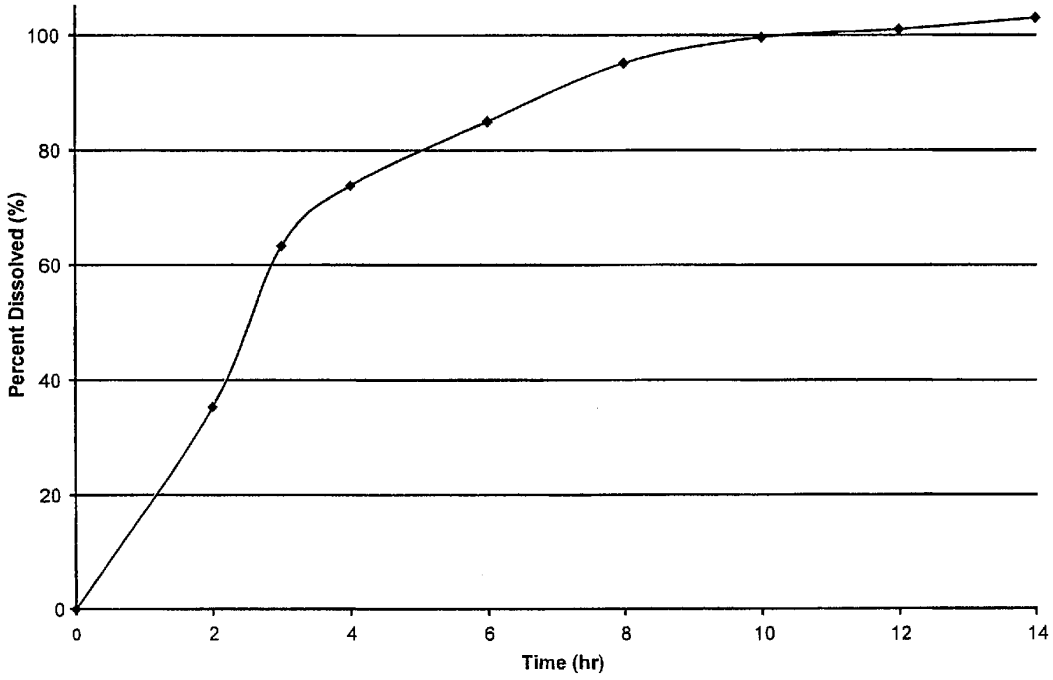

Dissolution Profile of SPD465 25mg Capsules Lot# A03547A
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 6

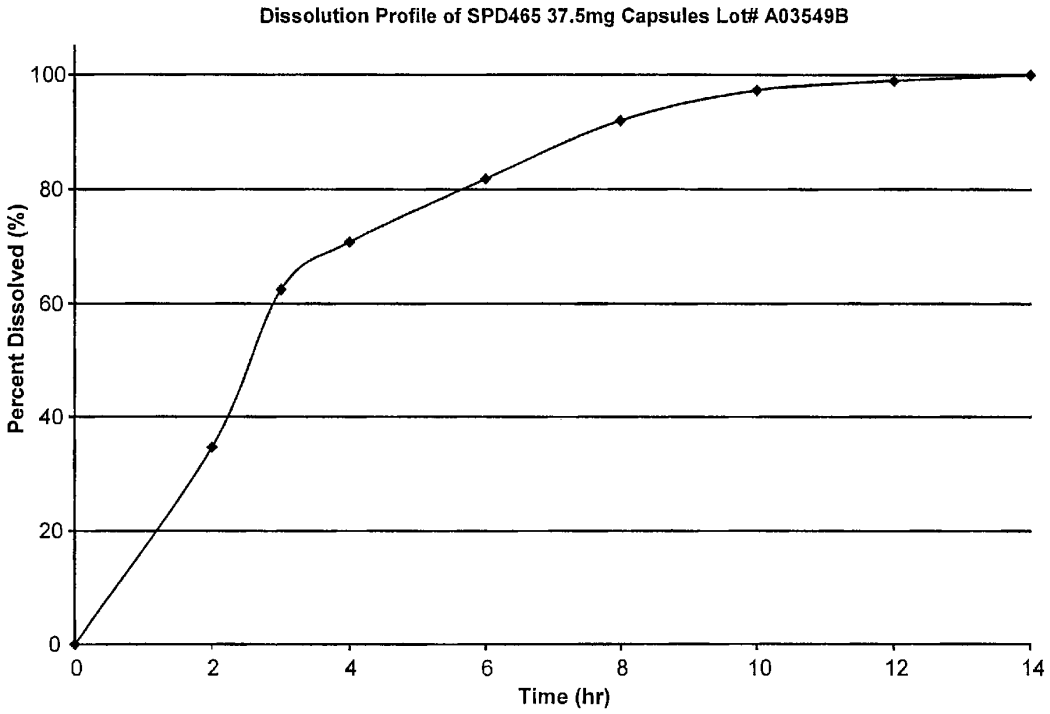

Dissolution Profile of SPD465 37.5mg Capsules Lot# A03549B
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 7

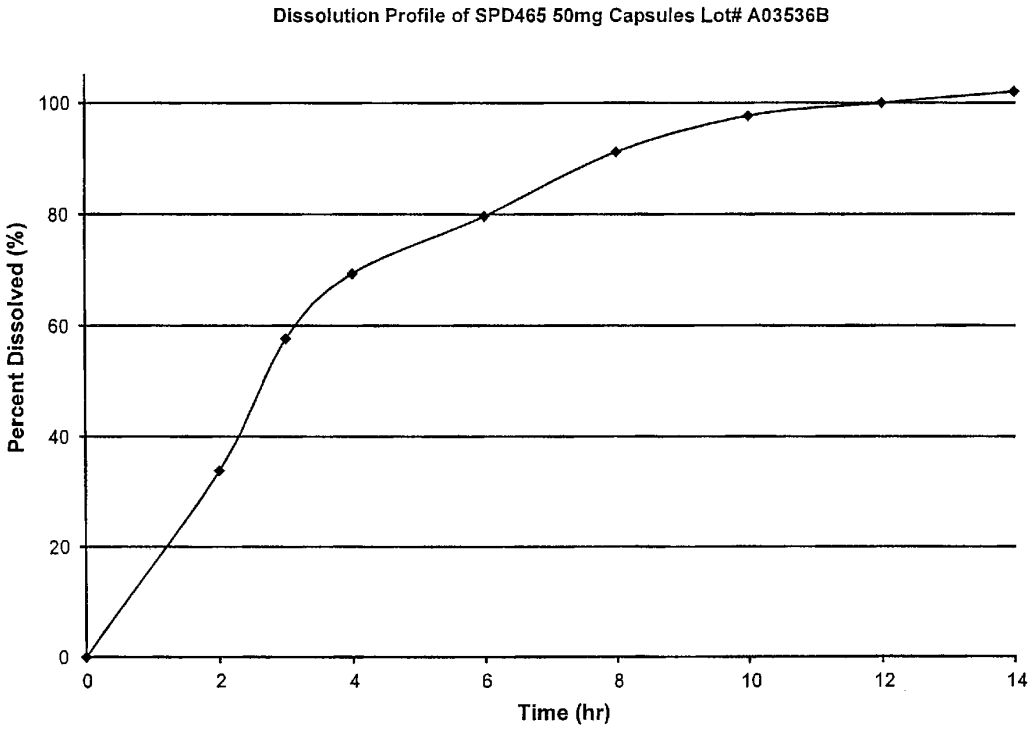

Dissolution Profile of SPD465 50mg Capsules Lot# A03536B
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 8

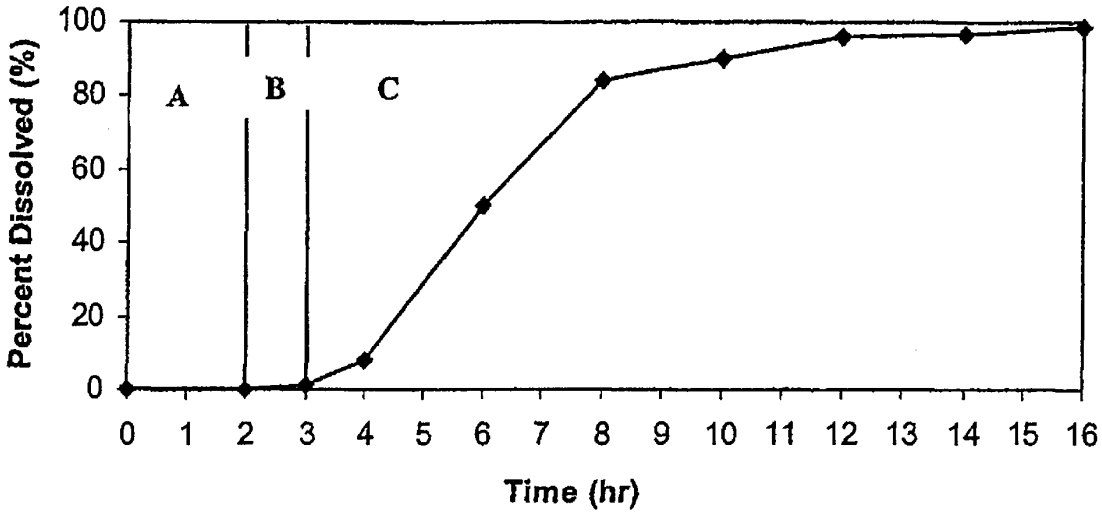

Percent Dissolved (%)
100
80
60
40
20
0
A
B
C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time (hr)

FIG. 9

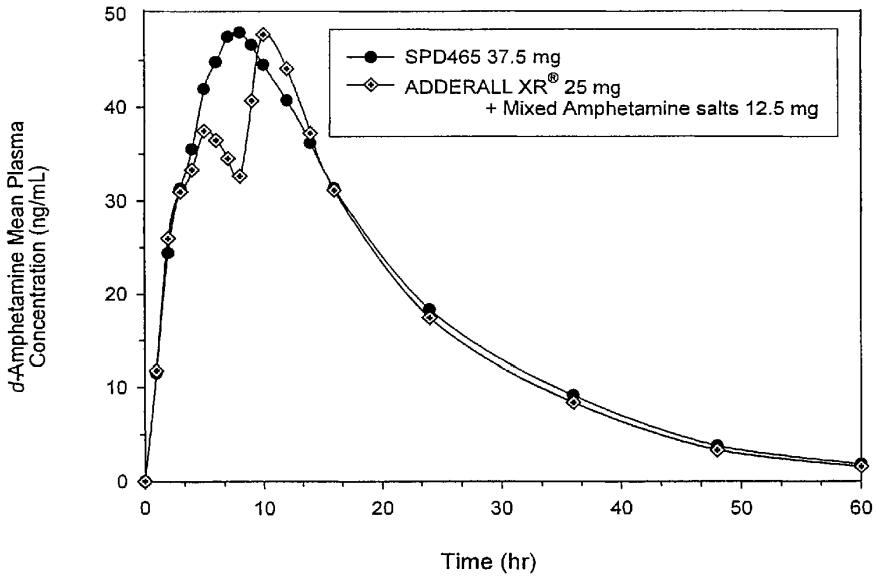

d-Amphetamine Mean Plasma Concentration (ng/mL)
50
40
30
20
10
0
SPD465 37.5 mg
ADDERALL XR® 25 mg
+ Mixed Amphetamine salts 12.5 mg
0 10 20 30 40 50 60
Time (hr)

FIG. 10

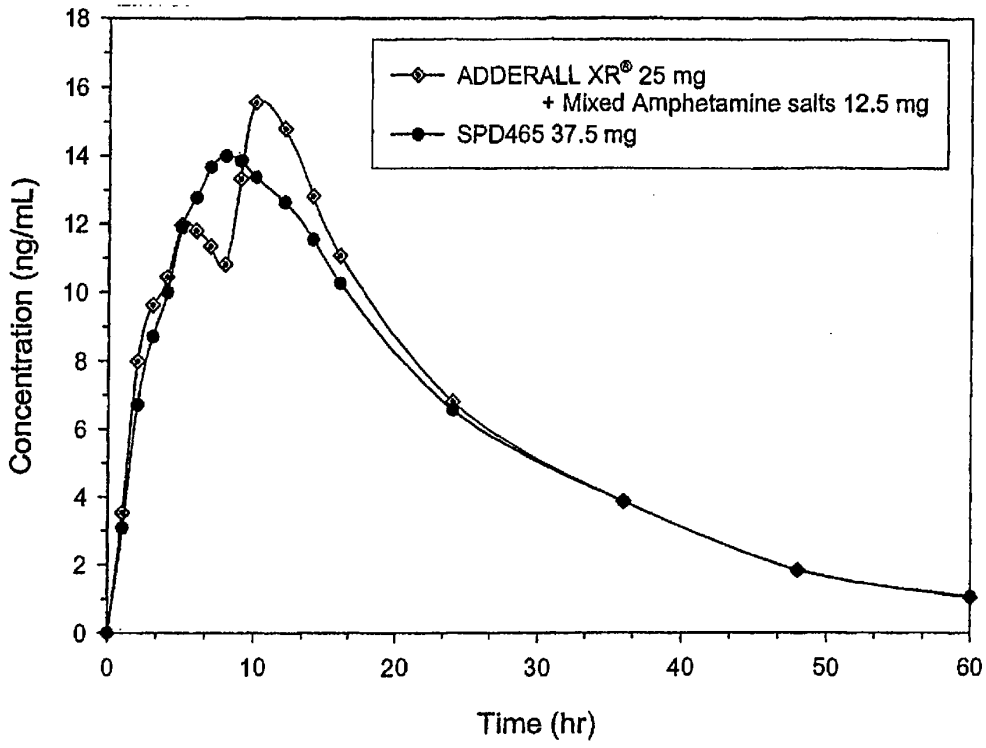

ADDERALL XR® 25 mg
+ Mixed Amphetamine salts 12.5 mg
SPD465 37.5 mg
Concentration (ng/mL)
Time (hr)
0
2
4
6
8
10
12
14
16
18
0
10
20
30
40
50
60

FIG. 11

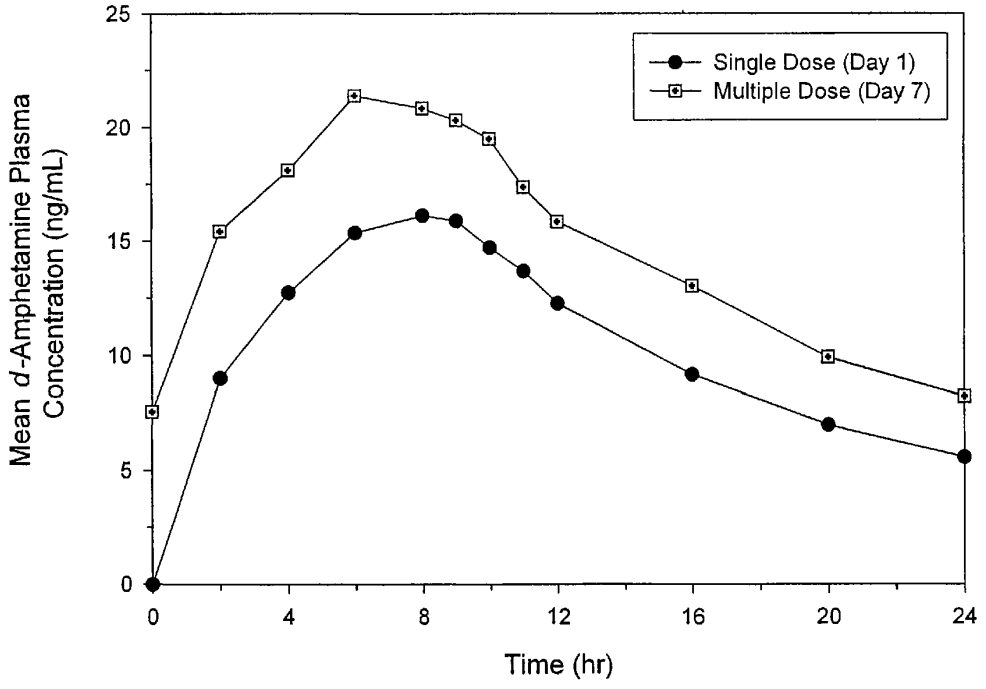

Single Dose (Day 1)
Multiple Dose (Day 7)
Mean d-Amphetamine Plasma Concentration (ng/mL)
Time (hr)
0
5
10
15
20
25
0
4
8
12
16
20
24

FIG. 12

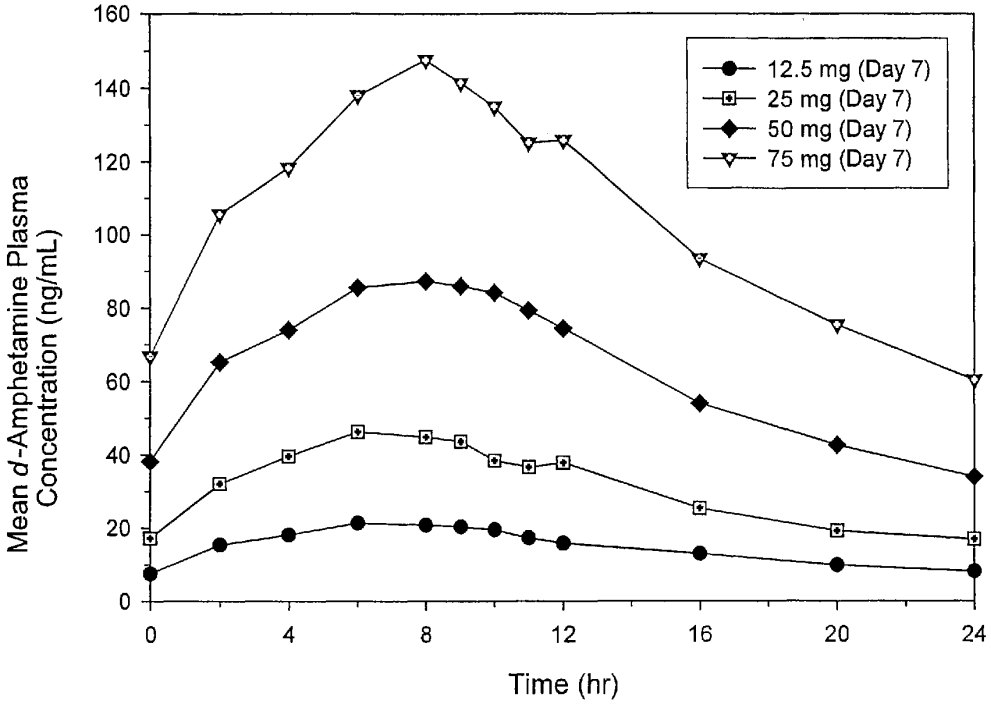

Mean d-Amphetamine Plasma Concentration (ng/mL)
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
Time (hr)
12.5 mg (Day 7)
25 mg (Day 7)
50 mg (Day 7)
75 mg (Day 7)

FIG. 13

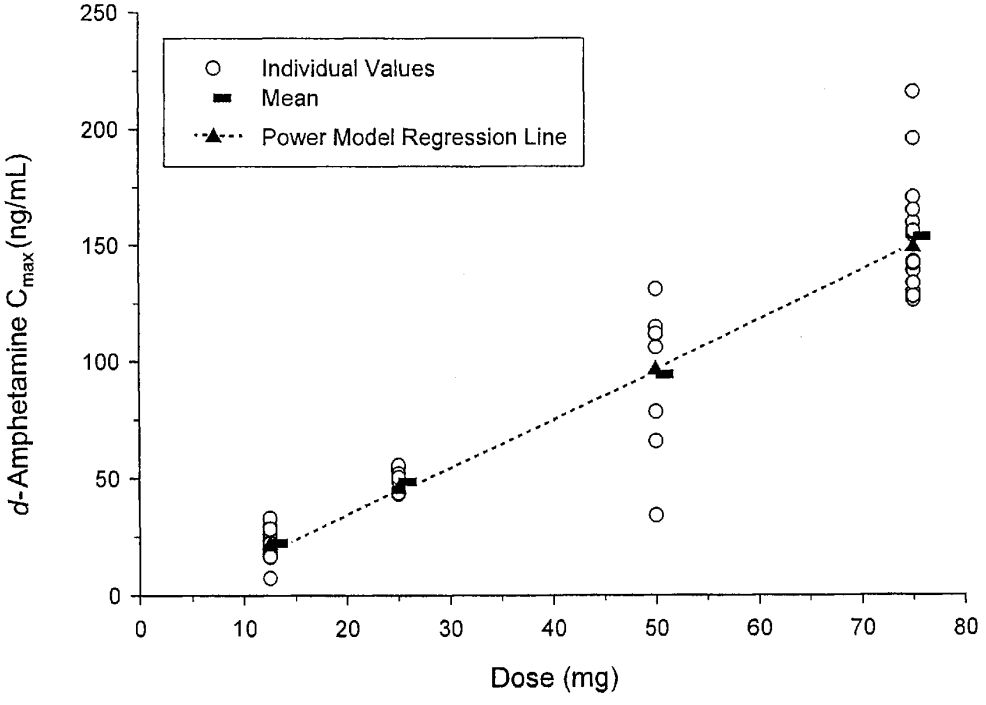

d-Amphetamine C_{max} (ng/mL)
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Dose (mg)
Individual Values
Mean
Power Model Regression Line

FIG. 14

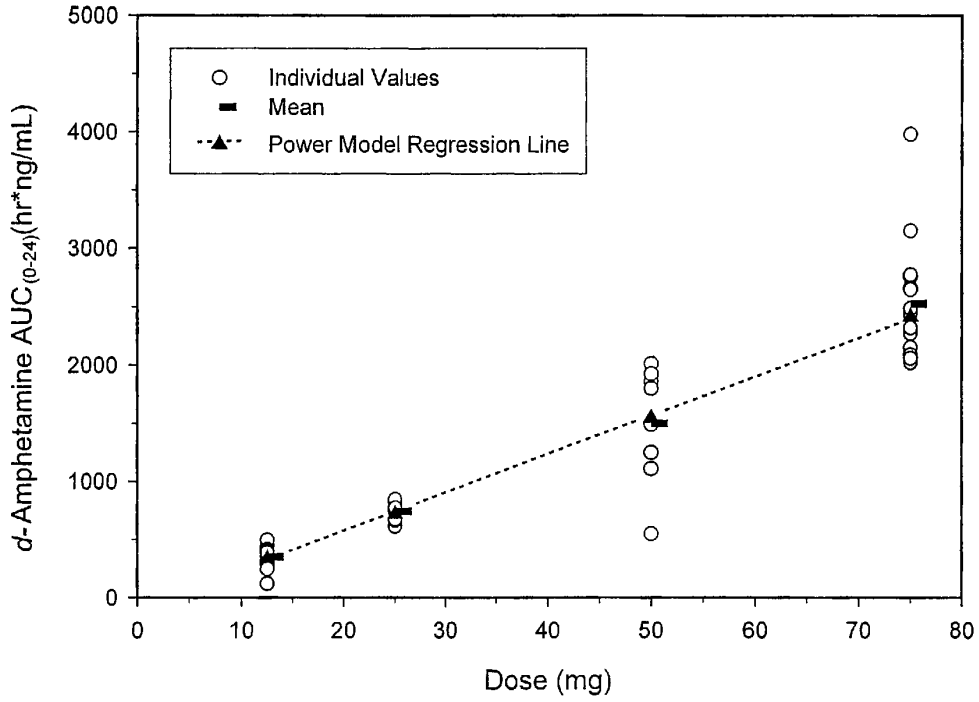

Individual Values
Mean
Power Model Regression Line
d-Amphetamine AUC(0-24)(hr*ng/mL)
Dose (mg)
0
1000
2000
3000
4000
5000
0
10
20
30
40
50
60
70
80

FIG. 15

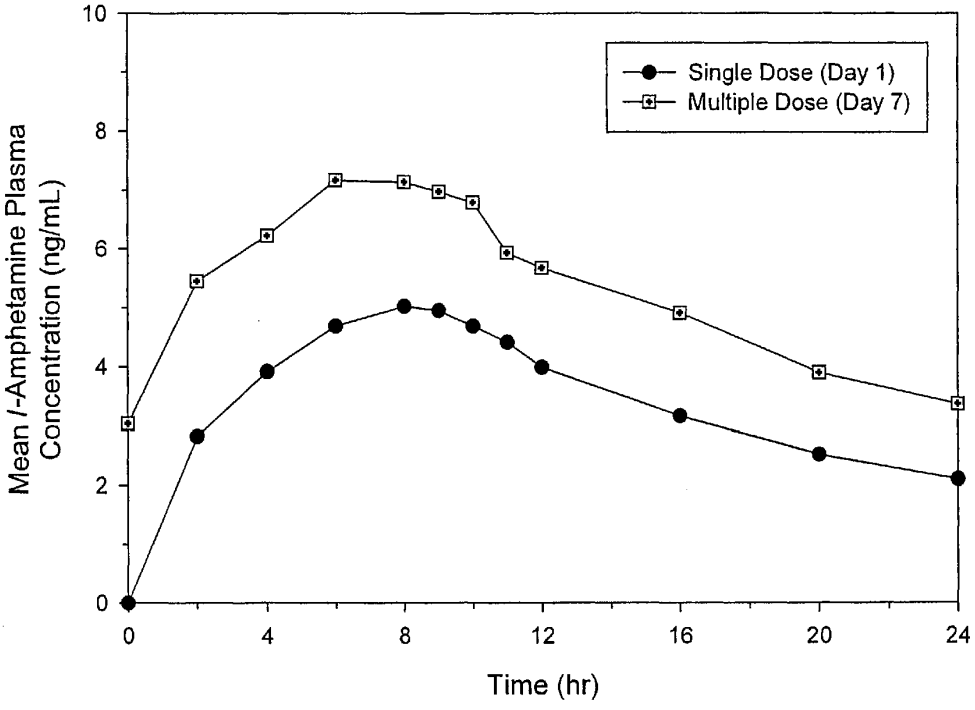

Single Dose (Day 1)
Multiple Dose (Day 7)
Mean l-Amphetamine Plasma Concentration (ng/mL)
Time (hr)
0
2
4
6
8
10
0
4
8
12
16
20
24

FIG. 16

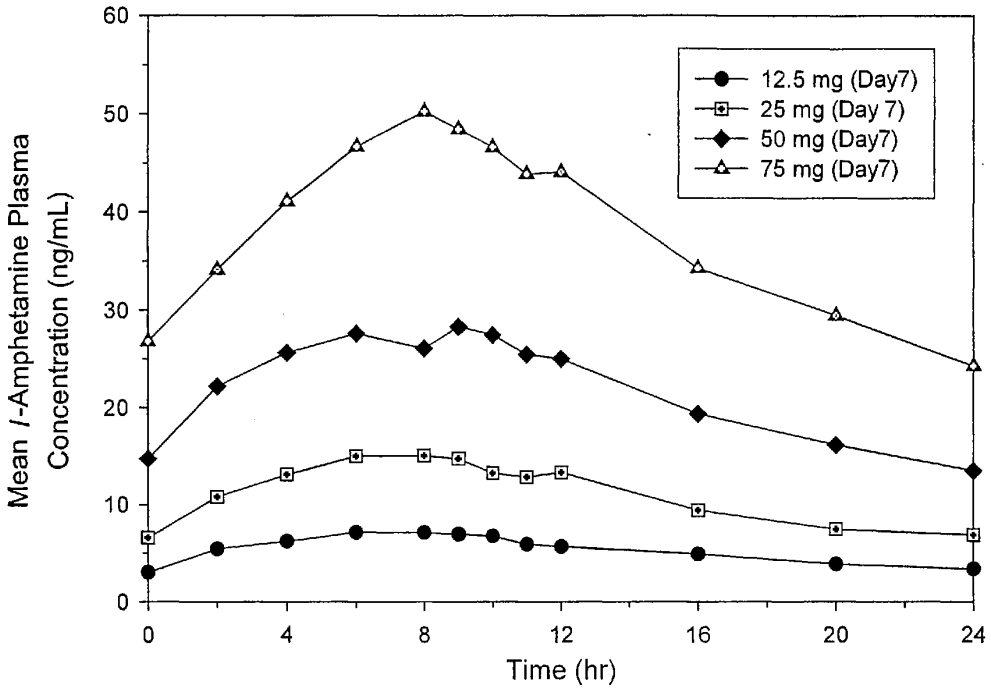

Mean l-Amphetamine Plasma Concentration (ng/mL)
Time (hr)
12.5 mg (Day7)
25 mg (Day 7)
50 mg (Day7)
75 mg (Day7)
0
10
20
30
40
50
60
0
4
8
12
16
20
24

FIG. 17

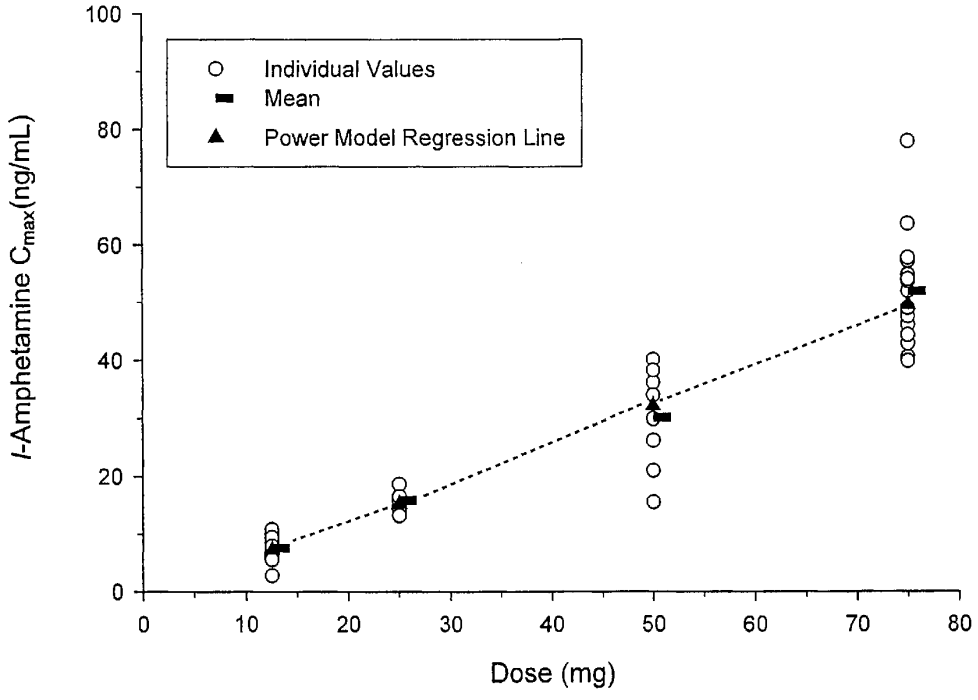
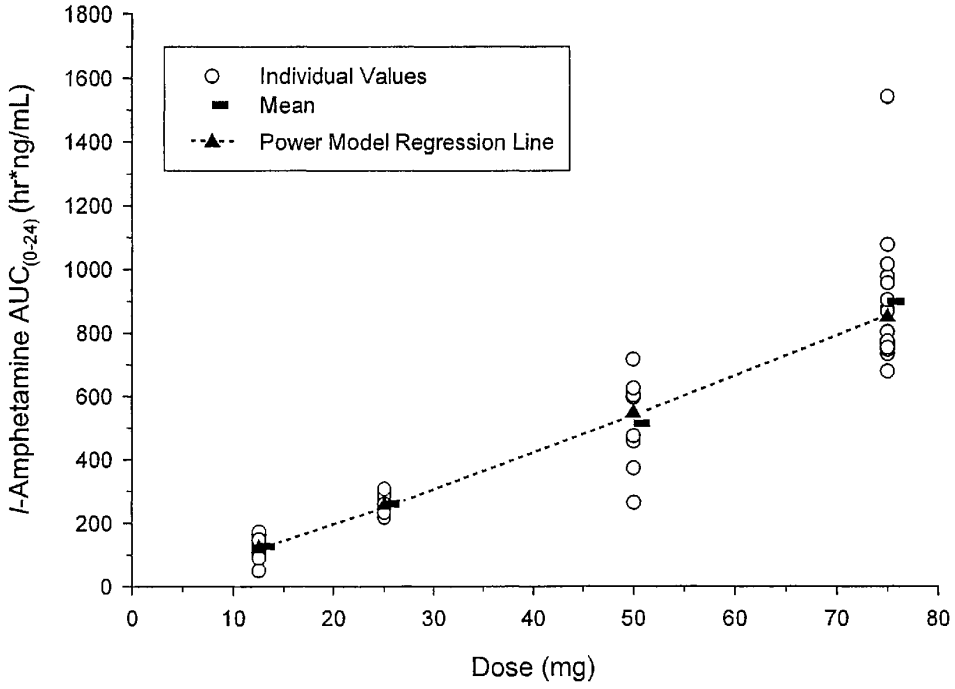

l-Amphetamine Cmax(ng/mL)
Dose (mg)
Individual Values
Mean
Power Model Regression Line
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80

FIG. 18


Individual Values
Mean
Power Model Regression Line
l-Amphetamine AUC(0-24) (hr*ng/mL)
Dose (mg)
0
200
400
600
800
1000
1200
1400
1600
1800
0
10
20
30
40
50
60
70
80

Electronic Acknowledgement Receipt

EFS ID:	1046167
Application Number:	11383066
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor:	Amir Shojaei
Customer Number:	07278
Filer:	Flynn Barrison/Daniel Harris
Filer Authorized By:	Flynn Barrison
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	12-MAY-2006
Filing Date:	
Time Stamp:	15:36:52
Application Type:	Utility
International Application Number:	

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part	Pages
1		00743927.PDF	440547	yes	69

	Multipart Description		
	Doc Desc	**Start**	**End**
	Transmittal letter	1	1
	Application Data Sheet	2	3
	Specification	4	50
	Claims	51	58
	Abstract	59	59
	Drawings	60	69

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing

Information:

Total Files Size (in bytes):	440547

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 11/07/2006

HSMITH1 SALE #00000001 Mailroom Dt: 05/12/2006 040100 11383066
01 FC : 1202 1,900.00 DA

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/383,066	05/12/2006	Amir Shojaei	20342/1202653-US8

CONFIRMATION NO. 7083

FORMALITIES LETTER

07278
DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

Date Mailed: 05/24/2006

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **300** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of **$1900** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$3030** for a Large Entity

- **$300** Statutory basic filing fee.
- **$130** Surcharge.

- The application search fee has not been paid. Applicant must submit **$500** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit **$200** to complete the examination fee for a large entity

- Total additional claim fee(s) for this application is **$1900**

  - **$1900** for **38** total claims over 20.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 3 - OFFICE COPY

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066

Filed: May 12, 2006

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM

Confirmation No.: 7083

Art Unit: N/A

Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

MS Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Notice to File Missing Parts of Application – Filing Date Granted mailed May 24, 2006, Applicant respectfully submits a Combined Declaration and Power of Attorney, a First Preliminary Amendment, a Supplemental Application Data Sheet, the Filing Fee for the Application (as shown on accompanying Fee Transmittal), a Petition for Extension of Time, and Part 2 Copy of Notice.

Please charge our Credit Card in the amount of $2,750.00 covering the fees set forth in 37 CFR 1.16(f), 1.16(a)(1), 1.16(k), 1.16(o), 1.17(a)(3), and 1.16(i). The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: October 24, 2006

Respectfully submitted,

By FRANK BARRISON (53,970)

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

M. Hasagawa

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/383,066	05/12/2006	Amir Shojaei	20342/1202653-US8

CONFIRMATION NO. 7083

07278
DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

DUE: July 24, 2006
Docketed on 6/6/06 by BWL for
Docketed without file ☐
Attorney _____

FORMALITIES LETTER

Date Mailed: 05/24/2006

(12-24-06)

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **300** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of **$1900** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$3030** for a Large Entity

- **$300** Statutory basic filing fee.
- **$130** Surcharge.

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- The application examination fee has not been paid. Applicant must submit **$200** to complete the examination fee for a large entity

- Total additional claim fee(s) for this application is **$1900**
  - **$1900** for **38** total claims over 20.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 1 - ATTORNEY/APPLICANT COPY

Supplemental Application Data Sheet

Application Information

Application number::	11/383,066
Filing Date::	05/12/06
Application Type::	Regular
Subject Matter::	Utility
Suggested Group Art Unit::	1615
CD-ROM or CD-R?::	None
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Title::	CONTROLLED DOSE DRUG DELIVERY SYSTEM
Attorney Docket Number::	20342/1202653-US8
Request for Early Publication?::	No
Request for Non-Publication?::	No
Total Drawing Sheets::	10
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Canada~~US~~
Status::	Full Capacity
Given Name::	Amir
Family Name::	Shojaei
City of Residence::	Phoenixville
State or Province of Residence::	PA
Country of Residence::	US

Street of mailing address::	241 Rivercrest Drive
City of mailing address::	Phoenixville
State or Province of mailing address::	PA
Postal or Zip Code of mailing address::	19460

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Stephanie
Family Name::	Read
City of Residence::	Philadelphia
State or Province of Residence::	PA
Country of Residence::	US
Street of mailing address::	237 Gay Street
City of mailing address::	Philadelphia
State or Province of mailing address::	PA
Postal or Zip Code of mailing address::	19128

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
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Given Name::	Richard
Middle Name::	A.
Family Name::	Couch
City of Residence::	Bryn Mawr
State or Province of Residence::	PA
Country of Residence::	US
Street of mailing address::	777 Woodleave Road
City of mailing address::	Bryn Mawr
State or Province of mailing address::	PA

Postal or Zip Code of mailing address:: 19010

Applicant Authority Type:: Inventor
Primary Citizenship Country:: United Kingdom
Status:: Full Capacity
Given Name:: Paul
Family Name:: Hodgkins
City of Residence:: Exton
State or Province of Residence:: PA
Country of Residence:: US
Street of mailing address:: 15 Landon Way
City of mailing address:: Exton
State or Province of mailing address:: PA
Postal or Zip Code of mailing address:: 19341

Correspondence Information

Correspondence Customer Number:: 07278

Representative Information

Representative Customer Number:: 07278

Domestic Priority Information

Foreign Priority Information

Assignee Information

Assignee name:: SHIRE LLC
Street of mailing address:: 9200 Brookfield Court

City of mailing address::	Florence
State or Province of mailing address::	KY
Postal or Zip Code of mailing address::	41042

PTO/SB/22 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2006 (Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)	Docket Number (Optional) 20342/1202653-US8
Application Number 11/383,066-Conf. #7083	Filed May 12, 2006
For CONTROLLED DOSE DRUG DELIVERY SYSTEM	
Art Unit N/A	Examiner Not Yet Assigned

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$120	$60	$
☐	Two months (37 CFR 1.17(a)(2))	$450	$225	$
X	Three months (37 CFR 1.17(a)(3))	$1020	$510	$ 1,020.00
☐	Four months (37 CFR 1.17(a)(4))	$1590	$795	$
☐	Five months (37 CFR 1.17(a)(5))	$2160	$1080	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

X Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

X The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 04-0100 . I have enclosed a duplicate copy of this sheet.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

X attorney or agent of record. Registration Number 52,392

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____ .

Frank Barrison (53970) — October 24, 2006
Signature — Date

Paul M. Zagar — (212) 527-7700
Typed or printed name — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of 1 forms are submitted.

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei

Application No.: 11/383,066	Confirmation No.:
Filed: May 12, 2006	Art Unit: N/A
For: CONTROLLED DOSE DRUG DELIVERY SYSTEM	Examiner: Not Yet Assigned

FIRST PRELIMINARY AMENDMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

LISTING OF CLAIMS

1. (Original) A pharmaceutical composition comprising:

(a) an immediate release bead comprising at least one amphetamine salt;

(b) a first delayed release bead comprising at least one amphetamine salt; and

(c) a second delayed release bead comprising at least one amphetamine salt;

wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt and the second delayed release bead provides sustained release of the at least one amphetamine salt.

2. (Original) The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

3. (Original) The pharmaceutical composition of claim 2, wherein the enteric coating is pH dependent.

4. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.

5. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coating.

6. (Original) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is bioequivalent to ADDERALL® XR followed by an immediate release amphetamine formulation administered 8 hours after the ADDERALL® XR;

wherein the combined dosage of the ADDERALL® XR and the immediate release formulation is equal to the dosage of the pharmaceutical composition.

7. (Original) The pharmaceutical composition of claim 1, wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a *d*-amphetamine C_{max} of about 50 ng/ml.

8. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1058 ng·hr/ml.

9. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1085 ng·hr/ml.

10. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine T_{max} is about 8.2 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

11. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine C_{max} after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 15 ng/ml.

12. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 354 ng·hr/ml.

13. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 373 ng·hr/ml.

14. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

15. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on a single core.

16. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.

17. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.

18. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.

19. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer over at least one enteric coating.

20. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.

21. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

22. (Original) The pharmaceutical composition of claim 21, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

23. (Original) The pharmaceutical composition of claim 1, wherein the composition does not exhibit a food effect.

24. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 12.5 mg.

25. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 18.75 mg.

26. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 25 mg.

27. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 31.25 mg.

28. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 37.5 mg.

29. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 43.75 mg.

30. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 50 mg.

31. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 62.5 mg.

32. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 75 mg.

33-58. (Canceled)

REMARKS

Claims 33-58 have been canceled, without prejudice to pursue them in one or more continuation applications. No new matter has been added. Claims 1-32 are pending and at issue.

Prompt and favorable consideration of the present application is earnestly solicited.

Dated: October 24, 2006

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION FOR PATENT APPLICATION

As the below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor of the subject matter which is described and claimed and for which a patent is sought on the invention entitled:

CONTROLLED DOSE DRUG DELIVERY SYSTEM

the specification of which was filed on May 12, 2006 as Application No. 11/383,066.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by an amendment, if any, specifically referred to herein. I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigned more than twelve months prior to this application.

I acknowledge the duty to disclose all information known to me that is material to patentability in accordance with Title 37, Code of Federal Regulations, § 1.56.

FOREIGN PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

[x] no such foreign applications have been filed

[ ] such foreign application have been filed as follows:

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Application Number	Country	Date of Filing	Priority Claimed Under 35 USC 119
			___ Yes No ___
			___ Yes No ___
			___ Yes No ___

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Application Number	Country	Date of Filing

CLAIM FOR BENEFIT OF EARLIER U.S. PROVISIONAL APPLICATIONS

I hereby claim priority benefits under Title 35, United States Code §119(e), of any United States provisional patent application(s) listed below:

[x] no such U.S. provisional applications have been filed.

[ ] such U.S. provisional application have been filed as follows:

Application Number	Date of Filing	Priority Claimed Under 35 USC 119
		___ Yes No ___
		___ Yes No ___
		___ Yes No ___

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of the United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information that is material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56 which became available to me between the filing date of the prior application and the national or PCT international filing date of this application:

[x] no such U.S./PCT applications have been filed.

[ ] such U.S./PCT application have been filed as follows:

Application Number	Date of Filing	Status (Patented/Pending/Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the practitioners under Customer Number

07278

jointly, and each of them severally, my attorneys at law/patent agent(s), with full power of substitution, delegation and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, and to transact all business in the U. S. Patent and Trademark Office connected therewith.

Please mail all correspondence to **Customer Number** 07278, whose address is:

Darby & Darby P.C.
P.O. Box 5257
New York, New York 10150-5257

Full name of sole or first inventor Amir Shojaei	
Sole or first inventor's signature	Date Aug 30 '2006
Residence Phoenixville, Pennsylvania	
Citizenship Canada	
Mailing Address 241 Rivercrest Drive Phoenixville, Pennsylvania 19460	

Full name of second inventor, if any Rick Couch	
Second inventor's signature	Date
Residence Bryn Mawr, Pennsylvania	
Citizenship US	
Mailing Address 777 Woodleave Road Bryn Mawr, Pennsylvania 19010	

Full name of third inventor, if any Paul Hodgkins	
Third inventor's signature	Date
Residence Exton, Pennsylvania	
Citizenship UK	
Mailing Address 15 Landon Way Exton, Pennsylvania 19341	

Full name of fourth inventor, if any Stephanie Read	
Fourth inventor's signature	Date
Residence Philadelphia, Pennsylvania	
Citizenship US	
Mailing Address 237 Gay Street, Phiadelphia, Pennsylvania 19128	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION FOR PATENT APPLICATION

As the below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor of the subject matter which is described and claimed and for which a patent is sought on the invention entitled:

CONTROLLED DOSE DRUG DELIVERY SYSTEM

the specification of which was filed on May 12, 2006 as Application No. 11/383,066.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by an amendment, if any, specifically referred to herein. I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigned more than twelve months prior to this application.

I acknowledge the duty to disclose all information known to me that is material to patentability in accordance with Title 37, Code of Federal Regulations, § 1.56.

FOREIGN PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

[x] no such foreign applications have been filed

[ ] such foreign application have been filed as follows:

EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Application Number	Country	Date of Filing	Priority Claimed Under 35 USC 119
			___ Yes No ___
			___ Yes No ___
			___ Yes No ___

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Application Number	Country	Date of Filing

CLAIM FOR BENEFIT OF EARLIER U.S. PROVISIONAL APPLICATIONS

I hereby claim priority benefits under Title 35, United States Code §119(e), of any United States provisional patent application(s) listed below:

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[ ] such U.S. provisional application have been filed as follows:

Application Number	Date of Filing	Priority Claimed Under 35 USC 119
		___ Yes No ___
		___ Yes No ___
		___ Yes No ___

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of the United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose all information that is material to patentability in accordance with Title 37, Code of Federal Regulations, §1.56 which became available to me between the filing date of the prior application and the national or PCT international filing date of this application:

[x] no such U.S./PCT applications have been filed.

[ ] such U.S./PCT application have been filed as follows:

Application Number	Date of Filing	Status (Patented/Pending/Abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the practitioners under Customer Number

07278

jointly, and each of them severally, my attorneys at law/patent agent(s), with full power of substitution, delegation and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, and to transact all business in the U. S. Patent and Trademark Office connected therewith.

Please mail all correspondence to **Customer Number** 07278, whose address is:

Darby & Darby P.C.
P.O. Box 5257
New York, New York 10150-5257

Attorney Docket No.: 20342/1202653-US8

Full name of sole or first inventor	
Amir Shojaei	
Sole or first inventor's signature	Date
Residence	
Phoenixville, Pennsylvania	
Citizenship US	
Mailing Address	
241 Rivercrest Drive Phoenixville, Pennsylvania 19460	

Full name of second inventor, if any	
~~Rick Couch~~ RICHARD A. COUCH	
Second inventor's signature Richard A. Couch	Date 27-Sep-06
Residence	
Bryn Mawr, Pennsylvania	
Citizenship US	
Mailing Address	
777 Woodleave Road Bryn Mawr, Pennsylvania 19010	

Full name of third inventor, if any	
Paul Hodgkins	
Third inventor's signature	Date
Residence	
Exton, Pennsylvania	
Citizenship UK	
Mailing Address	
15 Landon Way Exton, Pennsylvania 19341	

Full name of fourth inventor, if any	
Stephanie Read	
Fourth inventor's signature	Date
Residence	
Philadelphia, Pennsylvania	
Citizenship US	
Mailing Address	
237 Gay Street, Phiadelphia, Pennsylvania 19128	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION FOR PATENT APPLICATION

As the below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor of the subject matter which is described and claimed and for which a patent is sought on the invention entitled:

CONTROLLED DOSE DRUG DELIVERY SYSTEM

the specification of which was filed on May 12, 2006 as Application No. 11/383,066.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by an amendment, if any, specifically referred to herein. I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigned more than twelve months prior to this application.

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Application Number	Country	Date of Filing

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I hereby appoint the practitioners under Customer Number

07278

jointly, and each of them severally, my attorneys at law/patent agent(s), with full power of substitution, delegation and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, and to transact all business in the U. S. Patent and Trademark Office connected therewith.

Please mail all correspondence to **Customer Number** 07278, whose address is:

Darby & Darby P.C.
P.O. Box 5257
New York, New York 10150-5257

Full name of sole or first inventor Amir Shojaei	
Sole or first inventor's signature	Date
Residence Phoenixville, Pennsylvania	
Citizenship US	
Mailing Address 241 Rivercrest Drive Phoenixville, Pennsylvania 19460	

Full name of second inventor, if any Rick Couch	
Second inventor's signature	Date
Residence Bryn Mawr, Pennsylvania	
Citizenship US	
Mailing Address 777 Woodleave Road Bryn Mawr, Pennsylvania 19010	

Full name of third inventor, if any Paul Hodgkins	
Third inventor's signature	Date 31 Aug '06
Residence Exton, Pennsylvania	
Citizenship UK	
Mailing Address 15 Landon Way Exton, Pennsylvania 19341	

Full name of fourth inventor, if any Stephanie Read	
Fourth inventor's signature	Date
Residence Philadelphia, Pennsylvania	
Citizenship US	
Mailing Address 237 Gay Street, Phiadelphia, Pennsylvania 19128	

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My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor of the subject matter which is described and claimed and for which a patent is sought on the invention entitled:

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07278

jointly, and each of them severally, my attorneys at law/patent agent(s), with full power of substitution, delegation and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, and to transact all business in the U. S. Patent and Trademark Office connected therewith.

Please mail all correspondence to **Customer Number** 07278, whose address is:

Darby & Darby P.C.
P.O. Box 5257
New York, New York 10150-5257

Full name of sole or first inventor Amir Shojaei	
Sole or first inventor's signature	Date
Residence Phoenixville, Pennsylvania	
Citizenship US	
Mailing Address 241 Rivercrest Drive Phoenixville, Pennsylvania 19460	

Full name of second inventor, if any Rick Couch	
Second inventor's signature	Date
Residence Bryn Mawr, Pennsylvania	
Citizenship US	
Mailing Address 777 Woodleave Road Bryn Mawr, Pennsylvania 19010	

Full name of third inventor, if any Paul Hodgkins	
Third inventor's signature	Date
Residence Exton, Pennsylvania	
Citizenship UK	
Mailing Address 15 Landon Way Exton, Pennsylvania 19341	

Full name of fourth inventor, if any Stephanie Read	
Fourth inventor's signature	Date 14 Sept 2006
Residence Philadelphia, Pennsylvania	
Citizenship US	
Mailing Address 237 Gay Street, Phiadelphia, Pennsylvania 19128	

Electronic Patent Application Fee Transmittal

Application Number:	11383066
Filing Date:	12-May-2006
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Filer:	Marie Louise Collazo/Mami Hasegawa
Attorney Docket Number:	20342/1202653-US8
Filed as Large Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	300	300
Utility Search Fee	1111	1	500	500
Utility Examination Fee	1311	1	200	200
Pages:				
Claims:				
Claims in excess of 20	1202	12	50	600
Miscellaneous-Filing:				
Late filing fee for oath or declaration	1051	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1020	1020
Miscellaneous:				
		Total in USD ($)		**2750**

Electronic Acknowledgement Receipt

EFS ID:	1270464
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Marie Louise Collazo/Mami Hasegawa
Filer Authorized By:	Marie Louise Collazo
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	24-OCT-2006
Filing Date:	12-MAY-2006
Time Stamp:	15:05:25
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$2750
RAM confirmation Number	55
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1	Applicant Response to Pre-Exam Formalities Notice	00892983.PDF	40331	no	4
Warnings:					
Information:					
2	Application Data Sheet	00892984.PDF	22496	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Extension of Time	00892989.PDF	15183	no	1
Warnings:					
Information:					
4		00892991.PDF	39788	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
5	Oath or Declaration filed	00892995.PDF	182717	no	16
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	8752	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	309267		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei

Application No.: 11/383,066 | Confirmation No.: 7083

Filed: May 12, 2006 | Art Unit: N/A

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM | Examiner: Not Yet Assigned

SECOND PRELIMINARY AMENDMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

LISTING OF CLAIMS

1. (Original) A pharmaceutical composition comprising:

(a) an immediate release bead comprising at least one amphetamine salt;

(b) a first delayed release bead comprising at least one amphetamine salt; and

(c) a second delayed release bead comprising at least one amphetamine salt;

wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt and the second delayed release bead provides sustained release of the at least one amphetamine salt.

2. (Original) The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

3. (Original) The pharmaceutical composition of claim 2, wherein the enteric coating is pH dependent.

4. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.

5. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coating.

6. (Original) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is bioequivalent to ADDERALL® XR followed by an immediate release amphetamine formulation administered 8 hours after the ADDERALL® XR;

wherein the combined dosage of the ADDERALL® XR and the immediate release formulation is equal to the dosage of the pharmaceutical composition.

7. (Original) The pharmaceutical composition of claim 1, wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a *d*-amphetamine C_{max} of about 50 ng/ml.

8. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1058 ng·hr/ml.

9. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1085 ng·hr/ml.

10. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine T_{max} is about 8.2 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

11. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine C_{max} after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 15 ng/ml.

12. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 354 ng·hr/ml.

13. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 373 ng·hr/ml.

14. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

15. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on a single core.

16. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.

17. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.

18. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.

19. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer over at least one enteric coating.

20. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.

21. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

22. (Original) The pharmaceutical composition of claim 21, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

23. (Original) The pharmaceutical composition of claim 1, wherein the composition does not exhibit a food effect.

24. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 12.5 mg.

25. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 18.75 mg.

26. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 25 mg.

27. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 31.25 mg.

28. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 37.5 mg.

29. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 43.75 mg.

30. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 50 mg.

31. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 62.5 mg.

32. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 75 mg.

33-58. (Canceled)

59. (New) A pharmaceutical composition comprising:

at least one amphetamine salt and a pharmaceutically acceptable carrier;

wherein the composition provides an about bioequivalent plasma level of amphetamine in a patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® XR and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL® XR.

60. (New) The composition of claim 59, wherein the composition provides an about bioequivalent plasma level of d-amphetamine in the patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® XR and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL® XR.

61. (New) The composition of claim 59, wherein the composition provides an about bioequivalent plasma level of l-amphetamine in the patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® XR and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL® XR.

REMARKS

Claims 1-32 and 59-61 are pending with this amendment. Claims 33-35 were inadvertently canceled in the First Preliminary Amendment, filed October 24, 2006. To correct this inadvertent error, original claims 33-35 are added back as new claims 59-61. To correct a typographical error in original claims 33-35, new claims 59-61 recite "ADDERALL® XR." Support for this correction can be found in the specification at, for example, page 5, lines 8-10 and page 34, line 21 to page 39, line 7. No new matter has been added.

Dated: October 26, 2006

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 — Confirmation No.: 7083

Filed: May 12, 2006 — Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM — Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. A check for the fee set forth in 1. 17(p), presently believed to be $180, is enclosed.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(i) a check in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

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[x] 5. Other information being provided for the examiner's consideration follows:

[An Office Action, dated June 21, 2006, which issued during the prosecution of European Application No. 99 970 594.0 which corresponds to the present application.]

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Early and favorable consideration is earnestly solicited.

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Dated: October 26, 2006

Respectfully submitted,

By _____ (53,970)

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(Use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	11/383,066-Conf. #7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	20342/1202653-US8

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

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	BA	WO00/35450	06-22-2000	Paul D Goldenheim		
	BB	EP0 640 337	03-01-1995	Minoru Okada		
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/445

A1

(11) International Publication Number: **WO 00/35450**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/US99/30305

(22) International Filing Date: 17 December 1999 (17.12.99)

(30) Priority Data:
60/112,667 17 December 1998 (17.12.98) US

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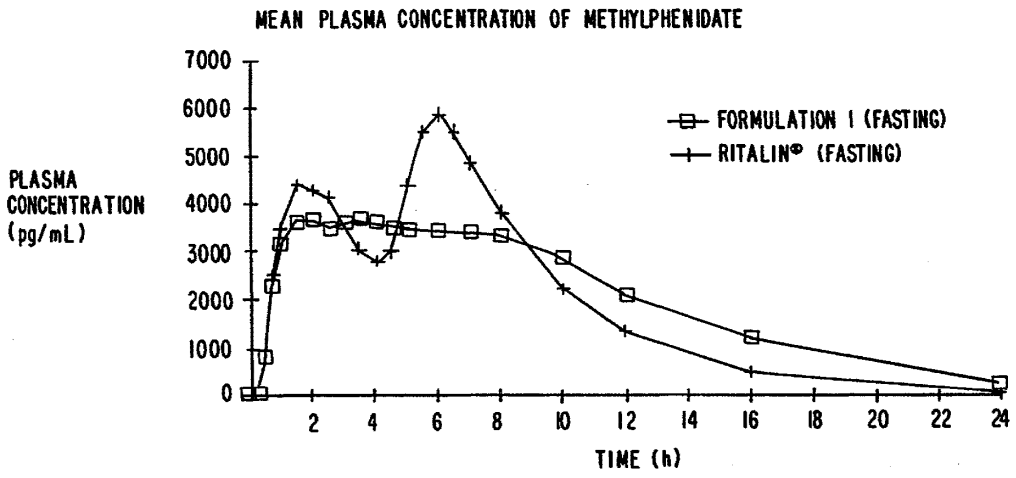
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: CONTROLLED/MODIFIED RELEASE ORAL METHYLPHENIDATE FORMULATIONS



(57) Abstract

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

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Controlled/Modified Release Oral Methylphenidate Formulations

This application claims priority from U.S. Provisional Application No. 60/112,667, filed December 17, 1998, the disclosure of which is hereby incorporated by reference.

Background of the Invention

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

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

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

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

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

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

Methylphenidate {dl-threo-methyl-2-phenyl-2-(2-piperidyl) acetate} is the psychostimulant used most frequently in the treatment of hyperactivity and attention deficit

disorder. It appears to have a higher incidence of positive effects and a lower incidence of adverse effects than other psychostimulants. The efficacy of methylphenidate ("MPH") in improving attention and behavioral symptoms has been supported by many studies.

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

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

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

OBJECTS AND SUMMARY OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

In certain further preferred embodiments, the formulation exhibits a bimodal release of active agent from the dosage form. Bimodal release of the active agent is characterized by the active agent being release from the dosage form by more than one distinct release rate. In

some embodiments, the release rates can be separated by a no-release or a substantially no-release interval, although this is not always necessary.

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

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

The present invention is further directed to an oral dosage form comprising an effective amount of methylphenidate or a pharmaceutically acceptable salt thereof and at least one release modifying material which causes the formulation to provide a in-vitro dissolution of the drug of from about 0 to about 45% released after 0.25 hour; from about 10 to about 50% released after about 1 hour; from about 30 to about 80% drug released after about 4 hours; not less than about 65% drug released after 8 hours; and not less than about 80% of the drug released after about 12 hours; the oral dosage form when orally administered to a human patient further providing a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration, and a duration of effect which lasts from about 8 to about 10 hours after oral administration, wherein the plasma concentration of the drug rapidly falls at about 8 to about 10 hours after oral administration to a level which is below the minimum effective plasma concentration. In certain preferred embodiments, the oral dosage form, when orally administered to a human patient, provides a peak plasma concentration from about 4 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral

dosage form. In certain preferred embodiments, the oral dosage form, when orally administered, provides a peak plasma concentration from about 5 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form. In certain further preferred embodiments, the oral dosage form provides peak plasma concentration from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration, and more preferably from about 1.0 to about 1.7 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration.

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

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

In certain preferred embodiments, an acrylic resin is utilized to provide the controlled slow release of therapeutically active ingredients over a predetermined or a specified period of time, the acrylic resin thereby comprising a significant part of the "base composition". Base compositions prepared from such acrylic resins provide sustained release of

therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration, generally oral administration, in humans or animals.

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION

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

The pharmacological properties of methylphenidate are essentially the same as the amphetamines. However, in contrast to amphetamines, methylphenidate is a mild CNS stimulant with more prominent effects on mental than motor activities. Methylphenidate

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

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

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

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

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

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

waning until after the school day ends, and preferably before dinner so that the drug does not have the side effect of acting as an appetite suppressant.

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

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

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

site. Under physiological conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium, providing for a steady state absorption.

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

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

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

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

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

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

Sustained Release Coatings

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

stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

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

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

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

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of

example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

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

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

Acrylic Polymers

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

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in

the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

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

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

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

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and

50% Eudragit® RS, and 10% Eudragit® RL: 90% Eudragit® RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

Plasticizers

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

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

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

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

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

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

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

The sustained release profile of the coated formulations of the invention can be altered, for example, by varying the amount of overcoating with the aqueous dispersion of

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

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

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

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color be added to Aquacoat via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to

water soluble polymer solution and then using low shear to the plasticized Aquacoat. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

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

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

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

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

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

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

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

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

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

In a particular preferred embodiment of the invention, the controlled/modified release methylphenidate formulation is prepared as a multilayered release (MLR) formulation comprising coated inert beads. A summary of one method of manufacturing such a formulation is outlined as follows. First, immediate release (IR) methylphenidate beads are prepared by spraying a solution of methylphenidate in water over sugar beads in a fluid bed dryer with a drug load of about 8%. The spray process is carried out in a fluid bed dryer,

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

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

Sustained Release Matrices

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

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

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

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

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

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

For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30°C to

about 100°C. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax.

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

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

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

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

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

In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A

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

Melt Extrusion Matrices

In certain preferred embodiments of the present invention, the sustained release matrices also be prepared via melt-granulation or melt-extrusion techniques. Such formulations are described in U.S. Patent Application Serial No. 08/334,209, filed November 4, 1994 and U.S. Patent Application Serial No. 08/833,948, filed April 10, 1997, both of which are hereby incorporated by reference in their entireties. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in U.S. Patent No. 4,861,598, assigned to the Assignee of the present invention and hereby incorporated by reference in its entirety.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids

during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

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

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

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

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, a therapeutically active agent, and an optional binder; heating the homogenous mixture; extruding the homogenous

mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

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

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

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

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

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

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

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

The sustained release formulations of the present invention preferably slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the therapeutically active agent, which is added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a

slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/ or the retardant material.

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

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

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

In certain preferred embodiments of the present invention, an effective amount of the drug in immediate release form is included in the drug formulation. The immediate release form of the drug is included in an amount which is effective to shorten the time to maximum concentration of the drug in the blood (e.g., plasma), such that time to T_{max} is shortened to a time of, e.g., from about 0.5 to about 2 hours. By including an amount of immediate release

drug in the formulation, the time to onset of action is significantly reduced, and is the same or earlier than that of the reference standard IR treatment (Ritalin IR).

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

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

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

Example 1
Methylphenidate HCl Immediate Release Beads

TABLE 1

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

Total	100.0

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

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

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

TABLE 2

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

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

Example 2

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

TABLE 3

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

The controlled-release coating is manufactured as follows:

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

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

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

TABLE 4

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

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

Examples 3 & 4

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

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

TABLE 5

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

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

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

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

TABLE 6

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

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

Example 5

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

TABLE 7

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

The enteric coating procedure is described below:

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

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

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

TABLE 8

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

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

Example 6
FORMULATIONS FOR CLINICAL TRIALS

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

Example 6A: (IR•EC•CR Beads)
Immediate Release (IR) Coating of Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

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

TABLE 9

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

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

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

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

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

The results are as follows:

TABLE 10

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

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

Example 6B: (IR + EC•CR Blend)
Combination of Immediate Release Methylphenidate Beads (IR) and Enteric Coated Controlled-Release (EC•CR) Methylphenidate Beads

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

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

Example 6C: (IR•CR Beads)
Immediate Release (IR) Coating of Controlled-Release (CR) Methylphenidate Beads

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

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

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

Table 11. Comparative Dissolution of Formulations

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

Example 7

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

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

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

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

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

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

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

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

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

This data is presented graphically in Figures 1-4. Figure 1 presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fasting conditions. Figure 2 presents the mean plasma concentration versus time for Formulation 1 and Ritalin® under fed conditions. Figure 3 presents the mean plasma concentration versus time for Formulation 1 under fed and fasting conditions. Figure 4 presents the mean plasma concentration versus time for Ritalin® under fed and fasting conditions.

Table 12. Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin®IR (fasting)

Sample Time (h)	Formulation 1			Ritalin		
	Concentration	SD(±)	CV(%)	Concentration	SD(±)	CV (%)
0.000	0.00	0.00	-	0.00	0.00	-
0.250	0.00	0.00	-	0.00	0.00	-
0.500	817.53	801.84	98.08	883.96	686.65	77.68
0.750	2268.79	1128.12	49.72	2485.74	828.38	33.33
1.00	3108.79	756.66	24.34	3468.74	1172.28	33.80
1.50	3597.88	740.36	20.58	4388.04	998.86	22.76
2.00	3675.60	1315.29	35.78	4289.39	1144.40	26.68
2.50	3469.81	882.62	25.44	4121.37	1014.57	24.62
3.00	3573.56	1031.61	28.87	3528.56	863.25	24.46
3.50	3637.01	1008.73	27.74	3020.93	716.36	23.71
4.00	3604.03	1071.59	29.73	2747.91	698.95	25.44
4.50	3494.44	1069.13	30.60	2958.49	799.89	27.04
5.00	3446.41	1069.50	31.03	4394.22	1603.40	36.49
5.50	-	-	-	5525.84	1766.58	31.97
6.00	3421.13	1166.25	34.09	5927.06	1955.99	33.00
6.50	-	-	-	5528.41	1758.49	31.81
7.00	3422.32	958.42	28.00	4860.45	1482.24	30.50
8.00	3338.59	724.49	21.70	3795.34	1500.79	39.54
10.0	2858.42	612.21	21.42	2223.48	926.11	41.65
12.0	2073.97	536.08	25.85	1334.71	523.37	39.21
16.0	1180.67	502.11	42.53	455.86	287.79	63.13
24.0	275.87	201.51	73.04	55.10	99.99	181.46

Table 13. Mean Plasma Concentrations (pg/mL) of Methylphenidate: Formulation 1 and Ritalin®IR (fed)

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

EXPERIMENTAL RESULTS

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

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

Analysis of Pharmacokinetic Data and Statistical Analysis

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

Time deviations during sampling for drugs with a $T_{max} \leq 4$ hours were treated as follows:

between 0 and 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of blood collection was < 10%. Above 6 hours post dose, the sampling time was used in the statistical analysis if the delay between the actual and scheduled time of plasma collection was < 15%. When sampling times were used

when previously described acceptance criteria, the corrected sampling items were used when performing pharmacokinetic parameters calculations. Sampling times are present in concentration tables and graphs of statistical report.

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

Areas under the Concentration-Time Curves

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

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

The AUC_{0-inf} was calculated as:

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

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

Maximum Observed Concentration and Time of Observed Peak Concentration

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

Half-Life and Elimination Rate Constant

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

TLIN and LQCT

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

Percent Drug Absorbed

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

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

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

RESULTS

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

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

Table 14. Pharmacokinetic Parameters for Formulation 1

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

Table 15. Pharmacokinetic Parameters for Ritalin® IR

Parameters	RITALIN® (fasting) Mean ± SD	CV (%)	RITALIN® (fed) Mean ± SD	CV (%)
AUC_{0-t} (pg.h/mL)	44644.22 ± 13806.82	30.93	52781.49 ± 15194.94	28.79
AUC_{0-inf} (pg.h/mL)	46466.23 ± 14012.73	30.16	54783.17 ± 15311.08	27.95
C_{max} (pg/mL)	6536.04 ± 1669.29	25.54	7571.74 ± 1534.58	20.27
T_{max} (h)	5.96 ± 0.54	9.09	3.54 ± 2.42	68.43
K_{el} (h^{-1})	0.2481 ± 0.0550	22.17	0.2449 ± 0.0719	29.37
$T_{½\ el}$ (h)	2.93 ± 0.71	24.10	3.08 ± 0.96	31.26

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

TABLE 16

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

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

TABLE 17

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

The results of the ANOVA and Duncan's Multiple Range Test performed on the lntransformed C_{max} data show a statistically significant difference between treatments for this parameter. According to Duncan's Multiple Range Test, the C_{max} of treatment 1 was not significantly different from the C_{max} of treatment 3. However, Duncan's Multiple Range Test detected statistically significant differences for C_{max} when comparing treatments 1 and 2 and

treatments 3 and 4. The statistical analyses performed on the data are summarized below in Table 18:

TABLE 18

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

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

The ANOVA and Duncan's Multiple Range Test performed on the $T_{½ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 3 for $T_{½ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 and treatments 3 and 4 for this parameter.

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

Summary and Analysis

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

Formulation 1 under fasting conditions are summarized in Table 20 below. Table 21 shows the comparative ratios for immediate release methylphenidate 10 mg (Ritalin® IR) and Formulation 1 under fed conditions.

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

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

Table 19. Formulation 1 (Fed) vs. Formulation 1 (Fast)

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

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

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

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

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

TABLE 20. Formulation 1 (Fast) vs Ritalin® (Fast)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	109.90%	111.65%	67.48%
90% Geometric C.I.[2]	102.59% - 117.74%	104.09% - 119.75%	60.28% - 75.54%

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

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

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

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

TABLE 21. Formulation 1 (Fed) vs. Ritalin® IR (Fed)

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	104.08%	105.86%	64.38%
90% Geometric C.I.[2]	97.15% - 111.50%	98.70% - 113.55%	57.51% - 72.07%

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

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

Conclusions

Review of individual plasma MPH time curves indicates the following:

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

A biphasic profile was apparent under fasted conditions in 7-10/12 subjects and in 8-10/12 under fed conditions. The mean curve showing a stable plateau under fasted conditions

is therefore not fully representative of the individual profiles. The enteric coat therefore gave rise to a biphasic profile in some subjects even under fasted conditions.

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

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

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

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

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

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

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

post-dose, are higher than those following the second dose of immediate release methylphenidate.

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

Example 8

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

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

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

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

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

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

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

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

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

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

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

Table 22. Pharmacokinetic Parameters for Formulation 2

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

Table 23. Pharmacokinetic Parameters for Formulation 3

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

Table 24. Pharmacokinetic Parameters for Ritalin SR®

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

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

TABLE 25

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

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

The ANOVA performed on the $T_{½ el}$ data detected a statistically significant difference between treatments for this parameter. Duncan's Multiple Range Test detected no statistically significant differences between treatments 1 and 2, treatments 3 and 4, and treatments 1 and 5 for $T_{½ el}$. However, Duncan's Multiple Range Test detected statistically significant differences between treatments 3 and 5 for this parameter.

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

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

TABLE 26

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

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

TABLE 27

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

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

The ANOVAs detected statistically significant differences between fed and fasting conditions, treatments 1 and 2, for the ln-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} and untransformed T_{max}, $T_{1/2el}$ and K_{el}. Duncan's Multiple Range Test detected statistically significant differences between treatments 1 and 2 for ln-transformed AUC_{0-t} and AUC_{0-inf} and untransformed T_{max}. However, Duncan's Multiple Range Test detected no statistically significant differences between treatments for ln-transformed C_{max} and untransformed $T_{1/2el}$

and K_{el}. All formulation ratios, as well as 90% geometric confidence intervals of the relative mean AUC_{0-t}, AUC_{0-inf} and C_{max} were found to be within the 80% to 125%, as is shown in Table 28 below. Thus, it appears that food increases the extent of absorption of methylphenidate for Formulation 2. However, this food effect was less than 20% on average.

TABLE 28

Formulation 2, Fed *versus* Fasting

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

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

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

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

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

TABLE 29

Formulation 3, Fed *versus* Fasting

	AUC_{0-t}	AUC_{0-inf}	C_{max}
Ratio[1]	113.35%	113.45%	117.96%
90% Geometric C.I.[2]	106.76% to120.33%	107.25% to 120.01%	109.35% to 127.25%

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

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

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

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

TABLE 30

Formulation 2 (Fasting) *versus* Ritalin SR (Fasting)

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

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

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

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

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

Table 31

Formulation 3 (Fasting) *versus* Ritalin SR (Fasting)

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

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

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

Conclusions

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

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

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

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

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

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

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

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

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

Conclusions- Examples 7 and 8

1. Formulation 1 has both a fast initial rate of rise, at least under fasted conditions and a prolonged duration. The transformation from a prolonged plateau profile under fasted conditions to a biphasic profile under fed conditions, is as predicted. Since these conditions represent the extremes of "food stress", one might predict that administration in association with normal meals and times would provide an intermediate profile. It is also possible that gastric emptying in children on a normal meal schedule will be faster than in adults fed a high fat meal – this will tend to make the second absorption phase occur earlier and produce lower concentrations from 12 hours onwards. Formulation 1 therefore meets the dual objectives of rapid onset and prolonged duration.

2. Formulation 2 is also very similar to Ritalin SR® under fasted conditions but shows a delayed peak under fed conditions such that plasma MPH concentrations are higher than Ritalin SR®(fasted) from 6 hours post dose onwards. The controlled release component in Formulation 2 is faster releasing than the one in Formulation 1 and plasma MPH concentrations are lower for Formulation 2 from about 10 hours post dose.

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

EXAMPLE 9

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

Assuming first order elimination of methylphenidate in human, the first order elimination rate constant was estimated from the linear terminal slope of plasma methylphenidate concentration curve (as plotted in log-linear paper) following oral administration of Ritalin IR. The absorption profile of Formulation 1 described above can be obtained following deconvolution calculation of the plasma drug concentration profile of the same using the Wagner-Nelsen Method ("Fundamentals of Clinical Pharmacokinetics" by John G. Wagner, Drug Intelligence Publications, Inc. 1975, page 174). The in-vitro drug dissolution profile correlates well with the in-vivo absorption profile, as shown in Figure 10. This correlation indicates that the in-vitro dissolution method can be used to predict in-vivo drug absorption.

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

Example 10

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

Table 32

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

Method of Manufacture:

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

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

Table 33- In-Vitro Dissolution

Hour	% Dissolved	Target % Dissolved
1	31	31
3	61	58
8	89	98

Example 11

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

TABLE 34

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

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

TABLE 35

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

Example 12

In Example 12, another method of producing controlled release Methylphenidate HCl tablets in accordance with the present invention is utilized, via a direct compression technique.

The ingredients of Example 12 are set forth in Table 36 below:

TABLE 36

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

Method of Manufacture:

The ingredients are blended. The blended material is compressed into tablets.

When these tablets were tested for dissolution using the same methodology noted above, the results were as set forth in Table 37 below:

TABLE 37

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

Example 13

In Example 13, the method of producing controlled release Methylphenidate HCl tablets in accordance with Example 12 is utilized, via a direct compression technique to produce another formulation. The ingredients of Example 13 are set forth in Table 38 below:

TABLE 38

Ingredient	mg/tablet
Methylphenidate HCl	15.0
Lactose DT	15.0
Eudragit L100-55	15.0
Methocel	52.0
Talc	2.0
Magnesium Stearate	1.0
	100

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

TABLE 39

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

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

WHAT IS CLAIMED IS:

1. An oral dosage form comprising an effective amount of methylphenidate or a pharmaceutically acceptable salt thereof and at least one release modifying material which causes the formulation to provide a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration, a peak plasma concentration from about 3 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form, wherein the peak plasma concentration is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration, and wherein the duration of effect provided by the methylphenidate contained in the formulation falls below effective plasma concentrations at about 8 to about 12 hours after oral administration.

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

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

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

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

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

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

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

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

8. An oral dosage form comprising an effective amount of methylphenidate or a pharmaceutically acceptable salt thereof and at least one release modifying material which causes the formulation to provide an in-vitro dissolution of the drug of from about 0 to about 45% released after 0.25 hour; from about 10 to about 50% released after about 1 hour; from about 30 to about 80% drug released after about 4 hours; not less than about 65% drug released after 8 hours; and not less than about 80% of the drug released after about 12 hours; the oral dosage form when orally administered to a human patient further providing a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration, and a duration of effect which lasts from about 8 to about 10 hours after oral administration, wherein the plasma concentration of the drug rapidly falls at about 8 to about 10 hours after oral administration to a level which is below the minimum effective plasma concentration.

9. The oral dosage form of claim 8, which when orally administered provides a peak plasma concentration from about 4 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form.

10. The oral dosage form of claim 8, which when orally administered provides a peak plasma concentration from about 5 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form.

11. The oral dosage form of claim 8, wherein the peak plasma concentration is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration.

12. The oral dosage form of claim 8, wherein the peak plasma concentration is from about 1.0 to about 1.7 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration.

FIG.1

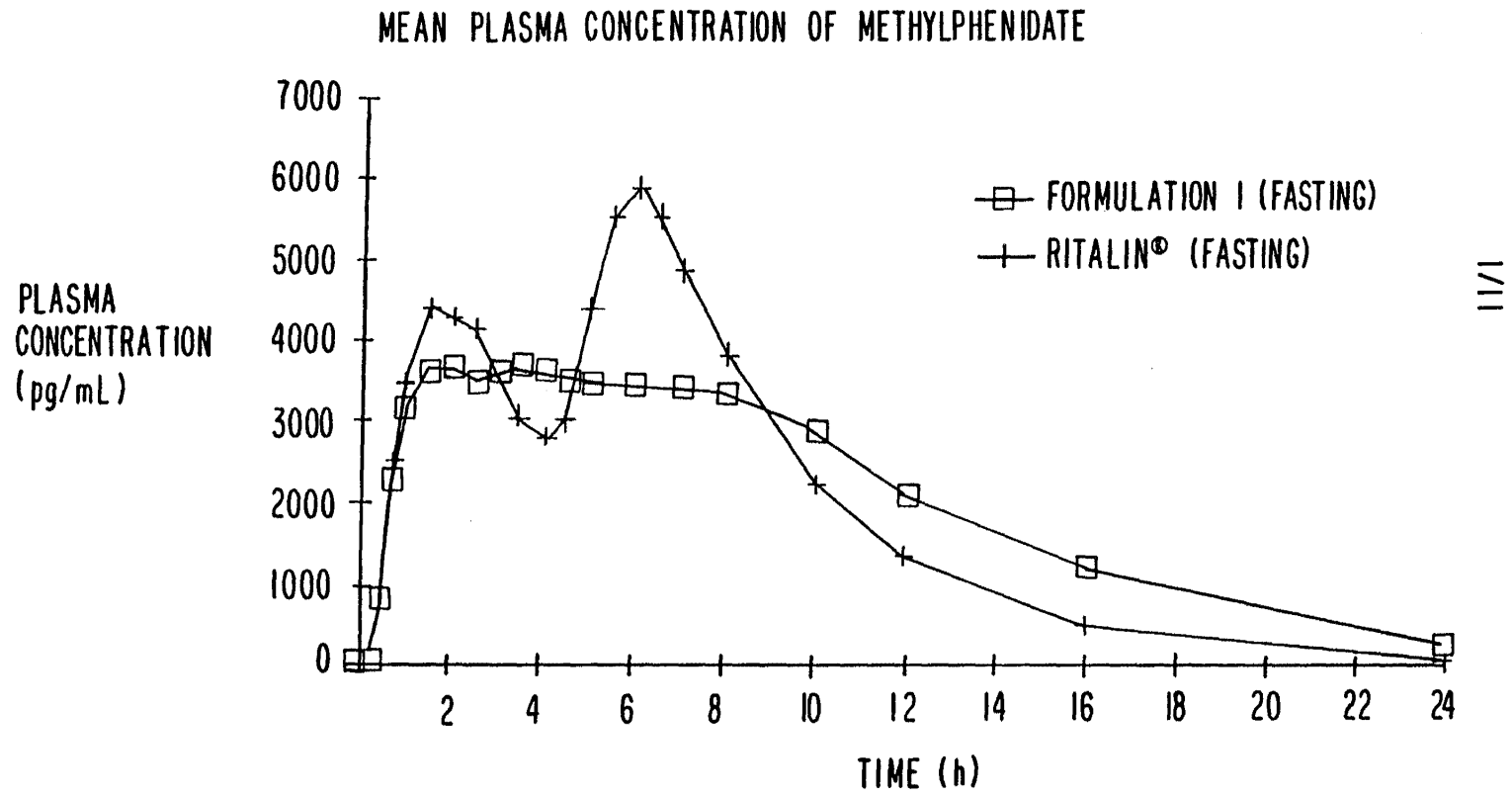


FIG. 2

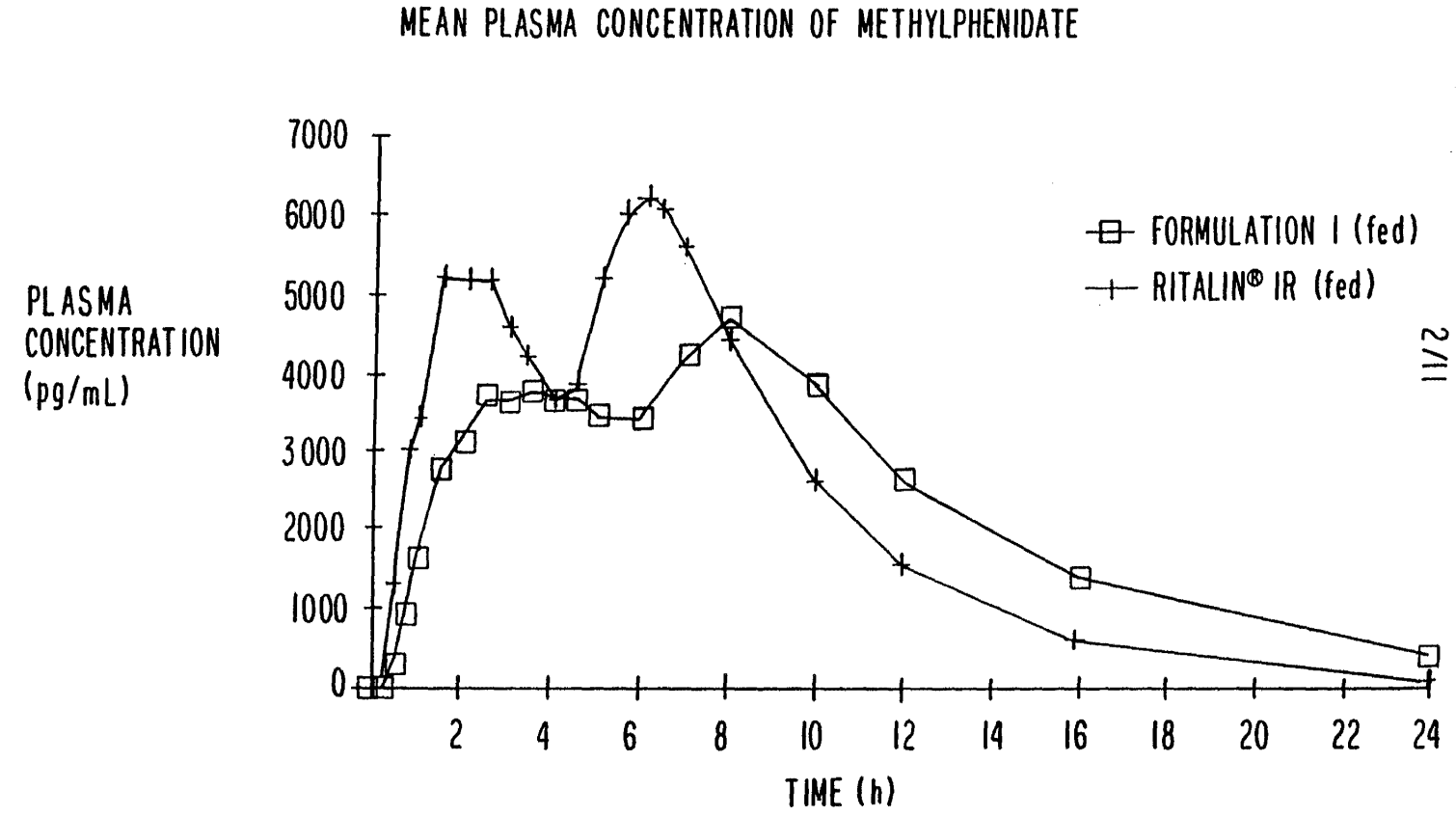


FIG.3

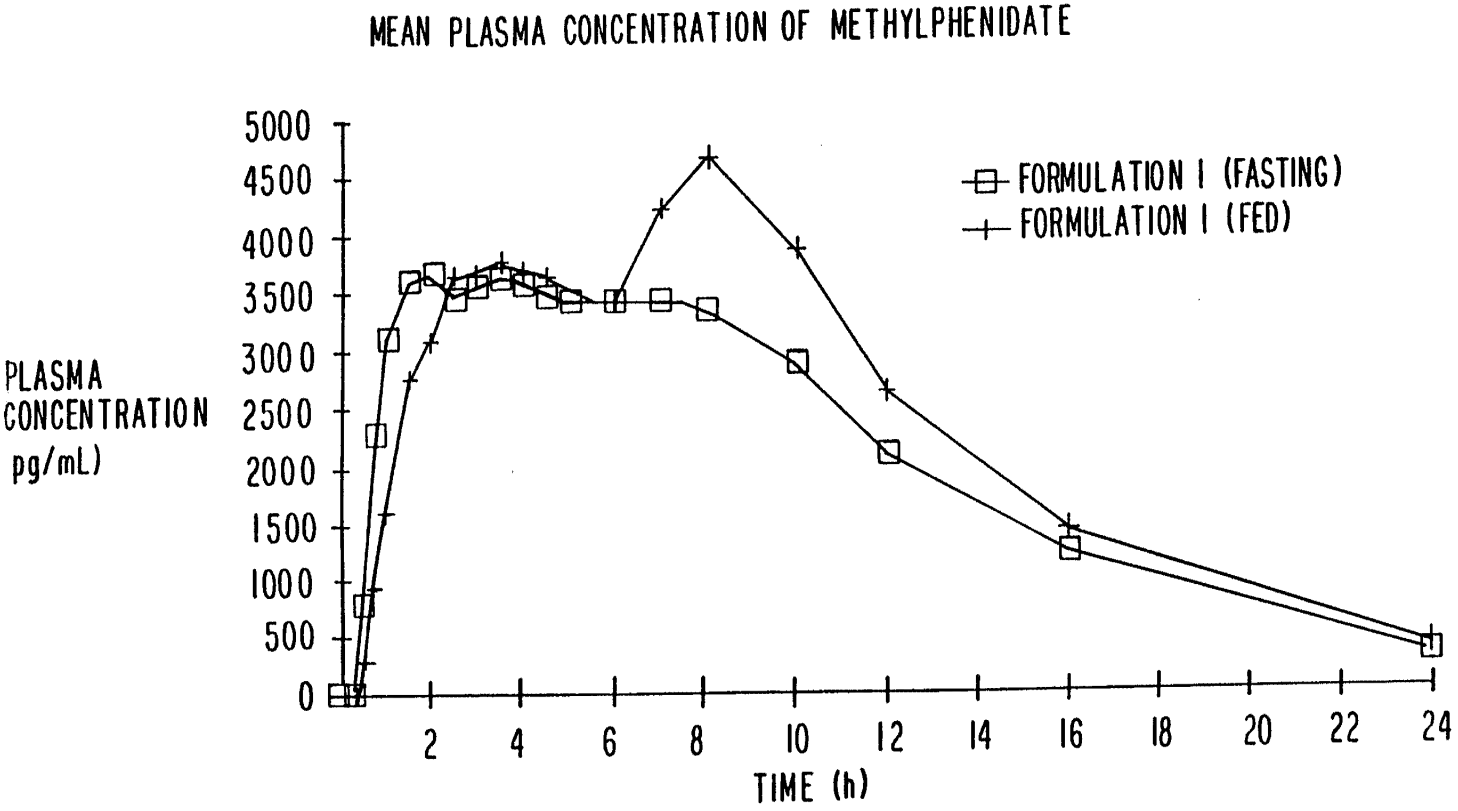


FIG.4

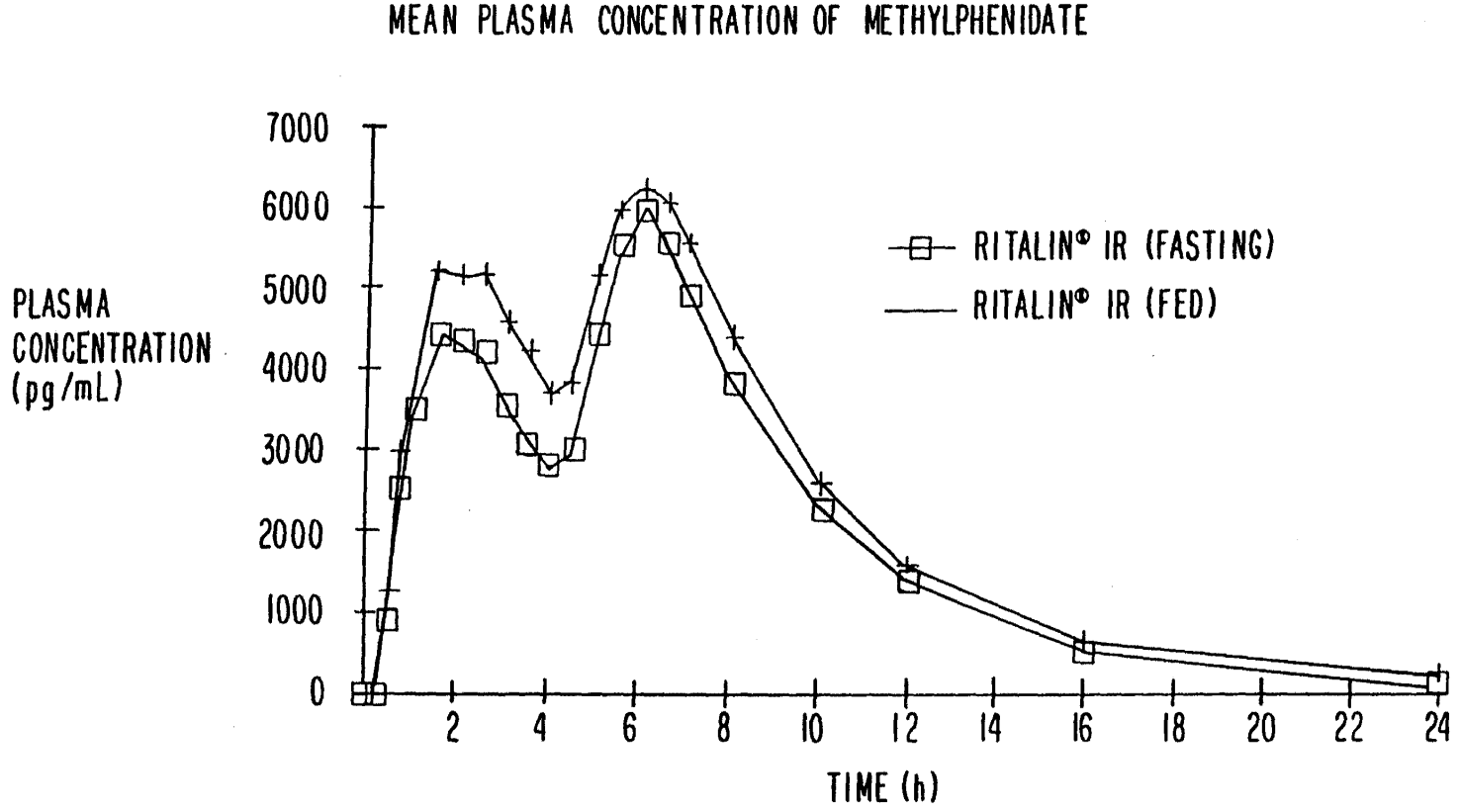


FIG.5

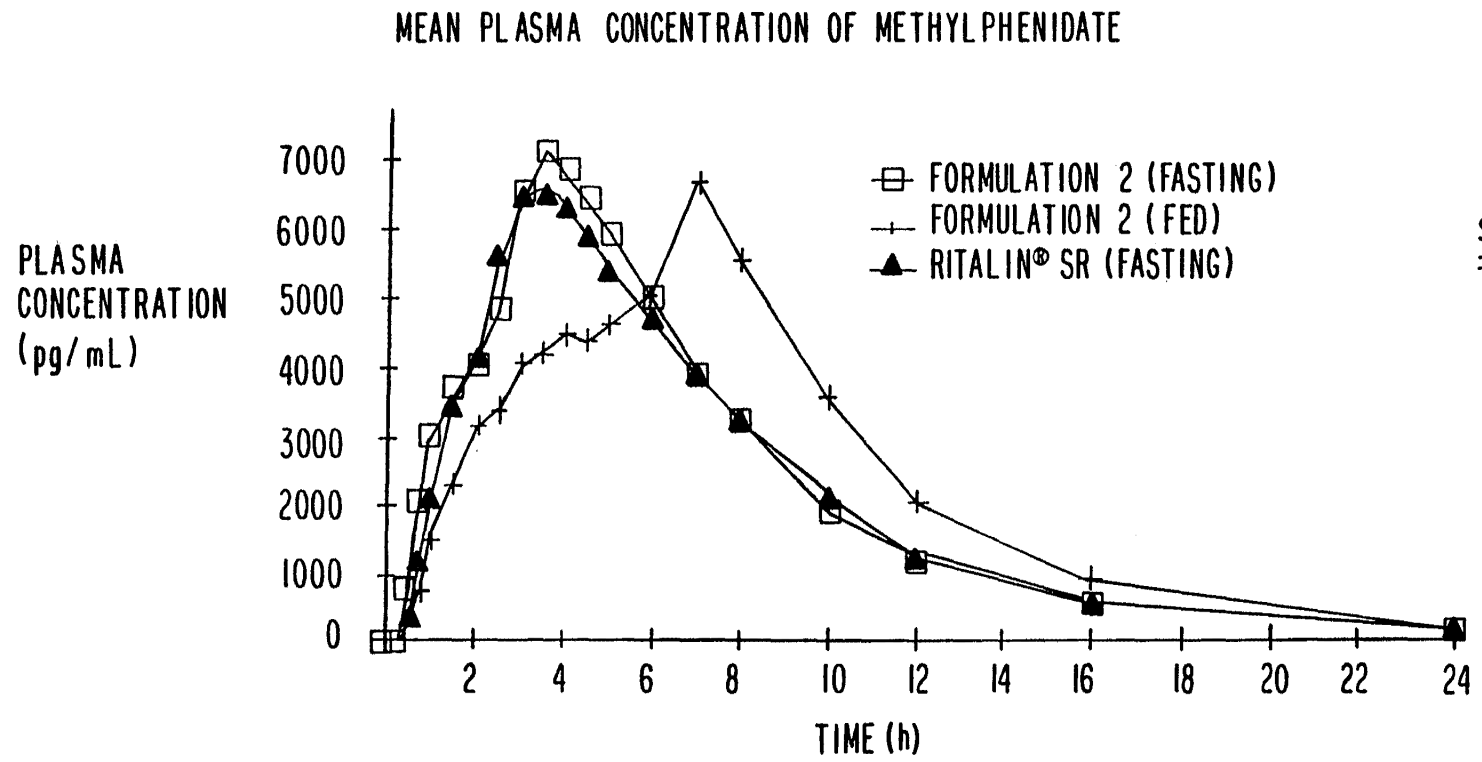


FIG.6

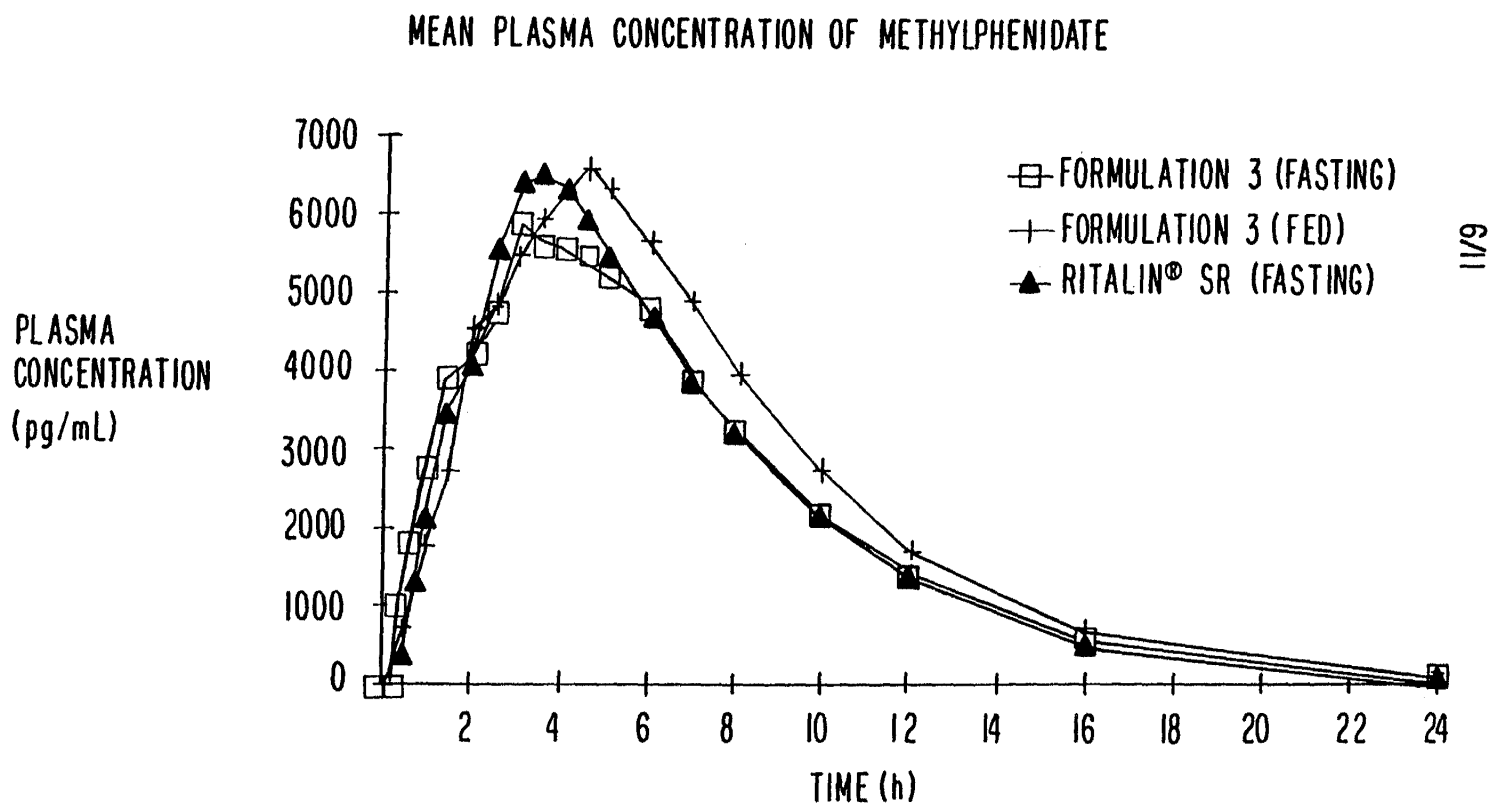


FIG. 7

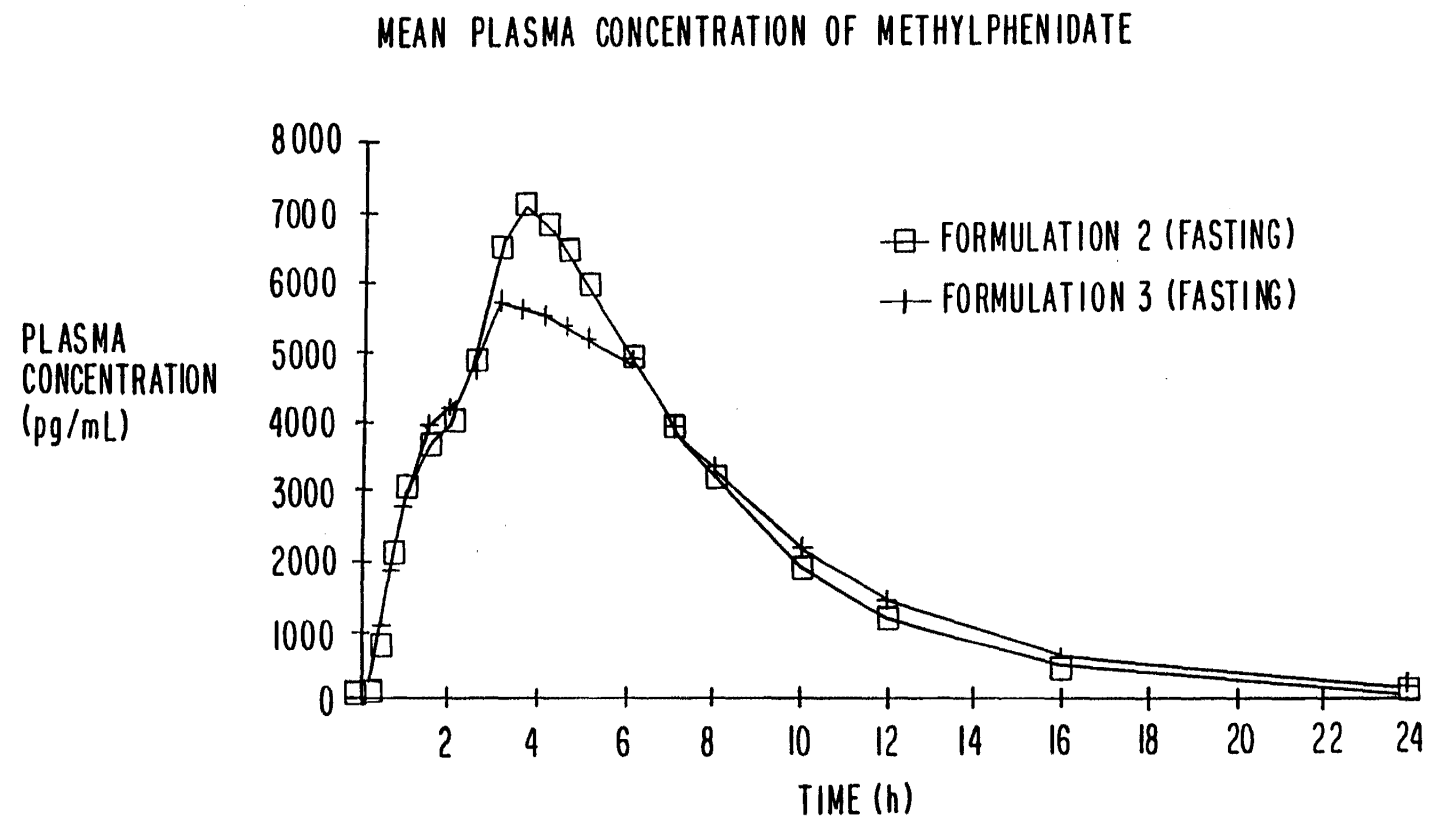


FIG.8

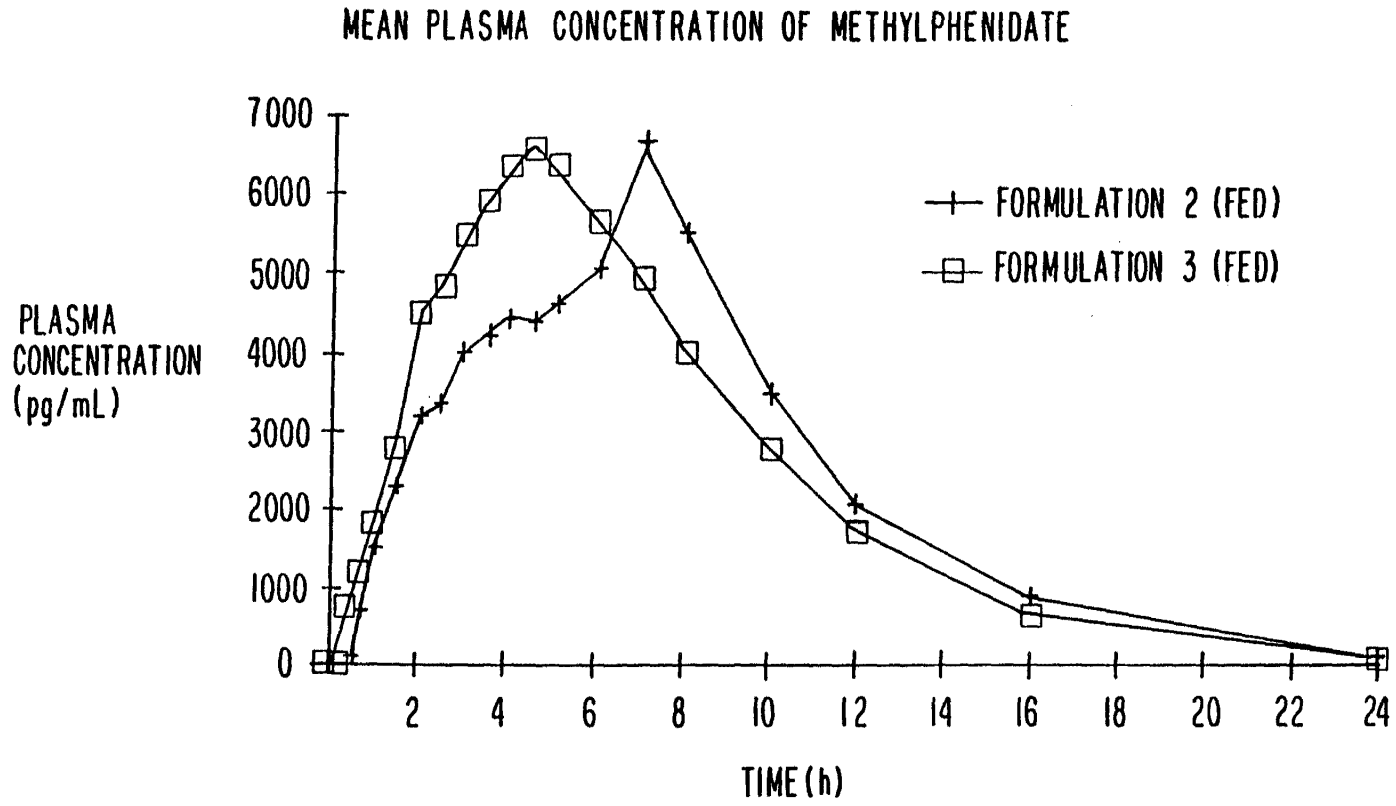


FIG.9

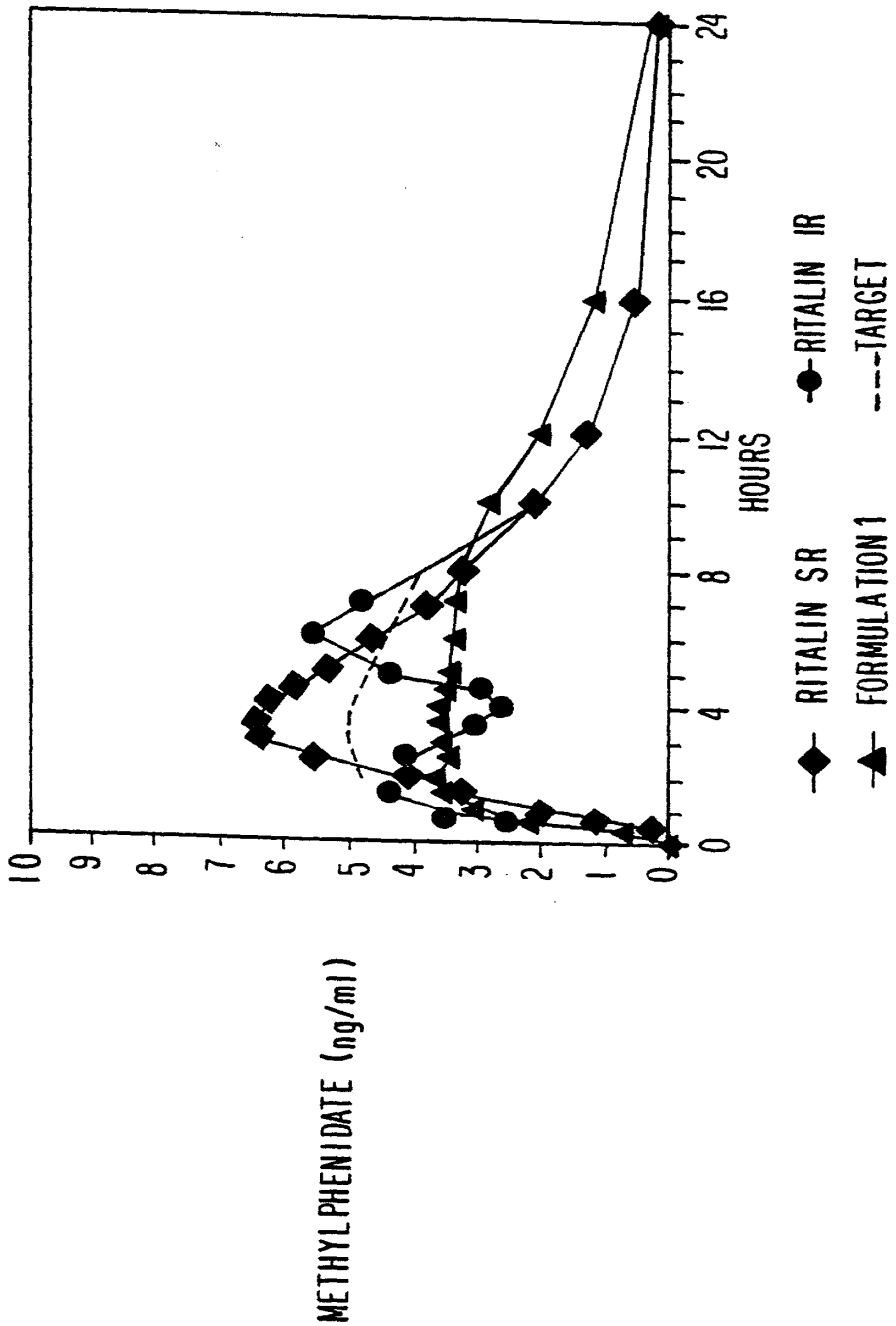

METHYLPHENIDATE (ng/ml)
0
1
2
3
4
5
6
7
8
9
10
HOURS
0
4
8
12
16
20
24
RITALIN SR
FORMULATION 1
RITALIN IR
TARGET

FIG.10

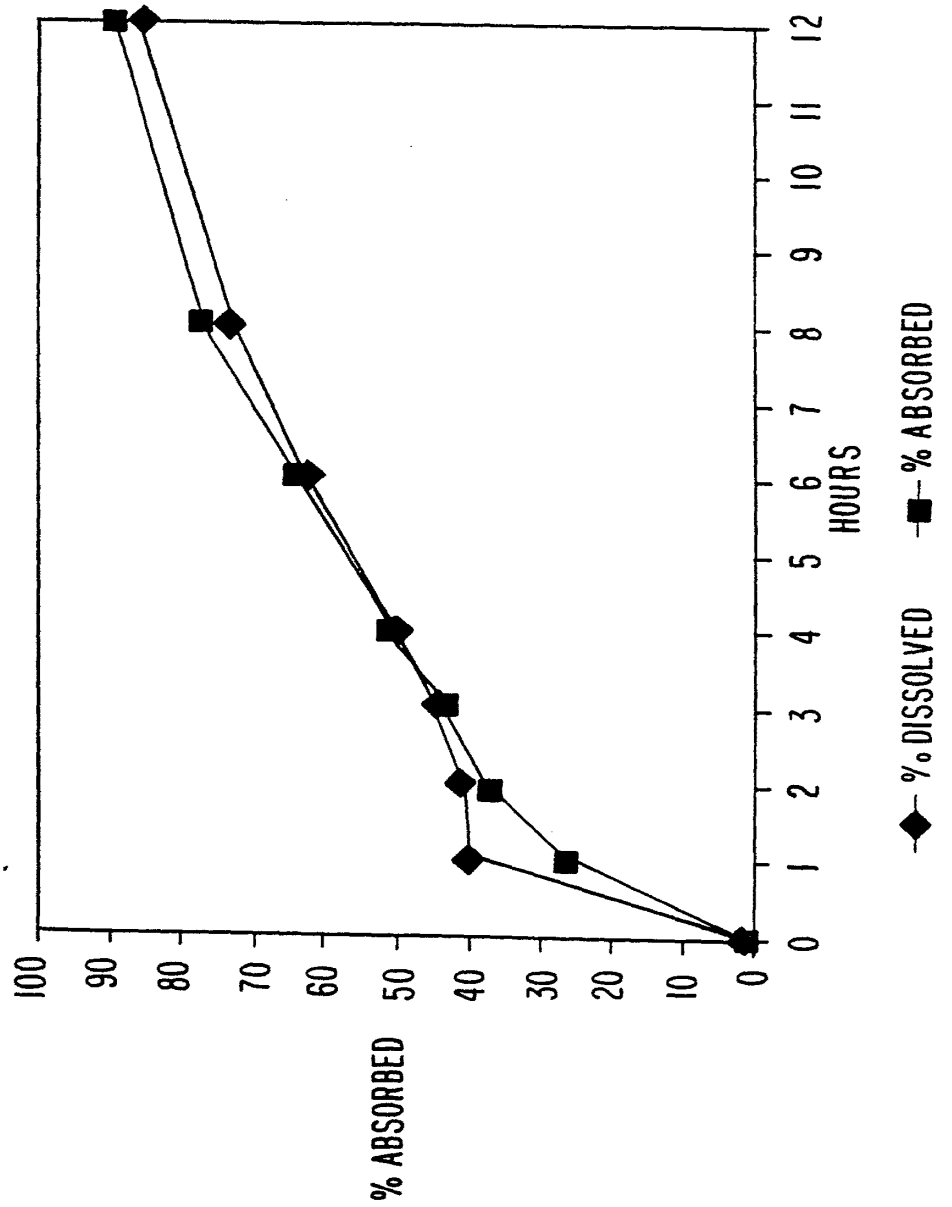
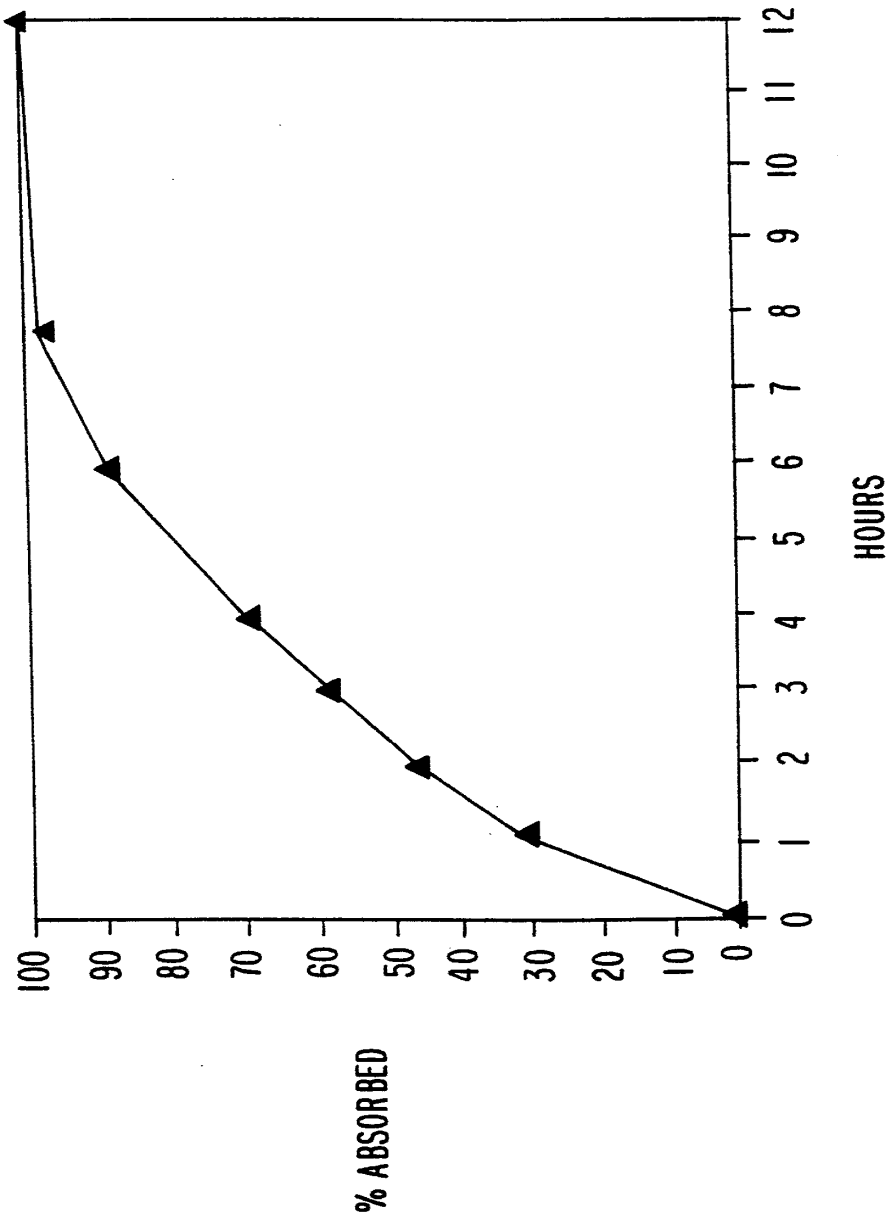

% ABSORBED
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
HOURS
% DISSOLVED
% ABSORBED

FIG. 11


% ABSORBED
100
90
80
70
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30
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2
3
4
5
6
7
8
9
10
11
12
HOURS

INTERNATIONAL SEARCH REPORT

Inte. ional application No.
PCT/US99/30305

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/445
US CL :514/317

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

HCAPLUS, MEDLINE, USPATFULL, BIOSCI- methylphenidate or other pharmacologically active agents in oral modified or controlled release dosage forms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,286,493 A (OSHLACK et al.) 15 February 1994, entire document, especially column 4 and claims 9, 23, and 32.	1-12
Y	Database HCAPLUS on STN, American Chemical Society, AN 1997:686114, ERRAMOUSPE et al. 'Effect on dissolution from halving methylphenidate extended-release tablets,' abstract, Ann. Pharmacother., 1997, 31(10), 1123-1126, see abstract.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 MARCH 2000	05 APR 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer M. MOEZIE Telephone No. (703) 308-1235

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 640 337 A2**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **94113304.3**

(51) Int. Cl.[6]: **A61K 9/28**, A61K 9/54

(22) Date of filing: **25.08.94**

(30) Priority: **25.08.93 JP 210453/93**

(43) Date of publication of application:
01.03.95 Bulletin 95/09

(84) Designated Contracting States:
BE CH DE ES FR GB IT LI NL SE

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(54) Controlled release-initiation and controlled release-rate pharmaceutical composition.

(57) A controlled release-initiation and controlled release-rate pharmaceutical composition in which a drug-containing composition is coated with a membrane layer comprising a water insoluble high polymer and silicone. The starting time for the release of drugs from the controlled release-initiation and controlled release-rate pharmaceutical composition of this invention and the drug-releasing rate thereafter can be controlled at will.

EP 0 640 337 A2

FIELD OF THE INVENTION

This invention relates to a controlled release-initiation and controlled release-rate pharmaceutical composition in which the starting time of the release of a drug from a preparation and the releasing rate of the drug after commencement of its release can be controlled at will.

BACKGROUND OF THE INVENTION

When a pharmaceutical composition is applied to patients, it is necessary to guarantee its efficacy and safety, as well as its specificity corresponding to each purpose.

Because of this, great concern has been directed toward the development of a system in which a pharmaceutical composition is designed in such a dosage form that a drug of interest is delivered to a target site for a necessary period of time in a required amount.

In order to satisfy such a requirement, sustained release preparations which can give prolonged duration of action of a drug by controlling the releasing rate of the drug from the preparation have already been developed and put into practical use. In addition, other types of pharmaceutical compositions which can control commencement of the release of drugs have been proposed in recent years, such as a preparation in which a drug is released when the coat membrane of the preparation is disrupted due to swelling of a water swelling material (JP-A-62-30709 (corresponding to U.S. Patent 4,871,549) and JP-A-4-338323; the term "JP-A" as used herein means an "unexamined published Japanese patent application"), a preparation in which a water repellent salt such as magnesium stearate, calcium stearate or the like fatty acid metal salt and an acrylic polymer are used in its coat membrane in order to give the preparation a lag time before the release of its ingredients (JP-A-4-235123 (corresponding to U.S. Patent 5,137,733)) and a preparation in which mutual interaction between Eudragit RS (manufactured by Rohm Pharma GMBH) and an organic acid is applied (Abstract of Papers, 7th Annual Meeting of The Japanese Society of Pharmacy, p.84, 1991).

However, since drugs are produced with various purposes, development of a pharmaceutical composition having various drug release mechanisms which can respond to these purposes has been called for in the field of medicine.

SUMMARY OF THE INVENTION

In view of the above, an object of the present invention is to provide a pharmaceutical composition of new construction in which the starting time of the release of a drug from the preparation and the releasing rate of the drugs, after commencement of its release, can be controlled.

With the aim of overcoming the aforementioned problems involved in conventional compositions, the inventors of the present invention have conducted intensive studies and found that, when a drug-containing composition is coated with a membrane layer comprising a water insoluble high polymer and silicone, the starting time of the release of the drug can be controlled at will by changing the thickness of the membrane, and the releasing rate of the drug after commencement of its release can be controlled by changing the composition of the membrane. The present invention has been accomplished on the basis of these findings.

Thus, the present invention provides a controlled release-initiation and controlled release-rate pharmaceutical composition in which a drug-containing composition is coated with a membrane layer which contains a water insoluble high polymer and silicone.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the results of dissolution tests carried out in Test Example 1 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 1 and comparative preparations obtained in Comparative Example 1. In Fig. 1, the curves, -o-, -□-, -●- and -■- stand for the results of Example 1-1, Example 1-2, Comparative Example 1-1 and Comparative Example 1-2, respectively.

Fig. 2 is a graph showing the results of tests of excretion into urine carried out in Test Example 2 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 2. In Fig. 2, the curves, -o- and -□- stand for the results of Example 2-1 and Example 2-2, respectively.

Fig. 3 is a graph showing the results of dissolution tests carried out in Test Example 3 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 3. In Fig. 3, the curves, -o-, -□- and -△- stand for the results of Example 3-1, Example 3-2 and Example 3-3, respectively.

Fig. 4 is a graph showing the results of dissolution tests carried out in Test Example 4 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 4. In Fig. 4, the curves, -o-, -□- and -△- stand for the results of Example 4-1, Example 4-2 and Example 4-3, respectively.

Fig. 5 is a graph showing the results of dissolution tests carried out in Test Example 5 using the controlled release-initiation and controlled release-

rate pharmaceutical compositions obtained in Example 5. In Fig. 5, the curves, -o-, -●-, -□- and -■- stand for the results of Example 5-1, Example 5-2, Example 5-3 and Example 5-4, respectively.

Fig. 6 is a graph showing the results of dissolution tests carried out in Test Example 6 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 6. In Fig. 6, the curves, -o-, -□- and -△- stand for the results of Example 6-1, Example 6-2 and Example 6-3, respectively.

Fig. 7 is a graph showing the results of dissolution tests carried out in Test Example 7 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 7. In Fig. 7, the curves, -o-, -□- and -△- stand for the results of Example 7-1, Example 7-2 and Example 7-3, respectively.

Fig. 8 is a graph showing the results of dissolution tests carried out in Test Example 8 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 8. In Fig. 8, the curves, -o- and -□- stand for the results of Example 8-1 and Example 8-2, respectively.

Fig. 9 is a graph showing the result of a dissolution test carried out in Test Example 9 using the controlled release-initiation and controlled release-rate pharmaceutical composition obtained in Example 9. In Fig. 9, the curve, -o-stands for the result of Example 9-1.

Fig. 10 is a graph showing the result of a dissolution test carried out in Test Example 10 using the controlled release-initiation and controlled release-rate pharmaceutical composition obtained in Example 10. In Fig. 10, the curve, -o- stands for the result of Example 10-1.

Fig. 11 is a graph showing the result of a dissolution test carried out in Test Example 11 using the controlled release-initiation and controlled release-rate pharmaceutical composition obtained in Example 11. In Fig. 11, the curve, -△- stands for the result of Example 11-1.

Fig. 12 is a graph showing the results of dissolution tests carried out in Test Example 12 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 1 and comparative preparations obtained in Comparative Example 2. In Fig. 12, the curves, -o-, -□-, -●- and -▲- stand for the results of Example 1-1, Example 1-2, Comparative Example 2-1 and Comparative Example 2-2, respectively.

Fig. 13 is a graph showing the results of dissolution tests carried out in Test Example 13 using the controlled release-initiation and controlled release-rate pharmaceutical compositions obtained in Example 1 and comparative preparations obtained in Comparative Example 3. In Fig. 13, the curves, -o-, -□-, -●- and -▲- stand for the results of Example 1-1, Example 1-2, Comparative Example 3-1 and Comparative Example 3-2, respectively.

DETAILED DESCRIPTION OF THE INVENTION

In the pharmaceutical composition of the present invention, a composition containing a drug of interest forms the central core of the preparation, which may be used in the crystalline form of the drug as such or as any of the usually used solid dosage forms such as fine granules, granules, beads, tablets and the like, by mixing the drug with pharmaceutically acceptable carrier, such as fillers, binders, lubricants and the like. As occasion demands, the central core composition may be coated with a water soluble high polymer, an acid soluble high polymer, an enteric high polymer, a water insoluble high polymer, wax or the like. Though not particularly limited, typical examples of the drug to be contained in the central core composition include: drugs for use in the treatment of central nervous system related diseases, such as hypnotics, sedatives, antiepileptics, antipyretics, analgesics, antiinflammatory agents, stimulants, antihypnotics, antidinics, pyschoneurosis treating drags and the like; drugs for use in the treatment of pripheral nervous system related diseases, such as skeletal muscle relaxants, autonomic agents, autonomic blocking agents, preparations containing plant extracts and the like; drugs for use in the treatment of sensory organ related diseases, such as opthalmic preparations, otorhinologic preparations and the like; drugs for use in the treatment of circulatory organ related diseases, such as cardiotonics, antiarrhythmic agents, diuretics, hypotensive agents, capillary stabilizers, vasoconstrictors, vasodilators, antiarteriosclerosis agents and the like; drugs for use in the treatment of respiratory organ related diseases, such as respiratory stimulants, respiratory depressants, antitussives and the like; drugs for use in the treatment of digestive organ related diseases, such as peptic ulcer treating drugs, stomachics, digestants, antracids, cathartics, cholagogues, intestinal function controlling drugs and the like; hormones, such as hormones and hormone antagonists and the like; drugs for use in the treatment of urogental organ and anus related diseases, such as urinary antiseptics oxytocics, urogenital drugs, hemorrhoid treating drugs, rectal preparations and the like; metabolic drugs, such as vitamins, aphrodisiacs, drugs for blood and body fluid, drugs for hepatic disease, antidotes, habitual intoxication treating agents, arthrifuges, enzyme preparations, antidiabetic drugs and the like; drugs for use in the treatment of tissue and cell function related diseases, such as cell activation drugs, antimalignant neoplastic

agents and the like; drugs for use in the treatment of pathogenic organisms related diseases, such as antibiotics, chemotherapeutic agents, antiprotozoan agents, anthelmintics and the like; and narcotics such as alkaloid-type narcotics, non-alkaloid-type narcotics and the like.

Illustrative examples of the water insoluble high polymer to be used in the membrane layer of the pharmaceutical composition of the present invention include: water insoluble high polymers such as a terpolymer composed of ethyl acrylate, methyl methacrylate and ethyl trimethylammonium chloride methacrylate, ethyl cellulose and the like; and enteric high polymers which are insoluble under acidic condition, such as a copolymer composed of methacrylic acid and ethyl acrylate, a copolymer composed of methacrylic acid and methyl methacrylate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethyl cellulose, cellulose acetate phthalate and the like. Of these high polymers, the ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer is particularly preferred, because it is most effective in prolonging the duration before drug-releasing while using (lag time) a lesser amount of coating. Preferably, the terpolymer has an ethyl acrylate:methyl methacrylate:ethyl trimethylammonium chloride methacrylate weight ratio of 1:2:0.1 to 1:2:0.2. Its commercially available examples include Eudragit RS and Eudragit RL (manufactured by Rohm Pharma GMBH).

The water insoluble high polymers exemplified above may be used alone or as a mixture of two or more, preferably in a range of from 20 to 95% by weight based on the total weight of the membrane layer.

The lag time and drug-releasing rate can be controlled by adding a small amount of a water soluble high polymer to the aforementioned water insoluble high polymer. Preferred examples of the water soluble high polymer include hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyethylene glycol and the like, preferably in a range of from 1 to 4% by weight based on the total weight of the membrane layer.

A silicone resin or a silicone oil, particularly dimethylpolysiloxane having a viscosity of 95 to 1,100 centistokes, is used preferably as the silicone to be contained in the membrane layer. The silicone may be contained in the membrane layer in an amount of preferably from 5 to 200% by weight, more preferably from 10 to 100% by weight, based on the aforementioned water insoluble high polymer.

It is preferable to add a silicone hold carrier to the membrane layer. Addition of a silicone hold carrier renders possible not only the inclusion of a large amount of silicone in the membrane layer but also the production of a highly stable pharmaceutical composition whose lag time before the release of a drug and the drug-releasing rate thereafter do not change even when a large amount of silicone is included in the membrane layer.

The silicone hold carrier is not particularly limited, provided that it can disperse and retain a liquid silicone in the water insoluble high polymer, but is selected preferably from talc, light anhydrous silicic acid, microcrystalline cellulose, starch and the like, of which light anhydrous silicic acid is particularly preferred. Preferably, the silicone hold carrier is used in the form of a fine powder having a large surface area. The silicone hold carrier is used in an amount of preferably from 0 to 200% by weight based on the silicone to be used.

A plasticizer may be further added to the membrane layer. Examples of useful plasticizers include triethyl citrate, triacetin, polyethylene glycol, castor oil, polyoxysorbitan monooleate, glycerine fatty acid ester and the like, which is preferably used in an amount of from 2 to 50% by weight based on the water insoluble high polymer.

The membrane layer to be coated may be used in an amount of generally from 2 to 200% by weight based on the central core weight, though it varies depending on the type of drug to be used, size and shape of the central core, intended lag time and release rate and composition of the membrane. In general, it is necessary to increase the coating quantity when a longer lag time is required, and the coating quantity also becomes large when the central core is small.

The pharmaceutical composition of the present invention can be produced by making central cores in the usual way and then coating each core with a membrane layer which contains a water insoluble high polymer and silicone.

Central cores can be produced by various known processes, such as a process in which fine granules and granules are produced by wet or dry granulation, a process in which these fine granules and granules are made into tablets by compression molding, a process in which tablets are produced by direct compression tableting, a process in which granules and beads are produced by rotary granulation, a process in which fine granules, granules and beads are produced by extrusion granulation and a process in which granules and beads are produced by extrusion granulation and subsequent treatment with Marumerizer (Fuji Paudal Co., Ltd.) or the like. Coating of the membrane layer may be effected by spray-coating the central cores with the membrane layer composition in a fluidized bed or a pan.

The controlled release-initiation and controlled release-rate pharmaceutical composition of the

present invention may be further combined with an immediate-release preparation or with another inventive controlled release-initiation and controlled release-rate pharmaceutical composition having different lag times.

The controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention once made into fine granules, granules, beads or tablets may be further made into a capsular dosage form by packing them into capsules, or the inventive fine granules, granules or beads may be made into tablets together with appropriate fillers, binders, lubricants and the like.

Since the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention can start the release of a drug from the preparation after a predetermined lag time, it can be made into sustained release preparations having various drug-releasing patterns by combining it with an immediate-release preparation or other preparations having different lag times. In addition, since the release of a drug can be set to a pulse type, the same blood concentration transition as the case of the administration of an immediate-release preparation several times a day can be obtained by once a day administration of the inventive preparation.

When a drug to which first-past effect exerts an adverse influence is applied in the form of a conventional sustained-release preparation, bioavailability thereof is extremely reduced. In accordance with the present invention, however, the decrease of bioavailability of such drug can be lessen because the inventive preparation can be set to a pulse type drug release pattern in which a drug of interest is released quickly at predetermined drug release starting times.

EXAMPLES

The following examples are provided to further illustrate the present invention. It is to be understood, however, that the examples are for purpose of illustration only and are not intended as a definition of the limits of the present invention. The term "%" as used herein means "% by weight".

EXAMPLE 1

A 1,500 g portion of trapidil was mixed with 100 g of hydroxypropyl cellulose and pulverized into fine powder. While spraying a solution of 20 g of hydroxypropyl cellulose dissolved in 380 g of ethyl alcohol, 1,280 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm, manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 5 hours of drying at 60 °C. The resulting granules were treated with screens and those which passed through a 12 mesh screen (sieve opening, 1.41 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as uncoated granules.

Next, 1,000 g of the uncoated granules thus obtained were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 8% hydroxypropylmethyl cellulose, 2% talc, 45% ethyl alcohol and 45% purified water until a 10% increase in the weight of the uncoated granules was attained. In this way, central cores of the present invention were obtained.

Thereafter, 250 g of the thus obtained central cores were put in a fluidised bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 60% (Example 1-1) or 90% (Example 1-2) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained in a dosage form of granules.

COMPARATIVE EXAMPLE 1

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Next, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 83% ethyl alcohol until a 60% (Comparative Example 1-1) or a 90% (Comparative Example 1-2) increase in the weight of the granules was attained. In this way, the comparative and controlled release-rate pharmaceutical compositions were obtained in a dosage form of granules.

TEST EXAMPLE 1

The inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 obtained in Example 1 and the silicone-free comparative pharmaceutical compositions 1-1 and 1-2 obtained in Comparative Example 1 were subjected to a trapidil dissolution test in accordance with the paddle method of The Pharmacopeia of Japonica, 12th revision, using phosphate buffer (pH 6.8) as a test solution. The results are shown in Fig. 1.

As is apparent from Fig. 1, in comparison with the comparative pharmaceutical compositions 1-1 and 1-2, the controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 of the present invention, having the same

coating ratios, are capable of releasing trapidil after a lag time.

EXAMPLE 2

The inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 obtained as granules in Example 1 were separately packed in hard capsules in such an amount that each capsule contained 150 mg of trapidil, thereby obtaining inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 2-1 and 2-2 in a dosage form of capsules.

TEST EXAMPLE 2

Each of the controlled release-initiation and controlled release-rate pharmaceutical compositions 2-1 and 2-2 of the present invention obtained in Example 2 was administered to healthy male adults in a dose of one capsule per adult in order to measure excretion rate of trapidil into urine. The results are shown in Fig. 2.

As is apparent from Fig. 2, trapidil in the inventive controlled release-initiation and controlled release-rate pharmaceutical compositions 2-1 and 2-2 is excreted after 3 and 7 hours of lag time, respectively.

EXAMPLE 3

A 1,500 g portion of trapidil was mixed with 100 g of hydroxypropyl cellulose and pulverized into fine powder. While spraying a solution of 20 g of hydroxypropyl cellulose dissolved in 380 g of ethyl alcohol, 1,280 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm, manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 5 hours of drying at 60 °C. The resulting granules were treated with screens and those which passed through a 12 mesh screen (sieve opening, 1.41 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as central cores of the present invention.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 6% Eudragit RS, 4% dimethylpolysiloxane, 2% light anhydrous silicic acid, 0.5% glycerine fatty acid ester and 87.5% ethyl alcohol until a 50% (Example 3-1), a 70% (Example 3-2) or a 90% (Example 3-3) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained.

TEST EXAMPLE 3

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 3-1, 3-2 and 3-3 of the present invention obtained in Example 3 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 3.

As is apparent from Fig. 3, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases. In addition, release of trapidil after lag time occurs at the same rate independent of the coating ratio.

EXAMPLE 4

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 20% Eudragit RS, 4% dimethylpolysiloxane, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 60% increase in the weight of the granules was attained, thereby obtaining a controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention (Example 4-1).

In the same manner, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 14% Eudragit RS, 6% dimethylpolysiloxane, 3% light anhydrous silicic acid, 2% glycerine fatty acid ester and 75% ethyl alcohol until a 70% increase in the weight of the granules was attained, thereby obtaining the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention (Example 4-2).

Also, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 10% Eudragit RS, 9% dimethylpolysiloxane, 5% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 100% increase in the weight of the granules was attained, thereby obtaining the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention (Example 4-3).

TEST EXAMPLE 4

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 4-1, 4-2 and 4-3 of the present invention obtained in Example 4 was measured in the same manner as described in Test

Example 1. The results are shown in Fig. 4.

As is apparent from Fig. 4, each of the inventive pharmaceutical compositions releases trapidil after a lag time, and the releasing rate of trapidil after the lag time can be controlled by changing the membrane composition.

EXAMPLE 5

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 16% Eudragit RS, 4% dimethylpolysiloxane, 3% light anhydrous silicic acid, 2% glycerine fatty acid ester and 75% ethyl alcohol until a 50% (Example 5-1), an 80% (Example 5-2), a 110% (Example 5-3) or a 140% (Example 5-4) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained.

TEST EXAMPLE 5

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 5-1, 5-2, 5-3 and 5-4 of the present invention obtained in Example 5 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 5.

As is apparent from Fig. 5, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases, thus showing that the release-starting time can be changed at will.

EXAMPLE 6

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RL, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 60% (Example 6-1), an 80% (Example 6-2) or a 100% (Example 6-3) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained.

TEST EXAMPLE 6

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 6-1, 6-2 and 6-3 of the present invention obtained in Example 6 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 6.

As is apparent from Fig. 6, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases, thus showing that the release-starting time can be changed at will.

EXAMPLE 7

A 400 g portion of phenylpropanolamine hydrochloride was mixed with 800 g of corn starch and pulverized into fine powder. While spraying a solution of 40 g of hydroxypropyl cellulose dissolved in 760 g of ethyl alcohol, 1,280 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm, manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 5 hours of drying at 60 °C. The resulting granules were treated with screens and those which passed through a 12 mesh screen (sieve opening, 1.41 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as uncoated granules.

Next, 1,000 g of the uncoated granules thus obtained were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 8% hydroxypropylmethyl cellulose, 2% talc, 45% ethyl alcohol and 45% purified water until a 10% increase in the weight of the uncoated granules was attained. In this way, central cores of the present invention were obtained.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 40% (Example 7-1), an 80% (Example 7-2) or a 120% (Example 7-3) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained in a dosage form of granules.

TEST EXAMPLE 7

Dissolution of phenylpropanolamine hydrochloride from the controlled release-initiation and controlled release-rate pharmaceutical compositions 7-1, 7-2 and 7-3 of the present invention obtained in

Example 7 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 7.

As is apparent from Fig. 7, each of the inventive pharmaceutical compositions releases phenylpropanolamine hydrochloride quickly after a lag time, and the lag time becomes longer as the coating ratio increases. In addition, the release of phenylpropanolamine hydrochloride after lag time occurs at the same rate independent of the coating ratio.

EXAMPLE 8

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12.5% Eudragit RS, 5% dimethylpolysiloxane, 6.25% talc, 1.25% glycerine fatty acid ester and 75% ethyl alcohol until a 40% (Example 8-1) or a 65% (Example 8-2) increase in the weight of the granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical compositions of the present invention were obtained in a dosage form of granules.

TEST EXAMPLE 8

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical compositions 8-1 and 8-2 of the present invention obtained in Example 8 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 8.

As is apparent from Fig. 8, each of the inventive pharmaceutical compositions releases trapidil quickly after a lag time, and the lag time becomes longer as the coating ratio increases, thus showing that the release-starting time can be changed at will.

EXAMPLE 9

A 150 g portion of diclofenac sodium salt was mixed with 1,295 g of corn starch and pulverized into a fine powder. While spraying a solution of 33 g of hydroxypropyl cellulose dissolved in 627 g of ethyl alcohol, 1,051 g of the fine powder was applied to 400 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm, manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 4 hours of drying at 60 °C. The resulting granules were treated with screens and those which passed through a 14 mesh screen (sieve opening, 1.19 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as central cores.

Thereafter, 500 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until an 80% increase in the weight of the granules was attained (Example 9-1). In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition 9-1 of the present invention was obtained in a dosage form of granules.

TEST EXAMPLE 9

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical composition 9-1 of the present invention obtained in Example 9 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 9.

As is apparent from Fig. 9, the inventive pharmaceutical composition releases diclofenac sodium salt after 4 hours of lag time.

EXAMPLE 10

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 6.75% ethyl cellulose, 0.45% polyvinyl pyrrolidone, 4.8% dimethylpolysiloxane, 2.4% light anhydrous silicic acid, 0.6% glycerine fatty acid ester and 85% ethyl alcohol until a 70% increase in the weight of the granules was attained (Example 10-1). In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

TEST EXAMPLE 10

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical composition 10-1 of the present invention obtained in Example 10 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 10.

As is apparent from Fig. 10, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention releases trapidil quickly after a lag time.

EXAMPLE 11

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit S100, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 100% increase in the weight of the granules was attained (Example 11-1). In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

TEST EXAMPLE 11

Dissolution of trapidil from the controlled release-initiation and controlled release-rate pharmaceutical composition 11-1 of the present invention obtained in Example 11 was measured in the same manner as described in Test Example 1. The results are shown in Fig. 11.

As is apparent from Fig. 11, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention releases trapidil quickly after a lag time.

EXAMPLE 12

A 900 g portion of theophylline was mixed with 100 g of talc and pulverized into fine powder. While spraying a solution of 20 g of hydroxypropyl cellulose dissolved in 380 g of ethyl alcohol, 800 g of the fine powder was applied to 200 g of Nonpareil 103 (spherical sugar having a particle size of 500 to 710 μm, manufactured by Freund Industrial Co., Ltd.) to effect rolling granulation, followed by 3 hours of drying at 60 °C. The resulting granules were treated with screens and those which passed through a 14 mesh screen (sieve opening, 1.19 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as central cores.

Thereafter, 400 g of the thus obtained uncoated granules were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 8% dimethylpolysiloxane, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 25% increase in the weight of the uncoated granules was attained. In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

EXAMPLE 13

A 500 g portion of pranoprofen was mixed with 500 g of microcrystalline cellulose, and the mixture was kneaded by adding 200 g of purified water, made into granules by extrusion granulation using a 0.8 mm screen and then treated with Marumerizer. After 5 hours of drying at 60 °C, the resulting granules were treated with screens and those which passed through a 14 mesh screen (sieve opening, 1.19 mm) but not a 32 mesh screen (sieve opening, 0.50 mm) were collected as uncoated granules.

Thereafter, 500 g of the thus obtained uncoated granules were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 14% Eudragit RS, 7% dimethylpolysiloxane, 3% light anhydrous silicic acid, 1% glycerine fatty acid ester and 75% ethyl alcohol until a 50% increase in the weight of the uncoated granules was attained. In this way, a controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of granules.

EXAMPLE 14

A mixture consisting of 100 g chlorpheniramine maleate, 400 g microcrystalline cellulose, 490 g lactose and 10 g magnesium stearate was applied to a tablet machine to obtain uncoated tablets (80 mg/tablet) as central cores.

Thereafter, 500 g of the thus obtained central cores were put in a coating pan and sprayed with a coating solution composed of 7.5% Eudragit RS, 3% dimethylpolysiloxane, 1.5% light anhydrous silicic acid, 0.5% glycerine fatty acid ester and 87.5% ethyl alcohol until the weight of each tablet was increased to 10 mg. In this way, the controlled release-initiation and controlled release-rate pharmaceutical composition of the present invention was obtained in a dosage form of tablets.

COMPARATIVE EXAMPLE 2

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester, 8% corn oil and 75% ethyl alcohol until a 60% (Comparative Example 2-1) or 90% (Comparative Example 2-2) increase in the weight of the granules was attained. In this way, comparative pharmaceutical compositions in which silicone in the coating membrane was replaced by corn oil were obtained in a dosage form

of granules.

TEST EXAMPLE 12

Dissolution of trapidil from the comparative pharmaceutical compositions 2-1 and 2-2 obtained in Comparative Example 2, in which silicone in the coating membrane was replaced by corn oil, was measured in the same manner as described in Test Example 1. The results are shown in Fig. 12, together with the results of the controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 of the present invention obtained in Example 1.

As is apparent from Fig. 12, the lag time prior to the commencement of drug-releasing cannot be obtained in the corn oil-applied comparative pharmaceutical compositions.

COMPARATIVE EXAMPLE 3

Central cores containing trapidil were obtained in the same manner as described in Example 1.

Thereafter, 250 g of the thus obtained central cores were put in a fluidized bed coating apparatus and sprayed with a coating solution composed of 12% Eudragit RS, 4% light anhydrous silicic acid, 1% glycerine fatty acid ester, 8% liquid paraffin and 75% ethyl alcohol until a 60% (Comparative Example 3-1) or a 90% (Comparative Example 3-2) increase in the weight of the granules was attained. In this way, comparative pharmaceutical compositions in which silicone in the coating membrane was replaced by liquid paraffin were obtained in a dosage form of granules.

TEST EXAMPLE 13

Dissolution of trapidil from the comparative pharmaceutical compositions 3-1 and 3-2 obtained in Comparative Example 3, in which silicone in the coating membrane was replaced by liquid paraffin, was measured in the same manner as described in Test Example 1. The results are shown in Fig. 13, together with the results of the controlled release-initiation and controlled release-rate pharmaceutical compositions 1-1 and 1-2 of the present invention obtained in Example 1.

As is apparent from Fig. 13, the lag time prior to the commencement of drug-releasing cannot be obtained in the liquid paraffin-applied comparative pharmaceutical compositions.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

Claims

1. A controlled release-initiation and controlled release-rate pharmaceutical composition comprising a drug-containing composition coated with a membrane layer comprising a water insoluble high polymer and silicone.

2. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 1, wherein said water insoluble high polymer is at least one compound selected from the group consisting of ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer, ethyl cellulose and enteric high polymer.

3. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 2, wherein said enteric high polymer is methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethyl cellulose or cellulose acetate phthalate.

4. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 1, wherein said silicone is a silicone resin or a silicone oil.

5. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 1, wherein said membrane layer contains a silicone hold carrier.

6. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 1, wherein said drug-containing composition comprises a therapeutically-effective amount of a drug and a pharmaceutically acceptable carrier.

7. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 1, wherein said membrane layer is present in an amount of from 2% to 200% based on the weight of the drug-containing composition, said water insoluble high polymer is present in an amount of from 20% to 95% by weight based on the total weight of the membrane layer, and said silicone is present in an amount of from 5% to 200% by weight based on the weight of the water insoluble high polymer.

8. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 1, wherein said membrane layer further comprises a water soluble high polymer.

9. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 8, wherein said water soluble high polymer is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone and polyethylene glycol.

10. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 2, wherein said water insoluble high polymer is ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer.

11. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 10, wherein said terpolymer has an ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate weight ratio of from 1:2:0.1 to 1:2:0.2.

12. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 4, wherein said silicone is dimethylpolysiloxane.

13. The controlled release-initiation and controlled release-rate pharmaceutical composition as claimed in claim 5, wherein said silicone hold carrier is selected from the group consisting of talc, light anhydrous silicic acid, microcrystalline cellulose and starch.

14. A method for preparing a pharmaceutical composition according to any preceding claim, comprising the step of coating a drug-containing composition with a membrane-forming composition comprising a water insoluble high polymer and a silicone.

15. The method according to claim 14, wherein the step of coating is controlled so that the membrane has a predetermined thickness to enable the starting time at which the drug is released to be controlled; and the composition of the membrane layer is formulated to enable the rate at which the drug is released to be controlled.

16. The method according to claim 14 or claim 15, wherein the membrane is used in an amount of 2% to 200% by weight based on the drug-containing composition weight.

17. The method according to claim 14, wherein the water insoluble high polymer is at least one compound selected from the group consisting of ethyl acrylate/methyl methacrylate/ethyl trimethylammonium chloride methacrylate terpolymer, ethyl cellulose and enteric high polymer.

18. The method according to claim 17, wherein said enteric high polymer is methacrylic acid/ethyl acrylate copolymer, methacrylic acid/methyl methacrylate copolymer, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethyl cellulose or cellulose acetate phthalate.

19. The method according to claim 14, wherein said silicone is a silicone resin or a silicone oil.

20. The method according to claim 14, wherein the membrane further comprises a silicone hold carrier.

21. The use of a composition comprising a water insoluble high polymer and silicone for coating a drug-containing composition for enabling the release-initiation and release-rate of the drug from the resulting pharmaceutical composition to be controlled.

Fig. 1

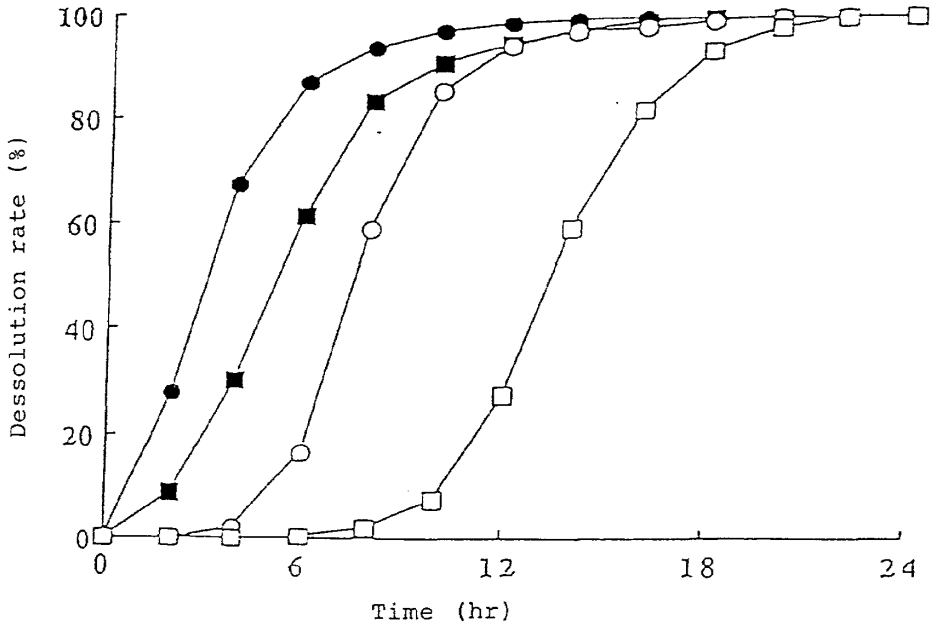


Fig. 2

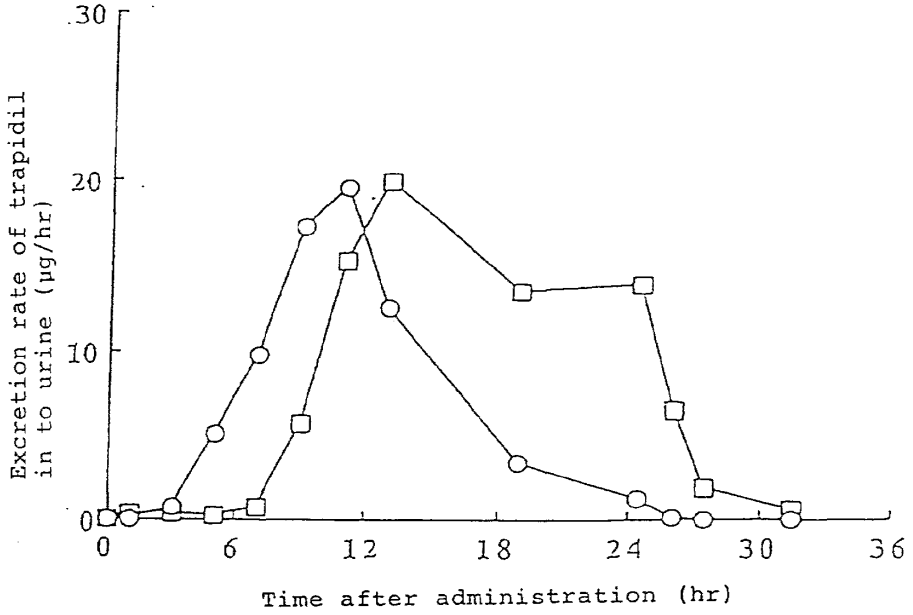

30
20
10
0
Excretion rate of trapidil in to urine (μg/hr)
0
6
12
18
24
30
36
Time after administration (hr)

Fig. 3

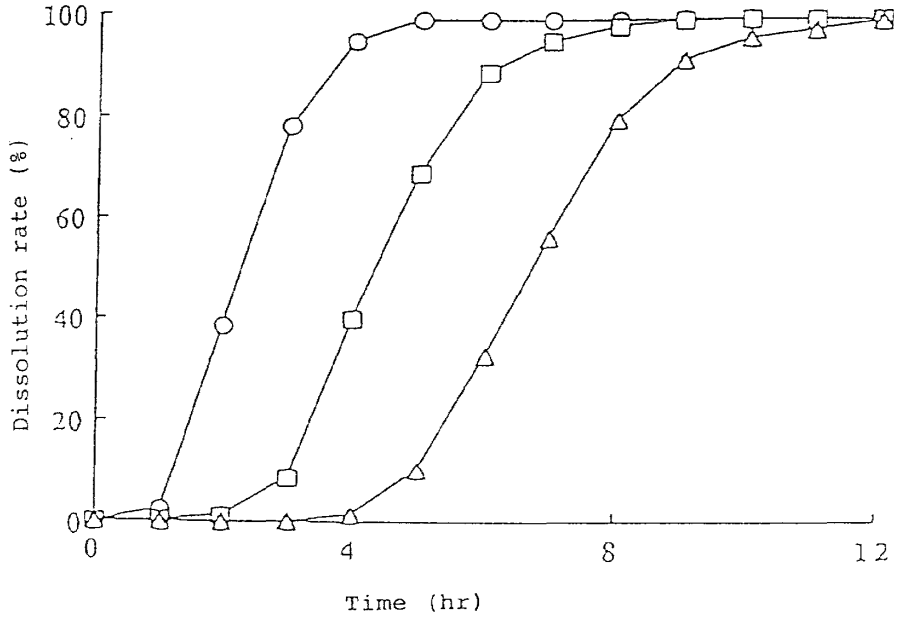
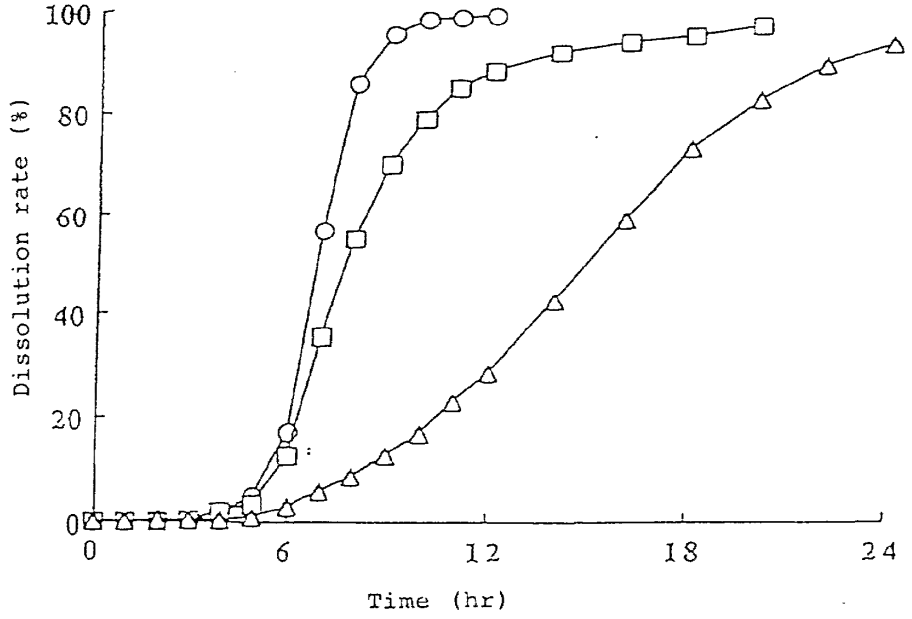

100
80
60
40
20
0
Dissolution rate (%)
0
4
8
12
Time (hr)

Fig. 4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40
20
0
Dissolution rate (%)
0
6
12
18
24
Time (hr)

Fig. 5

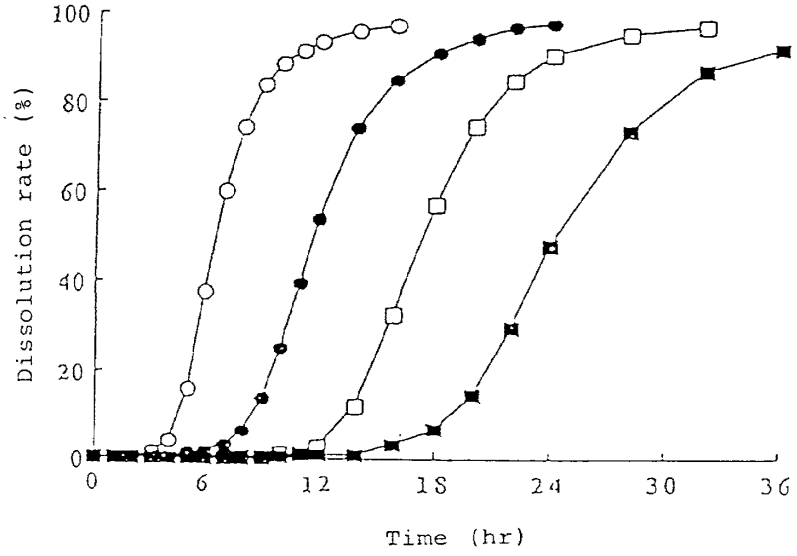

100
80
60
40
20
0
Dissolution rate (%)
0
6
12
18
24
30
36
Time (hr)

Fig. 6

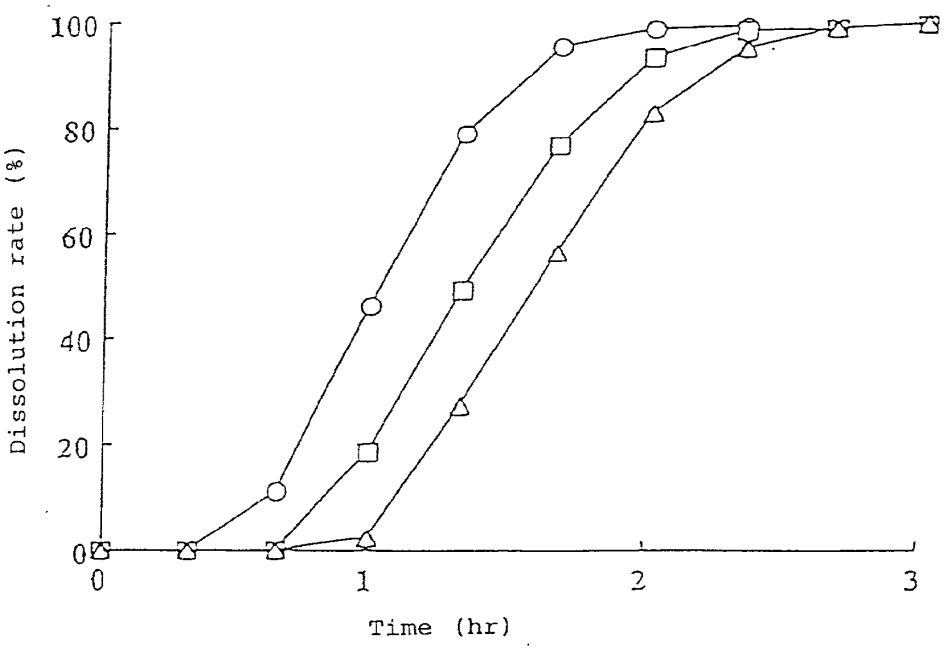


Fig. 7

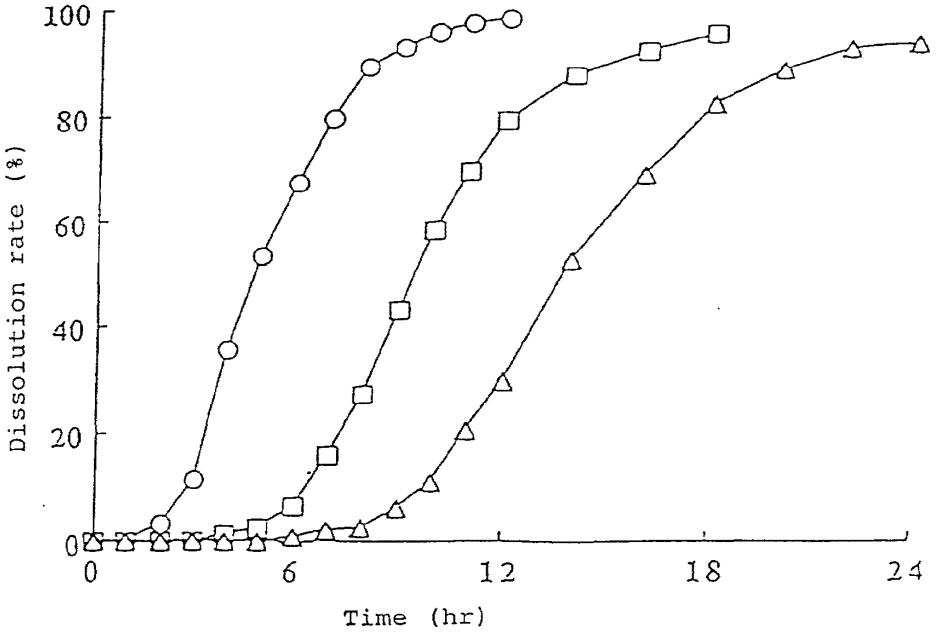


Fig. 8

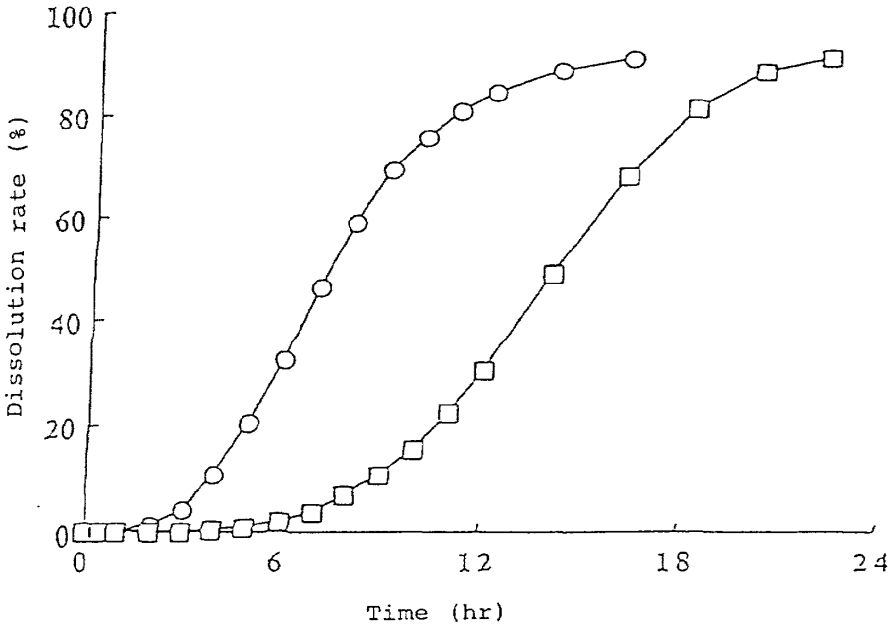


Fig. 9

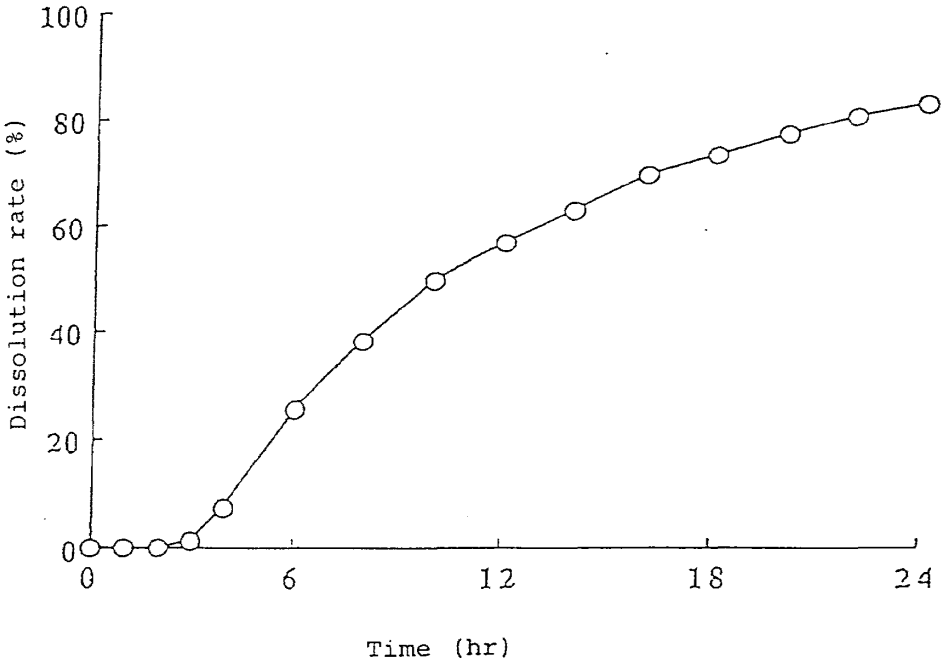


Fig. 10

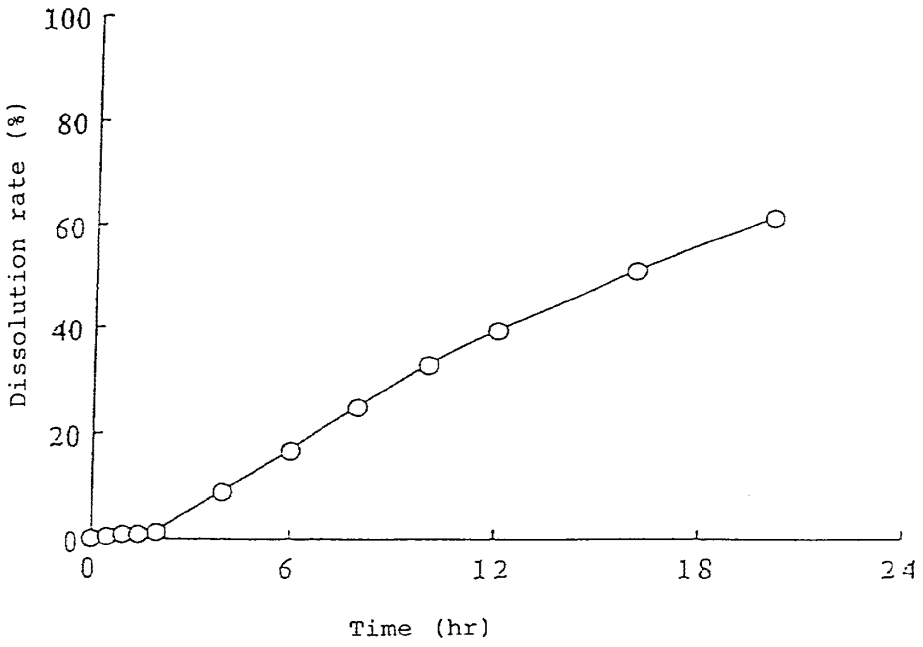


Fig. 11

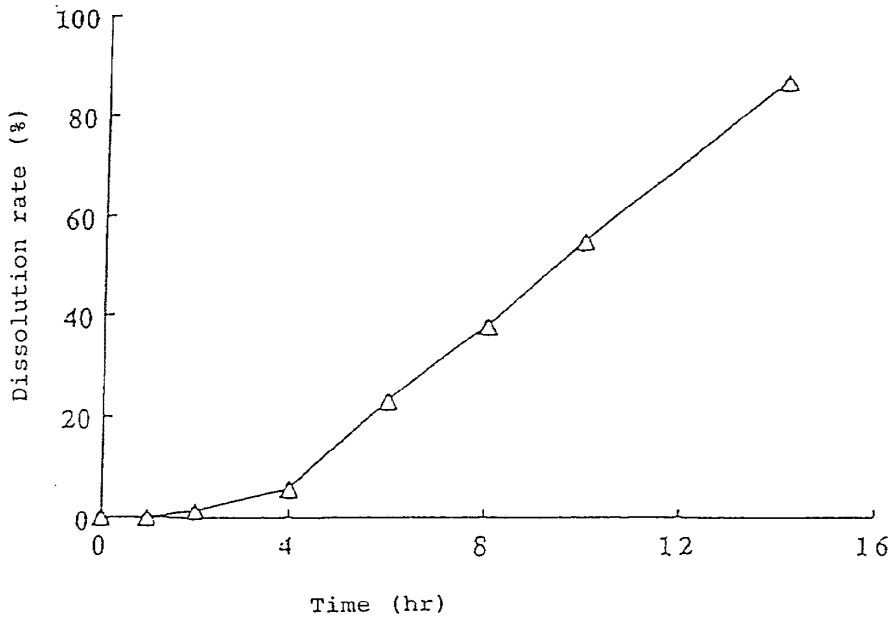


Fig. 12

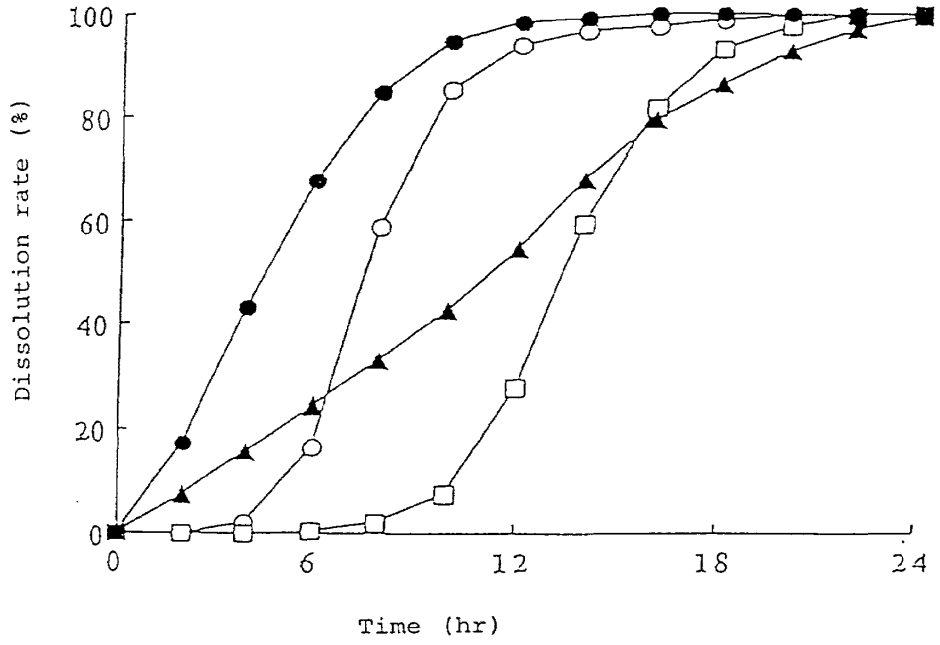
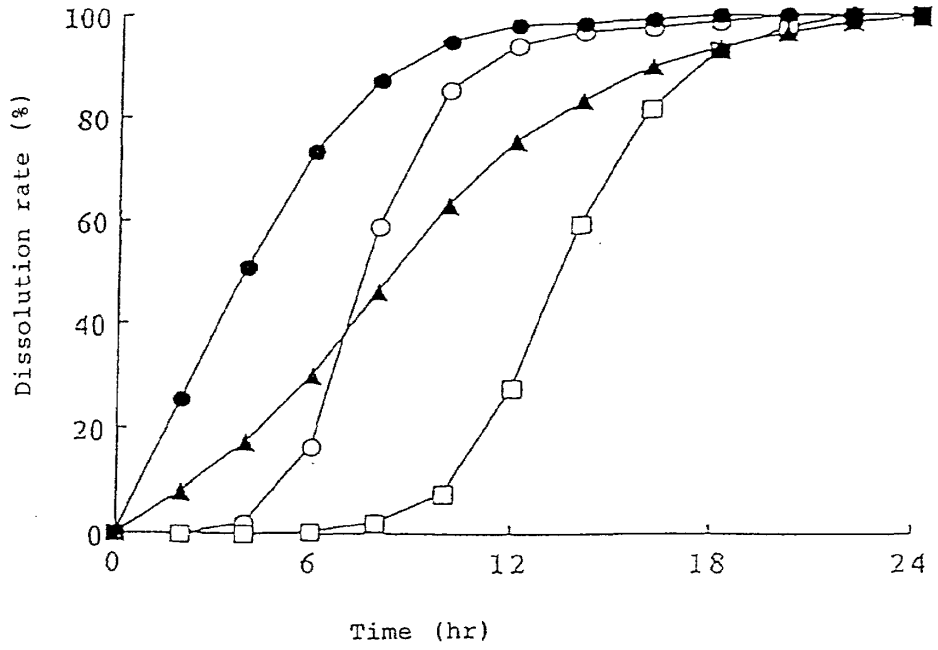


Fig. 13



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **A61K 31/445**	**A1**	**(11) International Publication Number:** **WO 99/03471** **(43) International Publication Date:** 28 January 1999 (28.01.99)

(21) International Application Number: PCT/US98/12057

(22) International Filing Date: 9 June 1998 (09.06.98)

(30) Priority Data:
08/892,190 14 July 1997 (14.07.97) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: IMPROVED DELIVERY OF MULTIPLE DOSES OF MEDICATIONS

(57) Abstract

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

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IMPROVED DELIVERY OF MULTIPLE DOSES OF MEDICATIONS

FIELD OF THE INVENTION

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

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

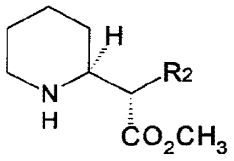
The administration of dosage forms which contain an immediate dosage and a delayed second dosage provides for reduced abuse potential, improved convenience of administration, and better patient compliance, especially when methylphenidate is used to treat certain central nervous system disorders.

BACKGROUND OF THE INVENTION

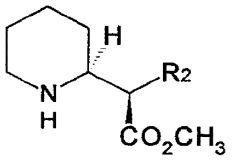
Attention Deficit Disorder (ADD), a commonly diagnosed nervous system illness in children, is generally treated with methylphenidate hydrochloride (available commercially as, e.g., Ritalin®). Symptoms of ADD include distractibility and impulsivity. A related disorder, termed Attention Deficit Hyperactivity Disorder (ADHD), is further characterized by symptoms of hyperactivity, and is also treated with

methylphenidate hydrochloride. Methylphenidate drugs have also been used to treat cognitive decline in patients with Acquired Immunodeficiency Syndrome (AIDS) or AIDS related conditions. *See, e.g.,* Brown, G., *Intl. J. Psych. Med.* 25(1): 21-37 (1995); Holmes et al., *J. Clin. Psychiatry* 50: 5-8 (1989).

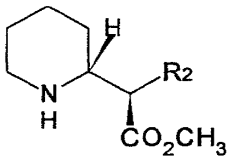
Methylphenidate exists as four separate optical isomers as follows:



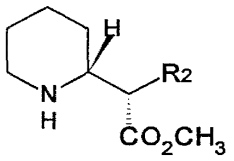
l-threo



d-erythro



d-threo



l-erythro

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

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

The *threo* racemate (pair of enantiomers) of methylphenidate is a mild central nervous system stimulant with pharmacological activity qualitatively similar to that of amphetamines. Undesirable side effects associated with the use of the *dl-threo* racemate of methylphenidate include anorexia, weight loss, insomnia, dizziness and

dysphoria. Furthermore, the racemate, which is a Schedule II controlled substance, produces a euphoric effect when administered intravenously or through inhalation or ingestion, and thus carries a high potential for abuse.

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

SUMMARY OF THE INVENTION

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

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

sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion.

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

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

methacrylate copolymer in a quantity sufficient to provide a dose of methylphenidate delayed by from about 2 hours to about 7 hours following ingestion. The components of the two groups of particles can vary as described hereinabove. The initial dose can be administered separately from the delayed dose, if desired.

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

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

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

As discussed, the four isomers have exhibited varying levels of therapeutic activity, and have been shown to differ generally in producing unwanted side effects. The present invention provides dosage forms which maximize therapeutic effectiveness and minimize undesirable side effects. In certain preferred embodiments, the dosage forms of the present invention provide administration of the two *threo* forms of methylphenidate. In particularly preferred embodiments, the dosage forms of the present invention provide administration of a single isomer, *d-threo*-methylphenidate, albeit in two or more doses.

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

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

Figure 2 is a schematic representation of the plasma concentration of drug resulting from a release profile according to Figure 1. The maximum concentration due to the first dose, C_1, occurs at t_1, preferably from about 1 hour to about 3 hours after ingestion, most preferably about 2 hours after ingestion. The release of the first dose is

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

$$|C_1 - C_2| / C_1$$

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

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

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

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

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

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

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

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

Quaternary ammonium groups in copolymers useful in forming coatings for use in the dosage forms of the present invention can be derived from monomers comprising quaternary ammonium groups. Preferably, the monomers are alkyl esters of acrylic or methacrylic acid, comprising alkyl groups having from 1 to 6 carbon atoms and a quaternary ammonium group in the alkyl portion. Monomers comprising quaternary ammonium groups can be prepared, for example, by reaction of monomers containing amino groups with alkylating agents such as, for example, alkyl halides, especially methyl

chloride. Suitable monomers containing amino groups include 2-(N,N-dibutylamino) ethyl acrylate, 2-(N,N-dibutylamino) ethyl methacrylate, 4-diethylamino-1-methyl-butyl acrylamide, and 4-diethylamino-1-methyl-butyl methacrylamide. Other useful monomers containing amino groups are disclosed in U.S. Patent No. 5,422,121, the disclosure of which is incorporated herein by reference. Particularly preferred as a monomer comprising a quaternary ammonium group is trimethylammonioethyl methacrylate chloride (TAMCl).

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

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

copolymers of methyl methacrylate, ethyl acrylate, and TAMCl, in ratios of 2:1:0.1 for the first copolymer and 2:1:0.2 for the second copolymer.

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

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

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

The quantity of filler used in preparing coatings for the dosage forms of the present invention should be sufficient to minimize agglomeration of the particles. Agglomeration is highly undesirable because the agglomerates, rather than discrete particles, will become coated. Agglomerates are susceptible to breaking into discrete particles, which will be partially uncoated, resulting in unwanted variability in release

rates. Preferably, the amount of filler is from about 30 percent to about 50 percent by weight, based on the total weight of the dry polymer, commonly referred to as "total solids". More preferably the amount of filler is from about 35 percent to about 45 percent of total solids, and most preferably about 40 percent.

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

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

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

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

Following the formation of suitable particles, those particles to be used to deliver the delayed dose are then coated with a polymer-containing coating as described herein. The amount of coating to be used in forming the dosage forms, particularly the delayed dose, of the present invention, will be determined by the desired delivery properties, including the amount of drug to be delivered, the delay time required, and the size of the particles. Preferably, the coating on the particles providing the delayed dose, including all solid components of the coating such as copolymer, filler, plasticizer and optional additives and processing aids, is from about 10 percent to about 60 percent, more preferably from about 20 percent to about 50 percent, most preferably from about 30 percent to about 40 percent, of the total final weight of the particles. The appropriate

amount of coating can advantageously be determined using *in vitro* measurements of drug release rates obtained with selected amounts of coating. The coating can be deposited by any method known to those skilled in the art, such as spray application. Spraying can be carried out by pan coating or by use of a fluid bed, such as the Wurster fluid bed described for use in depositing a drug.

After deposition of the drug, a sealant can be applied to any and/or all of the particles, prior to application of the polymeric coating. A sealant provides a physical barrier between the drug and the coating, to minimize or prevent interaction between the drug and the coating. Suitable sealants can be prepared from materials such as biologically inert, permeable, pharmaceutically acceptable polymers, such as, for example, hydroxypropylalkylcelluloses, wherein "alkyl" refers to C_1-C_6 hydrocarbon chains. Exemplary materials include hydroxypropyl methylcellulose, hydroxypropylethylcellulose, hydroxypropyl propylcellulose, and hydroxypropylbutylcellulose. Hydroxypropylmethylcellulose is preferred. While other materials are known to those skilled in the art for use as sealants, such as, for example, cellulose acetate methyl carbamate, cellulose acetate diethyl aminoacetate, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, semipermeable cross-linked polymers such as poly(vinylbenzyltrimethyl)ammonium chloride, these are not preferred as they may affect the release rate of certain drugs including *d*-MPD. A sealant can be prepared by adding the material to water, and agitating for a time and at a rate sufficient to form a solution. The formation of a solution will be indicated, for example, by transparency and the absence of visually observable suspended material. The amount of material added to the water is not critical but is determined by viscosity. A solution which is too viscous will present difficulties in spraying. Generally, the amount of material should not exceed about 20 weight/volume percent, i.e., 20 g sealant material per 100 ml of water. Preferably, the amount of material in the water is from about 5 percent to about 15 weight/ volume percent, and more preferably about 10 weight/volume percent.

Following deposition of the optional sealant and the coating, the coated particles are cured. "Curing" means that the particles are held at a controlled temperature for a time sufficient to provide stable release rates. Stability in release rate is indicated when further curing does not affect the release rate. In contrast, instability of release rate means that as the cure time is increased, the release rate continues to vary. Curing for a

sufficient time ensures that substantially the same release rate is obtained with all particles of a particular size coated with a given amount of a given coating composition. A suitable curing time can be determined by one of skill in the art without undue experimentation, by noting the variability in *in vitro* release times as curing time is varied. As a general guideline, many formulations can be cured in about 24 hours.

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

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

According to the invention, a first and a second group of particles can be administered simultaneously as part of one dosage form. Any dosage form can be used.

For example, the two groups of particles can be combined within a capsule. Alternatively, the two groups of particles can be pressed into a solid form such as a tablet. In pressing the particles into a solid form, suitable processing aids known to those skilled in the art can be used. Alternatively, particles coated to provide a delayed dose of a medication can be dispersed within or blended with, the medication in powder form.

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

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

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

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

Example 1: Preparation of layered pellets containing *d*-MPD hydrochloride

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

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

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

Example 2: Preparation of Coated Pellets containing *d*-MPD hydrochloride

A dispersion of 844 g of Eudragit® RS30D (ammoniomethacrylate copolymer from Hüls America, Somerset, NJ; EA/MMA/TAMCl 1:2:0.1), was screened through a 60 mesh screen, then stirred for 15 minutes. A dispersion of 44 g of Eudragit® RL30D (EA/MMA/TAMCl 1:2:0.2) was similarly screened and stirred. The two

dispersions were combined and stirred for 15 minutes, forming a combined dispersion. Triethyl citrate (TEC; from Moreflex, Greensboro, NC; 54 g) was added, followed by an additional 15 minutes of stirring. Deionized water (664 g) was added, followed by 15 minutes of stirring. Talc (108 g; from Luzenac, Englewood, CO) was added, followed by further stirring for 15 minutes.

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

Example 3: Evaluation of drug release profile for coated pellets prepared according to Example 2

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

Dissolution measurements

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

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

Example 4: Comparative Example

A dispersion of 911.25 g of Eudragit® RS30D was passed through a 60 mesh screen and mixed with a similarly screened dispersion of 101.25 g of Eudragit®

RL30D for 15 minutes at moderate speed. Triethyl citrate (61 g) was added, followed by an additional 15 minutes of mixing. After mixing, 991.5 g of deionized water, then 61 g of talc were added with 15 additional minutes of mixing following each addition. The resulting dispersion (1600 g) was sprayed onto 800 g of layered sealed pellets prepared according to Example 1.

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

Example 5: Comparative Example

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

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

TABLE 1: RELEASE TIMES

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

What is claimed is:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22. The dosage form of claim 1 wherein said delay is from about 4 hours to about 5 hours.

23. A dosage form for once-daily oral administration of a methylphenidate drug comprising:

a) particles comprising from about 2% by weight to about 99% by weight of said methylphenidate drug, in admixture with one or more binders,

b) a coating exterior to said methylphenidate drug, comprising an ammonio methacrylate copolymer in a quantity sufficient to provide a dose of said methylphenidate delayed by from about 2 hours to about 7 hours following administration, and

c) on the exterior surface of said coating, a layer comprising said methylphenidate drug, to provide a substantially immediate dose of said methylphenidate upon administration.

24. The dosage form of claim 23 wherein said methylphenidate is *dl-threo*-methylphenidate hydrochloride.

25. The dosage form of claim 23 wherein said methylphenidate is *d-threo*-methylphenidate hydrochloride.

26. The dosage form of claim 23 wherein said coating comprises a first ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 30:1 to about 40:1, and a second ammonio methacrylate copolymer comprising, as polymerized units, acrylic groups and trimethylammonioethyl methacrylate in a ratio of from about 15:1 to about 20:1.

27. A dosage form for the oral administration of *d-threo*-methylphenidate hydrochloride comprising two groups of particles, each containing *d-threo*-methylphenidate, wherein:

a) said first group of particles comprises *d-threo*-methylphenidate hydrochloride and provides a substantially immediate dose of said *d-threo* methylphenidate upon ingestion by a mammal, and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of *d-threo*-methylphenidate hydrochloride in admixture with one or more binders, said coating comprising a pharmaceutically acceptable ammonio methacrylate copolymer in an amount sufficient to provide a dose of said *d-threo*-methylphenidate delayed by from about 2 hours to about 7 hours following said ingestion.

28. A dosage form of a pharmaceutically acceptable salt of *d-threo*-methylphenidate providing an *in vitro* release profile comprising two pulses of drug release, wherein said pulses are temporally separated by from about 2 hours to about 7 hours.

29. A dosage form of a pharmaceutically acceptable salt of *d-threo*-methylphenidate providing an *in vivo* plasma concentration of said *d-threo*-methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about 2 hours to about 7 hours, and wherein the magnitude of said maxima differ by no more than about 30 percent.

30. A dosage form according to claim 23 wherein said ammoniomethacrylate copolymer comprises a first copolymer of methyl methacrylate, ethyl acrylate and TAMCl in a ratio of 2:1:0.1 and a second copolymer of methyl methacrylate, ethyl acrylate, and TAMCl in a ratio of 2:1:0.2.

31. A method for treating disease in a patient in need of treatment comprising administering to the patient a dosage form providing once-daily oral administration of *d-threo*-methylphenidate hydrochloride, said dosage form comprising two groups of particles, each containing *d-threo*-methylphenidate, wherein:

a) said first group of particles comprises from about 2% to about 99% by weight of *d-threo*-methylphenidate hydrochloride and provides a substantially immediate dose of said *d-threo* methylphenidate upon ingestion by a mammal; and

b) said second group of particles comprises coated particles, said coated particles comprising from about 2% to about 75% by weight of *d-threo*-methylphenidate in admixture with one or more binders, and a coating consisting of an ammonio methacrylate copolymer in an amount sufficient to provide a dose of said *d-threo*-methylphenidate hydrochloride delayed by from about 4 hours to about 7 hours following said ingestion.

32. A dosage form of a pharmaceutically acceptable salt of a methylphenidate providing an *in vitro* release profile comprising two pulses of drug release, wherein said pulses are temporally separated by from about two hours to about seven hours.

33. A dosage form of a pharmaceutically acceptable salt of a methylphenidate providing an *in vivo* plasma concentration of said methylphenidate comprising two maxima, wherein said maxima are temporally separated by from about two hours to about seven hours and wherein the magnitude of said maxima differ by no more than about 30%.

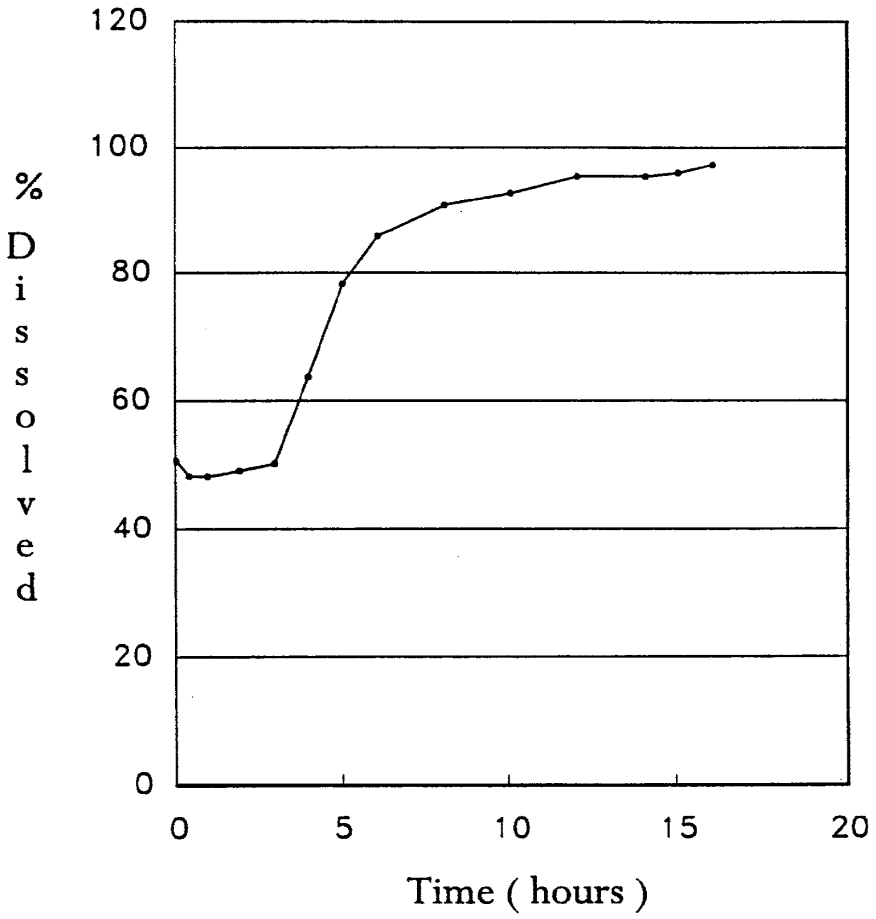


FIG. 1

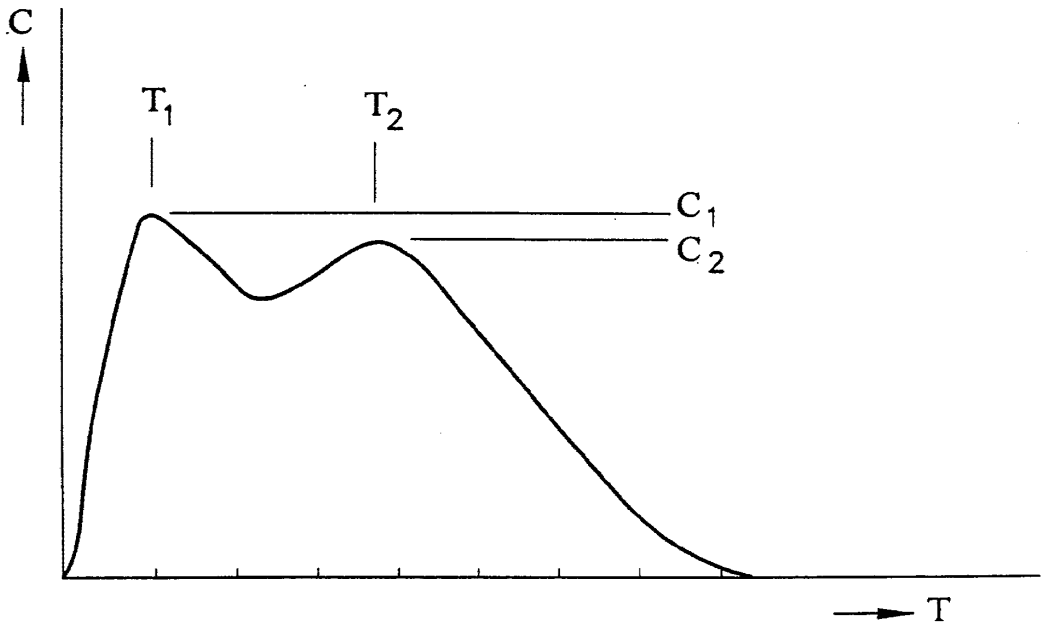


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12057

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/445
US CL :514/317
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,137,300 A (SHETH et al.) 30 January 1979.	1-33
A	US 5,202,128 A (MORELLA et al.) 13 April 1993.	1-33
A	US 5,512,293 A (LANDRAU et al.) 30 April 1996.	1-33
A	US 5,593,694 A (HAYASHIDA et al.) 14 January 1997	1-33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 JULY 1998	Date of mailing of the international search report 19 AUG 1998
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Form PCT/ISA/210 (second sheet)(July 1992)★

(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 200013350 B2
(10) Patent No. 770645

(54) Title
Multiparticulate modified release composition

(51)6 International Patent Classification(s)
A61K 009/20 A61K 009/58
A61K 009/24 A61K 009/62
A61K 009/54

(21) Application No: 200013350 (22) Application Date: 1999.11.01

(87) WIPO No: WO00/25752

(30) Priority Data

(31) Number	(32) Date	(33) Country
60/106726	1998.11.02	US

(43) Publication Date : 2000.05.22
(43) Publication Journal Date : 2000.07.20
(44) Accepted Journal Date : 2004.02.26

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(56) Related Art
US 5445829
US 5837284
US 4888178

13350/00

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/20, 9/24, 9/54, 9/58, 9/62 — A1

(11) International Publication Number: **WO 00/25752**

(43) International Publication Date: 11 May 2000 (11.05.00)

(21) International Application Number: PCT/US99/25632

(22) International Filing Date: 1 November 1999 (01.11.99)

(30) Priority Data:
60/106,726 2 November 1998 (02.11.98) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: MULTIPARTICULATE MODIFIED RELEASE COMPOSITION

(57) Abstract

The invention relates to a multiparticulate modified release composition that in operation delivers an active ingredient in a pulsed or bimodal manner. The multiparticulate modified release composition comprises an immediate release component and a modified release component; the immediate release component comprising a first population of active ingredient containing particles and the modified release component comprising a second population of active ingredient containing particles coated with a controlled release coating; wherein the combination of the immediate release and modified release components in operation deliver the active ingredient in a pulsed or a bimodal manner. The invention also relates to a solid oral dosage form containing such a multiparticulate modified release composition. The plasma profile achieved by the multiparticulate modified release composition is advantageous in reducing patient tolerance to the active ingredient and in increasing patient compliance by reducing dosage frequency.

MULTIPARTICULATE MODIFIED RELEASE COMPOSITION

Field of the Invention

The present invention relates to a multiparticulate modified release composition. In particular the present invention relates to a multiparticulate modified release composition that in operation delivers an active ingredient in a pulsatile manner. The present invention further relates to solid oral dosage forms containing such a multiparticulate controlled release composition.

Description of the Prior art

The plasma profile associated with the administration of a drug compound may be described as a "pulsatile profile" in which pulses of high active ingredient concentration, interspersed with low concentration troughs, are observed. A pulsatile profile containing two peaks may be described as "bimodal". Similarly, a composition or a dosage form which produces such a profile upon administration may be said to exhibit "pulsed release" of the active ingredient.

Conventional frequent dosage regimes in which an immediate release (IR) dosage form is administered at periodic intervals typically gives rise to a pulsatile plasma profile. In this case, a peak in the plasma drug concentration is observed after administration of each IR dose with troughs (regions of low drug concentration) developing between consecutive administration time points. Such dosage regimes (and their resultant pulsatile plasma profiles) have particular pharmacological and therapeutic effects associated with them. For example, the wash out period provided by the fall off of the plasma concentration of the active ingredient between peaks has been thought to be a contributing factor in reducing or preventing patient tolerance to various types of drugs.

Many controlled release drug formulations are aimed at producing a zero-order release of the drug compound. Indeed, it is often a specific object of these formulations to

minimise the peak-to-trough variation in drug plasma levels associated with conventional frequent dosage regimes. However, some of the therapeutic and pharmacological effects intrinsic in a pulsatile system may be lost or diminished as a result of the constant or nearly constant plasma levels achieved by zero-order release drug delivery systems. Thus, a modified release composition or formulation which substantially mimics the release of frequent IR dosage regimes, while reducing the need for frequent dosing, is desirable.

A typical example of a drug which may produce tolerance in patients is methylphenidate. Methylphenidate, or α-phenyl-2-piperidine acetic acid methyl ester, is a stimulant affecting the central nervous and respiratory systems and is primarily used in the treatment of attention deficit disorder. After absorption from the gastrointestinal tract (GIT), drug effects persist for 3 - 6 hours after oral administration of conventional IR tablets or up to about 8 hours after oral administration of extended release formulations. The total dosage is typically in the range of 5 - 30 mg per day, in exceptional cases rising to 60 mg / day. Under conventional dosage regimes, methylphenidate is given twice daily, typically with one dose given before breakfast and a second dose given before lunch. The last daily dose is preferably given several hours before retiring. Adverse effects associated with methylphenidate treatment include insomnia and the development of patient tolerance.

WO 98/14168 (Alza Corp.) teaches a dosage form and a method of administering methylphenidate in a sustained and constantly ascending rate. The dosage form disclosed comprises a plurality of beads comprising a hydrogel matrix with increasing amounts of the active ingredient therein, coated with varying amounts of a release rate controlling material. Appropriate combinations of the active ingredient dose and the number and thickness coating layers can be selected to give an ascending release profile in which the plasma concentration of the active ingredient continually increases over a given period of time. In contrast to the present invention, an object of WO 98/14168 is to provide a dosage form to specifically avoid uneven blood levels (characterised by peaks and troughs) associated with conventional treatments using immediate release dosage formulations.

WO 97/03672 (Chiroscience Ltd.) discloses that methylphenidate exhibits a therapeutic effect when administered in the form of a racemic mixture or in the form of a single isomer (such as the RR d-threo enantiomer). Further, WO 97/03763 (Chiroscience Ltd.) discloses a sustained release formulation containing dtmp. This disclosure teaches the use of a composition comprising a coating through which the dtmp passes in order to attain sustained release and achieve serum levels (of the active ingredient) of at least 50% c_{max} over a period of at least 8 hours. Thus, this formulation does not deliver the active ingredient in a pulsatile manner.

Shah *et al., J. Cont. Rel.* (1989) 9:169-175 discloses that certain types of hydroxypropyl methylcellulose ethers compressed into a solid dosage form with a therapeutic agent may give a bimodal release profile. However, it was noted that while polymers from one supplier yielded a bimodal profile, the same polymers with almost identical product specifications obtained from a different source gave non-bimodal release profiles.

Giunchedi *et al., Int. J. Pharm* (1991) 77:177-181 discloses the use of a hydrophilic matrix multiple-unit formulation for the pulsed release of ketoprofen. Giunchedi *et al.* teach that ketoprofen is rapidly eliminated from the blood after dosing (plasma half-life 1-3 hours) and consecutive pulses of drug may be more beneficial than constant release for some treatments. The multiple-unit formulation disclosed comprises four identical hydrophilic matrix tablets placed in a gelatin capsule. Although the *in vivo* studies show two peaks in the plasma profile there is no well defined wash out period and the variation between the peak and trough plasma levels is small.

Conte *et al., Drug Dev. Ind. Pharm,* (1989) 15:2583-2596 and EP 0 274 734 (Pharmidea Srl) teach the use of a three layer tablet for delivery of ibuprofen in consecutive pulses. The three layer tablet is made up of a first layer containing the active ingredient, a barrier layer (the second layer) of semi-permeable material which is interposed between the first layer and a third layer containing an additional amount of active ingredient. The barrier layer and the third layer are housed in an impermeable casing. The first layer dissolves upon contact with a dissolving fluid while the third layer is only available after dissolution or

rupture of the barrier layer. In such a tablet the first portion of active ingredient must be released instantly. This approach also requires the provision of a semi-permeable layer between the first and third layers in order to control the relative rates of delivery of the two portions of active ingredient. Additionally, rupture of the semi-permeable layer leads to uncontrolled dumping of the second portion of the active ingredient which may not be desirable.

US 5,158,777 (E. R. Squibb & Sons Inc.) discloses a formulation comprising captopril within an enteric or delayed release coated pH stable core combined with additional captopril which is available for immediate release following administration. In order to form the pH stable core, chelating agents such as disodium edetate or surfactants such as polysorbate 80 are used either alone or in combination with a buffering agent. The compositions have an amount of captopril available for immediate release following oral administration and an additional amount of pH stabilised captopril available for release in the colon.

US 4,728,512, US 4,794,001 and US 4,904,476 (American Home Products Corp.) relate to preparations providing three distinct releases. The preparation contains three groups of spheroids containing an active medicinal substance: the first group of spheroids is uncoated and rapidly disintegrates upon ingestion to release an initial dose of medicinal substance; the second group of spheroids is coated with a pH sensitive coat to provide a second dose; and the third group of spheroids is coated with a pH independent coat to provide to third dose. The preparation is designed to provide repeated release of medicinal substances which are extensively metabolised presystemically or have relatively short elimination half-lives.

U.S. Pat. No. 5,837,284 (Mehta et al) discloses a methylphenidate dosage form having immediate release and delayed release particles. The delayed release is provided by the use of ammonio methacrylate pH independent polymers combined with certain fillers.

Accordingly, the present invention desirably provides a multiparticulate modified release composition containing an active ingredient which in operation produces a plasma profile substantially similar to the plasma profile produced by the administration of two or more IR dosage forms given sequentially.

The present invention also desirably provides a multiparticulate modified release composition which in operation delivers an active ingredient in a pulsatile manner.

The present invention also desirably provides a multiparticulate modified release composition which substantially mimics the pharmacological and therapeutic effects produced by the administration of two or more IR dosage forms given sequentially.

The present invention also desirably provides a multiparticulate modified release composition which substantially reduces or eliminates the development of patient tolerance to the active ingredient of the composition.

The present invention also desirably provides a multiparticulate modified release composition in which a first portion of the active ingredient is released immediately upon administration and a second portion of the active ingredient is released rapidly after an initial delay period in a bimodal manner.

The present invention also desirably provides a multiparticulate modified release composition capable of releasing the active ingredient in a bimodal or multi-modal manner in which a first portion of the active ingredient is released either immediately or after a delay time to provide a pulse of drug release and one or more additional portions of the active ingredient are released each after a respective lag time to provide additional pulses of drug release.

The invention also desirably provides a solid oral dosage forms comprising a multiparticulate modified release composition of the present invention.

The present invention also desirably provides the provision of a once daily dosage form of methylphenidate which, in operation, produces a plasma profile substantially similar to the plasma profile produced by the administration of two immediate release dosage forms given sequentially and a method for treatment of attention deficit disorder based on administration of such a dosage form.

The present invention provides a multiparticulate modified release composition containing at least one active ingredient and having a first component comprising a first population of active ingredient-containing particles and at least one subsequent component, each subsequent component comprising a subsequent population of active ingredient-containing particles, the active ingredient contained in the first and subsequent components being the same or different; wherein the at least one subsequent population of active ingredient containing particles further comprises a modified release coating or, alternatively or additionally, a modified release matrix material, such that the composition following oral delivery to a subject delivers the active ingredient or active ingredients in a pulsatile manner.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

Brief Description of the Invention

The present invention provides a multiparticulate modified release composition having a first component comprising a first population of active ingredient-containing particles and a second component comprising a second population of active ingredient-containing particles. The active ingredient contained in the first and second components can be the same or different arid active ingredient-containing particles of the second component are coated with a modified release coating. Alternatively or additionally, the second population of active ingredient containing particles further comprises a modified release matrix material. Following oral delivery, the composition in operation delivers the active ingredient or active ingredients in a pulsatile manner.

In a preferred embodiment of a multiparticulate modified release composition according to the invention the first component is an immediate release component.

The modified release coating applied to the second population of active ingredient containing particles causes a lag time between the release of active ingredient from the first population of active ingredient containing particles and the release of active ingredient from the second population of active ingredient containing particles. Similarly, the presence of a modified release matrix material in the second population of active ingredient containing particles causes a lag time between the release of active ingredient from the first population of active ingredient containing particles and the release of active ingredient from the second population of active ingredient containing particles. The duration of the lag time may be varied by altering the composition and/or the amount of the modified release coating and/or altering the composition and/or amount of modified release matrix material utilised. Thus, the duration of the lag time can be designed to mimic a desired plasma profile.

Because the plasma profile produced by the multiparticulate modified release composition upon administration is substantially similar to the plasma profile produced by the administration of two or more IR dosage forms given sequentially, the multiparticulate controlled release composition of the present invention is particularly useful for administering active ingredients for which patient tolerance may be problematical. This multiparticulate modified release composition is therefore advantageous for reducing or minimising the development of patient tolerance to the active ingredient in the composition.

In a preferred embodiment of the present invention, the active ingredient is methylphenidate and the composition in operation delivers the active ingredient in a bimodal or pulsed manner. Such a composition in operation produces a plasma profile which substantially mimics that obtained by the sequential administration of two IR doses as, for instance, in a typical methylphenidate treatment regime.

The present invention also provides solid oral dosage forms comprising a composition according to the invention.

The present invention further provides a method of treating an animal, particularly a human in need of treatment utilising the active ingredient, comprising administering a therapeutically effective amount of a composition or solid oral dosage form according to the invention to provide pulsed or bimodal administration of the active ingredient

Advantages of the present invention include reducing the dosing frequency required by conventional multiple IR dosage regimes while still maintaining the benefits derived from a pulsatile plasma profile. This reduced dosing frequency is particularly advantageous in the case of children in that it eliminates the need for dosing during the middle of the school day which can be both disruptive and embarrassing for the patient. It is also advantageous in terms of patient compliance to have a formulation which may be administered at reduced frequency. The reduction in dosage frequency made possible by utilising the present invention would contribute to reducing health care costs by reducing the amount of time

spent by health care workers on the administration of drugs. In the case of methylphenidate, and other controlled substances, the use of a once-daily formulation (in place of multiple IR doses) reduces or eliminates the need for the storage of controlled substances on the premises of schools or other institutions.

Description of the Drawings

Figure 1 shows methylphenidate plasma profiles following oral administration of the following three formulations to human volunteers: A – 20 mg methylphenidate formulation having an immediate release component comprising particles containing a total of 10 mg methylphenidate (according to Table 1 (ii)) and a modified release component comprising particles containing a total of 10 mg methylphenidate (according to Table 2 (viii); IR particles coated to a 30% weight gain); B – 20 mg methylphenidate formulation having an immediate release component comprising particles containing a total 10 mg methylphenidate (according to Table 1 (ii)) and a modified release component comprising particles containing a total of 10 mg methylphenidate (according to Table 2 (vii); IR particles coated to a 30% weight gain); and Control - two doses of 10 mg Ritalin® Hydrochloride (IR) tablets administered at times 0 and 4 hours (total of 20 mg methylphenidate administered).

Detailed Description of the Invention

The term "particulate" as used herein refers to a state of matter which is characterised by the presence of discrete particles, pellets, beads or granules irrespective of their size, shape or morphology. The term "multiparticulate" as used herein means a plurality of discrete, or aggregated, particles, pellets, beads, granules or mixture thereof irrespective of their size, shape or morphology.

The term "modified release" as used herein in relation to the composition according to the invention or a coating or coating material or used in any other context means release which is not immediate release and is taken to encompass controlled release, sustained release and delayed release.

The term "time delay" as used herein refers to the duration of time between administration of the composition and the release of the active ingredient from a particular component.

The term "lag time" as used herein refers to the time between delivery of active ingredient from one component and the subsequent delivery of active ingredient from another component.

The invention will be described in detail with respect to methylphenidate as a specific example of an active ingredient particularly suited to formulation in a multiparticulate modified release composition according to the present invention.

The multiparticulate modified release composition of the invention may have more than two active ingredient-containing components. In this case the release of active ingredient from the second and subsequent components is modified such that there is a lag time between the release of active ingredient from the first component and each subsequent component. The number of pulses in the profile arising from such a composition in operation will depend on the number of active ingredient containing components in the composition. A composition containing three active ingredient-containing components will give rise to three pulses in the profile.

Any active ingredient for which it is useful to combine the advantages of a pulsatile plasma profile with a reduced frequency dosage regime may be used in practice of the present invention. Particularly useful in the practice of the invention include active ingredients whose pharmacological and/or therapeutic effects benefit from having a wash-out period between plasma concentration peaks, such as those active ingredients susceptible to the development of patient tolerance. Example active ingredients include but are not limited to peptides or proteins, hormones, analgesics, anti-migraine agents, anti-coagulant agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins and antidiuretic agents, drug compounds acting on the central nervous system such as cerebral stimulants, for example methylphenidate; pain management

active ingredients; alkaloids such as opiates, for example morphine; cardiovascular drugs, such as nitrates; and agents for treating rheumatic conditions. It is further appreciated that the present invention may be used to deliver a number of drugs including, but not limited to, peptides, proteins or hormones such as insulin, calcitonin, calcitonin gene regulating protein, atrial natriuretic protein, colony stimulating factor, betaseron, erythropoietin (EPO), interferons such as α,β or γ interferon, somatropin, somatotropin, somastostatin, insulin-like growth factor (somatomedins), luteinizing hormone releasing hormone (LHRH), tissue plasminogen activator (TPA), growth hormone releasing hormone (GHRH), oxytocin, estradiol, growth hormones, leuprolide acetate, factor VIII, interleukins such as interleukin-2, and analogues thereof; analgesics such as fentanyl, sufentanil, butorphanol, buprenorphine, levorphanol, morphine, hydromorphone, hydrocodone, oxymorphone, methadone, lidocaine, bupivacaine, diclofenac, naproxen, paverin, and analogues thereof; anti-migraine agents such as sumatriptan, ergot alkaloids, and analogues thereof; anti-coagulant agents such as heparin, hirudin; and analogues thereof; anti-emetic agents such as scopolamine, ondansetron, domperidone, metoclopramide, and analogues thereof; cardiovascular agents, anti-hypertensive agents and vasodilators such as diltiazem, clonidine, nifedipine, verapamil, isosorbide-5-mononitrate, organic nitrates, agents used in treatment of heart disorders, and analogues thereof; sedatives such as benzodiazepines, phenothiozines, and analogues thereof; chelating agents such as deferoxamine, and analogues thereof; anti-diuretic agents such as desmopressin, vasopressin, and analogues thereof; anti-anginal agents such as nitroglycerine, and analogues thereof; anti-neoplastics such as fluorouracil, bleomycin, and analogues thereof; prostaglandins and analogues thereof; and chemotherapy agents such as vincristine, and analogues thereof.

The active ingredient in each component may be the same or different. For example, a composition in which the first component contains a first active ingredient and the second component comprises a second active ingredient may be desirable for combination therapies. Indeed, two or more active ingredients may be incorporated into the same component when the active ingredients are compatible with each other. A drug compound present in one component of the composition may be accompanied by, for example, an enhancer compound

or a sensitiser compound in another component of the composition, in order to modify the bioavailability or therapeutic effect of the drug compound.

As used herein, the term "enhancer" refers to a compound which is capable of enhancing the absorption and/or bioavailability of an active ingredient by promoting net transport across the GIT in an animal, such as a human. Enhancers include but are not limited to medium chain fatty acids; salts, esters, ethers and derivatives thereof, including glycerides and triglycerides; non-ionic surfactants such as those that can be prepared by reacting ethylene oxide with a fatty acid, a fatty alcohol, an alkylphenol or a sorbitan or glycerol fatty acid ester; cytochrome P450 inhibitors, P-glycoprotein inhibitors and the like; and mixtures of two or more of these agents.

The proportion of active ingredient contained in each component may be the same or different depending on the desired dosing regime. The active ingredient may be present, in the first component individually or in combination with the active ingredient (or active ingredients) in the second component, in any amount sufficient to elicit a therapeutic response. The active ingredient (or active ingredients), when applicable, may be present either in the form of one substantially optically pure enantiomer or as a mixture, racemic or otherwise, of enantiomers. The active ingredient is preferably present in a composition in an amount of from 0.1 – 500 mg, preferably in the amount of from 1-100 mg. When the active ingredient is methylphenidate, it is preferably present in the first component in an amount of from 0.5 - 60 mg; more preferably the active ingredient is present in the first component in an amount of from 2.5 - 30 mg. The active ingredient is present in the subsequent components in an amount within a similar range to that described for the first component.

The time release characteristics for the release of the active ingredient from each of the components may be varied by modifying the composition of each component, including modifying any of the excipients or coatings which may be present. In particular the release of the active may be controlled by changing the composition and/or the amount of the modified release coating on the particles, if such a coating is present. If more than one modified release component is present, the modified release coating for each of these

components may be the same or different. Similarly, when modified release is facilitated by the inclusion of a modified release matrix material, release of the active ingredient may be controlled by the choice and amount of modified release matrix material utilised. The modified release coating may be present, in each component, in any amount that is sufficient to yield the desired delay time for each particular component. The modified release coating may be preset, in each component, in any amount that is sufficient to yield the desired time lag between components.

The lag time or delay time for the release of the active ingredient from each component may also be varied by modifying the composition of each of the components, including modifying any excipients and coatings which may be present. For example the first component may be an immediate release component wherein the active ingredient is released substantially immediately upon administration. Alternatively, the first component may be, for example, a time-delayed immediate release component in which the active ingredient is released substantially immediately after a time delay. The second component may be, for example, a time-delayed immediate release component as just described or, alternatively, a time-delayed sustained release or extended release component in which the active ingredient is released in a controlled fashion over an extended period of time.

As will be appreciated by those skilled in the art, the exact nature of the plasma concentration curve will be influenced by the combination of all of these factors just described. In particular, the lag time between the delivery (and thus also the on-set of action) of the active ingredient in each component may be controlled by varying the composition and coating (if present) of each of the components. Thus by variation of the composition of each component (including the amount and nature of the active ingredient(s)) and by variation of the lag time, numerous release and plasma profiles may be obtained. Depending on the duration of the lag time between the release of active ingredient from each component and the nature of the release from each component (i.e. immediate release, sustained release etc.), the pulses in the plasma profile may be well separated and clearly defined peaks (e.g. when the lag time is long) or the pulses may be superimposed to a degree (e.g. in when the lag time is short).

In a preferred embodiment, the multiparticulate modified release composition according to the present invention has an immediate release component and at least one modified release component, the immediate release component comprising a first population of active ingredient containing particles and the modified release components comprising second and subsequent populations of active ingredient containing particles. The second and subsequent modified release components may comprise a controlled release coating. Additionally or alternatively, the second and subsequent modified release components may comprise a modified release matrix material. In operation, administration of such a multiparticulate modified release composition having, for example, a single modified release component results in characteristic pulsatile plasma concentration levels of the active ingredient in which the immediate release component of the composition gives rise to a first peak in the plasma profile and the modified release component gives rise to a second peak in the plasma profile. Embodiments of the invention comprising more than one modified release component give rise to further peaks in the plasma profile.

Such a plasma profile produced from the administration of a single dosage unit is advantageous when it is desirable to deliver two (or more) pulses of active ingredient without the need for administration of two (or more) dosage units. Additionally, in the case of some disorders it is particularly useful to have such a bimodal plasma profile. For example, a typical methylphenidate treatment regime consists of administration of two doses of an immediate release dosage formulation given four hours apart. This type of regime has been found to be therapeutically effective and is widely used. The plasma profile produced by such an administration regime is illustrated by the "Control" curve in Figure 1. As previously mentioned, the development of patient tolerance is an adverse effect sometimes associated with methylphenidate treatments. It is believed that the trough in the plasma profile between the two peak plasma concentrations is advantageous in reducing the development of patient tolerance by providing a period of wash out of the active ingredient. Drug delivery systems which provide zero order or pseudo zero order delivery of the active ingredient do not facilitate this wash out process.

Any coating material which modifies the release of the active ingredient in the desired manner may be used. In particular, coating materials suitable for use in the practice of the invention include but are not limited to polymer coating materials, such as cellulose acetate phthalate, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, ammonio methacrylate copolymers such as those sold under the Trade Mark Eudragit® RS and RL, poly acrylic acid and poly acrylate and methacrylate copolymers such as those sold under the Trade Mark Eudragit® S and L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium carmellose, sodium carboxymethyl starch, poly vinyl alcohol, hydroxyethyl cellulose, methyl cellulose, gelatin, starch, and cellulose based cross-linked polymers –in which the degree of crosslinking is low so as to facilitate adsorption of water and expansion of the polymer matrix, hydoxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, aminoacryl-methacrylate copolymer (Eudragit® RS-PM, Rohm & Haas), pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (m. wt. ~5k - 5,000k), polyvinylpyrrolidone (m. wt. ~10k - 360k), anionic and cationic hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (m. wt. ~30k - 300k), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, Polyox® polyethylene oxides (m. wt. ~100k - 5,000k), AquaKeep® acrylate polymers, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, sodium starch glucolate (e.g. Explotab®; Edward Mandell C. Ltd.); hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro cellulose, carboxymethyl cellulose, cellulose ethers, polyethylene oxides (e.g. Polyox®, Union Carbide), methyl ethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, collagen, starch, maltodextrin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of methacrylic acid or methacrylic acid (e.g. Eudragit®, Rohm and Haas), other acrylic acid derivatives, sorbitan

esters, natural gums, lecithins, pectin, alginates, ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as arabic, karaya, locust bean, tragacanth, carrageens, guar, xanthan, scleroglucan and mixtures and blends thereof. As will be appreciated by the person skilled in the art, excipients such as plasticisers, lubricants, solvents and the like may be added to the coating. Suitable plasticisers include for example acetylated monoglycerides; butyl phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthalyl ethyl glycolate; glycerin; propylene glycol; triacetin; citrate; tripropioin; diacetin; dibutyl phthalate; acetyl monoglyceride; polyethylene glycols; castor oil; triethyl citrate; polyhydric alcohols, glycerol, acetate esters, gylcerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidised tallate, triisoctyl trimellitate, diethylhexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate.

When the modified release component comprises a modified release matrix material, any suitable modified release matrix material or suitable combination of modified release matrix materials may be used. Such materials are known to those skilled in the art. The term "modified release matrix material" as used herein includes hydrophilic polymers, hydrophobic polymers and mixtures thereof which are capable of modifying the release of an active ingredient dispersed therein *in vitro* or *in vivo*. Modified release matrix materials suitable for the practice of the present invention include but are not limited to microcrytalline cellulose, sodium carboxymethylcellulose, hydoxyalkylcelluloses such as hydroxypropylmethylcellulose and hydroxypropylcellulose, polyethylene oxide, alkylcelluloses such as methylcellulose and ethylcellulose, polyethylene glycol, polyvinylpyrrolidone, cellulose acteate, cellulose acetate butyrate, cellulose acteate phthalate, cellulose acteate trimellitate, polyvinylacetate phthalate, polyalkylmethacrylates, polyvinyl acetate and mixture thereof.

A multiparticulate modified release composition according to the present invention may be incorporated into any suitable dosage form which facilitates release of the active

ingredient in a pulsatile manner. Typically, the dosage form may be a blend of the different populations of active ingredient containing particles which make up the immediate release and the modified release components, the blend being filled into suitable capsules, such as hard or soft gelatin capsules. Alternatively, the different individual populations of active ingredient containing particles may be compressed (optionally with additional excipients) into mini-tablets which may be subsequently filled into capsules in the appropriate proportions. Another suitable dosage form is that of a multilayer tablet. In this instance the first component of the multiparticulate modified release composition may be compressed into one layer, with the second component being subsequently added as a second layer of the multilayer tablet. The populations of active ingredient containing particles making up the composition of the invention may further be included in rapidly dissolving dosage forms such as an effervescent dosage form or a fast-melt dosage form.

The composition according to the invention comprises at least two populations of active ingredient containing particles which have different *in vitro* dissolution profiles.

Preferably, in operation the composition of the invention and the solid oral dosage forms containing the composition release the active ingredient such that substantially all of the active ingredient contained in the first component is released prior to release of the active ingredient from the second component. When the first component comprises an IR component, for example, it is preferable that release of the active ingredient from the second component is delayed until substantially all the active ingredient in the IR component has been released. Release of the active ingredient from the second component may be delayed as detailed above by the use of a modified release coating and/or a modified release matrix material.

More preferably, when it is desirable to minimise patient tolerance by providing a dosage regime which facilitates wash-out of a first dose of active ingredient from a patient's system, release of the active ingredient from the second component is delayed until substantially all of the active ingredient contained in the first component has been released, and further delayed until at least a portion of the active ingredient released from the first

component has been cleared from the patient's system. In a preferred embodiment, release of the active ingredient from the second component of the composition in operation is substantially, if not completely, delayed for a period of at least about two hours after administration of the composition.

When the active ingredient is methylphenidate, release of the active ingredient from the second component of the composition in operation is substantially, if not completely, delayed for a period of at least about four hours, preferably about four hours, after administration of the composition.

In the following Examples all percentages are weight by weight unless otherwise stated. The term "purified water" as used throughout the Examples refers to water that has been purified by passing it through a water filtration system.

Example 1. Multiparticulate modified release composition containing methylphenidate.

A multiparticulate modified release composition according to the present invention comprising an immediate release component and a modified release component and containing methylphenidate as the active ingredient is prepared as follows.

(a) Immediate release component.

A solution of methylphenidate HCl (50:50 racemic mixture) is prepared according to any of the formulations given in Table 1. The methylphenidate solution is then coated onto non-pareil seeds to a level of approximately 16.9% solids weight gain using, for example, a Glatt GPCG3 (Glatt, Protech Ltd., Leicester, UK) fluid bed coating apparatus to form the IR particles of the immediate release component.

Table 1: Immediate release component solutions

Ingredient	Amount, % (w/w) (i)	(ii)
Methylphenidate HCl	13.0	13.0
Polyethylene Glycol 6000	0.5	0.5
Polyvinylpyrrolidone	3.5	
Purified Water	83.5	86.5

(b) Modified release component.

Methylphenidate containing delayed release particles are prepared by coating immediate release particles prepared according to Example 1(a) above with a modified release coating solution as detailed in Table 2. The immediate release particles are coated to varying levels up to approximately to 30 % weight gain using, for example, a fluid bed appratus.

Table 2: Modified release component coating solutions

Ingredient	Amount, % (w/w) (i)	(ii)	(iii)	(iv)	(v)	(vi)	(vii)	(viii)
Eudragit® RS 12.5	49.7	42.0	47.1	53.2	40.6	-	-	25.0
Eudragit® S 12.5	-	-	-	-		54.35	46.5	-
Eudragit® L 12.5	-	-	-	-	-	-	-	25.0
Polyvinylpyrrolidone	-	-	-	0.35	0.3	-	-	-
Diethylphthalate	0.5	0.5	0.6	1.35	0.6	1.3	1.1	-
Triethylcitrate	-	-	-	-	-	-	-	1.25
Isopropyl alcohol	39.8	33.1	37.2	45.1	33.8	44.35	49.6	46.5
Acetone	10.0	8.3	9.3	-	8.4	-	-	-
Talc[1]	-	16.0	5.9	-	16.3	-	2.8	2.25

[1]Talc is simultaneously applied during coating for formulations in column (i), (iv) and (vi).

(c) Dissolution testing

pH independent coated components ((i) to (v) Table 2) are tested *in vitro* in USP Type 1 apparatus (100 rpm) according to the following protocol: the sample is placed in 0.01 N HCl (900 ml), pH 2.0, 37°C for all of the sampling time points.

pH dependent coated components ((vi) to (viii) Table 2) are tested in USP Type 1 apparatus (100 rpm) according to a modified version of the United States Pharmacopoeia method for enteric protection (USP 23, 1995, p.1795): the sample is placed for 2 hours in 0.01 N HCl and then transferred to phosphate buffer pH 6.8 for the remainder of the sampling time points.

IR components were formulated using three different sizes of non-pareil seeds having diameter dimensions of 0.5 - 0.6, 0.6 - 0.71 and 0.71 - 0.85 mm, respectively. The IR particles formed by coating 0.5 - 0.6, 0.6 – 0.71 and 0.71 - 0.85 mm non-pareil seeds were found to release 100 % of the active ingredient within 20 minutes in aqueous media.

Dissolution data for the modified release components prepared according to Example 1(b) above are shown in Tables 3 (a) to 3 (c). This data shows that release characteristics of the modified release component can be varied by changing the composition and thickness of the coating applied.

Table 3 (a): Dissolution data for modified release components formulated with coating solutions given in Table 2

Coating formulation	(i)	(i)	(i)	(ii)	(ii)	(ii)	(iii)	(iii)
Coating level (% weight gain)	4 %	6 %	10 %	4 %	6 %	8 %	4 %	6 %
Time (hr)	% Active ingredient released							
1	0	0	0	8.5	1.3	1.4	6.1	3.0
2	17.0	3.3	0	36.9	7.1	3.7	21.3	8.2
4	51.5	22.1	0	80.0	40.3	15.1	62.3	26.3
6	75.8	46.5	0	92.8	72.4	31.2	82.1	52.6
8	86.0	65.5	10.2	97.5	83.0	47.5	91.3	73.0
10	91.3	76.5	17.3	-	-	-	97.7	86.5

(the notation "-" indicates no measurement taken)

Table 3 (b): Dissolution data for modified release components formulated with coating solutions given in Table 2

Coating formulation	(iv)	(iv)	(iv)	(v)	(v)
Coating level (% weight gain)	10 %	15 %	20 %	10 %	12.5 %
Time (hr)	% Active ingredient released				
1	3.5	0.9	1.1	1.3	1.0
2	13.4	5.4	2.9	6.1	2.9
4	47.1	22.5	13.8	42.4	21.2
6	80.0	52.0	36.9	77.5	54.4
8	94.8	70.3	61.0	92.4	79.7
10	103	81.5	76.1	-	-

(the notation "-" indicates no measurement taken)

Table 3 (c): Dissolution data for modified release components formulated with coating solutions given in Table 2

Coating formulation	(vi)	(vi)	(vi)	(vi)*	(vii)	(vii)	(viii)	(viii)
Coating level (% weight gain)	5 %	10 %	15 %	15 %	15 %	20 %	20 %	30 %
Time (hr)	% Active ingredient released							
1	33.2	0.4	0	0	3.9	0.6	3.8	2.1
2	80.6	9.8	0	0.5	52.0	12.4	7.4	3.1
4	92.2	43.5	10.1	44.0	85.0	61.6	43.7	8.9
6	93.9	61.6	29.9	80.2	89.9	75.3	72.4	36.9
8	94.3	67.5	48.4	69.0	91.4	79.6	79.2	63.9
10	94.4	-	60.0	-	-	-	79.5	73.4

(the notation "-" indicates no measurement taken; "*" indicates pH of phosphate buffer was 7.4 instead of 6.8)

(d) Encapsulation of immediate and delayed release particles.

The immediate and delayed release particles prepared according to Example 1(a) and (b) above are encapsulated in size 2 hard gelatin capsules to an overall 20 mg dosage strength using, for example, a Bosch GKF 4000S encapsulation apparatus. The overall dosage strength of 20 mg methylphenidate was made up of 10 mg from the immediate release component and 10 mg from the modified release component.

Table 4 shows the dissolution profiles for two multiparticulate modified release compositions prepared using the immediate release coating solution given in Table 1 (ii) and the modified release coating solutions given in Table 2 (vii) and (viii). These results indicate that approximately 50% of the methylphenidate HCl active ingredient was released within the first half hour with release from the modified release component being delayed for about four hours.

Table 4. Dissolution data for compositions containing an IR component and a modified release component

MR coating formulation	(vii)	(viii)
Coating level (% weight increase)	30 %	30 %
0	0	0
0.5	49.7	50.2
1	49.7	50.5
2	49.8	51.1
4	56.1	54.1
6	65.2	68.0
8	72.2	81.8
10	76.6	87.0

The dissolution profiles shown in Table 4 indicate that the compositions containing the pH dependent coated components release the methylphenidate active ingredient in a pulsed manner. A first pulse occurs before 1 hour followed by a plateau region where the

release of further amounts of the active ingredient is suppressed. The plateau region is in turn followed by a second pulse of active ingredient release as indicated by the increase in drug concentration from 4 hours onward.

Example 2. Multiparticulate modified release composition containing methylphenidate.

Multiparticulate modified release methylphenidate compositions according to the present invention having an immediate release component and a modified release component having a modified release matrix material are prepared according to the formulations shown in Table 5 (a) and (b).

Table 5 (a): 100 mg of IR component is encapsulated with 100 mg of modified release (MR) component to give a 20 mg dosage strength product

IR component	% (w/w)	MR component	% (w/w)
Methylphenidate HCl	10	Methylphenidate HCl	10
Microcrytalline cellulose	40	Microcrytalline cellulose	40
Lactose	45	Eudragit® RS	45
Povidone	5	Povidone	5

Table 5 (b): 50 mg of IR component is encapsulated with 50 mg of modified release (MR) component to give a 20 mg dosage strength product.

IR component	% (w/w)	MR component	% (w/w)
Methylphenidate HCl	20	Methylphenidate HCl	20
Microcrytalline cellulose	50	Microcrytalline cellulose	50
Lactose	28	Eudragit® S	28
Povidone	2	Povidone	2

(e) In vivo release

In a human cross-over biostudy, fasted healthy volunteers were dosed with 20 mg methylphenidate HCl compositions according to the present invention to compare the

bioavailability of methylphenidate HCl in these compositions relative to Ritalin® (Novartis; 10 mg dosed twice at a four hour interval). Pharmacokinetic assessment was based on the plasma levels of methylphenidate measured by blood sampling at regular intervals up to 48 hours after administration. Blood samples were also taken for pre- and post-study screening.

Referring now to Figure 1, the plasma profiles labelled "A" (modified component comprises IR particles coated with coating Table 2 (viii) at 30 %) and "B" (modified component comprises IR particles coated with coating Table 2 (vii) at 30 %) correspond to the plasma concentrations of methylphenidate observed in human volunteers after oral administration of the multiparticulate modified release compositions prepared according to Example 1. In both cases the plasma profile is qualitatively similar to the control, typical of prior art treatments (labelled "Control" in Figure 1), which consists of two doses of Ritalin® IR given sequentially, four hours apart.

For the multiparticulate modified release composition according to the present invention prepared according to Example 1 above, the first peak in the plasma profile associated with the immediate release component is similar in terms of c_{max} and peak width to the peak associated with the first dose of Ritalin® in the control profile. Profile A shows that the trough characteristic of the conventional twice daily administration (as exemplified by the control profile) is mimicked by the composition prepared according to the invention. Profile B also shows a significant fall off after the initial peak in plasma concentration. For both multiparticulate modified release compositions, the effect of the modified release component is to increase plasma concentrations four hours after administration resulting in a second peak level. This observed effect again mimics the control.

From Figure 1 it is clear that the multiparticulate modified release compositions prepared according to the present invention mimic a typical twice daily treatment (represented by the control) in terms of the plasma profile achieved upon administration. This *in vivo* release of methylphenidate from compositions according to the invention was achieved without any loss in bioavailability compared to Ritalin® dosed twice daily.

In a separate study, 34 children with ADHD were dosed with 20 mg methylphenidate HCl compositions according to the present invention. A simulated classroom design was used to compare formulations "A" and "B" (corresponding to the "A" and "B" formulations described above) with placebo. Pharmacodynamic assessments were conducted over a 9 hour time period which measured both attention and deportment as measured on the SKAMP scale and functional outcome as measured by the number of math problems attempted and the number of correct answers. Each formulation demonstrated a statistical difference from placebo on all efficacy measurements. The individual efficacy evaluations showed that the "A" and "B" formulations proved to be similar with regard to deportment. With regard to attention and functional outcome, the children on the "A" formulation appeared to focus more on the tasks at hand and attempted more math problems more quickly between 4 and 6 hours than the children taking the "B" formulation.

The present invention is not to be limited in scope by the specific embodiments described herein. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the following claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS

1. A multiparticulate modified release composition containing at least one active ingredient and having a first component comprising a first population of active ingredient-containing particles and at least one subsequent component, each subsequent component comprising a subsequent population of active ingredient-containing particles, the active ingredient contained in the first and subsequent components being the same or different; wherein the at least one subsequent population of active ingredient containing particles further comprises a modified release coating or, alternatively or additionally, a modified release matrix material, such that the composition following oral delivery to a subject delivers the active ingredient or active ingredients in a pulsatile manner.

2. The multiparticulate modified release composition according to claim 1, wherein the composition comprises a first component and one subsequent component.

3. The multiparticulate modified release composition according to claim 1 or claim 2, wherein the first component comprises an immediate release component and the subsequent component is a modified release component.

4. The multiparticulate modified release composition according to claim 3, wherein the modified release component comprises particles having a modified release coating.

5. The multiparticulate modified release composition according to claim 3, wherein the modified release component comprises a modified release matrix material.

6. The multiparticulate modified release composition according to any one of the preceding claims, wherein the first population of active ingredient-containing particles and the at least one subsequent population of active ingredient-containing particles comprise the same active ingredient.

7. The multiparticulate modified release composition according to anyone of the preceding claims, wherein the first population of active ingredient-containing particles contains two or more active ingredients

8. The multiparticulate modified release composition according to any one of the preceding claims, wherein the at least one subsequent population of active ingredient-containing particles contains two or more active ingredients.

9. The multiparticulate modified release composition according any one of the preceding claims, wherein the active ingredient comprises substantially one optically pure enantiomer or a mixture, racemic or otherwise, of enantiomers.

10. The multiparticulate modified release composition according to any one of the preceding claims, wherein at least one of the first and subsequent components further comprise an enhancer.

11. The multiparticulate modified release composition according to any one of the preceding claims, wherein the amount of active ingredient contained in the first and subsequent components is the same or different.

12. The multiparticulate modified release composition according to claim 11 wherein the amount of active ingredient contained in each component is from about 0.1 mg to about 1 g.

13. The multiparticulate modified release composition according to claim 6, wherein the active ingredient is methylphenidate or a pharmaceutically acceptable salt thereof, an enantiomer or mixtures thereof or mixtures thereof.

14. The multiparticulate modified release composition according to any one of the preceding claims, wherein the first and subsequent populations of active ingredient-containing particles have different in vitro dissolution profiles.

15. The multiparticulate modified release composition according to any one of the preceding claims, wherein the first component is an immediate release component and the at least one subsequent component is a modified release component.

16. The multiparticulate modified release composition according to claim 15, which in operation releases substantially all of the active ingredient from the first population of active ingredient-containing particles prior to release of the active ingredient from the subsequent population of active ingredient-containing particles.

17. The multiparticulate modified release composition according to any one of the preceding claims, wherein the in vivo release of the active ingredient in the subject mimics the *in vivo* release of the same active ingredient administered in the form of two or more doses of immediate release forms of the active ingredient.

18. The multiparticulate modified release composition according to claim 16, wherein the mean in vitro dissolution profile in aqueous media is such that about 50 to 100 % of the active ingredient contained in the first population of active ingredient containing particles is released within four hours of administration of the composition, and about 30 to 100 % of the active ingredient contained in the subsequent population of active ingredient containing particles is released between four and eight hours after administration of the composition.

19. The multiparticulate modified release composition according to claim 18, wherein the mean *in vitro* dissolution profile in aqueous media is such that about 80 to 100 % of the active ingredient contained in the first population of active ingredient-containing particles is released within four hours of administration of the composition, and about 60 to 100 % of the active ingredient contained in the subsequent population active ingredient-containing particles is released between four and eight hours after administration of the composition.

20. A solid oral dosage form comprising a multiparticulate modified release composition according to any one of the preceding claims.

21. The solid oral dosage form according to claim 20 comprising a blend of first and subsequent active ingredient-containing particles filled into hard gelatin or soft gelatin capsules.

22. The solid oral dosage form according to claim 20 or 21, wherein the first and subsequent components are separately and independently compressed into mini-tablets and filled into hard or soft gelatin capsules.

23. The solid oral dosage form according to any one of claims 20 to 22, wherein the first component is compressed into the first layer of a multilayer tablet and the at least

one subsequent component is compressed into a subsequent layer of the multilayer tablet.

24. The solid oral dosage form according to any one of claims 20 to 23, wherein the first and subsequent components are incorporated in a rapidly dissolving dosage foam.

25. The solid oral dosage form according to any one of claims 20 to 24, wherein the rapidly dissolving dosage form is a fast-melt tablet dosage form.

26. Use of a multiparticulate modified release composition according to any one of the preceding claims in the preparation of a medicament for the treatment of a condition which is characterised by the build up of patient tolerance to the at least one active ingredient contained in the composition.

27. Use of a multiparticulate modified release composition according to any one of the preceding claims in the preparation of a medicament for the treatment of attention deficit disorder.

28. A method of treatment of a condition which is characterised by the build up of patient tolerance to an active ingredient administered in the treatment of the condition comprising administering a therapeutically effective amount of a multiparticulate modified release composition according to any one of the preceding claims.

29. A method of treatment of attention deficit disorder comprising administering a therapeutically effective amount of a multiparticulate modified release composition according to any one of the preceding claims.

30. The composition according to claim 3, wherein the modified release component comprises a pH dependent polymer coating that releases a pulse of active ingredient from the modified release component following a delay time.

31. The composition according to claim 30, wherein the pH dependent polymer coating comprises methacrylate copolymers.

32. The composition according to claim 30, wherein the pH dependent polymer coating comprises a mixture of methacrylate and ammonio methacrylate copolymers in

a ratio sufficient to achieve a pulse of active ingredient from the modified release component following a delay time.

33. The composition according to claim 32, where the ratio of methacrylate to ammonio methacrylate copolymers is 1:1.

34. A multiparticulate modified release composition according to any one of claims 1 to 19 or 30 to 33 substantially as hereinbefore described with particular reference to the examples and/or the preferred embodiments.

35. A solid oral dosage form according to any one of claims 20 to 25 substantially as hereinbefore described with particular reference to the examples and/or the preferred embodiments.

36. The use of a multiparticulate modified release composition according to claim 26 or claim 27 substantially as hereinbefore described with particular reference to the examples and/or the preferred embodiments.

37. A method of treatment of a condition according to claim 28 substantially as hereinbefore described with particular reference to the examples and/or the preferred embodiments.

38. A method of treatment of attention deficit disorder according to claim 29 substantially as hereinbefore described with particular reference to the examples and/or the preferred embodiments.

Dated this third day of December 2003

Elan Corporation, plc
Patent Attorneys for the Applicant:

F B RICE & CO

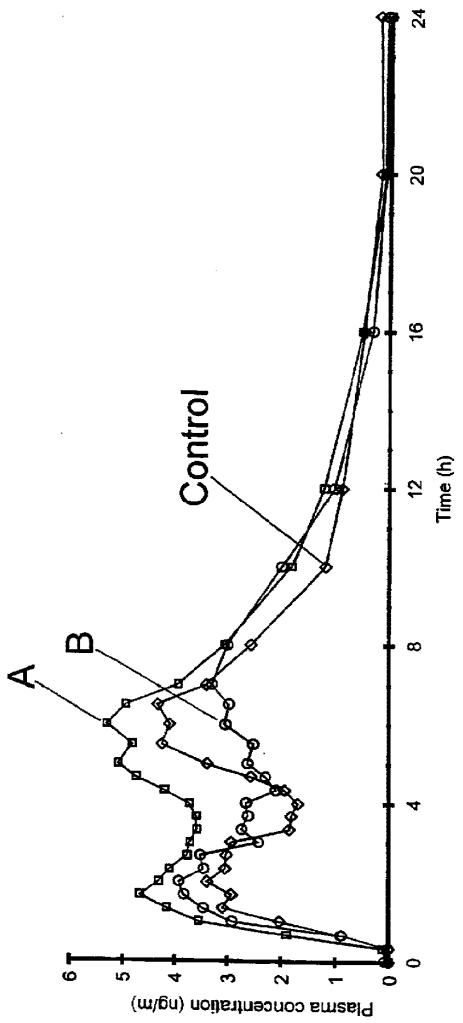

Plasma concentration (ng/m)
0
1
2
3
4
5
6
Time (h)
0
4
8
12
16
20
24
A
B
Control

Figure 1

Electronic Patent Application Fee Transmittal

Application Number:	11383066
Filing Date:	12-May-2006
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Filer:	Marie Louise Collazo/Mami Hasegawa
Attorney Docket Number:	20342/1202653-US8
Filed as Large Entity	

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1202	3	50	150
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**150**

Electronic Acknowledgement Receipt

EFS ID:	1275951
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Marie Louise Collazo/Mami Hasegawa
Filer Authorized By:	Marie Louise Collazo
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	26-OCT-2006
Filing Date:	12-MAY-2006
Time Stamp:	15:21:50
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$150
RAM confirmation Number	115
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1		00895897.PDF	46518	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed	00895901.PDF	46107	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	NPL Documents	00895904.PDF	94697	no	4
Warnings:					
Information:					
4	Foreign Reference	00892942.PDF	3556543	no	85
Warnings:					
Information:					
5	Foreign Reference	00892872.PDF	1118112	no	22
Warnings:					
Information:					
6	Foreign Reference	00892853.PDF	1495254	no	32
Warnings:					
Information:					
7	Foreign Reference	1202.pdf	1068513	no	33
Warnings:					
Information:					

8	Fee Worksheet (PTO-875)	fee-info.pdf	8158	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	7433902	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 11/383,066

CLAIMS AS FILED - PART I

5/12/06

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	58 minus 20=	* 38
INDEPENDENT CLAIMS	3 minus 3 =	*
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	395	OR	BASIC FEE	790.00
X$25		OR	X50	1900
X100		OR	X200	
180.00		OR	360.00	
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

10/24/06

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 32	Minus	** 58	=
Independent	* 1	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$25		OR	X$50	
X100		OR	X200	
+180		OR	+360	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

10/26/06

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 35	Minus	** 58	=
Independent	* 2	Minus	*** 3	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$25		OR	X$50	
X100		OR	X200	
+180		OR	360	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

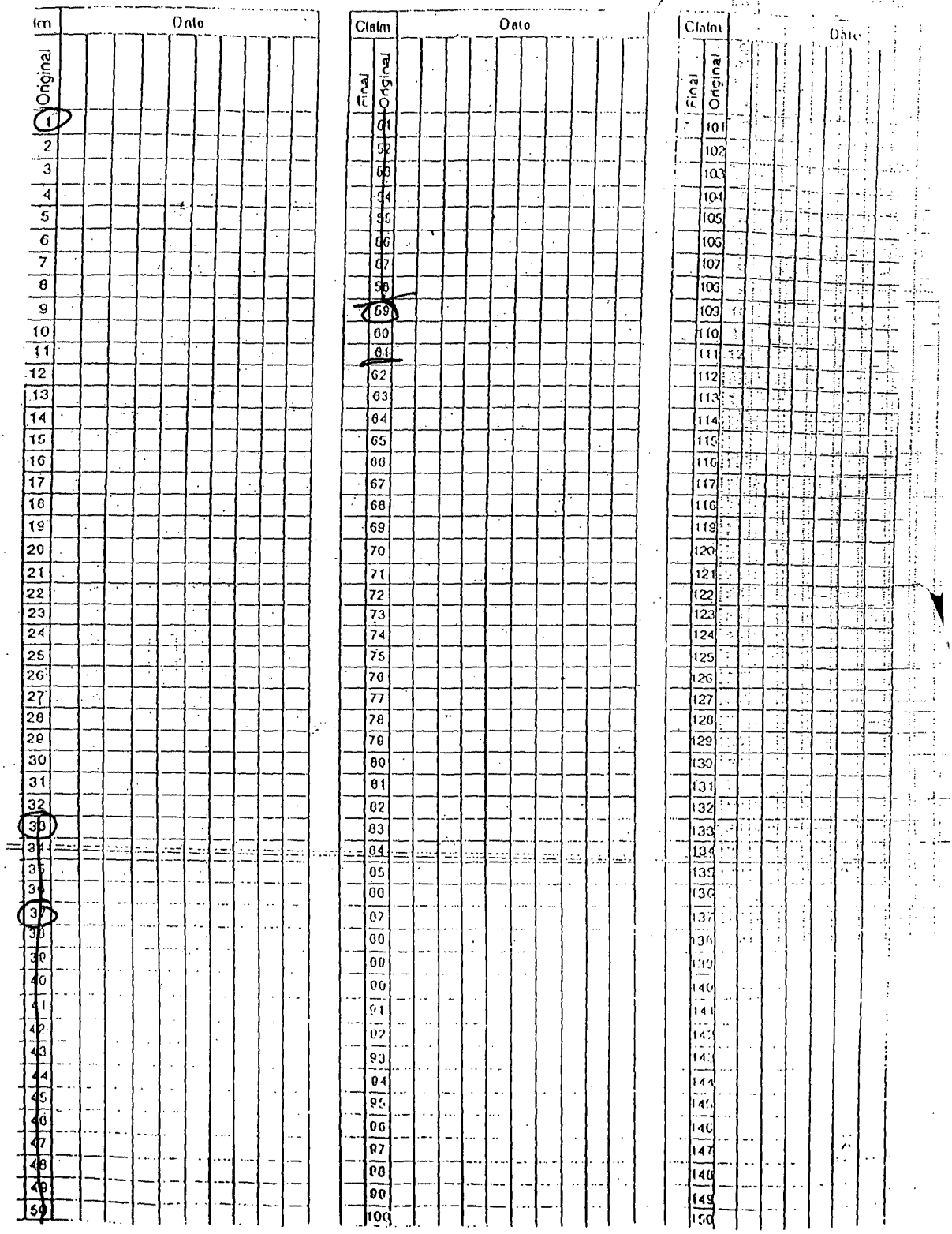
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$25		OR	X$50	
X100		OR	X200	
+180		OR	+360	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

111383,066

INDEX OF CLAIMS

✓ ..... Rejected
= ..... Allowed
– (Through numeral)... Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected



Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 — Confirmation No.: 7083

Filed: May 12, 2006 — Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM — Examiner: Not Yet Assigned

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. A check for the fee set forth in 1. 17(p), presently believed to be $180, is enclosed.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(i) a check in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[x] A. Pursuant to the 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the **U.S. Patent(s) and/or U.S. Patent Application Publication(s)** on PTO/SB08 is/are not being submitted.

[ ] B. Document(s) _____is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[ ] 3. Cite No(s). _____ are not in the English language. In accordance with 1.98(c), Applicant states:

[ ] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application , or English-language abstract (or claim) is enclosed.

[ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

☐ 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

☒ 5. Other information being provided for the examiner's consideration follows:

An International Search Report, dated November 21, 2006, which issued during the prosecution of International Application No. PCT/US06/18453 which corresponds to the present application.

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: December 6, 2006

Respectfully submitted,

By MARIE COLLADO 44085

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

PTO/SB/08A/B (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/383,066-Conf. #7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	20342/1202653-US8

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-6,322,819	12-27-2001	Burnside et al.	
	AB*	US-6,605,300	08-12-2003	Burnside et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		International Search Report dated November 21, 2006 issued for corresponding International Application No. PCT/US06/18453.	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

Examiner Signature		Date Considered	

00934273.doc

Electronic Acknowledgement Receipt

EFS ID:	1358166
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Jay Philip Lessler/Lillian Garcia
Filer Authorized By:	Jay Philip Lessler
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	07-DEC-2006
Filing Date:	12-MAY-2006
Time Stamp:	12:22:44
Application Type:	Utility

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	00937451.pdf	49605	no	5
Warnings:					

Information:					
This is not an USPTO supplied IDS fillable form					
2	NPL Documents	00937461.pdf	220161	no	9
Warnings:					
Information:					
			Total Files Size (in bytes):	269766	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 | Confirmation No.: 7083

Filed: May 12, 2006 | Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM | Examiner: Not Yet Assigned

REQUEST FOR REFUND

Mail Stop 16
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby request a refund of the $1,900 excess claim fee erroneously charged to our Deposit Account No. 04-0100 on November 7, 2006 for the above-identified application. A copy of the Deposit Account Statement received from the United States Patent and Trademark Office for the month of November 2006 is attached.

The application was initially filed on May 12, 2006 with 58 claims. In a Response to the Notice to File Missing Parts dated October 24, 2006, Applicants canceled claims 33 through 58 in a First Preliminary Amendment and paid the required fee of $600.00 for 12 excess claims. In a Second Preliminary Amendment dated October 26, 2006, one (1) independent claim (claim 59) and two (2) dependent claims (claims 60 and 61) were added bringing the total number of claims to 35 and paid the required fee of $150.00 for three (3) more excess claims.

Accordingly, Applicants respectfully request a refund of $1,900.00. Please credit the refund to Deposit Account No. 04-0100 in the name DARBY & DABY P.C.

Dated: December 11, 2006

Respectfully submitted,

By _____
Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

United States Patent and Trademark Office

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Deposit Account Statement

Requested Statement Month:	November 2006
Deposit Account Number:	040100
Name:	DARBY & DARBY P.C.
Attention:	ANGELINA DILULLO
Address:	805 THIRD AVENUE
City:	NEW YORK
State:	NY
Zip:	10022-7513
Country:	UNITED STATES

DATE	SEQ	POSTING REF TXT	ATTORNEY DOCKET NBR	FEE CODE	AMT	BAL
11/01	45	11278922	05986/1200450US1	8021	$40.00	$38,336.0
11/01	947	7090181	20339/0205650-US0	8021	$40.00	$38,296.0
11/01	202	11110575	08226/1203032-US2	1251	$120.00	$38,176.0
11/02	1776	11555672	08226/0205412-US0	1011	$300.00	$37,876.0
11/02	1779	11555672	08226/0205412-US0	1201	$400.00	$37,476.0
11/02	1778	11555672	08226/0205412-US0	1311	$200.00	$37,276.0
11/02	1777	11555672	08226/0205412-US0	1111	$500.00	$36,776.0
11/02	1781	11555675	08226/0205279-US0	1011	$300.00	$36,476.0
11/02	1782	11555675	08226/0205279-US0	1111	$500.00	$35,976.0
11/02	1783	11555675	08226/0205279-US0	1311	$200.00	$35,776.0
11/02	1784	11555675	08226/0205279-US0	1201	$200.00	$35,576.0
11/02	1811	60863966	01946/0205635-US0	1005	$200.00	$35,376.0
11/02	103	60803450	09857/0204691-USO	8007	$20.00	$35,356.0
11/02	384	11462441	20561/1203257-US1	8021	$40.00	$35,316.0
11/02	466	11510479	02140/1203115-US1	8021	$40.00	$35,276.0
11/03	54	60760054	01011/0203898-US0	8007	$20.00	$35,256.0
11/06	309	60717546	04366/0203258-US0	8007	$20.00	$35,236.0
11/07	144	0142670567	03946/000N203-USO	8014	$25.00	$35,211.0
11/07	149	0142670589	03946/000N203-US0	8014	$25.00	$35,186.0
11/07	81	11592795	11,061,561 03981 10078631US1	1011	$300.00	$34,886.0
11/07	83	11592795	11,061,561	1311	$200.00	$34,686.0
11/07	85	11592795	11,061,561	1202	$750.00	$33,936.0
11/07	86	11592795	11,061,561	1203	$360.00	$33,576.0
11/07	84	11592795	11,061,561	1201	$200.00	$33,376.0
11/07	82	11592795	11,061,561	1111	$500.00	$32,876.0
11/07	1	11383066	20342/1202653-US8	1202	$1,900.00	$30,976.0
11/08	102	11272569	20342/1202326-US3	8007	$280.00	$30,696.0

Electronic Acknowledgement Receipt

EFS ID:	1270464
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Marie Louise Collazo/Mami Hasegawa
Filer Authorized By:	Marie Louise Collazo
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	24-OCT-2006
Filing Date:	12-MAY-2006
Time Stamp:	15:05:25
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$2750
RAM confirmation Number	55
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1	Applicant Response to Pre-Exam Formalities Notice	00892983.PDF	40331	no	4
Warnings:					
Information:					
2	Application Data Sheet	00892984.PDF	22496	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Extension of Time	00892989.PDF	15183	no	1
Warnings:					
Information:					
4		00892991.PDF	39788	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	6

Warnings:					
Information:					
5	Oath or Declaration filed	00892995.PDF	182717	no	16
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	8752	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	309267		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066

Filed: May 12, 2006

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM

Confirmation No.: 7083

Art Unit: N/A

Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

MS Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Notice to File Missing Parts of Application – Filing Date Granted mailed May 24, 2006, Applicant respectfully submits a Combined Declaration and Power of Attorney, a First Preliminary Amendment, a Supplemental Application Data Sheet, the Filing Fee for the Application (as shown on accompanying Fee Transmittal), a Petition for Extension of Time, and Part 2 Copy of Notice.

Please charge our Credit Card in the amount of $2,750.00 covering the fees set forth in 37 CFR 1.16(f), 1.16(a)(1), 1.16(k), 1.16(o), 1.17(a)(3), and 1.16(i). The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: October 24, 2006

Respectfully submitted,

By (53,970)

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei

Application No.: 11/383,066 — Confirmation No.:

Filed: May 12, 2006 — Art Unit: N/A

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM — Examiner: Not Yet Assigned

FIRST PRELIMINARY AMENDMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 6 of this paper.

LISTING OF CLAIMS

1. (Original) A pharmaceutical composition comprising:

(a) an immediate release bead comprising at least one amphetamine salt;

(b) a first delayed release bead comprising at least one amphetamine salt; and

(c) a second delayed release bead comprising at least one amphetamine salt;

wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt and the second delayed release bead provides sustained release of the at least one amphetamine salt.

2. (Original) The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

3. (Original) The pharmaceutical composition of claim 2, wherein the enteric coating is pH dependent.

4. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.

5. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coating.

6. (Original) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is bioequivalent to ADDERALL® XR followed by an immediate release amphetamine formulation administered 8 hours after the ADDERALL® XR;

wherein the combined dosage of the ADDERALL® XR and the immediate release formulation is equal to the dosage of the pharmaceutical composition.

7. (Original) The pharmaceutical composition of claim 1, wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a *d*-amphetamine C_{max} of about 50 ng/ml.

8. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1058 ng·hr/ml.

9. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1085 ng·hr/ml.

10. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine T_{max} is about 8.2 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

11. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine C_{max} after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 15 ng/ml.

12. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 354 ng·hr/ml.

13. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 373 ng·hr/ml.

14. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

15. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on a single core.

16. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.

17. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.

18. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.

19. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer over at least one enteric coating.

20. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.

21. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

22. (Original) The pharmaceutical composition of claim 21, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

23. (Original) The pharmaceutical composition of claim 1, wherein the composition does not exhibit a food effect.

24. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 12.5 mg.

25. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 18.75 mg.

26. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 25 mg.

27. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 31.25 mg.

28. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 37.5 mg.

29. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 43.75 mg.

30. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 50 mg.

31. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 62.5 mg.

32. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 75 mg.

33-58. (Canceled)

REMARKS

Claims 33-58 have been canceled, without prejudice to pursue them in one or more continuation applications. No new matter has been added. Claims 1-32 are pending and at issue.

Prompt and favorable consideration of the present application is earnestly solicited.

Dated: October 24, 2006

Respectfully submitted,

By _____
Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

M. Hasagawa

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NUMBER
11/383,066	05/12/2006	Amir Shojaei	20342/1202653-US8

CONFIRMATION NO. 7083

07278
DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

DUE: July 24, 2006
Docketed on 6/6/06 by BWL for
Docketed without file ☐
Attorney _____

FORMALITIES LETTER

Date Mailed: 05/24/2006

(12-24-06)

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  Applicant must submit $ **300** *to complete the basic filing fee for a non-small entity. If appropriate, applicant may make a written assertion of entitlement to small entity status and pay the small entity filing fee (37 CFR 1.27).*
- The oath or declaration is missing. *A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.*
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- Additional claim fees of **$1900** as a non-small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $130 for a non-small entity, must be submitted with the missing items identified in this letter.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is **$3030** for a Large Entity

- **$300** Statutory basic filing fee.
- **$130** Surcharge.

- The application search fee has not been paid. Applicant must submit **$500** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit **$200** to complete the examination fee for a large entity

- Total additional claim fee(s) for this application is **$1900**

  - **$1900** for **38** total claims over 20.

Replies should be mailed to: Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

A copy of this notice MUST be returned with the reply.

Office of Initial Patent Examination (571) 272-4000, or 1-800-PTO-9199, or 1-800-972-6382
PART 1 - ATTORNEY/APPLICANT COPY

Electronic Acknowledgement Receipt

EFS ID:	1275951
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Marie Louise Collazo/Mami Hasegawa
Filer Authorized By:	Marie Louise Collazo
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	26-OCT-2006
Filing Date:	12-MAY-2006
Time Stamp:	15:21:50
Application Type:	Utility

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$150
RAM confirmation Number	115
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1		00895897.PDF	46518	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed	00895901.PDF	46107	no	5
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	NPL Documents	00895904.PDF	94697	no	4
Warnings:					
Information:					
4	Foreign Reference	00892942.PDF	3556543	no	85
Warnings:					
Information:					
5	Foreign Reference	00892872.PDF	1118112	no	22
Warnings:					
Information:					
6	Foreign Reference	00892853.PDF	1495254	no	32
Warnings:					
Information:					
7	Foreign Reference	1202.pdf	1068513	no	33
Warnings:					
Information:					

8	Fee Worksheet (PTO-875)	fee-info.pdf	8158	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	7433902	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei

Application No.: 11/383,066 — Confirmation No.: 7083

Filed: May 12, 2006 — Art Unit: N/A

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM — Examiner: Not Yet Assigned

SECOND PRELIMINARY AMENDMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

LISTING OF CLAIMS

1. (Original) A pharmaceutical composition comprising:

(a) an immediate release bead comprising at least one amphetamine salt;

(b) a first delayed release bead comprising at least one amphetamine salt; and

(c) a second delayed release bead comprising at least one amphetamine salt;

wherein the first delayed release bead provides pulsed release of the at least one amphetamine salt and the second delayed release bead provides sustained release of the at least one amphetamine salt.

2. (Original) The pharmaceutical composition of claim 1, wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

3. (Original) The pharmaceutical composition of claim 2, wherein the enteric coating is pH dependent.

4. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.

5. (Original) The pharmaceutical composition of claim 2, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coating.

6. (Original) The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is bioequivalent to ADDERALL® XR followed by an immediate release amphetamine formulation administered 8 hours after the ADDERALL® XR;

wherein the combined dosage of the ADDERALL® XR and the immediate release formulation is equal to the dosage of the pharmaceutical composition.

7. (Original) The pharmaceutical composition of claim 1, wherein administration of a 37.5 mg dose of the pharmaceutical composition to a human patient results in a *d*-amphetamine C_{max} of about 50 ng/ml.

8. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1058 ng·hr/ml.

9. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 1085 ng·hr/ml.

10. (Original) The pharmaceutical composition of claim 1, wherein the *d*-amphetamine T_{max} is about 8.2 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

11. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine C_{max} after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 15 ng/ml.

12. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to the last measured time ($AUC_{0\text{-last}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 354 ng·hr/ml.

13. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine area under the curve from time 0 to time infinity ($AUC_{0\text{-inf}}$) after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient is about 373 ng·hr/ml.

14. (Original) The pharmaceutical composition of claim 1, wherein the *l*-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

15. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on a single core.

16. (Original) The pharmaceutical composition of claim 1, wherein the immediate release bead and at least one delayed release bead are present on different cores.

17. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is coated onto a core.

18. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is incorporated into a core.

19. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer over at least one enteric coating.

20. (Original) The pharmaceutical composition of claim 2, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.

21. (Original) The pharmaceutical composition of claim 1, wherein the at least one amphetamine salt is selected from the group consisting of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, amphetamine sulfate, and mixtures thereof.

22. (Original) The pharmaceutical composition of claim 21, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

23. (Original) The pharmaceutical composition of claim 1, wherein the composition does not exhibit a food effect.

24. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 12.5 mg.

25. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 18.75 mg.

26. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 25 mg.

27. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 31.25 mg.

28. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 37.5 mg.

29. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 43.75 mg.

30. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 50 mg.

31. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 62.5 mg.

32. (Original) The composition of claim 6, wherein the amount of at least one amphetamine salt is about 75 mg.

33-58. (Canceled)

59. (New) A pharmaceutical composition comprising:

at least one amphetamine salt and a pharmaceutically acceptable carrier;

wherein the composition provides an about bioequivalent plasma level of amphetamine in a patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® XR and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL® XR.

60. (New) The composition of claim 59, wherein the composition provides an about bioequivalent plasma level of d-amphetamine in the patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® XR and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL® XR.

61. (New) The composition of claim 59, wherein the composition provides an about bioequivalent plasma level of l-amphetamine in the patient compared to an equivalent amount of at least one amphetamine salt contained in the combination of ADDERALL® XR and an immediate release amphetamine salt composition when the immediate release composition is administered to the patient about 8 hours after the ADDERALL® XR.

REMARKS

Claims 1-32 and 59-61 are pending with this amendment. Claims 33-35 were inadvertently canceled in the First Preliminary Amendment, filed October 24, 2006. To correct this inadvertent error, original claims 33-35 are added back as new claims 59-61. To correct a typographical error in original claims 33-35, new claims 59-61 recite "ADDERALL® XR." Support for this correction can be found in the specification at, for example, page 5, lines 8-10 and page 34, line 21 to page 39, line 7. No new matter has been added.

Dated: October 26, 2006

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

Electronic Acknowledgement Receipt

EFS ID:	1365275
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Marie Louise Collazo/Mami Hasegawa
Filer Authorized By:	Marie Louise Collazo
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	11-DEC-2006
Filing Date:	12-MAY-2006
Time Stamp:	15:36:54
Application Type:	Utility

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Refund Request	00941249.PDF	212275	no	26
Warnings:					

Information:	
Total Files Size (in bytes):	212275

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

12-11-06

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 — Confirmation No.: 7083

Filed: May 12, 2006 — Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM — Examiner: Not Yet Assigned

REQUEST FOR REFUND

Mail Stop 16
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby request a refund of the $1,900 excess claim fee erroneously charged to our Deposit Account No. 04-0100 on November 7, 2006 for the above-identified application. A copy of the Deposit Account Statement received from the United States Patent and Trademark Office for the month of November 2006 is attached.

The application was initially filed on May 12, 2006 with 58 claims. In a Response to the Notice to File Missing Parts dated October 24, 2006, Applicants canceled claims 33 through 58 in a First Preliminary Amendment and paid the required fee of $600.00 for 12 excess claims. In a Second Preliminary Amendment dated October 26, 2006, one (1) independent claim (claim 59) and two (2) dependent claims (claims 60 and 61) were added bringing the total number of claims to 35 and paid the required fee of $150.00 for three (3) more excess claims.

{W:\20342\1202653us8\00934136.DOC }

Adjustment date: 12/12/2006 SDENBOB1
11/07/2006 HSMITH1 00000001 040100 11383066
01 FC:1202 1900.00 CR

Accordingly, Applicants respectfully request a refund of $1,900.00. Please credit the refund to Deposit Account No. 04-0100 in the name DARBY & DABY P.C.

Dated: December 11, 2006

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

United States Patent and Trademark Office

Return To: USPTO Home Page | Finance Online Shopping Page

Deposit Account Statement

Requested Statement Month:	November 2006
Deposit Account Number:	040100
Name:	DARBY & DARBY P.C.
Attention:	ANGELINA DILULLO
Address:	805 THIRD AVENUE
City:	NEW YORK
State:	NY
Zip:	10022-7513
Country:	UNITED STATES

DATE	SEQ	POSTING REF TXT	ATTORNEY DOCKET NBR	FEE CODE	AMT	BAL
11/01	45	11278922	05986/1200450US1	8021	$40.00	$38,336.(
11/01	947	7090181	20339/0205650-US0	8021	$40.00	$38,296.(
11/01	202	11110575	08226/1203032-US2	1251	$120.00	$38,176.(
11/02	1776	11555672	08226/0205412-US0	1011	$300.00	$37,876.(
11/02	1779	11555672	08226/0205412-US0	1201	$400.00	$37,476.(
11/02	1778	11555672	08226/0205412-US0	1311	$200.00	$37,276.(
11/02	1777	11555672	08226/0205412-US0	1111	$500.00	$36,776.(
11/02	1781	11555675	08226/0205279-US0	1011	$300.00	$36,476.(
11/02	1782	11555675	08226/0205279-US0	1111	$500.00	$35,976.(
11/02	1783	11555675	08226/0205279-US0	1311	$200.00	$35,776.(
11/02	1784	11555675	08226/0205279-US0	1201	$200.00	$35,576.(
11/02	1811	60863966	01946/0205635-US0	1005	$200.00	$35,376.(
11/02	103	60803450	09857/0204691-USO	8007	$20.00	$35,356.(
11/02	384	11462441	20561/1203257-US1	8021	$40.00	$35,316.(
11/02	466	11510479	02140/1203115-US1	8021	$40.00	$35,276.(
11/03	54	60760054	01011/0203898-US0	8007	$20.00	$35,256.(
11/06	309	60717546	04366/0203258-US0	8007	$20.00	$35,236.(
11/07	144	0142670567	03946/000N203-USO	8014	$25.00	$35,211.(
11/07	149	0142670589	03946/000N203-US0	8014	$25.00	$35,186.(
11/07	81	11592795	11,061,561	1011	$300.00	$34,886.(
11/07	83	11592795	11,061,561	1311	$200.00	$34,686.(
11/07	85	11592795	11,061,561	1202	$750.00	$33,936.(
11/07	86	11592795	11,061,561	1203	$360.00	$33,576.(
11/07	84	11592795	11,061,561	1201	$200.00	$33,376.(
11/07	82	11592795	11,061,561	1111	$500.00	$32,876.(
11/07	1	11383066	20342/1202653-US8	1202	$1,900.00	$30,976.(
11/08	102	11272569	20342/1202326-US3	8007	$280.00	$30,696.(

BEST AVAILABLE COPY

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 | Confirmation No.: 7083

Filed: May 12, 2006 | Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM | Examiner: Not Yet Assigned

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. A check for the fee set forth in 1. 17(p), presently believed to be $180, is enclosed.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(i) a check in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[x] A. Pursuant to the 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the **U.S. Patent(s) and/or U.S. Patent Application Publication(s)** on PTO/SB08 is/are not being submitted.

[ ] B. Document(s) _____is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[ ] 3. Cite No(s). _____ are not in the English language. In accordance with 1.98(c), Applicant states:

[ ] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application , or English-language abstract (or claim) is enclosed.

[ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

☐ 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

☐ 5. Other information being provided for the examiner's consideration follows:

[A/An _____ Search Report, dated_____, which issued during the prosecution of _____Application No._____ which corresponds to the present application.]

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of' the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: January 9, 2007

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
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(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/383,066-Conf. #7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	20342/1202653-US8

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*If known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-6,228,398	5/8/01	Devane, et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

{W:\20342\1202653us8\00964919.doc		Date Considered	

Electronic Acknowledgement Receipt

EFS ID:	1426855
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Jeffrey C. Pepe/Dwight Peck
Filer Authorized By:	Jeffrey C. Pepe
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	09-JAN-2007
Filing Date:	12-MAY-2006
Time Stamp:	16:49:25
Application Type:	Utility

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	00965330.PDF	48912	no	5
Warnings:					

Information:	
This is not an USPTO supplied IDS fillable form	
Total Files Size (in bytes):	48912

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

04-02-07 IFW

Express Mail Label No. _____ Dated: _____

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 Confirmation No.: 7083

Filed: May 12, 2006 Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM Examiner: Not Yet Assigned

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

01051488

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. Payment in the amount of the fee set forth in 1.17(p), presently believed to be $180, is indicated below.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(i) a check in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[x] A. Pursuant to the 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the **U.S. Patent(s) and/or U.S. Patent Application Publication(s)** on PTO/SB08 is/are not being submitted.

[ ] B. Document(s) _____is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[ ] 3. Cite No(s). _____ are not in the English language. In accordance with 1.98(c), Applicant states:

[ ] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application , or English-language abstract (or claim) is enclosed.

[ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

[x] 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

[ ] 5. Other information being provided for the examiner's consideration follows:

[A/An _____ Search Report, dated_____, which issued during the prosecution of _____Application No._____ which corresponds to the present application.]

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: March 30, 2007

Respectfully submitted,

By _____

Paul M. Zagar
Registration No.: 52,392
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

PTO/SB/08a/b (07-06)
Approved for use through 09/30/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA	US-6,913,768	07-05-2005	Couch et al.	
	AB	US-6,764,696	07-20-2004	Pather et al.	
	AC	US-6,749,867	06-15-2004	Robinson et al.	
	AD	US-5,846,568	12-08-1998	Olinger et al.	
	AE	US-5,773,031	06-30-1998	Shah et al.	
	AF	US-5,733,575	03-31-1998	Mehra, et al.	
	AG	US-5,618,559	04-08-1997	Desai, et al.	
	AH	US-5,501,861	03-26-1996	Makino et al.	
	AI	US-5,422,121	06-06-1995	Lehmann et al.	
	AJ	US-5,411,745	05-02-1995	Oshlack et al.	
	AK	US-5,202,159	04-13-1993	Chen et al.	
	AL	US-5,137,733	08-11-1992	Noda et al.	
	AM	US-4,794,001	12-27-1988	Mehta et al.	
	AN	US-3,979,349	09-07-1976	H. Fink	
	AO	US-3,365,365	01-23-1968	J.A. Butler et al.	
	AP	US-3,066,075	11-27-1962	DEUTSCH MARSHALL E	
	AQ	US-3,048,526	08-07-1962	C. L. Boswell	
	AR	US-2,738,303	03-13-1956	R. H. Blythe	
	AS	US-2,099,402	11-16-1937	J. W. Keller	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	BA	AU-109,438	01-11-1940	I. Lipowski		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Examiner's signature		Date Considered	

PTO/SB/08a/b (07-06)
Approved for use through 09/30/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	Adderall XR Package Inset, Sept. (2004)	
	CB	Agyilirah GA and Banker SB, Polymers for Enteric Coating applications, Polymers for Controlled Drug Delivery (Peter J. Tarcha ed. 1991) 39-66	
	CC	American Chemical Society, Polymer Preprints, pp. 633-634, Vol. 34, No. 1, March 1993	
	CD	Ansel, et al., Rate Controlled Dosage Forms and Drug Delivery Systems, Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. (1995), 213-222	
	CE	Answering Expert Report of Dr. Alexander M. Klibanov, expert for Shire Laboratories, Inc., April 25, 2005	
	CF	Answering Expert Report of Robert Langer, Sc. D. Regarding United States Patent Nos. 6,322,819 and 6,605,300, expert for Shire Laboratories Inc., dated April 25, 2005	
	CG	Barr Laboratories' Objections and Responses to Plaintiff Shire Laboratories Inc.'s Fifth Set of Interrogatories (No. 17), dated September 3, 2004	
	CH	Barr Laboratories' Amended Answer, Affirmative Defenses And Counterclaims *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-1219-PKC	
	CI	Barr Laboratories' Answer, Affirmative Defenses, and Counterclaims, dated September 25, 2003	
	CJ	Barr Laboratories Inc.'s Objections and Responses to Shire Laboratories Inc.'s Second Set of Interrogatories (Nos. 8-11), dated February 18, 2004	
	CK	Barr Laboratories Inc.'s Objections and Responses to Shire Laboratories Inc.'s Fourth Set of Interrogatories (Nos.15-16), dated July 9, 2004	
	CL	Barr Laboratories' Memorandum in Support of Its Motion to Amend Its Pleadings and exhibits thereto, dated September 10, 2004	
	CM	Barr Laboratories' Memorandum in Support of Its Motion to Compel Production, dated September 13, 2004	
	CN	Barr Laboratories' Supplemental Objections and Responses to Plaintiff Shire Laboratories Inc.'s Third Set of Interrogatories (Nos. 12-14)(Redacted), dated August 27, 2004	
	CO	Barr Laboratories, Inc.'s '300 Notification Pursuant to §505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)(2)(B)(ii) and 21 C.F.R. § 314.95)	
	CP	Barr Laboratories, Inc.'s '819 Notification Pursuant to §505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)(2)(B)(ii) and 21 C.F.R. § 314.95)	
	CQ	Bauer, et al., Cellulose Acetate Phthalate (CAP) and Trimellitate (CAT), Coated Pharmaceutical Dosage Forms (1998), 102-104	
	CR	Bodmeier et al., the Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Catinoc Polymer Dispersions, Eudragit RS, RL 30D, Pharmaceutical Research Vol. 13, No. 1, 1996, 52-56	
	CS	Brown et al., Behavior and Motor Activity Response in Hyperactive Children and Plasma Amphetamine Levels Following a Sustained Release Preparation, Journal of the American Academy of Child Psychiatry, 19:225-239, 1980	
	CT	Brown et al., Plasma Levels of d-Amphetamine in Hyperactive Children, Psychopharmacology 62, 133-140, 1979	
	CU	Burns et al., A study of Enteric-coated Liquid-filled Hard Gelatin Capsules with Biphasic Release Characteristics, International Journal of Pharmaceutics 110 (1994) 291-296	
	CV	C. Lin et al., Bioavailability of d-pseudoephedrine and Azatadine from a Repeat Action Tablet Formulation, J Int Med Res (1982), 122-125	
	CW	C. Lin et al., Comparative Bioavailability of d-Pseudoephedrine from a Conventional d-Pseudoephedrine Sulfate Tablet and from a Repeat Action Tablet, J Int Med Res (1982) 10,	

Examiner's signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 3 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

		126-128	
	CX	Chan, Materials Used for Effective Sustained-Release Products, Proceedings of the International Symposium held on 29th to 31st of January 1987 (The Bombay College of Pharmacy 1988), 69-84	
	CY	Chan, New Polymers for Controlled Products, Controlled Release Dosage Forms Proceedings of the International Symposium held on 29th to 31st of January 1987 (The Bombay College of Pharmacy 1988) 59-67	
	CZ	Chang et al., Preparation and Evaluation of Shellac Pseudolatex as an Aqueous Enteric Coating Systems for Pellets, International Journal of Pharmaceuticals, 60 (1990) 171-173	
	CA1	Charles S. L. Chlao and Joseph R. Robinson, Sustained-Release Drug Delivery Systems, Remington: The Science and Pratice of Pharmacy, Tenth Edition (1995) 1660-1675	
	CB1	Civil Docket For Case #: 1:03-cv-01164-GMS *Shire Laboratories, Inc. v. Impax Laboratories, Inc.*, Civil Action No. 03-CV-01164-GMS	
	CC1	Civil Docket For Case #: 1:03-cv-01219-PKC-DFE *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-1219-PKC	
	CD1	Civil Docket For Case #: 1:03-cv-06632-VM-DFE *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-6632-PKC	
	CE1	Civil Docket For Case #: 1:05-cv-00020-GMS *Shire Laboratories, Inc. v. Impax Laboratories, Inc.*, Civil Action No. 05-20-GMS	
	CF1	Cody et al., Amphetamine Enantiomer Excretion Profile Following Administration of Adderall, Journal of Analytical Toxicology, Vol. 2, October 2003, 485-492	
	CG1	Complaint for Declaratory Judgment, Impax Laboratories, Inc. v. Shire International Laboratories, Inc. (Civ. Action No. 05772) and Exhibits attached thereto	
	CH1	Daynes, Treatment of Noctural Enuresis with Enteric-Coated Amphetamine, The Practitioner, No. 1037, Vol. 173, November 1954	
	CI1	Deposition of Transcript of Beth Burnside, dated 2/2/05	
	CJ1	Deposition of Transcript of Beth Burnside, dated 2/3/05	
	CK1	Deposition of Transcript of Charlotte M. McGuiness, dated 8/6/04	
	CL1	Deposition of Transcript of Donald John Treacy, Jr., dated 8/31/04	
	CM1	Deposition of Transcript of Edward Rudnic, dated 7/28/04	
	CN1	Deposition of Transcript of James J. Harrington, dated July 27, 2005	
	CO1	Deposition of Transcript of Kimberly Fiske, dated 9/17/04	
	CP1	Deposition of Transcript of Richard Rong-Kun Chang, dated 1/20/05	
	CQ1	Deposition of Transcript of Richard A. Couch, dated 9/14/04	
	CR1	Deposition of Transcript of Robert Schaffer, dated August 17, 2005	
	CS1	Deposition of Transcript of Xiaodi Guo, dated 1/24/05	
	CT1	Deposition of Transcript of Xiaodi Guo, dated 7/26/04	
	CU1	Deposition transcript of Honorable Gerald J. Mossinghoff and exhibits thereto, dated June 8, 2005	
	CV1	Deposition Transcript of Richard Chang, dated 9/8/04	
	CW1	Edward Stempel, Prolonged Drug Action, HUSA's Pharmaceutical Dispensing, Sixth Edition, 1996, 464, 481-485	
	CX1	Expert Report of Dr. Joseph R. Robinson, expert for Barr Laboratories and exhibits thereto, February 28, 2005	
	CY1	Expert Report of the Honorable Gerald J. Mossinghoff, expert for Barr Laboratories, Inc. and exhibits thereto, March 16, 2005	
	CZ1	Freedom of Information Request Results for - Dexadrine (SmithKline Beecham): 5/20/1976 Disclosable Approval Information	
	CA2	Fukumori, Coating of Multiparticulates Using Polymeric Dispersions, Multiparticulate Oral Drug Delivery (Swarbrick and Selassie eds. 1994),79-110	
	CB2	Garnett et al., Pharmacokinetic Evaluation of Twice-Daily Extended-Release	

Examiner's signature		Date Considered	

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Substitute for form 1449A/B/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	11/383,066-Conf.#7083
				Filing Date	May 12, 2006
				First Named Inventor	Amir Shojaei
				Art Unit	1615
(Use as many sheets as necessary)				Examiner Name	M. Young
Sheet	4	of	7	Attorney Docket Number	20342/1202653-US8

		Carbamazepine(CBZ) and Four-Times- Daily Immediate-Release CBZ in Patients with Epilepsy, Epilepsia 39(3): 274-279, 1998	
	CC2	Glatt, The World of the Fluid Bed, Fluid Bed Systems, 1-19	
	CD2	Goodhart et al., An evaluation of Aqueous Film-forming Dispersions for Conrolled Release, Pharmaceutical Technology, April 1984, 64-71	
	CE2	Greenhill et al., A Pharmacokinetic/Pharmacodynamic Study Comparing a Single Morning Dose of Adderall to Twice-Daily Dosing in Children with ADHD. J. Am. Acad. Adolesc. Psychiatry, 42:10, October 2003	
	CF2	Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (1997)	
	CG2	Guidance for Industry: Food- Effect Bioavailability and Fed Bioequivalence Studies (2002)	
	CH2	Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms (1997)	
	CI2	Hall HS and Pondell RE, Controlled Release Technologies: Methods, Theory, and Applications, pp. 133-154 (Agis F. Kydonieus ed. 1980)	
	CJ2	Handbook of Pharmaceutical Excipients: Ethycellulose, Polymethacrylates, 4th ed. (2003), 237-240, 462-468	
	CK2	Handbook of Pharmaceutical Excipients: Polymethacrylates, 2nd Ed. (1994), 361-366	
	CL2	Hans-Martin Klein & Rolf W. Gunther, Double Contrast Small Bowl Follow-Through with an Acid-Resistant Effervescent Agent, Investigative Radiology Vol. 28, No. 7, July 1993, 581-585	
	CM2	Harris, et al., Aqueous Polymeric Coating for Modified-Release Pellets, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms (McGinity ed., 1989), 63-79	
	CN2	Hawley's Condensed Chemical Dictionary 13th Ed. 1997, 584, 981	
	CO2	Holt, Bioequivalence Studies of Ketoprofen: Product formulation, Pharmacokinetics, Deconvolution, and In Vitro- In Vivo correlations, Thesis submitted to Oregon State University, August 20, 1997 (1997)	
	CP2	Husson et al., Influence of Size Polydispersity on Drug Release from Coated Pellets, International Journal of Pharmaceutics, 86 (1992) 113-121, 1992	
	CQ2	Impax Laboratories Answer And Affirmative Defenses *Shire Laboratories, Inc. v. Impax Laboratories, Inc.*, Civil Action No. 03-CV-01164-GMS	
	CR2	Impax Laboratories, Inc.'s First Supplemental Responses to Shire Laboratories Inc.'s First Set of Interrogatories (Nos. 11-12) dated 3/28/05	
	CS2	Impax Laboratories, Inc.'s Memorandum in Support of the Motion to Amend Its Answer dated 2/25/05 and exhibits thereto	
	CT2	Impax Laboratories, Inc.'s Reply Memorandum in Support of the Motion to Amend Its Answer dated 3/18/05 and exhibits thereto	
	CU2	Impax Laboratories, Inc's First Amended Answer and Affirmative Defenses, dated May 2, 2005	
	CV2	Ishibashi et al., Design and Evaluation of a New Capsule-type Dosage Form for Colon-targeted Delivery of Drugs, International Journal of Pharmaceutics 168, (1998) 31-40	
	CW2	J. Sjogren, Controlled Release Oral Formulation technology, Rate Control in Drug Therapy, (1985) 38-47	
	CX2	Jarowski, The Pharmaceutical Pilot Plant, Pharmaceutical Dosage Forms: Tablets, Vol. 3, 2nd Ed. (1990), 303-367	
	CY2	Kao et al., Lag Time Method to Delay Drug release to Various Sites in the Gastrointestinal Tract, Journal of Controlled Release 44(1997) 263-270	
	CZ2	Kiriyama et al., The Bioavailability of Oral Dosage Forms of a New HIV-1 Protease Inhibitor, KNI-272, in Beagle Dogs, Biopharmaceutics & Drug Disposition, Vol. 17 125-234 (1996)	
	CA3	Klaus Lehmann, Coating of Multiparticulates Using Polymeric Solutions, Multiparticulate Oral Drug Delivery (Swarbrick and Sellassie ed., 1994) 51-78	
	CB3	Krowczynski & Brozyna, Extended-Release Dosage Forms, pp. 123-131 (1987)	
	CC3	Leon Lachman, Herbert A. Liebeman, Joseph L. Kanig, The Theory and Practice of Industrial Pharmacy, Second Edition (1976) 371-373	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

	CD3	Leopold & Eikeler, Eudragit E as Coating Material for the pH-Controlled Drug Release in the Topical Treatment of Inflammatory Bowel Disease (IBD), Journal of Drug Targeting, 1998, Vol. 6, No. 2, pp. 85-94	
	CE3	Lin & Cheng, In-vitro Dissolution Behaviour of Spansule-type Micropellets Prepared by Pan Coating Method, Pharm. Ind. 51 No. 5 (1989) 528-531	
	CF3	Liu et al., Comparative Release of Phenylprepanolamine HCl from Long-Acting Appetite Suppressant Product: Acutrim vs. Dexatrim, Drug Development and Industral Pharmacy, 10(10), 1639-1661 (1984)	
	CG3	Marcotte, et al., Kinetics of Protein Diffusion from a Poly(D, L-Lactide) Reservoir System. Journal of Pharmaceutical Sciences Vol. 79, No.5, May 1990	
	CH3	Mathir, et al., In vitro characterization of a controlled-release chloropheniramine maleate delivery system prepared by the air-suspension technique, J. microencapsulation, Vol. 14, No. 6,743-751 (1997)	
	CI3	McGough, et al., Pharmacokinetics of SL1381 (Adderall XR), an Extended-Release Formulation of Adderall, Journal of the American Academy of Child & Adolescent Psychiatry, Vol. 42, No. 6, June 2003, 684-691	
	CJ3	McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed. (1994), 97,972	
	CK3	Mehta, et al., Evaluation of Fluid-bed Processes for Enteric Coating Systems, Pharmaceutical Technology, April 1986, 46-56	
	CL3	Moller, Dissolution Testing of delayed Release Preparations, Proceedings of the International Symposium held on 29th to 31st of January 1987 (the Bombay College of Pharmacy 1988), 85-111	
	CM3	Response to Office Action filed May 2, 2006 in U.S. Patent Application No. 11/091/010	
	CN3	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed February 3, 2006	
	CO3	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed July 13, 2006	
	CP3	Response to Office Action filed July 18, 2006 in U.S. Patent Application No. 11/091,010	
	CQ3	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed October 10, 2006	
	CR3	Office Action mailed March 2, 2005 in European Patent Application No. 99 970594.0-2123	
	CS3	Opening Expert Report of Dr. Michael Mayersohn, expert for Impax Laboratories Inc. and exhibits thereto , March 12, 2005	
	CT3	Opening Expert Report of Dr. Walter Chambliss, expert for Impax Laboratories, Inc. and exhibits thereto, March 15, 2005	
	CU3	Order Construing The Terms Of U.S. Patent Nos. 6,322,819 And 6,605,300 *Shire Laboratories, Inc. v. Impax Laboratories, Inc.*, Civil Action No. 03-CV-01164-GMS	
	CV3	PDR Drug information for Ritalin LA Capsules, April (2004)	
	CW3	Pelham, et al., A Comparision of Morning-Only and Morning/Late Afternoon Adderall to Morning-Only, Twice-daily, and Three Times-Daily Methyphenidate in Children with Attention-Deficit/Hyperactivity Disorder, Pediatrics,Vol. 104, No. 6, December 1999	
	CX3	Physicians' Desk Reference: Adderall, 51st Ed. (1997)	
	CY3	Physicians' Desk Reference: Adderall, 56th Ed. (2002)	
	CZ3	Physicians' Desk Reference: Dexedrine, 56th ed. (2002)	
	CA4	Physicians' Desk Reference: Ritalin, 56th Ed. (2002)	
	CB4	Porter and Bruno, Coating of Pharmaceutical Solid-Dosage Forms, 77-160	
	CC4	Prescribing Information: Dexedrine, brand of dextroamphetamine sulfate (2001)	
	CD4	R. Bianchini & C. Vecchio, Oral Controlled Release Optimization of Pellets Prepared by Extrusion- Spheronization Processing, IL Farmaco 44(6), 645-654, 1989	
	CE4	Rambali, et al., Using experimental design to optimize the process parameters in fluidized bed granulation on a semi-full scale, International Journal of Pharmaceutics 220 (2001) 149-160	
	CF4	Remington: The Science and Practice of Pharmacy, Basic Pharmacokinetics, 16th Ed. (1980), 693	
	CG4	Remington: The Science and Practice of Pharmacy, Elutriation, 20th Ed.(2000), 690	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Application Number	11/383,066-Conf.#7083
				Filing Date	May 12, 2006
				First Named Inventor	Amir Shojaei
				Art Unit	1615
(Use as many sheets as necessary)				Examiner Name	M. Young
Sheet	6	of	7	Attorney Docket Number	20342/1202653-US8

	CH4	Remington's Pharmaceutical Sciences, Fifteenth Edition (1975) 1624-1625	
	CI4	Remington's Pharmaceutical Sciences, RPS XIV, 1700-1714	
	CJ4	Reply to Barr Laboratories Inc.'s Amended Answer, Affirmatice Defenses And Counterclaims *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-1219-PKC	
	CK4	Reply to Barr Laboratories Inc.'s Amended Answer, Affirmatice Defenses And Counterclaims *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-6632-PKC	
	CL4	Rong-Kun Chang and Joseph R. Robinson, Sustained Drug Release from Tablets and Particles Through Coating, Pharmaceutical Dosage Forms: Tablets (Marcel Dekker, Inc. 1990), 199-302	
	CM4	Rong-Kun Chang et al., Formulation Approaches for Oral Pulsatile Drug Delivery, American Pharmaceutical Review	
	CN4	Rong-Kun Chang, A Comparision of Rheological and Enteric Properties among Organic Solutions, Ammonium Salt Aqueous Solutions, and Latex Systems of Some Enteric Polymers, Pharmaceutical Technology, October 1990, Vol. 14, No. 10, 62-70	
	CO4	Rosen, et al., Absorption and Excretion of Radioactively Tagged Dextroamphetamine Sulfate from a Sustained-Release Preparation, Journal of the American Medical Association, December 13, 1965, Vol. 194, No. 11, 1203-1205	
	CP4	Scheiffele, et al., Studies Comparing Kollicoat MAE 30 D with Commercial Cellulose Derivatives for Enteric Coating on Caffeine Cores, Drug Development and Industrial Pharmacy, 24(9), 807-818 (1998), 807-818	
	CQ4	Serajuddin, et al., Selection of Solid Dosage Form Composition through Drug-Excipient Compatibility Testing, Journal of Pharmaceutical Sciences Vol. 88, No. 7, July 1999, 696-704	
	CR4	Shargel; Pharmacokinetics of Oral Absorption, Applied Biopharmaceutics & Pharmacokinetics. 5th Ed. (225), 164-166	
	CS4	Sheen et al., Aqueous Film Coating Studies of Sustained Release Nicotinic Acid Pellets: An In-Vitro Evaluation, Drug Development and Industrial Pharmacy, 18(8), 851-860 (1992)	
	CT4	Shire Laboratories Inc.'s Opposition to Barr Laboratories' Motion to Amend Its Answers and Counterclaims, September 15, 2004	
	CU4	Slattum, et al., Compararision of Methods for the Assessment of Central Nervous System Stimulant Response after Dextroamphetamine Administration to Healthy Male Volunteers, J. clin Pharmacol (1996) 36,1039-1050	
	CV4	Sprowls' American Pharmacy: An Introduction to Pharmaceutical Techniques and Dosage Forms, 7th Ed. (1974), 387-388	
	CW4	Sriamornsak, et al., Development of Sustained Release Theophylline Pellets Coated with Calcium Pectinate, Journal of Controlled Release 47 (1997) 221-232	
	CX4	Stevens, et al., Controlled, Multidose, Pharmacokinetic Evaluation of Two Extended-Release Carbamazepine Formulations (carbatrol and Tegretol-XR), Journal of Pharmaceutical Sciences Vol. 87, No. 12, December 1998, 1531-1534	
	CY4	Teva Notice letter dated February 21, 2005	
	CZ4	Teva Notice letter dated June 1, 2005	
	CA5	The Merck Index: Amphetamine, 12th Ed., 620	
	CB5	The Merck Index: Amphetamine, 13th Ed. (2001), 97, 1089	
	CC5	The United States Pharmacopeia 23, National Formulary 18 (1995) pp. 1791-1799	
	CD5	The United States Pharmacopeia 26, National Formulary 21 (2003) pp. 2157-2165	
	CE5	The United States Pharmacopeia 27, National Formulary 22 (2004) pp. 2302-2312	
	CF5	Treatise on Controlled Drug Delivery, pp. 185-199 (Agis Kydonieus ed. 1992)	
	CG5	Tulloch, et al., SL 1381 (Adderall XR), a Two-component, Extended-Release Formulation of Mixed Amphetamine Salts: Bioavailability of Three Test formulations and Comparision of Fasted, Fed, and Sprinkled Administration, PHARMACOTHERAPY Vol. 22, No. 11, (2002), 1405-1415	
	CH5	Vasilevska, et al., Preparation and Dissolution Characteristics of Controlled Release Diltiazem	

Examiner's signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 7

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Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

		Pellets, Drug Development and Industrial Pharmacy, 18(15), 1649-1661 (1992)	
	CI5	Watano, et al., Evaluation of aqueous Enteric Coated Granules Prepared by Moisture Control Method in Tumbling Fluidized Bed Process, Chem. Pharm. Bull. 42(3) 663-667 (1994)	
	CJ5	Wesdyk, et al., Factors affecting differences in film thickness of beads coated in fluidized bed units, International Journal of Pharmaceutics, 93, 101-109, (1993)	
	CK5	Wouessidjewe, Aqueous polymethacrylate Dispersions as Coating Materials for Sustained and Enteric Release Systems, S.T.P. Pharma Sciences 7(6) 469-475 (1997)	
	CL5	Barr Laboratories' Amended Answer, Affirmative Defenses And Counterclaims *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-6632-PKC, dated September 27, 2004	
	CM5	Court Docket for Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated January 8, 2007	
	CN5	Complaint in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., and exhibits thereto, Case No. 2:06 -cv-00952-SD dated March 2, 2006	
	CO5	Answer and Counterclaims in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated July 24, 2006	
	CP5	Reply To Counterclaims in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated August 16, 2006	
	CQ5	Defendants' Responses to Plaintiff Shire's First Set of Interrogatories (1-12) in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated September 20, 2006	
	CR5	Defendants' Responses to Plaintiff's First Set of Request for the Production of Documents and Things (1-70) in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated October 4, 2006	
	CS5	Plaintiff's Response to Defendants' First Set of Interrogatories in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated October 11, 2006	
	CT5	Plaintiff's Response to Defendants' First Set of Production Requests in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated October 11, 2006	
	CU5	Defendants' Responses to Plaintiff's Second Set of Requests for the Production of Documents and Things (71-80) in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated November 8, 2006	
	CV5	Defendants' Responses to Plaintiff Shire's Second Set of Interrogatories (No. 13) in Shire Laboratories v. Teva Pharmaceuticals Industries Ltd., Case No. 2:06-cv-00952-SD dated November 8, 2006	
	CW5	Petition Under Section 8 and exhibits thereto, submitted to the Canadian Patent Office on December 4, 2006	
	CX5	Office Action in U.S. Patent Application Serial No. 11/091,011, mailed December 1, 2006	
	CY5	Response to Non-Final Office Action filed January 10, 2007 in U.S. Patent Application No. 11/091,011	
	CZ5	Response to Non-Final Office Action filed January 10, 2007 in U.S. Patent Application No. 11/091,010	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Examiner's signature		Date Considered	

Application No. (if known): 11/383,066 Attorney Docket No.: 20342/1202653-US8

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Supplemental Information Disclosure Statement (4 pages)
Form PTO/SB/08 (7 pages) with 157 references
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Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 | Confirmation No.: 7083

Filed: May 12, 2006 | Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. A check for the fee set forth in 1. 17(p), presently believed to be $180, is enclosed.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(p) a check in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[x] A. Pursuant to the Notice issued by the United States Patent and Trademark Office dated July 11, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the United States Patent on PTO/SB08 is/are not being submitted.

[ ] B. Document(s) _____ is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[x] 3. Cite Nos. 1-6 under Foreign Patent Docs. are not in the English language. In accordance with 1.98(c), Applicant states:

[x] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application, or English-language abstract (or claim) is enclosed.

[x] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached Notice; citation of the documents cited in the Notice shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

[ ] 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

[x] 5. Other information being provided for the examiner's consideration follows:

A Notice of Reason of Refusal, dated June 26, 2007, which issued during the prosecution of Japanese Application No. 2000-576830 which corresponds to the present application.

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

No fee is believed to be due for the filing of this Information Disclosure Statement. The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: August 20, 2007

Respectfully submitted,

By /FB/ Flynn Barrison (53,970)
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PTO/SB/08a (05-07)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11383066
	Filing Date	2006-05-12
	First Named Inventor	Amir Shojaei
	Art Unit	1615
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	20342/1202653-US8

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6475493		2002-11-05	Mulye	

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
1	1	59-082311	JP		1984-05-12	Shionogi & Co Ltd	Abstract Attached	☒
2	2	07-061922	JP		1995-03-07	SS Pharmaceut Co Ltd	Abstract Attached	☒
3	3	10-081634	JP		1998-03-31	Taisho Pharmaceut Co Ltd	Abstract Attached	☒

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11383066
	Filing Date	2006-05-12
	First Named Inventor	Amir Shojaei
	Art Unit	1615
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	20342/1202653-US8

4	4	09-267035	JP		1997-10-14	Kanegafuchi Chemical Ind Co Ltd	Abstract Attached	☒
5	5	03-148215	JP		1991-06-25	Nippon Shinyaku Co Ltd	Abstract Attached	☒
6	6	09-249557	JP		1997-09-22	Shionogi & Co	Abstract Attached	☒
7	7	98/14168	WO		1998-04-09	ALZA Corporation		☐
8	8	97/03673	WO		1997-02-06	Chiroscience Limited		☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	WIGAL, et al., Evaluation of Individual Subjects in the Analog Classroom Setting; II. Effects of Dose of Amphetamine (Adderall), Psychopharmacology Bulletin, Vol. 34, No. 4, Pages 833-838, 1998	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11383066
	Filing Date	2006-05-12
	First Named Inventor	Amir Shojaei
	Art Unit	1615
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	20342/1202653-US8

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/FB/ Flynn Barrison (53,970)	Date (YYYY-MM-DD)	2007-08-20
Name/Print	Paul M. Zagar	Registration Number	52392

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

CITED REFERENCE 4

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 59-082311
(43)Date of publication of application : 12.05.1984

(51)Int.Cl. A61K 9/16
// A61K 9/48
A61K 31/545

(21)Application number : 57-194154
(22)Date of filing : 04.11.1982

(71)Applicant : SHIONOGI & CO LTD
(72)Inventor : TAKAGISHI YASUSHI
NODA KINSABURO

(54) SUSTAINED RELEASE PREPARATION OF CEPHALEXIN

(57)Abstract:
PURPOSE: The titled preparation useful for infectious diseases, obtained by blending an entric component of cephalexin with a rapidly dissolving component of it in a specific ratio, coating the enteric component with a copolymer methacrylic acid and methyl methacrylate, shellac, etc. in a specific thickness.
CONSTITUTION: A rapidly dissolving cephalexin (rapidly dissolving component for short) is blended with an entric cephalexin (enteric component for short) in a ratio of 3:7 (weight on calculated as potency), to give a sustained release preparation of cephalexin. In the operation, the enteric component used is obtained by coating granules of the rapidly dissolving component with an enteric coating base consisting of a copolymer of methacrylic acid, methyl methacrylate, shellac, talc, stearic acid, and a plasticizer, having about 6 dissolution pH until the weight of the granules is increased by 0.3W0.6. This sustained release preparation exhibits sufficient effect by administration of every 12hr, and administration during sleeping hours can be avoided.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

⑲ 日本国特許庁（JP）　⑪ 特許出願公開

⑫ 公開特許公報（A）　昭59—82311

⑤1Int. Cl.³	識別記号	庁内整理番号	⑬公開 昭和59年(1984)5月12日
A 61 K 9/16		7057—4C	
// A 61 K 9/48		7057—4C	発明の数 1
31/545		7169—4C	審査請求 未請求

（全 5 頁）

⑤4セフアレキシン持効性製剤

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⑦1特 願 昭57—194154
⑫2出 願 昭57(1982)11月4日

⑦2発 明 者 高岸靖
芦屋市潮見町27—1

明 細 書

1.発明の名称

セフアレキシン持効性製剤

2.特許請求の範囲

1) 速溶性セフアレキシン（以下速溶成分という）と腸溶性セフアレキシン（以下腸溶成分という）との組合せよりなるセフアレキシン持効性製剤において，該腸溶成分が，速溶成分の粒状剤に，メタクリル酸とメタクリル酸メチルとの共重合体，セラック，タルク，ステアリン酸および可塑剤を含み，溶出pHが約6である腸溶性コーティングを，該粒状剤の重量が0.3ないし0.6増大する迄，施したものであり，かつ該組合せ比率が力価換算重量で，速溶成分：腸溶成分＝約3：7であることを特徴とするセフアレキシン持効性製剤。

2) 該速溶成分が粒状剤であつて，腸溶成分粒状剤との混合物であることを特徴とする特許請求の範囲1)に記載のセフアレキシン持効性製剤。

3) 該速溶成分が，該腸溶成分粒状剤の腸溶性コーティング層の外側に，層状に付着させたものであることを特徴とする特許請求の範囲1)に記載のセフアレキシン持効性製剤。

4) 両成分が顆粒または細粒であつて，一投与単位またはその分数単位として分包したことを特徴とする特許請求の範囲1)に記載のセフアレキシン持効性製剤。

5) 両成分が顆粒（細粒）またはビーズであつて，一投与単位またはその分数単位として硬質ゼラチンカプセル内に充填したことを特徴とする特許請求の範囲1)に記載のセフアレキシン持効性製剤。

3.発明の詳細な説明

本発明はセフアレキシン持効性製剤に関する。

セフアレキシンは，多くのセフアロスポリン系抗生物質中，経口投与が可能なものの一つであり，内服後，その殆んどが速やかに吸収され，体内で代謝されることなく，主として尿中に排泄されるもので，多くの感染症に対して有効であり，安全性も高いところから極めて有用なものである。しかしながら，排泄が早いため1日4回すなわち6時間毎というような頻回投与が必要であり，持効

性製剤が待望されていた。

従来，セファレキシンのような殺菌型抗菌形式を有する抗生物質は，一般に，患者におけるその抗生物質の有効血中濃度を，一たん起炎菌の最小発育阻止濃度（ＭＩＣ）より，はるかに高い濃度にするように投与すれば，その後は有効血中濃度が急激に低下しても，之を数回繰り返すことにより治療目的を達成しうるものであるとされていた。

ところが，本発明者らが行つた試験管内の細菌増殖阻害実験において，セファレキシンは，それがＭＩＣに達してさえ居れば，低濃度であつても長時間作用させた方が，高濃度における短時間作用より抗菌効果が大きいことが判明した。

この事実は生体内における抗菌効果においても共通することであり，したがつて低濃度・長時間作用を可能とするセファレキシン製剤は大きな治療効果を有するものと考えられ，種々の持効性製剤が提案された（たとえば，特公昭５５－４７６１１号参照）。

該公報においては，持効性セファレキシン製剤を得るにあたつて，1)「非圧縮製剤」が，消化管内移行速度などの点で好ましいこと，2)コーティング層の厚みなどを変化させることによつて製剤の崩壊時間を調節した「徐放性製剤」より，腸溶剤と速溶剤との組合せの方が主剤を有効に吸収させることができること，3)腸溶性コーティング層の溶出pHが約５．５から６．５の範囲にあることが好ましいことおよび4)速溶性成分と腸溶性成分の組成比が６０：４０から１５：８５の範囲とすることによつて有効血中濃度を期待通り長期に維持できるものであることが開示されている。

本発明者らは，上記目的を最も効果的に達成する腸溶性コーティングに関し種々検討を進めた結果，冒頭の特許請求の範囲に記載通りの発明を完成した。

すなわち本発明によれば，速溶性セファレキシン（以下速溶成分という）と腸溶性セファレキシン（以下腸溶成分という）との組合せよりなるセファレキシン持効性製剤において，該腸溶成分が速溶成分の粒状剤に，メタクリル酸とメタクリル酸メチルとの共重合体，セラック，タルク，ステアリン酸および可塑剤を含み，溶出pHが約６である腸溶性コーティングを，該粒状剤の重量が０．３ないし０．６増大する迄，施したものであり，かつ該組合せ比率が力価換算重量で，速溶成分：腸溶成分＝約３：７であることを特徴とするセファレキシン持効性製剤が提供される。

本発明において「粒状剤」とは，粒剤すなわち顆粒および細粒（約５００μ以下の粒剤），およびビーズなど一投与単位が多数個に分割されたものを指称し，公知の湿式押出し造粒あるいは転動造粒法によつて製造されるものがよい。両成分のうち，腸溶成分は粒状剤でなければならないが，これと組合せる速溶成分は粒状剤に限定されるべきでなく，混合粒状剤にあつては，とくに粒子径にこだわらず，さらに細かい粒子，散剤あるいは純末であつてもよい。こうした「組合せ」混合粒状剤は，これを一投与単位あるいはその分数単位として分包（たとえば，ストリップ・パツケージング）し，あるいは硬質ゼラチンカプセル内に充填したものであることが便利である。

腸溶性コーティング用の基剤は約６の溶出pHを有するものが良いことは既に開示されているが，そのうちでもメタクリル酸とメタクリル酸メチルとの共重合体が好ましい。また，もう一つの腸溶性基剤としてセラックを配合する。これは，個々の粒子を覆う腸溶皮膜の耐酸性を強化し，また粒子間付着を抑制し，作業を容易にする。両者の好ましい配合比率（重量）は，共重合体１重量部に対し０．５～０．２重量部である。

本発明における腸溶コーティング層には，上記のほか，タルク，ステアリン酸および可塑剤が適量配合される。タルクは層に適度の厚みを与えて皮膜を強化するとともに粒子同志の付着防止に役立ち，またステアリン酸は，同じく付着防止と皮膜の緻密化，強化に役立つとともに，流動性改善のためにも有用である。タルクは腸溶性基剤合計の１重量部に対して０．５～１．５重量部，またステアリン酸は同じく０．１～０．３重量部で配合することが好ましい。また，可塑剤として腸溶性コーテ

イング基剤に対して一般に用いられる任意のものを基剤1重量部に対して0.15～0.4重量部程度配合することが好ましい。好適な可塑剤はグリセリン脂肪酸エステル（食品添加物）であるが，このほか無害なフタル酸エステル類，PEG，PPG，トリアセチンなども用いうる。

本発明において，腸溶成分のコーティング層の厚みは重要であり，裸顆粒に対し，その重量が0.3ないし0.6増大する迄前記のコーティング組成物を付着させることが好ましい。任意のコーティング方法が利用可能であるが，スプレーコーティングが最も普通の方法である。

また，本発明は前記の両粒状剤の混合物である態様のほか，腸溶性コーティングを施したセファレキシン粒状剤の外側に，さらに速溶性セファレキシン成分を層状に付着させた，いわゆる二重粒剤の態様においても実施しうる。この実施態様は混合物態様の場合，しばしば生じ得る，両成分の偏析を避けることができ有意義である。

この態様は，たとえば，セファレキシン（速溶成分）をけんだくさせた白糖シラップを，腸溶性コーティングを施したセファレキシン粒状剤にスプレーコーティングを行うことによつて容易に実施しうる。

以下，顆粒製造の実施例によつて本発明をより詳細に説明する。

実施例

1) 裸顆粒の製造

セファレキシン763g（力価），乳糖148g，コーンスターチ52gからなる混合物に8%のデンプン糊液325gを加えて練合した。この練合物を円筒式製粒機で造粒したのち，60℃で1時間乾燥した。得られた乾燥物をフィッツパトリツクミルを用いて粉砕し，その後16メッシュ不通過部と24メッシュ通過部を除去してセファレキシンの裸顆粒を得た。

2) コーティング

上記1)で得た裸顆粒1000gを直径30cmのコーティングパンに入れ，下記組成のコーティング液を用いて常法によるスプレーコーティングを，被覆後の顆粒全重量が約1.41kgになるまで行い，腸溶性セファレキシン顆粒を得た。

記

オイドラギットL（メタクリル酸・メタクリル酸メチル共重合体の商品名）	57g
白色セラック（日局）	8g
タルク	55g
ステアリン酸	10g
グリセリン脂肪酸エステル（食品添加物）	15g
エタノール	387g
ジクロルメタン	339g
精製水	129g
計	1000g

3) 混合・分包

1)と同様にして別に製造した裸顆粒と，2)によつて得た腸溶性顆粒の力価を測定し，これらの力価比率が3：7となるように両顆粒を混合した。この混合顆粒を1ポケット当りの総セファレキシンが500mg力価に相当する量にストリップパッケージングマシンで分包した。

4) 二重顆粒の製造

上記2)と同様の腸溶性コーティングを施した腸溶性顆粒1000g（セファレキシン540g（力価）含有）を直径30cmのコーティングパンに入れ，下記組成のコーティング液を用いて，常法によるスプレーコーティングを，被覆後の顆粒全重量が約1543gになるまで行い，腸溶成分および速溶成分をそれぞれ7：3の力価比率で含む二重顆粒を得た。

記

50%白糖シラップ	622g
セファレキシン	232g（力価）
着色料	0.1g
計	854.1g

このようにして得られた製剤について，日本抗生物質医薬品基準（1981年）にもとづく力価試験を行つたところ，全力価が表示力価の95～108%にあること，および製剤中の胃溶性粒の

力価が２７～３４％であることを認めた。また日本薬局方第１０版記載の溶出試験法，第２法（パドル法）を行つた結果，U.V.吸収（２６２nm）において上記力価に相当する量の胃溶性および腸溶性セファレキシンの存在を認めた。なお，同法に準じ，腸溶性粒のみの溶出試験を，pH５４の試験液を用いて行つたところ，１２０分後に３％程度のセファレキシンの溶出を認めるのみであつた。

一方，実施例の組成物からセラックを除いた組成物を用い，実施例に準じて腸溶性粒を製造したが，粒子同志の付着のためコーティング作業が困難であり，凝集粒子をときほぐす工程でコーティング層が破損し，腸溶特性を失う粒子が生じた。破損粒子を除去したのちの腸溶性粒について，上記のpH５４の試験液を用いた溶出試験を行つた結果，１５～２０％程度のセファレキシンの溶出を認めた。

また，実施例の製剤および対照裸顆粒を，大腸菌，シュードモナス，ストレプトマイセス，クレブシエラ，レツトゲレラおよびエンテロバクターに属する種々の細菌に起因する無症候性細菌尿患者に投与して，投与前後の尿中細菌数を実測したところ次表に示す結果を得た。

（以下余白）

表（生菌／ml）

患者群	投与前	投与後時間 3	6	9	12	22
第１群（９名，実施例製剤５００mg投与）	$\geqq 10^7$	10^4，$<10^3$，$<10^3$，$<10^3$，$<10^3$				
第２群（８名，対照裸顆粒２５０mg投与）	$\geqq 10^7$	10^4，10^4，5×10^4，10^5，10^5				
第３群（５名，対照裸顆粒５００mg投与）	$\geqq 10^7$	10^4，5×10^3，10^4，5×10^4，10^5				

上表より，本発明の製剤を投与された患者群の尿中細菌数は投与後６時間で10^3個以下に減少し以後この値を保つのに対し，対照裸顆粒２５０mg投与群では，３時間後に一たん10^4個迄減少するものの，その後増大をつづけ10^5個に達することがわかる。また対照裸顆粒５００mg投与群では，６時間から１２時間までの期間に限つて，２５０mg投与群に対する有意な差が認められるが２２時間では２５０mg投与群と変らなくなる。

このことは，本発明の製剤が単回投与後６時間を超えても，なお尿中細菌の増殖阻止に有効に作用しているのに対し，同力価の対照製剤は３時間程度しか有効でない事実を裏付けている。

叙上のように，本発明を実施した製剤は，１２時間毎の投与で充分な治療効果を発揮しうるのに対し，在来の製剤では就眠時間中の服用を不可避とする６時間毎の投与でも不充分な効果しか得られないことが裏付けられた。ことに通院患者の場合は，就眠時間中の服用を強制することが困難であり，しばしば治療日数長期化の原因となつてい

た状況が，本発明製剤を用いることにより改善され，本発明の実際的効果はきわめて大きいものであることを立証した。

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CITED REFERENCE 8

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 03-148215
(43)Date of publication of application : 25.06.1991

(51)Int.Cl. A61K 9/00
A61K 9/50
A61K 31/445

(21)Application number : 01-287048
(22)Date of filing : 01.11.1989

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(54) LAMINATED FORMULATION

(57)Abstract:
PURPOSE: To obtain sustained release laminated formulation of flavoxate hydrochloride useful for medical drug having stabilized release of drug, safety and reduced bitterness, etc., in administration by laminating sustained release part and quick release part respectively comprising specific substances.
CONSTITUTION: Two parts composed of a sustained release part comprising three layers of A) flavoxate hydrochloride-containing layer, B) intermediate layer and C) enteric skin substance layer and a quick release part comprising D) flavoxate hydrochloride-containing layer and E) acid-soluble skin substance layer are laminated to afford the aimed formulation. Combination of hydroxypropyl methyl cellulose acetate succinate as the C-layer component and starch as the B-layer component is effective. Mixing weight ratio of flavoxate hydrochloride in the quick release part and in the sustained release part is 1:0.5-4, preferably 1:1-4, especially 1:2.3.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

⑲日本国特許庁(JP) ⑪特許出願公開

⑫公開特許公報(A) 平3-148215

⑤1Int.Cl.⁵	識別記号	庁内整理番号
A 61 K 9/00	D	7624-4C
9/50	A	7624-4C
31/445	ACX	7252-4C

⑬公開 平成3年(1991)6月25日

審査請求 未請求 請求項の数 2 (全9頁)

⑤4発明の名称 積層製剤

⑳特 願 平1-287048

㉒出 願 平1(1989)11月1日

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最終頁に続く

明 細 書

1. 発明の名称

積 層 製 剤

2. 特許請求の範囲

(1) (a)塩酸フラボキサート含有層、(b)中間層、(c)腸溶性皮膜物質層、の上記(a)～(c)よりなる徐放部分、

(d)塩酸フラボキサート含有層、(e)酸可溶性皮膜物質層、の上記(d)及び(e)よりなる速放部分、

の二つの部分を積層してなることを特徴とする、塩酸フラボキサート徐放性積層製剤。

(2) (b)中間層の成分が殿粉であり、(c)腸溶性皮膜物質層の成分がヒドロキシプロピルメチルセルロースアセテートサクシネートである請求項1の塩酸フラボキサート徐放性積層製剤。

3. 発明の詳細な説明

【産業上の利用分野】

本発明は、徐放部分の外側に速放部分が形成される積層タイプの塩酸フラボキサート徐放性製剤に関する。

更に詳しくは、胃において速やかに溶出する速放部分と胃では溶出しにくく腸に至って溶出するように放出制御された徐放部分とが一体となっており、経口的に人に投与された場合に当該成分の放出を長時間に渡って持続せしめ、治療効果を有効にするものである。

従って本発明は医薬品の分野において利用される。

【従来の技術】

従来より塩酸フラボキサート製剤に関しては白糖等を施した糖衣錠、あるいはヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース等の皮膜を施したフィルムコーティング錠、または顆粒が市販され幅広く使用されている。

これらの塩酸フラボキサート製剤は優れた頻尿および残尿感治療効果が得られているが、消化管からの吸収がすみやかでありかつ生物学的半減期が1.2時間と短いことから、薬効持続時間が4～5時間と短く、従って1日3回分服する用法にならざるを得ない状況にある。

このために特にこの種の薬物を服用する対象として老人が多いことを考慮すれば、夜間頻尿による睡眠妨害等の苦痛を伴うことになる。

このような状況から服用後速やかに薬効を発揮し、しかも薬効の持続時間が長い塩酸フラボキサート製剤が要望されているがいまだ有用な製剤の出現を見ていない。

特開昭63－154619号公報には塩酸フラボキサートを含む速放性顆粒とこれに腸溶性皮膜物質を施した顆粒を一定の比率で混合し徐放性製剤とする旨の記載がなされている。

しかしながら本発明者らの詳細な研究によれば、塩酸フラボキサートとほとんどの腸溶性皮膜物質との間には両者の相互作用による皮膜の不溶化現象が認められ、その結果腸溶性皮膜物質が溶解する条件下においても皮膜本来のスムーズな溶解が妨げられ、従って塩酸フラボキサートの放出性に問題を生じることが判明しており、必ずしも満足すべき徐放性製剤とはいい難い。

またこのタイプの製剤の欠点として両顆粒の投与単位における組成割合が一定し難く幅広いバラツキが見られることが公知の事実として挙げられる。

原因は両顆粒の比重、大きさ、表面状態の違い、帯電性の違い等の要因からくる混合操作に難しさがあるものと思われるが、いずれにしても組成割合のバラツキは徐放性製剤の信頼性、有用性を損なう欠陥である。

更に、周知のように塩酸フラボキサートは強い苦味を有していることから、服用時のマスキングについても充分な配慮が必要である。

【発明が解決しようとする課題】

本発明者らは以上のような塩酸フラボキサートに係わる事情に鑑みて、鋭意研究を重ねた結果、塩酸フラボキサートと腸溶性皮膜物質との接触を回避するための特別の膜層及び特定の腸溶性皮膜物質の組成を見い出したことにより皮膜物質の不溶化及び薬物の放出性に関する問題を解消したこと、速放部分と徐放部分を一体化することによって組成割合のバラツキに関する問題を解消したこと、及び酸可溶性皮膜物質を被覆することによって苦味等のコンプライアンスに関する問題を改善することができ、本発明を完成するに至った。

即ち本発明の目的は上記の塩酸フラボキサートに係わる諸問題を解消し、服用時あるいは服用後のコンプライアンスに関する問題のないしかも安定した治療効果を有する塩酸フラボキサート徐放性製剤を提供することにある。

【課題を解決するための手段】

本発明において速放部分とは投与後胃内において速やかに薬物を放出し初期の薬効を呈する部分であり、徐放部分とは胃内では放出せず小腸上部以降の pH に至って薬物を放出し薬効を呈する部分である。

以下に顆粒タイプの剤形を主体に本発明を詳細に説明する。但し本発明はこれらの剤形に限定されるものではない。

本発明の塩酸フラボキサート徐放性積層製剤を得るためには、まず徐放部分を調製する。

徐放部分の調製方法は特に限定されたものではなく、従来の押出し造粒、破砕造粒、転動造粒等の方法を用いることができるが、最も簡便な例としては、遠心流動型コーティング造粒装置を用い、市販球形顆粒上に塩酸フラボキサートを順次被覆していく方法がある。

具体的には球形顆粒を遠心流動型コーティング造粒装置に投入し、遠心力（ローターの回転による）により回転せしめつつ、同時に造粒機の側壁と回転体との間（スリット）から吹出す空気流により制御された高さまで吹き上げ、その上方に位置するスプレーガンからショ糖、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルアルコール、ポリビニルピロリドン、メチルセルロース等の水溶液あるいは有機溶媒溶液を噴霧し、同時に造粒機の上方に位置する粉末導入口より塩酸フラボキサートを含むコーンスターチ、乳糖、低置換度ヒドロキシプロピルセルロース、結晶セルロース、タルク等の混合粉末を導入して造粒を行う。

続いてこの上に薬物の放出を制御するための腸

溶性皮膜物質を被覆する。

腸溶性皮膜物質としてはセルロースアセテートフタレート、ヒドロキシプロピルメチルセルロースフタレート、ヒドロキシプロピルメチルセルロースアセテートサクシネート、カルボキシメチルエチルセルロース、メタアクリル酸アクリル酸エチルコポリマー、メタアクリル酸メタアクリル酸メチルコポリマー等が用いられるが、本発明者らはこれらの腸溶性皮膜物質を被覆した顆粒について日局第2液による溶出試験、又は経時的pH変化溶出試験（上野和行、最近の製剤技術とその応用 P.124、医薬ジャーナル社）等を実施した場合に、ほとんどの腸溶性皮膜物質に皮膜の溶解遅延及びそれに伴う薬物の放出遅延が生じ、不溶化物が長時間に渡って残存する現象を見い出した。

原因は不明であるが、いずれにせよ放出調節機構の問題は徐放性製剤としての有用性を著しく阻害するものである。

本発明者らはかかる欠陥を改善する方法として、両者の間に一種のバリヤーとしての中間層を形成し、徐放部分の放出制御機構を保護することを企図した。

この目的の為に、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルアルコール、ポリビニルピロリドン、メチルセルロース等の水溶性高分子物質、乳糖、マンニトール、ショ糖等の水溶性物質、澱粉、リン酸水素カルシウム等の親水性物質、結晶セルロース、低置換度ヒドロキシプロピルセルロース等の膨潤性物質、タルク、ステアリン酸マグネシウム、高級脂肪酸、高級アルコール等の滑沢効果及び付着防止目的物質、炭酸ナトリウム、炭酸水素ナトリウム、炭酸カルシウム等のアルカリ性物質等のそれぞれ性質の異なる添加物と各々の腸溶性皮膜物質との組合せを逐一行い、相互作用について詳細に検討を行った。

その結果、これらの大半に不溶化物の残存及び薬物の放出遅延が認められ、充分な成果が得られなかった中にあって、ヒドロキシプロピルメチルセルロースアセテートサクシネートと中間層形成成分としての澱粉との組合せのみが唯一相互作用に対して有効であることを見い出し、本発明を完成させることができた。

中間層を設ける方法は特に限定されるものではないが、遠心流動型コーティング造粒装置中で徐放部造粒顆粒 100重量部に対して 1～100 重量部、好ましくは 5～50重量部を被覆する方法が良い。これ以下では均一な中間層を得ることが難しく従って放出性にバラツキを生じやすく、一方これ以上では中間層形成成分自身の崩壊性の影響が生じるため好ましくない。

中間層に用いる澱粉は特別な目的のない限り単独使用が好ましいが、他の添加物と少量を併用することは可能である。

このようにして中間層を設けた顆粒に対して腸溶性皮膜物質のヒドロキシプロピルメチルセルロースアセテートサクシネートを被覆する。その被覆量は徐放部造粒顆粒 100重量部に対して1～50重量部、好ましくは5～20重量部である。これ以下では胃内における対酸性が不十分となり、またこれ以上では小腸上部以降の pH での溶解が遅くなりバイオアベイラビリティに問題を生じることになる。

なお、腸溶性皮膜物質中には必要に応じてポリエチレングリコール、プロピレングリコール、クエン酸トリエチル、トリアセチン、グリセリン、グリセリン脂肪酸エステル等の可塑剤を添加することができる。

以上までの工程で得られた部分が徐放部分である。

次いでその上に、徐放部分の造粒と同じ要領で塩酸フラボキサートを含むコーンスターチ、乳糖、低置換度ヒドロキシプロピルセルロース、結晶セルロース、タルク等の混合粉末を被覆し速放部分を形成させる。

最終的に塩酸フラボキサートの苦味をマスクするために、酸可溶性皮膜物質であるポリビニルアセタルジエチルアミノアセテートを被覆する。その被覆量は徐放部造粒顆粒 100重量部に対して1～30重量部、好ましくは1～15重量部である。こ

れ以下では十分なマスキングとはならず口中で苦味を生じ、またこれ以上では酸性下において速やかな溶解を示しにくく従って初期の薬効が期待できない可能性がある。

更に塩酸フラボキサート製剤を服用する対象に老人が多いことを考慮するならば、無酸症状というものを軽視することはできない。その場合、上記のコーティング量であれば、pH6近辺においても日局第1液の酸性条件下と大きく変らない速放部分の薬物の放出性を示すことが明らかとなった。

ポリビニルアセタルジエチルアミノアセテートの被覆に関しては、必要に応じてポリエチレングリコール、プロピレングリコール、クエン酸トリエチル、トリアセチン、グリセリン、グリセリン脂肪酸エステル等の可塑剤を添加することができる。

本発明において、速放部分と徐放部分における塩酸フラボキサートの配合比率は、重量比で1：0.5～4好ましくは1：1～4、特に好ましくは1：2.3である。

配合比が1：0.5より少ない徐放部配合量では、従来の製品と殆ど同じ血中濃度パターンを示すため、本発明の持続性目的の達成が困難であり、1：5より大きい徐放部配合量では投与初期の血中濃度が上がらず、持続時間を延ばすことができない。

本発明の塩酸フラボキサート徐放性積層製剤における特徴の1つとして、速放部分と徐放部分を一体化したことが挙げられる。

速放部顆粒と徐放部顆粒の各々を混合して成るタイプの剤形では、両顆粒の投与単位における組成割合が一定しにくくバラツキが大きいことが公知の事実となっている。この原因は両顆粒の比重、大きさ、表面状態、帯電性等の要因からくる混合操作にあるものと考えられるが、いずれにしても組成割合のバラツキは徐放性製剤としての信頼性、有用性を損なう重大な欠陥である。

本発明者らは塩酸フラボキサートに関して詳細に検討を行い、その結果これらの欠陥を改善した本発明の積層タイプの徐放性製剤を発明したものである。

【実施例】

以下に実施例、比較例、及び試験例をあげて更に詳しく説明する。

実施例1

市販球形顆粒（フロイント社製、商品名：ノンパレル,14-20mesh）600gを遠心流動型コーティング造粒装置（フロイント社製、商品名：CF-360）に投入し、ヒドロキシプロピルセルロース(以下、HPCという)の5%溶液を噴霧しながら、塩酸フラボキサート560g、コーンスターチ300g、低置換度ヒドロキシプロピルセルロース70g、タルク40gの混合物を徐々に添加して造粒した後、引き続きコーンスターチ320gを中間層として被覆した。乾燥後、500gを流動層コーティング装置（富士産業製、商品名：STREA)に投入し、腸溶性皮膜物質ヒドロキシプロピルメチルセルロースアセテートサクシネート（以下、AQOAT-Mという）50g、クエン酸トリエチル10g、タルク15gを含むエタノール／水混合溶液1400mlを噴霧し徐放部顆粒を得た。

次いで徐放部顆粒555gを遠心流動型コーティング造粒装置に投入し、HPCの5%溶液を噴霧しながら塩酸フラボキサート60g、コーンスターチ45g、タルク3gの混合物を徐々に添加して速放部分を被覆した。

乾燥後、速放部被覆顆粒500gを流動層コーティング装置に投入しポリビニルアセタルジエチルアミノアセテート（以下、ABAという）15g、マクロゴール-6000 3.5g、タルク1.5gを含むエタノール溶液300mlを噴霧して本発明の塩酸フラボキサート徐放性積層製剤を得た。

比較例1

実施例1と同様の方法で徐放部分の造粒をした後、中間層を被覆することなく乾燥を行った。

乾燥後、顆粒500gについて同操作を行い、AQOAT-Mを被覆した徐放部顆粒を得た。

次いで徐放部顆粒500gを遠心流動型コーティング造粒装置に投入し、HPCの5%溶液を噴霧しながら塩酸フラボキサート65g、コーンスターチ47g、タルク3gの混合物を徐々に添加して速放部分を被覆した。

乾燥後、速放部被覆顆粒 500g を流動層コーティング装置に投入し、AEA 15g 、マクロゴール-6000 3.5g 、タルク 1.5g を含むエタノール溶液 300mℓを噴霧して塩酸フラボキサート徐放性積層製剤を得た。

比較例 2

比較例 1 における腸溶性皮膜物質AQOAT-Mの代わりに、ヒドロキシプロピルメチルセルロースフタレート（以下HP-55という）を用いて同様の操作を行い、塩酸フラボキサート徐放性積層製剤を得た。

比較例 3

比較例 1 における腸溶性皮膜物質AQOAT-Mの代わりに、メタアクリル酸アクリル酸エチルコポリマー（以下オイドラギットL30D-55という）を用いて同様の操作を行い、塩酸フラボキサート徐放性積層製剤を得た。

比較例 4

比較例 1 における腸溶性皮膜物質AQOAT-Mの代わりに、メタアクリル酸メタアクリル酸メチルコポリマー（以下オイドラギットL-100という）を用いて同様の操作を行い、塩酸フラボキサート徐放性積層製剤を得た。

比較例 5

比較例 1 における腸溶性皮膜物質AQOAT-Mの代わりに、カルボキシメチルエチルセルロース（以下CMECという）を用いて同様の操作を行い、塩酸フラボキサート徐放性積層製剤を得た。

比較例 6

中間層の成分の比較試験として、実施例 1 における中間層の成分であるコーンスターチの代りに、ヒドロキシプロピルメチルセルロースを徐放部造粒顆粒に対して重量比で10%量被覆して塩酸フラボキサート徐放性積層製剤を得た。

比較例 7

中間層の成分の比較試験として、実施例 1 における中間層の成分であるコーンスターチの代りに低置換度ヒドロキシプロピルセルロースを、徐放部造粒顆粒に対して重量比で20%量被覆して塩酸フラボキサート徐放性積層製剤を得た。

比較例 8

中間層の成分の比較試験として、実施例 1 における中間層の成分であるコーンスターチの代りに乳糖を、徐放部造粒顆粒に対して重量比で20%量被覆して塩酸フラボキサート徐放性積層製剤を得た。

比較例 9

実施例 1 における腸溶性皮膜物質AQOAT-Mの代わりに、HP-55を用いて同様の操作を行い、塩酸フラボキサート徐放性積層製剤を得た。

比較例10

中間層の成分の比較試験として、比較例 9 における中間層の成分であるコーンスターチの代りにヒドロキシプロピルメチルセルロースを徐放部造粒顆粒に対して重量比で10%量被覆して塩酸フラボキサート徐放性積層製剤を得た。

比較例11

中間層の成分の比較試験として、比較例 9 における中間層の成分であるコーンスターチの代りに低置換度ヒドロキシプロピルセルロースを、徐放部造粒顆粒に対して重量比で20%量被覆して塩酸フラボキサート徐放性積層製剤を得た。

比較例12

中間層の成分の比較試験として、比較例 9 における中間層の成分であるコーンスターチの代りに乳糖を、徐放部造粒顆粒に対して重量比で20%量被覆して塩酸フラボキサート徐放性積層製剤を得た。

試験例 1

実施例 1 及び比較例 1 ～ 5 で得られた顆粒について日局第 1 液及び第 2 液による溶出試験を行った。試験方法は塩酸フラボキサート 400mg相当量の顆粒を第 1 液で 2 時間行った後、試料を第 2 液に移し、引続き 3 時間の試験を行った。各時間でサンプリングを行い、吸光度法によって溶出量を求めた。液量は 900mℓとし、パドル法（100rpm）を用いた。

図 1 に示したように何れの顆粒も第 1 液においては速やかな放出が認められ、速放部分の薬物量30%を 2 時間に渡って維持している。しかしなが

ら第2液においてはかなり様子が異なっており、徐放部上に直接腸溶性皮膜物質を被覆した顆粒が緩慢な放出を示すのに対して、中間層形成成分であるコーンスターチを被覆した顆粒では明らかに速やかな放出が認められる。

表1には溶出試験中の顆粒の状況を示した。

表1

	5分後	30分	60分	120分	180分
例1	変化なし	一部 カケラ状	一部 カケラ状	ほとんど カケラ状	カケラ状 で残存
例2	顆粒同士 の付着 あり	同左 数個の塊	同左 ゴム状	同左 浮遊	上層に浮 遊残存
例3	顆粒同士 の付着 あり	同左 数個の塊	同左 浮遊 ゴム状	同左 浮遊	上層に浮 遊残存
例4	変化なし	同左	同左 一部 カケラ状	同左 一部 カケラ状	カケラ状 で残存
例5	変化なし	同左	同左 一部 カケラ状	ほとんど カケラ状	カケラ状 で残存

〔中間層を被覆しない顆粒の日局第2液における状況。例1～5は、比較例1～5を意味する。〕

徐放部上に直接腸溶性皮膜物質を被覆した顆粒では皮膜によって第2液における状況がそれぞれ異なり、AQOAT-M, CMEC, オイドラギットL-100 が顆粒のまま、又は一部の顆粒が破壊されたカケラ状で長時間に渡って残存するタイプであるのに対して、HP-55, オイドラギットL30D-55では、第2液に移して数分後より顆粒同士の付着凝集が起こり、この付着凝集体が長時間浮遊状態で残存する状況が見受けられた。

また表2に各々の腸溶性皮膜物質について3例づつの溶出試験結果を示した。

付着凝集を起こすタイプのものは当然のことながら放出性に大きなバラツキが見られる。

以上の溶出試験の結果より、塩酸フラボキサートと腸溶性皮膜物質間の不溶化現象に係わる問題を解消するためには中間層を設けることが有効であることが判明した。

表2

	中間層の有無	30 分	60 分	120 分	180 分
実施例1	あり	88.3± 5.3	92.0± 4.7	96.3± 4.1	99.2± 1.9
比較例1	なし	58.3± 8.6	62.1± 6.7	66.7± 5.3	76.3± 6.6
比較例2	なし	60.1±20.3	66.4±21.3	70.7±18.6	73.4±17.3
比較例3	なし	63.6±21.6	68.5±18.0	73.5±16.8	76.2±14.6
比較例4	なし	48.3± 7.2	51.4± 8.8	60.3± 6.6	66.5± 5.3
比較例5	なし	55.2± 8.5	60.2± 7.2	64.5± 7.8	70.8± 7.1
比較例9	あり	63.5±13.5	68.2±15.6	73.2±17.5	77.8±14.2

〔中間層の有無と日局第2液中での放出性（n＝3）を表す。単位（%）　平均値±標準偏差〕

試験例2

実施例1、比較例6、7、8、9、10、11、12で得られた顆粒について試験例1と同様の方法で溶出試験を実施し、中間層形成成分及び腸溶性皮膜物質の効果の比較を行った。

図2及び図3に示したように第2液に移行した後の薬物の放出性においては、コーンスターチを用いた顆粒が最も速やかな放出を示したのに対してヒドロキシプロピルメチルセルロース、低置換度ヒドロキシプロピルセルロース、乳糖を用いた顆粒では、中間層を被覆しない顆粒に比べれば若干の改善は見られたが（図1参照）、依然として塩酸フラボキサートと腸溶性皮膜物質との間の相互作用による不溶化物が認められ、それに伴って緩慢な薬物の放出性を示すものであった。

また、同図から明らかなように腸溶性皮膜物質としてはヒドロキシプロピルメチルセルロースアセテートサクシネートが優れていることが判明した。

これらの結果より、塩酸フラボキサートと腸溶

性皮膜物質との間の相互作用による皮膜物質の不溶化及び薬物の放出性に関する問題を改善するためには、徐放部上に澱粉を必須成分とした中間層を被覆し、これに腸溶性皮膜物質であるヒドロキシプロピルメチルセルロースアセテートサクシネートを被覆する方法が最も有効であることが判った。

試験例3

実施例1で得られた本発明の塩酸フラボキサート徐放性積層製剤を、健康成人に下記の試験条件に従って服用せしめ、塩酸フラボキサートの主代謝物である3-メチルフラボン-8-カルボン酸の尿中排泄量を測定し、徐放性製剤の評価を行った。

〔試験条件〕

5名の男子健康成人を被験者とし、絶食時（試験開始12時間前より試験当日の朝食）及び軽食後の2条件下に水 100mlと共に服用し、予め設定した採尿スケジュールに従って24時間まで採取した。両試験は1週間以上の休薬期間をおいて実施した。

服用量は、それぞれ塩酸フラボキサート徐放性積層製剤約 1.3g（塩酸フラボキサートとして400mg含有）を1日1回、対照としてブラダロン錠1錠（日本新薬社製、塩酸フラボキサートとして1錠に 200mg含有）を1日1回とした。

〔試験結果〕

試験結果を表3及び図4にそれぞれ示した。

（以下次頁）

表3 ヒト投与時における尿中排泄量に係わるパラメーター

	用量	Bmax (mg/hr)
①ブラダロン錠（絶食）	200mg	30.3±4.5
②徐放性積層顆粒（絶食）	400mg	31.3±7.5
③徐放性積層顆粒（非絶食）	400mg	38.9±8.9

	Tmax (hr)	B10hr	BBA(%)
①	1.2±0.5	80.1± 7.4	100.0
②	3.6±0.5	133.8±21.9	83.9
③	4.6±0.5	172.0±12.1	107.4

	MRT(hr)	VRT(hr²)
①	2.4±0.2	4.1±0.7
②	3.9±0.3	5.0±0.4
③	4.6±0.7	5.0±0.6

〔Bmax：最高尿中排泄速度
Tmax：最高尿中排泄速度到達時間
B10hr ：10時間までの尿中排泄量
BBA ：バイオアベイラビリティ
MRT ：平均滞留時間
VRT ：体内滞留時間の分散 〕

本発明の塩酸フラボキサート徐放性積層製剤は対照である錠剤と比較してバイオアベイラビリティの低下を伴うことなく、徐放性製剤の指標となるべき最高尿中排泄速度到達時間の明らかなる遅延、及び平均滞留時間における大幅な延長（絶食時においては 約1.6倍、非絶食時においては約2倍）が認められており、徐放性製剤として充分なる有用性を備えているものと言える。

加えて最高尿中排泄速度が通常用量（200 mg）と同程度を示すことから、本発明の塩酸フラボキサート徐放性積層製剤は体内における安全性についても優れているものである。

【発明の効果】

本発明の塩酸フラボキサート徐放性積層製剤は、塩酸フラボキサートと腸溶性皮膜物質との相互作用による皮膜物質の不溶化及び薬物の放出性に関する問題を改善するために中間層の成分である澱粉と腸溶性皮膜物質であるヒドロキシプロピルメチルセルロースアセテートサクシネートとを必須成分として用いることにより、安定した薬物の放

出を保証せしめ、徐放性製剤としての有用性を有意に高めた。

また速放部分と徐放部分を積層型として一体化することによって、従来の混合タイプに較べて安定した速放部分と徐放部分の薬物組成割合を持つ製剤を提供することを可能とし、更に苦味を改善するために酸可溶性皮膜物質によるマスキング層を設けたことの結果、当薬物が所持している服用時のコンプライアンスに関する問題をも改善することができた。

なお、本発明の塩酸フラボキサート徐放性積層製剤は成人1人あたり1回 0.5～3 g (塩酸フラボキサートとして 400mg) を朝、晩1日2回服用するものである。

4、図面の簡単な説明

図1は、実施例1及び比較例1、2、3、4、5で得られた各々の腸溶性皮膜物質からなる顆粒の中間層の有無に関する溶出試験結果を示す。

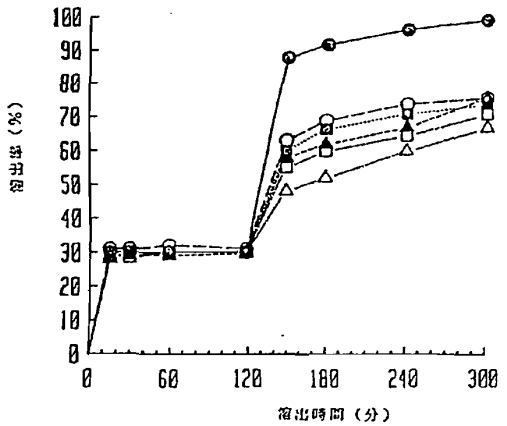
図2、図3は異なる中間層の成分を用いて実施例1、比較例6、7、8、9、10、11、12で得られた顆粒の溶出試験結果を示す。

図4は試験例3における本発明の製剤及び従来の製剤であるプラダロン錠投与後の3-メチルフラボン-8-カルボン酸尿中排泄速度曲線を示す。

出願人　日本新薬株式会社

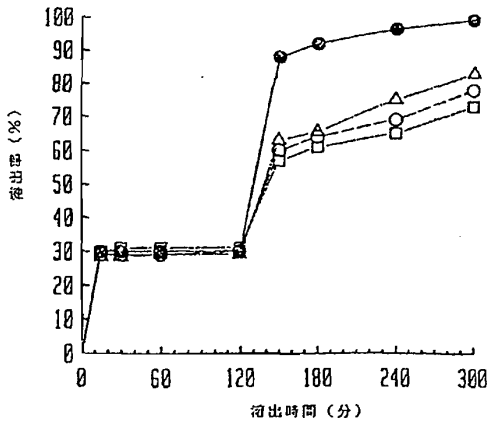
代理人　弁理士　片岡　宏

図1



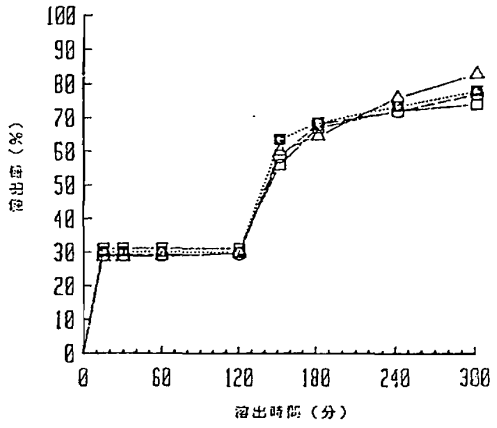
● ： 実施例1
▲ ： 比較例1
■ ： 比較例2
○ ： 比較例3
△ ： 比較例4
□ ： 比較例5

図2



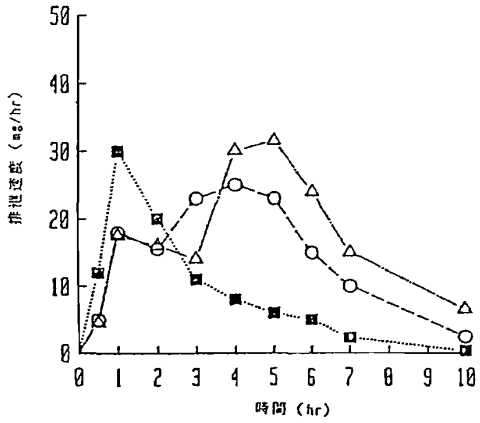
● ： 実施例1
○ ： 比較例6
△ ： 比較例7
□ ： 比較例8

図3



■：比較例 9
○：比較例10
△：比較例11
□：比較例12

図4



■：プラダロン錠（絶食）
○：徐放性徐放顆粒（絶食）
△：徐放性徐放顆粒（非絶食）

第1頁の続き

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CITED REFERENCE 5

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 07-061922
(43)Date of publication of application : 07.03.1995

(51)Int.Cl. A61K 9/32
A61K 9/52
A61K 47/32
A61K 47/38

(21)Application number : 05-210453
(22)Date of filing : 25.08.1993

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(54) RELEASE START CONTROLLING TYPE PHARMACEUTICAL PREPARATION

(57)Abstract:
PURPOSE: To obtain a release start controlling type pharmaceutical preparation capable of freely regulating the time for the relee of a medicine from the pharmaceutical preparation and the relee rate of the medicine after starting the release of the medicine.
CONSTITUTION: This release start controlling type pharmaceutical preparation is obtained by coating a central core containing a medicine with a coating layer containing a water-insoluble polymer and a silicone. When a holding material for the silicone (preferably light silicic anhydride) is further added to the coating layer, a large amount of the silicone can be contained in the coating layer and a pharmaceutical preparation good in stability without changing the time for the medicine to start the release and release rate with time even if the large amount of the silicone is contained can be obtained. Furthermore, the time for the medicine to start the release can freely be regulated by changing the thickness of the coating layer and the release rate of the medicine after starting the release can be regulated by changing the composition of the coating layer An ethyl acrylate-methyl methacrylate-trimethylammonium chloride ethyl methacrylate copolymer is preferred as the water-insoluble polymer in the coating layer and a silicone resin or a silicone oil is preferred as the silicone.

LEGAL STATUS

[Date of request for examination]	20.11.1996
[Date of sending the examiner's decision of rejection]	
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]	
[Date of final disposal for application]	
[Patent number]	2916978
[Date of registration]	23.04.1999
[Number of appeal against examiner's decision of rejection]	
[Date of requesting appeal against examiner's decision of rejection]	

CLAIMS

[Claim(s)]
[Claim 1] Emission initiation control mold pharmaceutical preparation characterized by covering the constituent containing a drug with the coat layer containing a water-insoluble nature macromolecule and silicone.
[Claim 2] Emission initiation control mold pharmaceutical preparation according to claim 1 which is one sort as which a water-insoluble nature giant molecule is chosen from ethyl-acrylate methacrylic acid methyl methacrylic acid chlorination trimethylammonium ethyl and a copolymer, ethyl cellulose, methacrylic acid, an ethyl acrylate and a copolymer, methacrylic acid, methacrylic acid methyl and a copolymer, hydroxypropylmethylcellulose phthalate, hydroxypropyl-methylcellulose acetate succinate, carboxy methyl ethyl cellulose, and cellulose acetate phthalate, or two sorts or more.
[Claim 3] Emission initiation control mold pharmaceutical preparation according to claim 1 whose silicone is silicone resin or silicone oil.
[Claim 4] Furthermore, emission initiation control mold pharmaceutical preparation according to claim 1 which contains the supporter of silicone in a coat layer.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the emission initiation control mold pharmaceutical preparation which can adjust freely the time amount to which a drug starts emission, and the drug release rate after drug release initiation from pharmaceutical preparation.
[0002]
[Description of the Prior Art] If drugs are in charge of the application, the singularity according to security and various purposes of effectiveness and safety is required. For this reason, the system by which it can move aside is demanded of the target site only for the initial complement as delivery over need time amount in the drug by devising dosage forms. Although the sustained release drug which adjusts the emission rate of the drug from pharmaceutical preparation, and already gives continuous effectiveness to this demand was put in practical use, the pharmaceutical preparation which controls time amount until emission of a drug begins in recent years was invented. As a coat of the pharmaceutical preparation which obtains the ragtime to what a coat is destroyed as such pharmaceutical preparation because the water bloating tendency matter expands, and a drug emits (JP,62-30709,A, JP,4-33823,A), and emission initiation The thing using the water-repellent salt and acrylic-acid system polymers of a fatty acid, such as magnesium stearate and calcium stearate, (JP,4-235123,A), [, such as a metal salt,] And the thing [the collection of the 7th annual convention lecture summaries of Academy of Pharmaceutical Science and Technology, Japan and p84 (1991)] using the interaction of OIDORAGITTO RS (product made from REMU Pharma) and an organic acid etc. is mentioned.
[0003]
[Problem(s) to be Solved by the Invention] However, there are various purposes in drugs and pharmaceutical preparation with the various drug release devices according to this is called for. Therefore, the purpose of this invention is to obtain the pharmaceutical preparation of a new configuration of that a drug can control the time amount which starts emission, and the drug release rate after drug release initiation from pharmaceutical preparation.
[0004]
[Means for Solving the Problem] As a result of this invention person's inquiring wholeheartedly in view of this actual condition, when covering the constituent containing a drug with the coat layer containing a water-insoluble nature macromolecule and silicone, a header and this invention were completed for the ability of the emission rate of the drug after emission initiation for the emission start time of a drug to be freely adjusted by changing the thickness of the coat layer, and to be adjusted by changing the presentation of a coat layer further.
[0005] That is, the emission initiation control mold pharmaceutical preparation characterized by this invention covering the constituent containing a drug with the coat layer containing a water-insoluble nature macromolecule and silicone is offered.
[0006] that to which the constituent containing a drug makes the core of pharmaceutical preparation in the pharmaceutical preparation of this invention -- it is -- the crystal of a drug -- what remained as it was, or added the excipient usually used for physic pharmaceutical preparation, a binder, lubricant, etc., and was used as various solid preparations generally used as

(19)日本国特許庁（ＪＰ）　(12)公開特許公報（A）　(11)特許出願公開番号

特開平7－61922

(43)公開日　平成７年(1995)３月７日

(51)Int.Cl.[6]		識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｋ	9/32				
	9/52	Ｊ			
	47/32	Ｃ			
		Ｄ			
	47/38	Ｃ			

審査請求　未請求　請求項の数４　ＯＬ　（全 10 頁）　最終頁に続く

(21)出願番号　特願平5－210453

(22)出願日　平成５年(1993)８月25日

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(54)【発明の名称】　放出開始制御型製剤

(57)【要約】
【構成】　薬物を含む中心核が、水不溶性高分子及びシリコーンを含有する皮膜層で被覆されたことを特徴とする放出開始制御型製剤。
【効果】　本発明の放出開始制御型製剤は、製剤から薬物が放出を開始する時間及び薬物放出開始後の薬物放出速度を自由に調節することができる。

1

【特許請求の範囲】

【請求項１】　薬物を含む組成物を、水不溶性高分子及びシリコーンを含有する皮膜層で被覆したことを特徴とする放出開始制御型製剤。

【請求項２】　水不溶性高分子がアクリル酸エチル・メタアクリル酸メチル・メタアクリル酸塩化トリメチルアンモニウムエチル・共重合体、エチルセルロース、メタアクリル酸・アクリル酸エチル・共重合体、メタアクリル酸・メタアクリル酸メチル・共重合体、ヒドロキシプロピルメチルセルロースフタレート、ヒドロキシプロピルメチルセルロースアセテートサクシネート、カルボキシメチルエチルセルロース及び酢酸フタル酸セルロースから選ばれる１種又は２種以上である請求項１記載の放出開始制御型製剤。

【請求項３】　シリコーンが、シリコーン樹脂又はシリコーンオイルである請求項１記載の放出開始制御型製剤。

【請求項４】　更に皮膜層にシリコーンの保持体を含む請求項１記載の放出開始制御型製剤。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明は製剤から薬物が放出を開始する時間、及び薬物放出開始後の薬物放出速度を自由に調節することのできる放出開始制御型製剤に関する。

【０００２】

【従来の技術】医薬品は、その適用にあたっては有効性、安全性の保障及びさまざまな目的に応じた特異性が要求される。このため、剤形を工夫することによって薬物を標的部位に必要時間にわたって必要量だけ送りとどけるシステムが要求されている。すでに、この要求に対し、製剤からの薬物の放出速度を調節し、持続的効果を与える徐放性製剤が実用化されているが、近年、薬物の放出が開始するまでの時間を制御する製剤が案出された。このような製剤としては、水膨潤性物質が膨脹することで皮膜が破壊され薬物が放出するもの（特開昭６２－３０７０９号公報、特開平４－３３８２３号公報）、放出開始までのラグタイムを得る製剤の皮膜として、ステアリン酸マグネシウム、ステアリン酸カルシウム等の脂肪酸の金属塩等の撥水性塩とアクリル酸系ポリマーを用いたもの（特開平４－２３５１２３号公報）、及びオイドラギットＲＳ（レーム・ファーマ社製）と有機酸の相互作用を利用したもの〔日本薬剤学会第７年会講演要旨集，ｐ８４，（１９９１）〕等が挙げられる。

【０００３】

【発明が解決しようとする課題】しかしながら、医薬品にはさまざまな目的があり、これに応じた種々の薬物放出機構を持つ製剤が求められる。従って、本発明の目的は製剤から薬物が放出を開始する時間及び薬物放出開始後の薬物放出速度をコントロールできる新たな構成の製剤を得ることにある。

2

【０００４】

【課題を解決するための手段】斯かる実情に鑑み、本発明者は鋭意研究を行った結果、薬物を含む組成物を水不溶性高分子及びシリコーンを含む皮膜層で被覆すれば、その皮膜層の厚さを変化させることで薬物の放出開始時間を自由に調節でき、更に皮膜層の組成を変えることで放出開始後の薬物の放出速度を調節できることを見出し、本発明を完成した。

【０００５】すなわち本発明は、薬物を含む組成物を、水不溶性高分子及びシリコーンを含有する皮膜層で被覆したことを特徴とする放出開始制御型製剤を提供するものである。

【０００６】本発明の製剤において、薬物を含む組成物は、製剤の中心核をなすものであり、薬物の結晶そのままで、又は医薬製剤に通常使用される賦形剤、結合剤、滑沢剤等を添加し、細粒、顆粒、ビーズ、錠剤等一般に医薬品として用いられている様々な固形剤としたものでもよい。また、この中心核組成物は、必要により、水可溶性高分子、酸可溶性高分子、腸溶性高分子、水不溶性高分子、ワックス等で被覆してもよい。ここで中心核組成物に含まれる薬物は特に制限されないが、例えば代表的なものとして、催眠鎮静薬、抗てんかん薬、解熱鎮痛消炎薬、興奮薬、覚醒薬、鎮暈薬、精神神経用薬等の中枢神経系用薬；骨格筋弛緩薬、自律神経薬、自律神経遮断薬、植物製剤等の末梢神経系用薬；眼科用薬、耳鼻科用薬等の感覚器官用薬；強心薬、不整脈用薬、利尿薬、血圧降下薬、血管補強薬、血管収縮薬、血管拡張薬、動脈硬化用薬等の循環器官用薬；呼吸促進薬、鎮咳去痰薬等の呼吸器官用薬；消化性潰瘍用薬、健胃消化薬、制酸剤、下剤、利胆薬、整腸薬等の消化器官用薬；ホルモン薬、抗ホルモン薬等のホルモン薬、尿路消毒薬、子宮収縮薬、泌尿生殖器官用薬、痔疾用薬、肛門用薬等の泌尿生殖器官及び肛門用薬；ビタミン、滋養強壮変質剤、血液及び体液用薬、肝臓疾患用薬、解毒薬、習慣性中毒用薬、痛風治療薬、酵素製剤、糖尿病治療薬等の代謝性医薬品；細胞賦活用薬、腫瘍用薬等の組織細胞の機能用医薬品；抗生物質、化学療法薬、抗原虫薬、駆虫薬等の病原生物に対する医薬品；アルカロイド系麻薬、非アルカロイド系麻薬等の麻薬等が挙げられる。

【０００７】本発明の製剤の皮膜層に用いる水不溶性高分子としては、アクリル酸エチル・メタアクリル酸メチル・メタアクリル酸塩化トリメチルアンモニウムエチルの３者の共重合体、エチルセルロース等の水不溶性高分子、メタアクリル酸・アクリル酸エチル共重合体、メタアクリル酸・メタアクリル酸メチル・共重合体、ヒドロキシプロピルメチルセルロースフタレート、ヒドロキシプロピルメチルセルロースアセテートサクシネート、カルボキシメチルエチルセルロース、酢酸フタル酸セルロース等の酸性条件下で不溶性の腸溶性高分子等が例示されるが、就中、アクリル酸エチル・メタアクリル酸メチ

ル・メタアクリル酸塩化トリメチルアンモニウムエチルの共重合体が少ないコーティングで放出開始までの時間（ラグタイム）を最も長くできる点で好ましい。アクリル酸エチル・メタアクリル酸メチル・メタアクリル酸塩化トリメチルアンモニウムエチルの共重合体の３者の重量比は１：２：０．１～１：２：０．２であるものが好ましく、市販のものとしては、オイドラギットＲＳ及びオイドラギットＲＬ（レーム・ファーマ社製）が例示される。

【０００８】水不溶性高分子は、１種でも２種以上を混合して用いてもよく、使用量は、皮膜層全体の２０～９５重量％の範囲が好ましい。

【０００９】上記の水不溶性高分子に少量の水可溶性高分子を必要により添加し、ラグタイム及び薬物の放出速度を調節することができる。このような水可溶性高分子としては、ヒドロキシプロピルメチルセルロース、ヒドロキシプロピルセルロース、ポリビニルピロリドン、ポリエチレングリコール等が好適な例として挙げられる。

【００１０】本発明において、皮膜層中に含有せしめるシリコーンとしては、シリコーン樹脂、シリコーンオイルが好ましく、特に粘度９５～１１００センチストークスのジメチルポリシロキサンが好ましい。皮膜層中のシリコーンは、前記の水不溶性高分子に対して５～２００重量％含有せしめることが好ましく、特に１０～１００重量％とすることが好ましい。

【００１１】また、本発明において、皮膜層中には、更にシリコーン保持体を添加することが好ましい。シリコーンの保持体は、皮膜層に大量のシリコーンを含有することを可能にするのみならず、大量のシリコーンを含有させても経時的に薬物が放出を開始するまでの時間や放出速度が変化しない安定性の良好な製剤とすることができる。

【００１２】シリコーンの保持体は液状のシリコーンを水不溶性高分子の中に分散させ保持でき得るものであれば、特に限定されないが、タルク、軽質無水ケイ酸、結晶セルロース、デンプン等が好ましく、特に、軽質無水ケイ酸が好ましい。また、保持体の形状は表面積の大きな微粉末が好ましい。保持体の添加量はシリコーンに対し、０～２００重量％とすることが好ましい。

【００１３】本発明において、皮膜層には更に可塑剤を添加することができる。このような可塑剤としては、クエン酸トリエチル、トリアセチン、ポリエチレングリコール、ひまし油、ポリオキシソルビタンモノオレエート、グリセリン脂肪酸エステル等が挙げられ、添加量は水不溶性高分子に対し２～５０重量％とすることが好ましい。

【００１４】皮膜層の被覆量は、薬物の種類、中心核の大きさ、形状、目的とする放出開始までの時間、放出速度、皮膜の構成成分により異なるので適宜決定すればよいが、一般的に中心核に対して２～２００重量％である。また、被覆量は、一般に放出開始までの時間が長いもの程多く必要で、中心核の小さなものも被覆量は多くなる。本発明の製剤を製造するには、常法により中心核を製造し、これに水不溶性高分子とシリコーンを含む皮膜層をコーティングすればよい。

【００１５】中心核の製造方法としては、湿式造粒あるいは乾式造粒により細粒や顆粒を製造する方法、更に、これらの造粒した細粒や顆粒を圧縮成型して錠剤にする方法、直接打錠により錠剤にする方法、転動造粒により顆粒やビーズを製造する方法、押し出し造粒により細粒、顆粒やビーズを製造する方法、押し出し造粒後にマルメライザー等で処理して顆粒やビーズを製造する方法等従来公知の方法が挙げられる。皮膜層のコーティングは、流動層に中心核を入れスプレーコーティングする方法、パンに中心核を入れスプレーコーティングする方法等により行うことができる。本発明の放出開始制御型製剤に更に速溶部を組み合わせたり、放出開始時間の異なる本発明の放出開始制御型製剤を組み合わせたりすることができる。本発明の細粒、顆粒、ビーズ、錠剤の放出開始制御型製剤はカプセルに充填しカプセル剤としてもよく、また、本発明の細粒、顆粒、ビーズを適当な賦形剤、結合剤、滑沢剤などと共に打錠し錠剤としてもよい。

【００１６】

【発明の効果】本発明の放出開始制御型製剤は、あらかじめ定められた放出開始時間に薬物を放出し始めるため、速溶部と合わせて、あるいは種々の放出開始時間の異なる製剤を組み合わせることにより、様々な放出パターンの徐放性製剤を得ることができる。更に、薬物の放出をパルス型に設定できるため、１日１回の服用で速放性の製剤を１日数回服用したのと同じ血中濃度推移にすることもできる。従って、初回通過効果により徐々に薬物を放出する通常の徐放化では生物学的利用能が大きく低下する薬物に対しても、本発明の放出開始制御型製剤は、あらかじめ定められた放出開始時間に薬物を急速に放出しはじめるようにパルス型に薬物の放出を設定することができるため、生物学的利用能の低下を少なくすることができる。

【００１７】

【実施例】次に、実施例を挙げて本発明を具体的に説明するが、本発明はこれに限定されるものではない。なお、以下「％」は重量％を示す。

【００１８】実施例１

トラピジル１５００ｇとヒドロキシプロピルセルロース１００ｇを混合した後、微粉砕した。ヒドロキシプロピルセルロース２０ｇをエチルアルコール３８０ｇに溶解した液を噴霧しながら、この粉砕末１２８０ｇをノンパレル１０３（球形白糖、粒径７１０－５００μｍ、フロイント産業（株）製）４００ｇに散布して転動造粒し、６０℃で５時間乾燥した後、１２メッシュ（目開き１．

４１㎜）を通過し３２メッシュ（目開き０．５０㎜）を通過しないものを素顆粒として得た。

【００１９】次いで、この素顆粒１０００ｇを流動層コーティング装置に入れ、素顆粒の重量増が１０％になるまで、ヒドロキシプロピルメチルセルロース８％、タルク２％、エチルアルコール４５％、精製水４５％の組成のコーティング液を噴霧し、本発明の中心核を得た。

【００２０】次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が６０％（実施例１－１）、９０％（実施例１－２）になるまで、オキドラギットＲＳ１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００２１】比較例１

実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が６０％（比較例１－１）、９０％（比較例１－２）になるまで、オイドラギットＲＳ１２％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール８３％の組成のコーティング液を噴霧し、顆粒剤として皮膜にシリコーンを含まない比較製剤を得た。

【００２２】試験例１

実施例１で得た本発明の放出開始制御型製剤、実施例１－１、１－２及び比較例１で得たシリコーンを含まない比較製剤、比較例１－１、１－２のトラピジルの溶出をパドル法（日本薬局方、第１２改正、溶出試験法）で、pH６．８のリン酸塩緩衝液を試験液として測定した。その結果を図１に示した。図１より、同じコーティング量の比較例１－１、１－２の比較製剤に比べ、本発明の放出開始制御型製剤は放出開始までのラグタイムの後にトラピジルを放出していることがわかる。

【００２３】実施例２

実施例１で得た本発明の放出開始制御型製剤の顆粒、実施例１－１及び１－２をそれぞれトラピジルの含量が１５０㎎になるように硬カプセルに充填して、カプセル剤として本発明の放出開始制御型製剤、実施例２－１及び２－２を得た。

【００２４】試験例２

実施例２で得た本発明の放出開始制御型製剤、実施例２－１及び２－２のそれぞれ１カプセルを健康成人男子に投与してトラピジルの尿中排泄速度を測定した。その結果を図２に示した。図２より、本発明の放出開始制御型製剤はそれぞれ３時間及び７時間のラグタイムの後、トラピジルが排泄されていることがわかる。

【００２５】実施例３

トラピジル１５００ｇとヒドロキシプロピルセルロース１００ｇを混合した後、微粉砕した。ヒドロキシプロピルセルロース２０ｇをエチルアルコール３８０ｇに溶解

した液を噴霧しながら、この粉砕末１２８０ｇをノンパレル１０３（球形白糖、粒径７１０－５００μｍ、フロイント産業（株）製）４００ｇに散布して転動造粒し、６０℃で５時間乾燥した後、１２メッシュ（目開き１．４１㎜）を通過し３２メッシュ（目開き０．５０㎜）を通過しないものを本発明の中心核として得た。次いで、この中心核２５０ｇを流動層コーティング装置に入れ、重量増が５０％（実施例３－１）、７０％（実施例３－２）、９０％（実施例３－３）になるまで、オイドラギットＲＳ６％、ジメチルポリシロキサン４％、軽質無水ケイ酸２％、グリセリン脂肪酸エステル０．５％、エチルアルコール８７．５％の組成のコーティング液を噴霧し、本発明の放出開始制御型製剤を得た。

【００２６】試験例３

実施例３で得た本発明の放出開始制御型製剤、実施例３－１、３－２、３－３のトラピジルの溶出を試験例１と同様にして測定した。その結果を図３に示した。図３より、本発明の製剤は放出開始までのラグタイムの後に速やかにトラピジルを放出し、放出開始までのラグタイムはコーティング量が増加するほど長くなることがわかる。更に、ラグタイム後のトラピジルの放出速度はコーティング量が異なる実施例でも同じになっていることがわかる。

【００２７】実施例４

実施例１と同様にしてトラピジルを含む中心核を得た。中心核２５０ｇを流動層コーティング装置に入れ、重量増が６０％になるまで、オイドラギットＲＳ２０％、ジメチルポリシロキサン４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、本発明の放出開始制御型製剤（実施例４－１）を得た。中心核２５０ｇを流動層コーティング装置に入れ、重量増が７０％になるまで、オイドラギットＲＳ１４％、ジメチルポリシロキサン６％、軽質無水ケイ酸３％、グリセリン脂肪酸エステル２％、エチルアルコール７５％の組成のコーティング液を噴霧し、本発明の放出開始制御型製剤（実施例４－２）を得た。中心核２５０ｇを流動層コーティング装置に入れ、重量増が１００％になるまで、オイドラギットＲＳ１０％、ジメチルポリシロキサン９％、軽質無水ケイ酸５％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、本発明の放出開始制御型製剤（実施例４－３）を得た。

【００２８】試験例４

実施例４で得た本発明の放出開始制御型製剤、実施例４－１、４－２、４－３のトラピジルの溶出を試験例１と同様にして測定した。その結果を図４に示した。図４より、本発明の製剤は放出開始までのラグタイムの後にトラピジルを放出し、ラグタイム後のトラピジルの放出速度は皮膜の組成を変えることで調節できることがわかる。

【００２９】実施例５
実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が５０％（実施例５－１）、８０％（実施例５－２）、１１０％（実施例５－３）、１４０％（実施例５－４）になるまで、オイドラギットＲＳ１６％、ジメチルポリシロキサン４％、軽質無水ケイ酸３％、グリセリン脂肪酸エステル２％、エチルアルコール７５％の組成のコーティング液を噴霧し、本発明の放出開始制御型製剤を得た。

【００３０】試験例５
実施例５で得た本発明の放出開始制御型製剤、実施例５－１、５－２、５－３、５－４のトラピジルの溶出を試験例１と同様にして測定した。その結果を図５に示した。図５より、本発明の放出開始制御型製剤は放出開始までのラグタイムの後に速やかにトラピジルを放出し、放出開始までのラグタイムはコーティング量が増加するほど長くなることがわかり、放出開始時間を自由に変えることができることがわかる。

【００３１】実施例６
実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が６０％（実施例６－１）、８０％（実施例６－２）、１００％（実施例６－３）になるまで、オイドラギットＲＬ１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、本発明の放出開始制御型製剤を得た。

【００３２】試験例６
実施例６で得た本発明の放出開始制御型製剤、実施例６－１、６－２、６－３のトラピジルの溶出をパドル法（日本薬局方、第１２改正、溶出試験法）で、pH６．８のリン酸塩緩衝液を試験液として測定した。その結果を図６に示した。図６より、本発明の放出開始制御型製剤は放出開始までのラグタイムの後に速やかにトラピジルを放出し、放出開始までのラグタイムはコーティング量が増加するほど長くなることがわかり、放出開始時間を自由に変えることができることがわかる。

【００３３】実施例７
塩酸フェニルプロパノールアミン４００ｇとコーンスターチ８００ｇを混合した後、微粉砕した。ヒドロキシプロピルセルロース４０ｇをエチルアルコール７６０ｇに溶解した液を噴霧しながら、この粉砕末１２８０ｇをノンパレル１０３（球形白糖、粒径７１０－５００μｍ、フロイント産業（株）製）４００ｇに散布して転動造粒し、６０℃で５時間乾燥した後、１２メッシュ（目開き１．４１㎜）を通過し３２メッシュ（目開き０．５０ｍｍ）を通過しないものを素顆粒とした。次いで、この素顆粒１０００ｇを流動層コーティング装置に入れ、素顆粒の重量増が１０％になるまで、ヒドロキシプロピルメチルセルロース８％、タルク２％、エチルアルコール４５％、精製水４５％の組成のコーティング液を噴霧し、中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、重量増が４０％（実施例７－１）、８０％（実施例７－２）、１２０％（実施例７－３）になるまで、オイドラギットＲＳ１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００３４】試験例７
実施例７で得た本発明の放出開始制御型製剤、実施例７－１、７－２、７－３の塩酸フェニルプロパノールアミンの溶出を試験例１と同様にして測定した。その結果を図７に示した。図７より、本発明の放出開始制御型製剤は放出開始までのラグタイムの後に速やかに塩酸フェニルプロパノールアミンを放出し、放出開始までのラグタイムはコーティング量が増加するほど長くなることがわかる。更に、ラグタイム後の塩酸フェニルプロパノールアミンの放出速度はコーティング量が異なる実施例でも同じになっていることがわかる。

【００３５】実施例８
実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が４０％（実施例８－１）、６５％（実施例８－２）になるまで、オイドラキッドＲＳ１２．５％、ジメチルポリシロキサン５％、タルク６．２５％、グリセリン脂肪酸エステル１．２５％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００３６】試験例８
実施例８で得た本発明の放出開始制御型製剤、実施例８－１、８－２のトラピジルの溶出を試験例１と同様にして測定した。その結果を図８に示した。図８より、本発明の放出開始制御型製剤は放出開始までのラグタイムの後に速やかにトラピジルを放出し、放出開始までのラグタイムはコーティング量が増加するほど長くなることがわかり、放出開始時間を自由に変えることができることがわかる。

【００３７】実施例９
ジクロフェナクナトリウム１５０ｇとコーンスターチ１２９５ｇを混合した後、微粉砕した。ヒドロキシプロピルセルロース３３ｇをエチルアルコール６２７ｇに溶解した液を噴霧しながら、この粉砕末１０５１ｇをノンパレル１０３（球形白糖、粒径７１０－５００μｍ、フロイント産業（株）製）４００ｇに散布して転動造粒し、６０℃で４時間乾燥した後、１４メッシュ（目開き１．１９㎜）を通過し３２メッシュ（目開き０．５０㎜）を通過しないものを中心核とした。次に、この中心核５００ｇを流動層コーティング装置に入れ、素顆粒の重量増

が８０％（実施例７－１）になるまで、オイドラギットＲＳ１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤の実施例９－１を得た。

【００３８】試験例９

実施例９で得た本発明の放出開始制御型製剤、実施例９－１のジクロフェナクナトリウムの溶出をパドル法（日本薬局方、第１２改正、溶出試験法）で、pH６．８のリン酸塩緩衝液を試験液として測定した。その結果を図９に示した。図９より、本発明の放出開始制御型製剤は放出開始まで４時間のラグタイムの後にジクロフェナクナトリウムを放出していることがわかる。

【００３９】実施例１０

実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が７０％（実施例１０－１）になるまで、エチルセルロース６．７５％、ポリビニルピロリドン０．４５％、ジメチルポリシロキサン４．８％、軽質無水ケイ酸２．４％、グリセリン脂肪酸エステル０．６％、エチルアルコール８５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００４０】試験例１０

実施例１０で得た本発明の放出開始制御型製剤、実施例１０－１のトラピジルの溶出をパドル法（日本薬局方、第１２改正、溶出試験法）で、pH６．８のリン酸塩緩衝液を試験液として測定した。その結果を図１０に示した。図１０より、本発明の放出開始制御型製剤は放出開始までのラグタイムの後に速やかにトラピジルを放出していることがわかる。

【００４１】実施例１１

実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が１００％（実施例１１－１）になるまで、オイドラギットＳ１００　１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００４２】試験例１１

実施例１１で得た本発明の放出開始制御型製剤、実施例１１－１のトラピジルの溶出をパドル法（日本薬局方、第１２改正、溶出試験法）で、pH６．８のリン酸塩緩衝液を試験液として測定した。その結果を図１１に示した。図１１より、本発明の放出開始制御型製剤は放出開始までのラグタイムの後に速やかにトラピジルを放出していることがわかる。

【００４３】実施例１２

テオフィリン９００ｇとタルク１００ｇを混合した後、微粉砕した。ヒドロキシプロピルセルロース２０ｇをエチルアルコール３８０ｇに溶解した液を噴霧しながら、この粉砕末８００ｇをノンパレル１０３（球形白糖、粒径７１０－５００μｍ、フロイント産業（株）製）２００ｇに散布して転動造粒し、６０℃で３時間乾燥した後、１４メッシュ（目開き１．１９㎜）を通過し３２メッシュ（目開き０．５０㎜）を通過しないものを中心核とした。次に、この素顆粒４００ｇを流動層コーティング装置に入れ、素顆粒の重量増が２５％になるまで、オイドラギットＲＳ１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００４４】実施例１３

プラノプロフェン５００ｇと結晶セルロース５００ｇを混合し、精製水２００ｇを添加して練合し、０．８㎜径のスクリーンで押し出し造粒した後、マルメライザーで処理して、６０℃で５時間乾燥した後、１４メッシュ（目開き１．１９㎜）を通過し３２メッシュ（目開き０．５０㎜）を通過しないものを素顆粒とした。次に、この素顆粒５００ｇを流動層コーティング装置に入れ、素顆粒の重量増が５０％になるまで、オイドラギットＲＳ１４％、ジメチルポリシロキサン７％、軽質無水ケイ酸３％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

【００４５】実施例１４

マレイン酸クロルフェニラミン１００ｇ、結晶セルロース４００ｇ、乳糖４９０ｇ、ステアリン酸マグネシウム１０ｇを混合したのち１錠の重量が８０㎎になるように打錠して素錠として中心核を得た。次に、この中心核５００ｇをコーティングパンに入れ、１錠当たりの重量増が１０㎎になるまで、オイドラギットＲＳ７．５％、ジメチルポリシロキサン３％、軽質無水ケイ酸１．５％、グリセリン脂肪酸エステル０．５％、エチルアルコール８７．５％の組成のコーティング液を噴霧し、錠剤として本発明の放出開始制御型製剤を得た。

【００４６】比較例２

実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が６０％（比較例２－１）、９０％（比較例２－２）になるまで、オイドラギットＲＳ１２％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、とうもろこし油８％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として皮膜をシリコーンに代えてとうもろこし油を含む比較製剤を得た。

【００４７】試験例１２

比較例２で得たシリコーンに代えてとうもろこし油を含

11

む比較製剤、比較例２－１、２－２のトラピジルの溶出を試験例１と同様にして測定した。その結果を、実施例１の本発明の放出開始制御型製剤、実施例１－１、１－２と共に図１２に示した。図１２より、とうもろこし油を用いた比較例２の比較製剤では放出開始までのラグタイムが得られないことがわかる。

【００４８】比較例３

実施例１と同様にしてトラピジルを含む中心核を得た。次に、この中心核２５０ｇを流動層コーティング装置に入れ、顆粒の重量増が６０％（比較例３－１）、９０％（比較例３－２）になるまで、オイドラギットＲＳ１２％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、流動パラフィン８％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として皮膜をシリコーンに代えて流動パラフィンを含む比較製剤を得た。

【００４９】試験例１３

比較例３で得たシリコーンに代えて流動パラフィンを含む比較製剤、比較例３－１、３－２のトラピジルの溶出を試験例１と同様にして測定した。その結果を、実施例１の本発明の放出開始制御型製剤、実施例１－１、１－２と共に図１３に示した。図１３より、流動パラフィンを用いた比較例３の比較製剤では放出開始までのラグタイムが得られないことがわかる。

【図面の簡単な説明】

【図１】実施例１で得た本発明の放出開始制御型製剤及び比較例１の比較製剤の試験例１による溶出試験の結果を示す図である。

12

＊【図２】実施例２で得た本発明の放出開始制御型製剤の試験例２による尿中排泄試験の結果を示す図である。

【図３】実施例３で得た本発明の放出開始制御型製剤の試験例３による溶出試験の結果を示す図である。

【図４】実施例４で得た本発明の放出開始制御型製剤の試験例４による溶出試験の結果を示す図である。

【図５】実施例５で得た本発明の放出開始制御型製剤の試験例５による溶出試験の結果を示す図である。

【図６】実施例６で得た本発明の放出開始制御型製剤の試験例６による溶出試験の結果を示す図である。

【図７】実施例７で得た本発明の放出開始制御型製剤の試験例７による溶出試験の結果を示す図である。

【図８】実施例８で得た本発明の放出開始制御型製剤の試験例８による溶出試験の結果を示す図である。

【図９】実施例９で得た本発明の放出開始制御型製剤の試験例９による溶出試験の結果を示す図である。

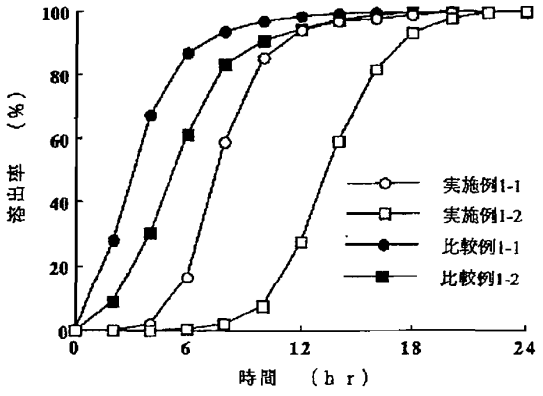
【図１０】実施例１０で得た本発明の放出開始制御型製剤の試験例１０による溶出試験の結果を示す図である。

【図１１】実施例１１で得た本発明の放出開始制御型製剤の試験例１１による溶出試験の結果を示す図である。

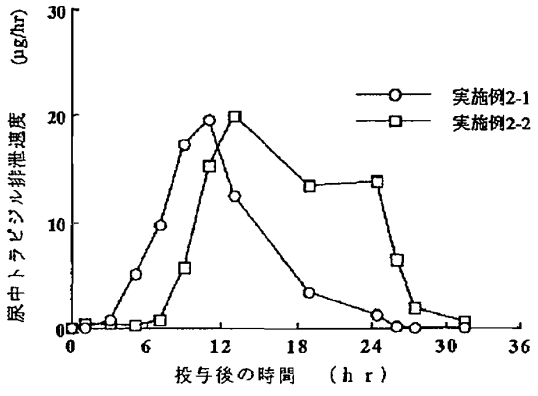
【図１２】実施例１で得た本発明の放出開始制御型製剤及び比較例２の比較製剤の試験例１２による溶出試験の結果を示す図である。

【図１３】実施例１で得た本発明の放出開始制御型製剤及び比較例３の比較製剤の試験例１３による溶出試験の結果を示す図である。

【図１】



【図２】



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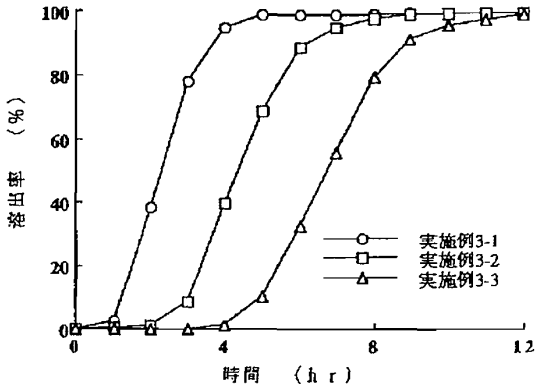

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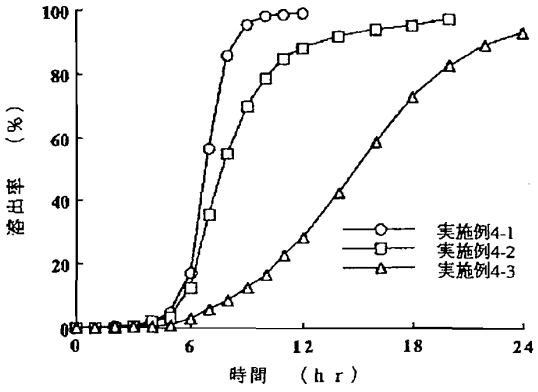
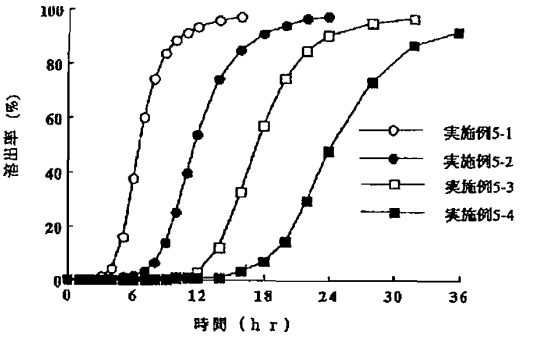
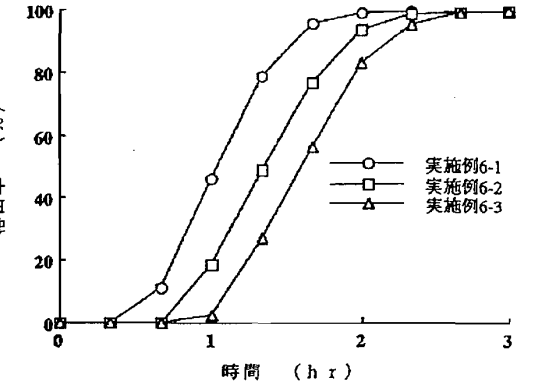


【図５】



【図６】



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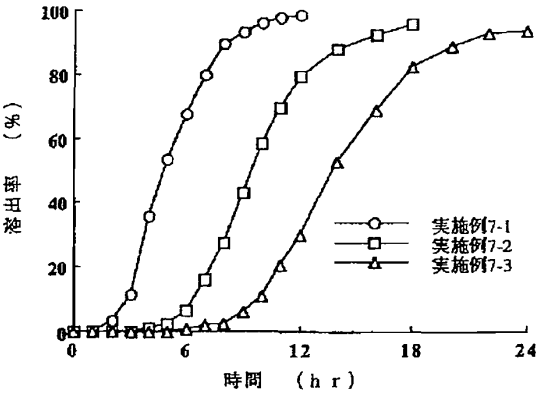

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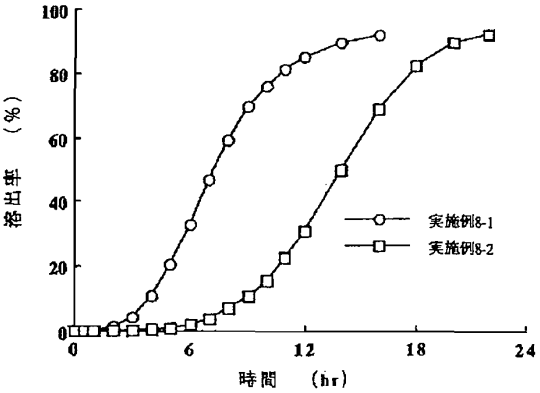

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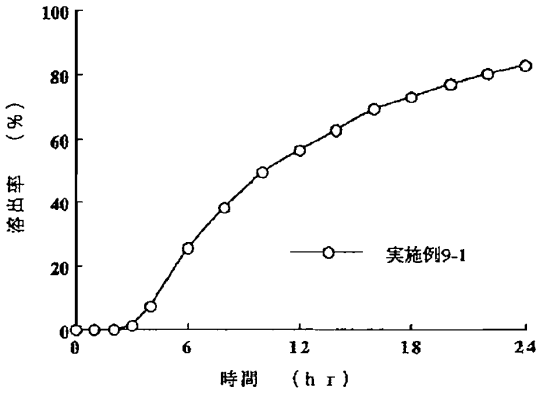
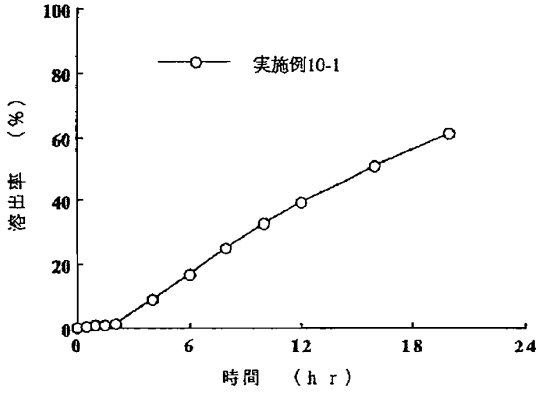
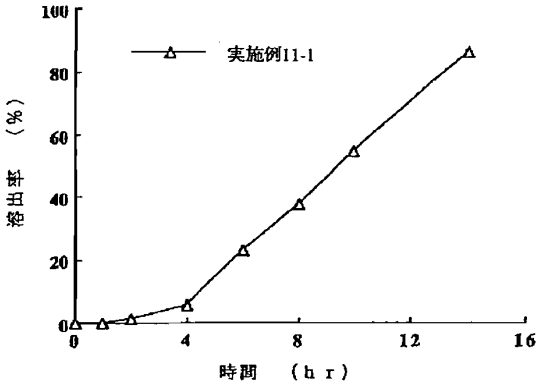


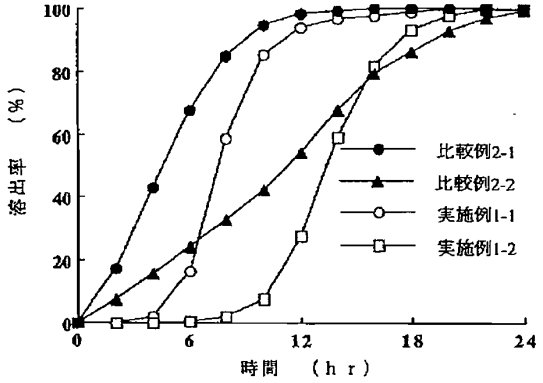
【図１０】



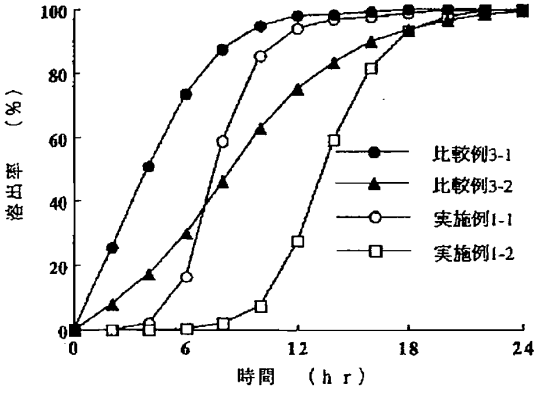
【図１１】



【図１２】



【図１３】



フロントページの続き

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	技術表示箇所
Ａ６１Ｋ　47/38		Ｄ		

【公報種別】特許法第１７条の２の規定による補正の掲載
【部門区分】第３部門第２区分
【発行日】平成１０年（１９９８）８月１８日

【公開番号】特開平７－６１９２２
【公開日】平成７年（１９９５）３月７日
【年通号数】公開特許公報７－６２０
【出願番号】特願平５－２１０４５３
【国際特許分類第６版】
A61K 9/32
9/52
47/32
47/38

【ＦＩ】
A61K 9/32
9/52 J
47/32 C
D
47/38 C
D

【手続補正書】
【提出日】平成８年１１月２０日
【手続補正１】
【補正対象書類名】明細書
【補正対象項目名】００３７
【補正方法】変更
【補正内容】
【００３７】実施例９
ジクロフェナクナトリウム１５０ｇとコーンスターチ１２９５ｇを混合した後、微粉砕した。ヒドロキシプロピルセルロース３３ｇをエチルアルコール６２７ｇに溶解した液を噴霧しながら、この粉砕末１０５１ｇをノンパレル１０３（球形白糖、粒径７１０－５００μｍ、フロイント産業（株）製）４００ｇに散布して転動造粒し、６０℃で４時間乾燥した後、１４メッシュ（目開き１．１９ｍｍ）を通過し３２メッシュ（目開き０．５０ｍｍ）を通過しないものを中心核とした。次に、この中心核５００ｇを流動層コーティング装置に入れ、素顆粒の重量増が８０％（実施例９－１）になるまで、オイドラギットＲＳ１２％、ジメチルポリシロキサン８％、軽質無水ケイ酸４％、グリセリン脂肪酸エステル１％、エチルアルコール７５％の組成のコーティング液を噴霧し、顆粒剤として本発明の放出開始制御型製剤を得た。

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 9/50, 9/20 — A3

(11) International Publication Number: WO 98/14168

(43) International Publication Date: 9 April 1998 (09.04.98)

(21) International Application Number: PCT/US97/16599

(22) International Filing Date: 16 September 1997 (16.09.97)

(30) Priority Data:

60/028,726	30 September 1996 (30.09.96)	US
60/030,514	12 November 1996 (12.11.96)	US
60/044,121	22 April 1997 (22.04.97)	US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

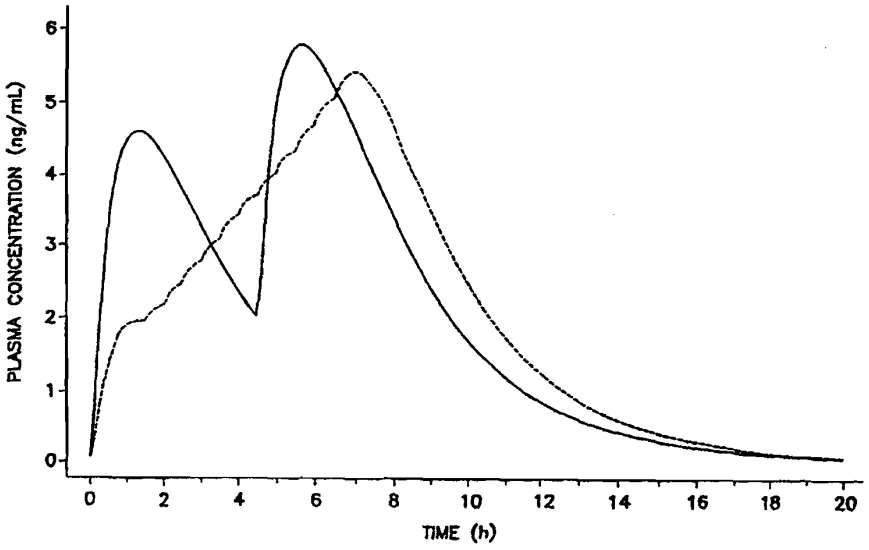
Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 30 July 1998 (30.07.98)

(54) Title: DOSAGE FORM PROVIDING A SUSTAINED AND ASCENDING DRUG RELEASE



(57) Abstract

A dosage form and a method are disclosed and claimed for administering a drug in a sustained and constantly ascending rate per unit time to provide an intended therapeutic effect while concomitantly lessening the development of unwanted effects.

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INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 97/16599

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/50 A61K9/20

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

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5 June 1998	12/06/1998

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2

INTERNATIONAL SEARCH REPORT

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PCT/US 97/16599

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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(11)Publication number : 09-267035
(43)Date of publication of application : 14.10.1997

(51)Int.Cl. B01J 2/16
B01J 2/00
B01J 2/28

(21)Application number : 08-248678
(22)Date of filing : 29.08.1996

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(72)Inventor : YANO YOSHIAKI
SUNADA KYUICHI

(30)Priority
Priority number : 08 37135 Priority date : 30.01.1996 Priority country : JP

(54) PRODUCTION OF NUCLEAR PARTICLE

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a process for production nuclear particles having a sharp grain size distribution and sufficient strength by executing granulation by controlling the liquid drops of a spray liquid to be sprayed in such a manner that the coarse liquid drops having specific grain sizes or above among these liquid drops attain specific vol.% or below while progressing coating.
SOLUTION: This process for producing the nuclear particles comprises executing granulation by spraying the spray liquid contg. a binder while forming a fluidized bed of ray material particles by using a combined type fluidized bed device accompanied with ≥1 kinds of rolling, stirring and jetting (including a Wurster type). In such a case, the viscosity of the spray liquid to be sprayed is ≤20 centipoises at 20° C and the granulation is executed while the coating is progressed by controlling the coarse liquid drops of the grain size ≥30μm among the liquid drops of the spray liquid to be sprayed to attain ≤10vol.%. The pharmaceuticals contain the resulted nuclear particles, the combined particles of the nuclear particles and functional blank materials and functional particles as well as combined particles. As a result, the nuclear particles having the sharp grain size distribution and the sufficient strength are produced. The nuclear particles are adequately usable as the nuclear particles for designing the combined particles by coating, addition working treatment, etc., on the particle surface by a wet process or dry process for the purposes of adding function, etc., thereto.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

CLAIMS

[Claim(s)]
[Claim 1] In the manufacture approach of the nuclear particle which performs a granulation while spraying the spray liquid containing a binder, forming the fluid bed of a raw material particle using rolling, stirring, and the compound-die fluid bed equipment accompanied by one or more sorts of a jet (the Wurster format is included) The manufacture approach of the nuclear particle characterized by corning advancing [control so that a rough drop with a particle size of 30 micrometers or more becomes below 10 volume % among the drops of the spray liquid with which the viscosity of the spray liquid sprayed is 20 or less centipoises, and is sprayed at 20 degrees C, and] coating.
[Claim 2] the manufacture approach of the nuclear particle characterize by control the amount of spraying of spray liquid in the manufacture approach of the nuclear particle which perform a granulation while spray the spray liquid containing a binder, form the fluid bed of a raw material particle using rolling, stirring, and the compound die fluid bed equipment accompanied by one or more sorts of a jet (the Wurster format be include) so that an exhaust-gas temperature become high 3 degrees C or more from the adiabatic saturation temperature under an equipment installation environment.
[Claim 3] The manufacture approach according to claim 2 characterized by controlling so that a rough drop with a particle size of 30 micrometers or more becomes below 10 volume % among the drops of the spray liquid sprayed.
[Claim 4] The manufacture approach according to claim 2 or 3 that the viscosity of spray liquid is 20 or less centipoises at 20 degrees C.
[Claim 5] claims 1-4 which are those in which spray liquid contains the SSL grade (viscosity is 2.0 to 2.9 centipoise under 20 degrees C with a 2-% of the weight water solution) of hydroxypropylcellulose as a binder at least -- either -- the manufacture approach of a publication.
[Claim 6] claims 1-5 whose ratios (d95/d5) of the particle size (d95) of 95 % of the weight of minus sieve passage accumulation to the particle size (d5) of 5 % of the weight of minus sieve passage accumulation of the last granulation object obtained are 3.0 or less -- either -- the manufacture approach of a publication.
[Claim 7] a claim -- the nuclear particle corned by the manufacture approach of a publication one to 6 either.
[Claim 8] The manufacture approach of the compound-ized particle characterized by making a nuclear particle compound-ize by making a coating coat form in the front face by spraying the solution containing a functional material and drying using a nuclear particle according to claim 7.
[Claim 9] The manufacture approach of the compound-ized particle characterized by making a nuclear particle compound-ize by blending the functional particle of a particle size smaller than this with a nuclear particle according to claim 7, applying mechanical consolidation and a shear to this, adhering and combining both.
[Claim 10] The compound-ized particle manufactured by the manufacture approach according to claim 8 or 9.
[Claim 11] Pharmaceutical preparation containing a compound-ized particle according to claim

10.

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the compound-ized particle obtained by the manufacture approach of the manufacture approach of the nuclear particle which has reinforcement more sharp [particle size distribution] in a detail, and sufficient, the nuclear particle obtained by the list by this manufacture approach, and the compound-ized particle using the nuclear particle, and this manufacture approach, and the pharmaceutical preparation containing these about the nuclear particle obtained by the manufacture approach list of a nuclear particle by this manufacture approach.
[0002]
[Description of the Prior Art] In recent years, the particle engineering which pursued the functionality of a particle by the advance of equipment etc. becomes possible, and positioning of a nuclear particle (heart matter) is very large in it. For example, by coating the surface layer of a nuclear particle (heart matter) with additives (basis), such as a material (functional material) which has functionality, such as emission control, and considering as multilayer structure etc., it is very useful to give functionality and it is used widely.
[0003] However, what is used as a nuclear particle (heart matter) is chosen from additives (basis) in many cases, and there is no example of having performed the particle design, using a principal component or a chief remedy as a nuclear particle not much. It is because it is required the mechanical strength which is extent which breaks at the time of that particle size distribution of a nuclear particle (heart matter) is sharp and coating actuation, or is not powdered, that it is a real ball as much as possible, etc., and this is considered to be the reason nil why such a technical difficulty is big.
[0004] Although it is conquerable to some extent about the problem of these reinforcement, a configuration, and particle size with after treatment, such as a powder cliff, especially about the sharpness of particle size distribution, it is not satisfactory, and considers as the difficult technical problem. Namely, although the granulation object which serves as a nucleus (heart) first by the general corning methods, such as the centrifugal corning method, the rolling corning method, a stirring mixing granulation method, the fluid bed corning method, the extrusion corning method, or a method of corning the compound die accompanied by these one or more sorts, is built Although the width of face of the particle size distribution is broadcloth therefore, the method of dividing this by the screen and preparing the particle of a required particle size as a nuclear particle is usual, time and effort is taken and there is a difficulty that productivity is low.
[0005] therefore, as an additive (basis) used widely for the application as a nuclear particle (heart matter) on an actual particle design for example, the spherical granulation which consists of white soft sugar and a starch system, a purified sucrose system, a lactose, a crystalline cellulose system, etc. like trade name Nonpareil (Freund Industrial make), although the spherical granulation of crystalline cellulose is similarly known like trade name cel FIA (Asahi Chemical Industry Co., Ltd. make) These are divided into a fraction with a desirable particle size of 150 micrometers or more by the screen after granulation, as already stated. It is a usual state to coat a case to build a layer by coating of a principal component or a chief remedy in the upper

(19)日本国特許庁（ＪＰ）　(12)公開特許公報（A）　(11)特許出願公開番号

特開平9－267035

(43)公開日　平成９年(1997)10月14日

(51)Int.Cl.[6]		識別記号	庁内整理番号	ＦＩ		技術表示箇所
Ｂ０１Ｊ	2/16			Ｂ０１Ｊ	2/16	
	2/00				2/00	Ｂ
	2/28				2/28	

審査請求　未請求　請求項の数11　ＦＤ　（全 9 頁）

(21)出願番号　特願平8－248678

(22)出願日　平成８年(1996)８月29日

(31)優先権主張番号　特願平8－37135

(32)優先日　平８(1996)１月30日

(33)優先権主張国　日本（ＪＰ）

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(54)【発明の名称】　核粒子の製造方法

(57)【要約】

【解決手段】転動、攪拌および噴流（ワースター形式を含む）の１種以上を伴う複合型流動層装置を用い、原料粒子の流動層を形成しつつ、結合剤を含むスプレー液を噴霧しながら造粒を行う核粒子の製造方法において、噴霧されるスプレー液の粘度が２０℃で２０センチポイズ以下であって、噴霧されるスプレー液の液滴のうち粒径３０μｍ以上の粗液滴が１０体積%以下になるように制御しコーティングを進行させながら造粒する核粒子の製造方法、得られた核粒子、核粒子と機能性素材・機能性粒子との複合化粒子、並びに複合化粒子を含有する製剤。

【効果】本発明によると、粒径分布がシャープで十分な強度を有する核粒子を製造することができる。本発明の核粒子は、機能性付加等の目的で湿式又は乾式で粒子表面にコーティング、付着加工処理等により複合化粒子を設計するための核粒子として好適に用いることができる。

1

【特許請求の範囲】

【請求項1】　転動、攪拌および噴流（ワースター形式を含む）の1種以上を伴う複合型流動層装置を用い、原料粒子の流動層を形成しつつ、結合剤を含むスプレー液を噴霧しながら造粒を行う核粒子の製造方法において、噴霧されるスプレー液の粘度が20℃で20センチポイズ以下であって、噴霧されるスプレー液の液滴のうち粒径30μm以上の粗液滴が10体積%以下になるように制御しコーティングを進行させながら造粒することを特徴とする核粒子の製造方法。

【請求項2】　転動、攪拌および噴流（ワースター形式を含む）の1種以上を伴う複合型流動層装置を用い、原料粒子の流動層を形成しつつ、結合剤を含むスプレー液を噴霧しながら造粒を行う核粒子の製造方法において、排気温度が装置設置環境下の断熱飽和温度より3℃以上高くなるようにスプレー液の噴霧量が制御されていることを特徴とする核粒子の製造方法。

【請求項3】　噴霧されるスプレー液の液滴のうち、粒径30μm以上の粗液滴が10体積%以下になるように制御することを特徴とする請求項2記載の製造方法。

【請求項4】　スプレー液の粘度が20℃で20センチポイズ以下である請求項2又は3記載の製造方法。

【請求項5】　スプレー液が少なくともヒドロキシプロピルセルロースのSSLグレード（粘度が2重量%水溶液で20℃下で2．0～2．9センチポイズ）を結合剤として含むものである請求項1～4いずれか記載の製造方法。

【請求項6】　得られる最終造粒物の篩下通過累積5重量%の粒径（d_5）に対する篩下通過累積95重量%の粒径（d_{95}）の比（d_{95}/d_5）が、3．0以下である請求項1～5いずれか記載の製造方法。

【請求項7】　請求項1～6いずれか記載の製造方法により造粒された核粒子。

【請求項8】　請求項7記載の核粒子を用いてその表面に機能性素材を含む溶液を噴霧し乾燥することでコーティング皮膜を形成させることにより核粒子を複合化させることを特徴とする複合化粒子の製造方法。

【請求項9】　請求項7記載の核粒子にこれより小さな粒径の機能性粒子を配合し、これに機械的な圧密、剪断をかけて両者を付着、結合させることにより核粒子を複合化させることを特徴とする複合化粒子の製造方法。

【請求項10】　請求項8または9記載の製造方法により製造された複合化粒子。

【請求項11】　請求項10記載の複合化粒子を含有する製剤。

【発明の詳細な説明】

【0001】

【発明の属する技術分野】本発明は、核粒子の製造方法並びに該製造方法により得られる核粒子に関し、より詳細には、粒径分布がシャープで十分な強度を有する核粒子の製造方法、並びに該製造方法により得られる核粒子、その核粒子を用いた複合化粒子の製造方法、該製造方法により得られる複合化粒子、これらを含有する製剤に関する。

2

【0002】

【従来の技術】近年、装置等の進歩により粒子の機能性を追求した粒子設計技術が可能となり、その中で核粒子（芯物質）の位置づけは極めて大きくなっている。例えば、核粒子（芯物質）の表面層に放出制御等の機能性を有する素材（機能性素材）などの添加剤（基剤）をコーティングし多層構造等とすることにより、機能性をもたせることは極めて有用であり汎用されている。

【0003】しかしながら、核粒子（芯物質）として用いるものは添加剤（基剤）の中から選択されることが多く、主成分もしくは主薬を核粒子として用いて粒子設計を行ったという例はあまりない。これは核粒子（芯物質）は粒径分布がシャープであることとコーティング操作時に割れたり粉化したりすることがない程度の機械的強度、また出来るだけ真球であること等が要求されるからであり、このような技術的難点が大きな理由と考えられる。

【0004】これら強度、形状、粒径の問題については粉がけ等の後処理によりある程度克服できるとはいうものの、特に粒径分布のシャープさについては満足のいくものではなく難しい課題とされている。即ち、遠心造粒法、転動造粒法、攪拌混合造粒法、流動層造粒法、押し出し造粒法、あるいはこれらの1種以上を伴う複合型の造粒法等の一般的造粒法によりまず核（芯）となる造粒物をつくるが、その粒径分布の幅がブロードであるが故に、これを篩により分けて必要な粒径の粒子を核粒子として調製する方法が通常であり、手間がかかり生産性が低いという難点がある。

【0005】従って、実際の粒子設計の上で核粒子（芯物質）としての用途で汎用される添加剤（基剤）として、例えば商品名ノンパレル（フロイント産業（株）製）の如く白糖・デンプン系、精製白糖系、乳糖・結晶セルロース系等よりなる球状顆粒や、同じく商品名セルフィア（旭化成工業（株）製）の如く結晶セルロースの球状顆粒が知られているが、これらは既に述べたように造粒後、篩により150μm以上の望ましい粒径の画分に分けられたものである。これら核粒子（芯物質）の上層に主成分もしくは主薬のコーティングにより層をつくり、さらにその上に放出制御する目的の場合には、機能性を有する添加剤（基剤）をコーティングして粒子設計するのが常である。この場合、適用する主成分もしくは主薬の含量に限度があるのが難点であり、これが粒子設計上の制限となり、ややもすれば得られた設計粒子もしくは製剤のサイズが大きくなる傾向がみられる。

【0006】仮に主成分もしくは主薬から核粒子を調製することが可能となれば設計粒子もしくは製剤中の主成

分もしくは主薬の含量を高含量とすることが可能であり、また必要に応じて剤形を小型化することが可能となる大きなメリットがある。

【0007】また主成分もしくは主薬が水溶性の場合には、それほど粒子を細かく粉砕する必要はないが、水に難溶性の場合には溶出性／溶解性を改善する意味で粒子の比表面積を大きくする目的で粉砕により粒子を細かくすることがなされる。この場合に核粒子（芯物質）調製を試みることは1次粒子が小さいことから極めて困難であるとともにその要望は高い。本発明者らはこのような観点から核粒子（芯物質）の調製に関し、鋭意検討を行った。

【0008】

【発明が解決しようとする課題】既に本発明者は、粒径が0．2mm以下の微細な造粒物を調製するために転動攪拌流動層造粒法およびワースター噴流層造粒法で高粘性、低粘性の結合剤をスプレー液組成として用いて検討を行い、低粘性の結合力の弱い結合剤を用いることで、出来るだけ粒子表面をコーティングしつつ造粒を行う操作をコントロールしやすいことを見出し、微細な造粒物の製造方法として出願を行っている（WO94／08709号公報）。

【0009】高粘性（高結合力）の結合剤を使用する場合、必要なスプレー液使用量も少なく、造粒の所要時間も短いメリットがあるが、一部急激な造粒が進行し粒子径の大きい粒子や団塊の産生等のため、その粒径分布のシャープさや目的とする粒径の粒子の収率について改善の余地がある。一方、低粘性（低結合力）の結合剤については必要なスプレー液使用量も多く、造粒の所要時間も長くその間に造粒物が物理的衝撃により粉化しやすい欠点はあるが、造粒をできるだけ抑制する意味で操作性は良い。さらに結合剤の展延性、浸透性が良好であるならば粒子表面を効果的にコーティングしながら造粒が進行し、望ましい微細粒子としての特性を有していることを見出している（平成6年度第11回製剤と粒子設計シンポジウム講演要旨集、p165～170、平成7年度日本薬剤学会第11年会講演要旨集、p94～95）。

【0010】しかしながら、まだ粒子径分布のシャープさにおいては存在する微粉量のため、核粒子（芯物質）としては改善の余地が残されていた。従って、本発明の目的は、粒径分布がシャープで十分な核粒子（芯物質）としての特性を有する造粒物の製造方法、及びその製造方法により得られる核粒子（芯物質）を提供することにある。またこの核粒子（芯物質）を用いてその表面にさらにコーティング等の加工処理を施して複合化粒子を製造することができる。

【0011】

【課題を解決するための手段】このような観点から、これ迄の技術を発展させ主成分もしくは主薬から核粒子（芯物質）を調製することのできる可能性と有用性について、本発明者らは鋭意検討を行った結果、以下の如く本発明に到達した。即ち、転動攪拌流動層造粒法およびワースター噴流層造粒法での造粒操作を考えたとき、結合剤を含むスプレー液の粗液滴の存在が造粒の支配因子とならないよう、出来るだけシャープな粒径分布を有する微小液滴によりコーティングできるよう制御しつつ造粒を進行させる必要がある。そのためには、結合剤の選択とスプレー液の送液速度、スプレー空気風量の選択が大きな影響を与えること、また装置槽内のスプレー液の噴霧による給気温度の断熱冷却曲線に従った低下の程度を製品温度もしくは排気温度としてコントロールしながら、必要量の結合剤を噴霧することが極めて重要な因子であることを見出した。

【0012】即ち、本発明の要旨は、（1）　転動、攪拌および噴流（ワースター形式を含む）の1種以上を伴う複合型流動層装置を用い、原料粒子の流動層を形成しつつ、結合剤を含むスプレー液を噴霧しながら造粒を行う核粒子の製造方法において、噴霧されるスプレー液の粘度が20℃で20センチポイズ以下であって、噴霧されるスプレー液の液滴のうち粒径30μm以上の粗液滴が10体積%以下になるように制御しコーティングを進行させながら造粒することを特徴とする核粒子の製造方法、（2）　転動、攪拌および噴流（ワースター形式を含む）の1種以上を伴う複合型流動層装置を用い、原料粒子の流動層を形成しつつ、結合剤を含むスプレー液を噴霧しながら造粒を行う核粒子の製造方法において、排気温度が装置設置環境下の断熱飽和温度より3℃以上高くなるようにスプレー液の噴霧量が制御されていることを特徴とする核粒子の製造方法、（3）　噴霧されるスプレー液の液滴のうち、粒径30μm以上の粗液滴が10体積%以下になるように制御することを特徴とする前記（2）記載の製造方法、（4）　スプレー液の粘度が20℃で20センチポイズ以下である前記（2）又は（3）記載の製造方法、（5）　スプレー液が少なくともヒドロキシプロピルセルロースのSSLグレード（粘度が2重量%水溶液で20℃下で2．0～2．9センチポイズ）を結合剤として含むものである前記（1）～（4）いずれか記載の製造方法、（6）　得られる最終造粒物の篩下通過累積5重量%の粒径（d_5）に対する篩下通過累積95重量%の粒径（d_{95}）の比（d_{95}／d_5）が、3．0以下である前記（1）～（5）いずれか記載の製造方法、（7）　前記（1）～（6）いずれか記載の製造方法により造粒された核粒子、（8）　前記（7）記載の核粒子を用いてその表面に機能性素材を含む溶液を噴霧し乾燥することでコーティング皮膜を形成させることにより核粒子を複合化させることを特徴とする複合化粒子の製造方法、（9）　前記（7）記載の核粒子にこれより小さな粒径の機能性粒子を配合し、これに機械的な圧密、剪断をかけて両者を付着、結合させることにより核粒子を複合化させることを特徴とする複合

化粒子の製造方法、（１０）　前記（８）または（９）記載の製造方法により製造された複合化粒子、（１１）　前記（１０）記載の複合化粒子を含有する製剤、に関する。

【００１３】

【発明の実施の形態】本発明の核粒子（芯物質）の製造方法は、転動、攪拌および噴流（ワースター形式を含む）の１種以上を伴う複合型流動層装置を用い、原料粒子の流動層を形成しつつ、低粘性、低結合性、展延性、浸透性を有する結合剤を含むスプレー液を噴霧しながらコーティングしつつ造粒を進行させる核粒子の製造方法において、噴霧されるスプレー液の液滴のうち粒径３０μｍ以上の粗液滴が１０体積％以下になるように制御されていることを特徴とするものであり、さらには排気温度が装置設置環境下の断熱飽和温度より高くなるよう、３℃以上、好ましくは４℃以上高くなるようにスプレー液の噴霧量が制御されていることを特徴とするものである。また、本発明の複合化粒子の製造方法は、本発明の核粒子の製造方法により得られた核粒子を用いその表面に機能性素材を含む溶液を噴霧し乾燥することでコーティング皮膜を形成させることにより、あるいは本発明の核粒子にこれより小さな粒径の機能性粒子を配合し、これに機械的な圧密、剪断をかけて両者を付着、結合させることにより製造することができる。本明細書においては、複合化粒子とは本発明の核粒子の表面が機能性素材（粒子）で処理された粒子を意味する。また、本明細書において、本発明の核粒子とは原料粒子（一次粒子）が造粒された造粒体を意味し、各種用途における芯物質として使用できるものであることから、「核粒子（芯物質）」と表示している。

【００１４】本発明の核粒子の製造方法に用いられる複合型流動層装置は、転動、攪拌および噴流（ワースター形式を含む）の１種以上を伴う複合型流動層装置であれば特に限定されることなく、公知の装置が使用できる。

【００１５】具体的には、例えば、ワースター（グラット社製）、スパイラフロー（フロイント産業（株）製）、マルチプレックス（パウレック（株）製）、スピラコータ（岡田精工（株）製）、アグロマスター（細川ミクロン（株）製）、ニューマルメライザー（不二パウダル（株）製）等が用いられる。

【００１６】本発明における具体的な造粒操作を簡単に述べると、例えば、あらかじめ粉砕もしくは未粉砕のかたちでの原料粒子（例えば薬物等）を上記の複合型流動層造粒装置に仕込み、さらに装置内での流動性確保の目的でさらにアエロジル等の流動化改善剤を適宜加えた後、原料粒子の流動層を形成しつつ、低粘性、低結合性、良展延性の特性を備えた結合剤として例えばヒドロキシプロピルセルロースのＳＳＬグレード（ＨＰＣ－ＳＳＬ；２０℃での２重量％水溶液の粘度が２．０～２．９センチポイズ）を少なくとも適当な濃度で含むスプレー液を必要量噴霧すればよい。

【００１７】このときスプレーの方式は底部から少し上の位置から下部にむけてのトップスプレーでも、底部から上部にむけてのボトムスプレーでも、また底部において接線方向にむけてのタンジェンシャルスプレーでもかわまないが、各々それぞれの特徴が一般的にみられるので、核粒子（芯物質）設計の対象とする粒子の粒径に応じてボトムまたはタンジェンシャルまたはトップのスプレー様式を選択すればよい。例えば粒径の数十μｍのより小さな粒子で粒径分布のシャープな粒子を得ようとすればボトムまたはタンジェンシャルスプレー様式を選択すればよい。勿論種々の様式を組み合わせて噴霧することもできる。

【００１８】また、スプレー液滴径が微小な程、且つその分布がシャープな程、コーティングしながら徐々に造粒してシャープな粒径分布を有する核粒子（芯物質）を調製するうえで有利なので、適当なスプレー液組成と濃度、スプレー風量を選択すればよい。勿論、スプレーノズルの性能がスプレー液滴に影響を与えるが、通常の装置に用いられているものを吟味して選択すればよい。

【００１９】なお、原料粒子（コーティングされたものや造粒進行中のものを含む）の流動層を形成するためには通常、加温された空気等が用いられる。

【００２０】原料粒子に関しては特に限定されないが、粉砕等により適度な粒径に調製された薬剤等が用いられる。本発明においては粒径分布が１０μｍ以下のシャープな粒度成分を有するようあらかじめ粉砕しておいた方が、造粒物の粒子表面の平滑度が高いという顕著な効果が得られる。勿論、造粒対象である原体が比較的そろった粒径を有する等の理由で粒径の大きい核粒子（芯物質）を調製するうえでは粉砕しないで用いても支障がない場合もあり得る。

【００２１】結合剤に関しては低粘性、低結合力、展延性、及び浸透性等の特性を有することが重要であり、このような機能を有するものとして、ヒドロキシプロピルセルロース、ポリビニルピロリドン、ヒドロキシプロピルメチルセルロース等を適当な希釈や添加剤等の添加により適宜調製して使用することが考えられるが、ヒドロキシプロピルセルロースのＨＰＣ－ＳＳＬ（日本曹達（株）製；２０℃での２重量％の水溶液の粘度が、２．０～２．９センチポイズ）が好ましい。

【００２２】スプレー液として通常用いる濃度は、上記目的の機能性や操作性の観点から粘性の指標として２０℃での粘度が２０センチポイズ以下であることが望ましく、１５センチポイズ以下であることがより望ましい。例えばコーティング効率と造粒の所要時間等との兼ね合いで５～８重量％程度のＨＰＣ－ＳＳＬ水溶液（２０℃での粘度が６～１５センチポイズ）が好ましく用いられる。

【００２３】勿論、上記の結合剤をエタノール等の溶媒

に溶解して用いることも可能であるが、操作性等から水系で使用することが望ましい。また種々の目的で界面活性剤等の添加剤（基剤）をスプレー液に添加することもできるが、スプレー液の液滴径、粘度、結合力、展延性等の上記目的の機能性を損なわない程度の性質、範囲であることが必要である。

【００２４】また目的や操作性等の理由からＨＰＣ－ＳＳＬ水溶液と種々の目的の添加剤（基剤）を含むＨＰＣ－ＳＳＬ水溶液を適宜使い分けすることも可能である。また、連続的もしくは段階的にスプレー液の成分や組成を変えることもできる。

【００２５】スプレー液滴の液滴径分布に関しては、本発明では噴霧されるスプレー液の液滴のうち、粒径３０μｍ以上の粗液滴が１０体積％以下になるように制御されていることが好ましく、より好ましくは３０μｍ以上の粗液滴が８体積％以下に制御されていることである。このようにスプレー液滴中の粗液滴の割合を低くして出来るだけシャープな粒径分布を有する微小液滴とすることによりコーティングを行いながら造粒を進行させ、得られる核粒子（芯物質）の粒径分布をシャープにすることができる。

【００２６】このようにスプレー液の液滴径を制御するには、上記のように結合剤の種類や濃度等によりスプレー液の粘度を調製したり、スプレー液の送液速度やスプレー空気風量を調整したりすること等により行うことができる。

【００２７】上記粘度のＨＰＣ－ＳＳＬ水溶液を使用する場合、粗液滴の割合はそれほど高いことはなく、仮に数体積％程度の粗液滴が存在しても結合力がそれほど強くないので造粒の支配因子とはならない。例えばＨＰＣ－ＳＳＬの５重量％水溶液においては、スプレー空気風量が３０～３５Ｌ／分の条件下で、スプレー液の送液速度の調整により液滴径の平均粒子径（d_{50}）は約１０μｍ前後で粒径３０μｍ以上の粗液滴は５～６体積％以下とすることができる。

【００２８】なお、本発明におけるスプレー液の液滴径は、レーザー光散乱式粒度分布測定装置（例えば実施例では東日コンピューターアプリケーションズ（株）製，ＬＳＤＡ－２４００Ａを使用）により測定されたものをさす。

【００２９】勿論、このときのスプレー液の送液速度は流動層内の温度コントロールと密接な関係を有し造粒に極めて大きな影響を与える。即ち、造粒操作時の環境（温度、湿度）で決まる断熱飽和温度への断熱冷却曲線にそった装置の入口の送風加熱空気温度から製品温度、排気温度への冷却について検討、考察を試みると、排気温度が断熱飽和温度より高くなるにつれ、その時のスプレー液は粒子へのコーティング性の付加の程度を高めながら送液され造粒が進行することが見出された。さらに充分なコーティングが進行しつつ造粒されるためには排気温度が断熱飽和温度より少なくとも３℃以上、好ましくは４℃以上となるようスプレー液が供給される必要があることを見出した。あまり排気温度が高過ぎるとスプレー液の送液が遅いことを示し、効率的ではなく、スプレー液の液滴の乾燥度が高まり粒子への噴霧および付着が均一に起こらなくなり、不都合をもたらす。従って、排気温度は断熱飽和温度より３～７℃、好ましくは４～７℃高いことがより好ましい。排気温度が断熱飽和温度より低いとスプレー液の供給が過剰であり流動層内の粒子が濡れすぎて流動性が低下し団塊等が生成しトラブルの原因となる。

【００３０】勿論、核粒子（芯物質）としての粒径分布のシャープさは上記の低粘性、低結合力、展延性、及び浸透性を有する適当な結合剤を用いることで、上記の操作条件のもとに断熱飽和温度より高い温度でコーティング造粒することにより主薬をベースとした粒径分布のシャープな粒子表面の平滑度の高い核粒子（芯物質）を得ることができる。最も好ましい均一なコーティング造粒を可能とするには、断熱飽和温度より３～７℃、好ましくは４～７℃高く制御する必要がある。即ち、本発明では、低粘性、低結合力、展延性、及び浸透性を有する結合剤、好ましくは、ＨＰＣ－ＳＳＬを用いて粘度が２０℃で２０センチポイズ以下のスプレー液濃度で排気温度が断熱飽和温度より高くなるよう、好ましくは３～７℃、さらに好ましくは４～７℃高くなるよう送液速度を調整し必要量を噴霧することで、より粒径分布のシャープなかつ粒子表面の平滑度の高い粒子強度のある核粒子（芯物質）を製造することができる。このように底部のディスクローターの攪拌により粉体の転動、攪拌による造粒と粉化のバランスがあるとは言え、断熱飽和温度を考慮した排気温度のコントロールは重要な因子である。もしこのような円滑な排気温度制御がなされなければ団塊ができたりして不均一な造粒が進行することになり、本発明の目的とする核粒子を製造することができなくなる。

【００３１】ローターの攪拌速度については、それを適宜調整することにより造粒粒子の粒径分布を調整できる。一般に攪拌速度が高いとより微細な方向に粒径をシフトさせることが可能であるが、このときスプレー条件を結合剤（例えば、ＨＰＣ－ＳＳＬ）濃度とスプレー量の視点で考慮することにより微粉の発生を阻止することができ粒径分布をシャープに保つことができる。

【００３２】スプレー液の噴霧速度は自ずから上記因子に支配されることになり、低粘性、低結合性で良好な展延性、浸透性を有する結合剤（例えば、ＨＰＣ－ＳＳＬ）のスプレー溶液を噴霧することで０．２～０．３ｍｍ以上の粒子成長は抑制され、むしろ底部でのローターによる攪拌、転動作用もしくは流動作用による粉化とのバランスはあるが、微粉をコーティング造粒する方向にむける結果となり粒径分布をシャープにする上で良好な

結果をもたらすことになる。

【００３３】原料粒子や造粒過程の粒子は底部でディスクローターの回転による攪拌、転動が行われる装置の場合には、底部で攪拌、転動および上部に向かっての流動や下部への下降と動きながらスプレーと流動乾燥を繰り返していくが、底部のディスクローターの回転速度を高くしたり流動層内の空気量をあげることで粒子運動はより活発になり、より微細な方へ粉化がおこる。このような複雑な現象をコントロールすることで希望の粒径の粒子を核粒子（芯物質）として設計、提供できる。

【００３４】このように、コーティング、攪拌、造粒、流動、粉化の過程がバランスよく進行することで、表面の平滑度の高い強度のある粒径分布のシャープな微細な核粒子（芯物質）を調製することができる。

【００３５】本発明で核粒子（芯物質）として得られる最終造粒物の篩下通過累積５重量%の粒径（d_5）に対する篩下通過累積９５重量%の粒径（d_{95}）の比（d_{95}／d_5）は３．０以下、好ましくは２．８以下であり、さらに好ましくは２．５以下であり、粒径分布はシャープである。

【００３６】本発明者による従来の技術では平均粒子径１００μm付近の領域の粒子設計においては、粉化（微粉）が多く、７５μm以下の造粒粒子の割合は１５～３０重量%程度を占めていたが、核粒子（芯物質）をめざした本発明造粒品では１５重量%以下と極めて改善されており、核粒子に適当なシャープな粒径分布を有している。

【００３７】勿論、さらに粒径の小さな核粒子（芯物質）を調製しようと思えば、粉砕等で出来るだけ小さくした１次粒子に対して本発明の方法を用い、造粒終点を調節することでさらに１００μm以下の核粒子（芯物質）を調製することが可能であり、これを用いて微小な複合化粒子を設計できる。またより大きな粒径の範囲の核粒子（芯物質）を調製しようと思えば、適当な粒径の原料粒子を用いたり本発明の方法の造粒終点をさらに延長することで、乾燥や流動による粉化と造粒過程のバランスを保ちながら適度な所望する粒径範囲の核粒子を得ることができる。

【００３８】このようにして得た核粒子（芯物質）は、複合型の流動層造粒装置（攪拌転動流動層装置、ワースター流動層装置）や遠心流動層造粒装置等を用いて核粒子（芯物質）の表面にさらに種々の目的の機能性をもった添加剤（機能性素材）を含む溶液を噴霧することでコーティング皮膜を形成させ、またはより小さな粒径の機能性粒子を乾式で機械的に圧密、剪断をかけて核粒子（芯物質）の表面に皮膜を形成させて本発明の複合化粒子を製造することができる。即ち、本発明において複合化粒子とは、核粒子の表面に機能性素材をコーティングしたものや、機能性粒子を付着させたものを意味する。複合化粒子の製造に用いられる機能性素材または機能性粒子としては、フィルムコーティング性の機能をもったもの、腸溶性コーティング性の機能をもったもの、胃溶性コーティング性の機能をもったもの、徐放性コーティング性の機能をもったもの、苦味マスキングコーティング性の機能をもったものなどが挙げられるが、本発明にいう機能とは上記のような機能のみに限定されず、糖衣用、光沢用などの機能をも含む広い概念である。

【００３９】複合化粒子を製造する場合の装置として、機能性素材を含む溶液を噴霧することでコーティング皮膜を形成させる場合、上記の如く転動、攪拌および噴流（ワースター形式を含む）の１種以上を伴う複合型流動層装置であれば特に限定されることはなく、核粒子（芯物質）を製造した装置と同じものを使うことができ、同一装置内で製造できるメリットがある。勿論、複合型流動層装置により核粒子（芯物質）を製造後に上記の如くの遠心流動層造粒装置を用いて複合化粒子を調製してもよいし、乾式の複合化装置を用いて調製することもできる。このような乾式の複合化装置としては、メカノフュージョンシステム装置（ホソカワミクロン（株）製）、ハイブリダイゼーションシステム装置（奈良機械（株）製）、シータコンポーザー（徳寿工作所（株）製）等が挙げられ、遠心流動層造粒装置としてはＣＦ－グラニュレーター（フロイント産業（株）製）が挙げられる。実際、転動複合型装置マルチプレクス（パウレック（株）製）を用いた湿式複合化およびシータコンポーザー（徳寿工作所（株）製）を用いた乾式複合化の実施例からも本発明造粒品の核粒子（芯物質）としての妥当性が確認された。

【００４０】本発明はまた、このようにして製造された複合化粒子を含有する製剤をも含む。かかる製剤としては、例えば、速溶性・速吸収性の製剤や徐放性・持続性の製剤等が含まれる。また経口製剤の観点だけではなく、その複合化粒子の粒径によっては、注射や点鼻投与、経肺吸入投与等の用途として利用が可能な製剤をも含むものである。

【００４１】核粒子（芯物質）製造のうえで原料粒子の粒径分布はシャープであることが必要であるが、そのための造粒対象の原体については造粒目的とする粒径より小さな適当な粒径を有するものであれば別に制限されるものではない。しかし、粉砕等の手段によりできるだけ微細な粒子に粒径を揃えることは転動攪拌造粒法においてコーティング造粒操作による造粒粒子表面の平滑度を保つ上で重要なことである。即ち、たとえ造粒粒子の真球度を高めることができなくとも表面の平滑度を高めることは表面に加工性をもたらす核粒子（芯物質）としての必要な特性になる。

【００４２】

【実施例】以下、実施例および比較例により本発明をさらに詳しく説明するが、本発明はこれらの実施例等によりなんら限定されるものではない。実施例１～２と比較

例1は、原料粒子が微細でない場合であり、スプレー液の微小液滴が粒径の大きい原料粒子の表面のコーティングに有効に働いてコーティング造粒が進行している（実施例1～2）が、その排気温度が断熱飽和温度に接近している場合には原料粒子が大きいために団塊が生成しやすい（比較例1）ことを示している。排気温度が断熱飽和温度より少なくとも3℃高い場合にシャープな粒径分布（d_{95}／d_s の比が3．0以下）の造粒物が得られている。

【0043】実施例3～4、比較例2は原料粒子が微細な場合であり、スプレー液の微小液滴が微細な原料粒子と衝突もしくは原料粒子を抱え込むかたちで造粒核が形成され少しずつ表面のコーティング造粒が進行し粒子が成長する例を示している。即ち、比較例2では実施例3と同一のスプレー液組成でほぼ同一の噴霧量と給気温度で造粒を行っているが、その排気温度が断熱飽和温度により近いことでその生成した造粒物の比較品IIの平均粒子径およびd_{95}／d_s の比が実施例3の本発明造粒品IIIよりも高い数値になっていることを示している。実施例3では断熱飽和温度と排気温度との差も3℃以上と大きくなり、造粒よりもコーティングの方に有利に働きながら十分なコーティングをしつつ造粒が進行していることを反映している。即ち、本発明造粒品III は比較品IIと比べて粒子がしまっていることが示されている。また実施例4は最初にＨＰＣ－ＳＳＬ7％濃度で断熱飽和温度付近でコーティング造粒を進め、さらに途中からＨＰＣ－ＳＳＬ5％濃度で断熱飽和温度より3～5℃程度高い温度で十分なコーティングを進行させつつ造粒によるシャープな粒径分布を有する本発明造粒品IVを得ている例を示している。実施例5～6では本発明造粒品を核粒子（芯物質）として用いた粒子の複合化の例を示した。

【0044】実施例1

1ｋｇの局方エテンザミド（粒径75μm以下が85重量%以上；150μm以上が2重量%以下）に対して20ｇのアエロジル＃200（日本アエロジル工業（株）製）を添加し転動流動層造粒装置、スピラコータ（岡田精工（株）製）に投入し、60℃に加温した12m^3／ｈｒの空気量を流動層内に送風しながら底部で180ｒｐｍの回転速度でディスクローターを回転し、粉体を転動かつ流動させた。このときの装置のおかれている外部環境下での断熱飽和温度は30℃であった。60℃の温風がスプレーにより断熱冷却曲線に沿って冷却されたときの排気温度が少なくとも34℃以上は確保できるよう5．8～6．5ｇ／分のスプレー速度でトップスプレーで噴霧を行った。スプレーの空気風量は30～35Ｌ／分であった。スプレー液の組成はステップ様式で段階的に変化させた。段階的に用いたスプレー液の組成およびスプレー量は順次、以下のとおりの①ＨＰＣ－ＳＳＬ8重量%濃度で250ｇスプレー、②ＨＰＣ－ＳＳＬ8重量%、添加剤の親水性界面活性剤の蔗糖脂肪酸エステル（ＤＫエステルＦ－160）0．5重量%濃度で210ｇスプレー、③ＨＰＣ－ＳＳＬ8重量%濃度で240ｇスプレーであった。このようにして中間造粒品を得たが、さらにＨＰＣ－ＳＳＬ5重量%濃度で400ｇスプレーを行い、造粒を終了した時点で、本発明造粒品Ｉを得た。本発明造粒品Ｉは中間造粒品と比べて造粒プロセスで流動しつつ粉化が多少おこっていることで、より小さな粒径の方にシフトしていたが、これは低濃度の結合剤に切り換えた効果と考えられる。排気温度は34～35℃であった。

【0045】ロボットシフター（セイシン企業（株）製、ＲＰＳ－85）による分析から本発明造粒品Ｉは約90重量%程度の粒子が粒径75～200μmの間に分布していた（中間造粒品；d_{50} 160μm、本発明造粒品Ｉ；d_{50} 114μm、d_{95}／d_s 比は約2．6であった）。

【0046】実施例2

800ｇの局方エテンザミド（粒径75μm以下が85重量%以上；150μm以上が2重量%以下）に対して16ｇのアエロジル＃200（日本アエロジル工業（株）製）を添加し転動流動層造粒装置、スピラコータ（岡田精工（株）製）に投入し、60℃に加温した12m^3／ｈｒの空気量を流動層内に送風しながら底部で140ｒｐｍの回転速度でディスクローターを回転し、粉体を転動かつ流動させた。このときの装置のおかれている外部環境下での断熱飽和温度は32℃であった。60℃の温風がスプレーにより断熱冷却曲線に沿って冷却されたときの排気温度が少なくとも36℃以上は確保できるよう5ｇ／分のスプレー速度でトップスプレーで噴霧を行った。スプレーの空気風量は30～35Ｌ／分、排気温度は36～37℃であった。スプレー液の組成はＨＰＣ－ＳＳＬ5重量%濃度で1700ｇの噴霧を行った時点で造粒を終了し、本発明造粒品IIを得た。本発明造粒品IIの平均粒子径（d_{50}）は144μmであった。d_{95}／d_s 比は約2．5であった。

【0047】比較例1

800ｇの局方エテンザミド（粒径75μm以下が85重量%以上；150μm以上が2重量%以下）に対して16ｇのアエロジル＃200（日本アエロジル工業（株）製）を添加し転動流動層造粒装置、スピラコータ（岡田精工（株）製）に投入し、60℃に加温した12m^3／ｈｒの空気量を流動層内に送風しながら底部で140ｒｐｍの回転速度でディスクローターを回転し、粉体を転動かつ流動させた。このときの装置のおかれている外部環境下での断熱飽和温度は33℃であった。60℃の温風がスプレーにより断熱冷却曲線に沿って冷却されたときの排気温度は34～36℃であり、6ｇ／分のスプレー速度でトップスプレーで噴霧を行った。スプレーの空気風量は30～35Ｌ／分であった。スプレー液の組成はＨＰＣ－ＳＳＬ5重量%濃度で1250ｇの噴

霧を行った時点で造粒を終了し、比較品Ｉを得た。断熱飽和温度より高めに操作したが原料粒子が微粉砕品でないためか、平均粒子径（d_{50}）は１２２μｍであり、粒径の大きい造粒体の生成がみられ粒径分布のシャープさの限界（d_{95}／d_5 比は１０以上）が推察された。

【００４８】実施例３

局方エテンザミド（粒径７５μｍ以下が８５重量％以上；１５０μｍ以上が２重量％以下）を粉砕することにより得たエテンザミド微粉砕粒子（平均粒子径５μｍ以下）５００ｇに対して１０ｇのアエロジル＃２００（日本アエロジル工業（株）製）を添加し、転動流動層造粒装置、マルチプレックス（パウレック（株）製）に投入し、６０℃に加温した３６m^3／ｈｒの空気量を流動層内に送風しながら底部で３００ｒｐｍの回転速度でディスクローターを回転し、粉体を転動かつ流動させた。このときの装置のおかれている外部環境下での断熱飽和温度は２３℃であった。６０℃の温風がスプレーにより断熱冷却曲線に沿って冷却されたときの排気温度は２６～２８℃であり、８ｇ／分のスプレー速度でトップスプレーで噴霧した。スプレーの空気風量は２０Ｌ／分、スプレー液の組成はＨＰＣ－ＳＳＬ７重量％濃度で９９０ｇの噴霧を行った時点で造粒を終了し、本発明造粒品III を得た。本発明造粒品III の平均粒子径（d_{50}）は１１７μｍであり、d_{95}／d_5 比は約２．８であった。

【００４９】比較例２

局方エテンザミド（粒径７５μｍ以下が８５重量％以上；１５０μｍ以上が２重量％以下）を粉砕することにより得たエテンザミド微粉砕粒子（平均粒子径５μｍ以下）５００ｇに対して１０ｇのアエロジル＃２００（日本アエロジル工業（株）製）を添加し、転動流動層造粒装置、マルチプレックス（パウレック（株）製）に投入し、６０℃に加温した３６m^3／ｈｒの空気量を流動層内に送風しながら底部で３００ｒｐｍの回転速度でディスクローターを回転し、粉体を転動かつ流動させた。このときの装置のおかれている外部環境下での断熱飽和温度は２３℃であった。６０℃の温風がスプレーにより断熱冷却曲線に沿って冷却されたときの排気温度は２３～２４℃であり、１０ｇ／分のスプレー速度でトップスプレーで噴霧した。スプレーの空気風量は２０Ｌ／分であった。スプレー液の組成はＨＰＣ－ＳＳＬ７重量％濃度で９９０ｇの噴霧を行った時点で造粒を終了し、比較品IIを得た。比較品IIの平均粒子径（d_{50}）は１４８μｍであり、d_{95}／d_5 比は約３．３であり、本発明造粒品III と比較して、核粒子としての粒子のしまりぐあいに劣っていた。

【００５０】実施例４

局方エテンザミド（粒径７５μｍ以下が８５重量％以上；１５０μｍ以上が２重量％以下）を粉砕することにより得たエテンザミド微粉砕粒子（平均粒子径５μｍ以下）５００ｇに対して１０ｇのアエロジル＃２００（日本アエロジル工業（株）製）を添加し、転動流動層造粒装置、マルチプレックス（パウレック（株）製）に投入し、６０℃に加温した３６m^3／ｈｒの空気量を流動層内に送風しながら底部で３００ｒｐｍの回転速度でディスクローターを回転し、粉体を転動かつ流動させた。このときの装置のおかれている外部環境下での断熱飽和温度は２３℃であった。最初ＨＰＣ－ＳＳＬ７重量％濃度で１０ｇ／分のスプレー速度で７００ｇの量を噴霧したが、このときの排気温度は２４～２５℃であった。次にＨＰＣ－ＳＳＬ５重量％濃度で８ｇ／分のスプレー速度で４００ｇの噴霧を排気温度２６～２７℃下で行い、本発明造粒品IVを得た。いずれもスプレーの空気風量は２０Ｌ／分であった。本発明造粒品IVの平均粒子径は１１０μｍであり、d_{95}／d_5 比は約２．６であった。

【００５１】実施例５

実施例１で得た本発明造粒品Ｉ（平均粒子径１１４μｍ）を核粒子（芯物質）として、１０ｇに対してカルナバワックス粉末を１ｇまたは２ｇ加えてシータコンポーザー（徳寿工作所（株）製）に投入し、クリアランス１ｍｍ、ベッセル２０ｒｐｍ、ロータ２０００ｒｐｍの条件で材料温度が４０～５０℃に加温されるよう３０分間高速回転混合させて複合化粒子とし、それぞれの複合化粒子の平均粒子径を比較した。本発明造粒品Ｉの平均粒子径は１１４μｍ、カルナバワックス１ｇ添加処理品の平均粒子径１４０μｍ、カルナバワックス２ｇ添加処理品の平均粒子径１６５μｍであり、核粒子の表面にカルナバワックス粒子が付着し、光沢性、滑沢性が付加された複合化粒子であることが示された。

【００５２】実施例６

転動流動層造粒装置、マルチプレックス（パウレック（株）製）で実施例４に従い、本発明造粒品IV（平均粒子径１１０μｍ）を得て後、さらに同装置にてこれを原料としてヒドロキシプロピルメチルセルロース／ポリエチレングリコール６０００／酸化チタン／水（６／１／１／９２）よりなるコーティングスプレー液を５重量％となるよう必要量を噴霧することにより、本発明造粒品IVを核粒子としてその表面にコーティング皮膜を形成した平均粒子径１６０μｍの複合化粒子を得た。このときのスプレー速度は４ｇ／分、ロータの回転速度は３００ｒｐｍ、送風空気風量は３６m^3／ｈｒ、給気温度は７５℃、断熱飽和温度は２５℃、排気温度は３２℃であった。

【００５３】

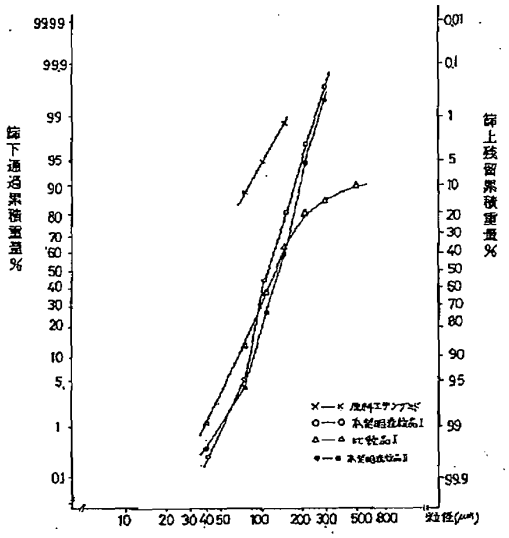
【発明の効果】本発明の核粒子の製造方法によると、粒径分布がシャープで十分な強度を有する核粒子を製造することができる。当該製造方法により得られる本発明の核粒子は上記のような粒径分布と強度を有するため、機能性付加等の目的で湿式又は乾式で粒子表面にコーティング、付着加工処理等により複合化粒子を設計するための核粒子として好適に用いることができる。

15　　16

【図面の簡単な説明】

【図１】図１は、実施例１～２、比較例１で得られた核＊粒子の粒径と篩下通過累積重量%、篩上残留累積重量%の関係を示す図である。

【図１】



CITED REFERENCE 6

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 10-081634
(43)Date of publication of application : 31.03.1998

(51)Int.Cl. A61K 47/02
A61K 9/16
A61K 9/22
A61K 45/00
A61K 47/36
A61K 47/38

(21)Application number : 09-185644
(22)Date of filing : 11.07.1997

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(30)Priority
Priority number : 08189071 Priority date : 18.07.1996 Priority country : JP

(54) BASE CONTROLLED IN DISSOLUTION TIME

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a base capable of providing a time limit release type preparation and a sustained release preparation capable of retarding dissolution time in digestive organs.
SOLUTION: This base comprises (A) one or two or more kinds of compounds selected from a group comprising an alkali metal salt of carboxymethyl cellulose, an alkali metal salt of carboxymethyl starch and an alkali metal salt of croscarboxylmethyl cellulose and (B) a water soluble alkali substance containing magnesium.

LEGAL STATUS

[Date of request for examination] 08.07.2004
[Date of sending the examiner's decision of rejection]
[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]
[Date of final disposal for application]
[Patent number]
[Date of registration]
[Number of appeal against examiner's decision of rejection]
[Date of requesting appeal against examiner's decision of rejection]
[Date of extinction of right]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] (A) a carboxymethyl cellulose -- alkali metal -- a salt -- carboxy methyl starch -- alkali metal -- a salt -- and -- a cross -- carboxyl -- methyl cellulose -- alkali metal -- a salt -- from -- becoming -- a group -- choosing -- having -- one -- a sort -- or -- two -- a sort -- more than -- and -- (-- B --) -- magnesium -- containing -- water solubility -- alkali -- the matter -- from -- becoming -- a basis .
[Claim 2] The basis according to claim 1 which is one sort chosen from the group which the water-soluble alkali matter containing magnesium becomes from a magnesium oxide, a magnesium hydroxide, and a magnesium carbonate, or two sorts or more.
[Claim 3] The basis according to claim 1 or 2 whose loadings of the water-soluble alkali matter which contains magnesium to one sort or two sorts or more of 1 weight sections chosen from the group which consists of the alkali-metal salt of a carboxymethyl cellulose, an alkali-metal salt of carboxy methyl starch, and an alkali-metal salt of cross carboxyl methyl cellulose are 0.2 - 5 weight section.
[Claim 4] Time limit emission mold pharmaceutical preparation characterized by covering a basis according to claim 1 to 3 in the outer shell layer of the main lock containing drugs.
[Claim 5] Gradual release-ized pharmaceutical preparation characterized by mixing and corning drugs and a basis according to claim 1 to 3.

[Translation done.]

(19)日本国特許庁（ＪＰ）　(12)公開特許公報（A）　(11)特許出願公開番号
特開平10－81634
(43)公開日　平成10年(1998)３月31日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ		技術表示箇所
Ａ６１Ｋ 47/02			Ａ６１Ｋ 47/02	Ｃ	
9/16			9/16	Ｋ	
9/22			9/22	Ｆ	
45/00			45/00		
47/36			47/36	Ｃ	

審査請求　未請求　請求項の数５　ＯＬ　（全 7 頁）　最終頁に続く

(21)出願番号　特願平9－185644
(22)出願日　平成９年(1997)７月11日
(31)優先権主張番号　特願平8－189071
(32)優先日　平８(1996)７月18日
(33)優先権主張国　日本（ＪＰ）

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(54)【発明の名称】　溶解時間を制御した基剤

(57)【要約】
【課題】　新たな時限放出型製剤、徐放化製剤を得ることが可能な基剤を提供する。
【解決手段】　（A）カルボキシメチルセルロースのアルカリ金属塩、カルボキシメチルスターチのアルカリ金属塩およびクロスカルボキシルメチルセルロースのアルカリ金属塩からなる群より選ばれる１種または２種以上、ならびに（B）マグネシウムを含有する水溶性のアルカリ物質からなる基剤。

1

【特許請求の範囲】

【請求項１】（Ａ）カルボキシメチルセルロースのアルカリ金属塩、カルボキシメチルスターチのアルカリ金属塩およびクロスカルボキシルメチルセルロースのアルカリ金属塩からなる群より選ばれる１種または２種以上、ならびに（Ｂ）マグネシウムを含有する水溶性のアルカリ物質からなる基剤。

【請求項２】マグネシウムを含有する水溶性のアルカリ物質が、酸化マグネシウム、水酸化マグネシウムおよび炭酸マグネシウムからなる群から選ばれる１種または２種以上である請求項１記載の基剤。

【請求項３】カルボキシメチルセルロースのアルカリ金属塩、カルボキシメチルスターチのアルカリ金属塩およびクロスカルボキシルメチルセルロースのアルカリ金属塩からなる群より選ばれる１種または２種以上の１重量部に対して、マグネシウムを含有する水溶性のアルカリ物質の配合量が０．２～５重量部である請求項１または２に記載の基剤。

【請求項４】　薬剤を含む中心錠の外殻層に、請求項１～３のいずれかに記載の基剤を被覆したことを特徴とする時限放出型製剤。

【請求項５】　薬剤および請求項１～３のいずれかに記載の基剤を混合し、造粒したことを特徴とする徐放化製剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は消化器官での溶解時間を遅延することができる基剤およびそれを利用した製剤に関する。

【０００２】

【従来の技術】近年、薬剤を疾患部位に直接作用させるために様々な薬物送達方法（ドラッグデリバリーシステム）が提唱されている。経口剤としては時限放出型製剤、徐放化製剤などが知られている。時限放出型製剤とは薬物を一定のラグタイムの後に放出する製剤のことであり、経口投与してから一定の時間を経過した後に薬物を放出する製剤である。

【０００３】時限放出型製剤としては、水不溶性物質で薬剤と膨潤剤を被覆し、時間経過と共に水分を吸収した膨潤剤が錠剤を内部から破裂させ、薬剤を放出する製剤が特開昭６２－３０７０９号公報などに記載されている。

【０００４】時限放出型製剤の持つ利点としては、一定の周期性を持って日内変動を繰り返す血圧や心拍数などに異常をきたす疾患や、起床時あるいは早朝に高い薬物血中濃度を必要とする喘息、腰痛、低血圧などの疾患の治療において有効なことである。

【０００５】また、近年これらの顆粒に腸溶性皮膜を施し、３～４時間の小腸通過時間に相当するラグタイムを有するシステムにより、薬物の大腸への送達が試みられ

2

ている。比較的消化酵素が少ない大腸へ薬物を送達することにより、従来経口投与しても胃－消化管経路を経るうちに酸や酵素により分解され不活性化される薬物（ペプチド剤など）の経口投与を可能にできるといった点で有用性は高い。大腸への薬物の送達は、錠剤または顆粒を大腸でのみ分解されるアゾ基を有するポリマーでコーティングするといった方法も提唱されているが、アゾ基を含むポリマーは、現在必ずしも安全性が確立されているとはいえない。また、生体内消化液のｐＨ変動（ｐＨ上昇）を利用して薬物を送達するシステムも提唱されているが、大腸への特異的な薬物送達の確実性には乏しい。

【０００６】一方、一定時間薬物を放出し続ける徐放化製剤も種々のものが知られているが、従来知られているものは、製造作業が煩雑、使用できる薬剤に制限があるなどの難点があった。

【０００７】

【発明が解決しようとする課題】ここで、薬剤層の外殻に遅溶性物質層を設け、錠剤の外部から遅溶性物質が徐々に溶解し、薬剤層まで到達した時点で薬剤が一気に放出される時限放出型製剤を開発すれば新たな薬物送達方法として有用性は高いが、そのような方法は現在まで知られていない。

【０００８】また、使用できる薬剤に制限が無く、簡便に製造できる徐放化製剤ができれば、医薬品の製剤として有用性は高い。

【０００９】本発明の目的は、新たな時限放出型製剤、徐放化製剤を得ることが可能な基剤を提供することにある。

【００１０】

【課題を解決するための手段】本発明者らは上記課題の解決のため鋭意検討した結果、カルボキシメチルセルロースのアルカリ金属塩、カルボキシメチルスターチのアルカリ金属塩およびクロスカルボキシルメチルセルロースのアルカリ金属塩からなる群より選ばれる１種または２種以上ならびにマグネシウムを含有する水溶性のアルカリ物質を配合した基剤は、消化器官における溶解に時間がかかり、かつ、基剤の構成およびその比率により溶解時間の調節が可能であることから時限放出型製剤、徐放化製剤の基剤として好ましいことを見いだし本発明を完成した。

【００１１】すなわち本発明は、（Ａ）カルボキシメチルセルロースのアルカリ金属塩、カルボキシメチルスターチのアルカリ金属塩およびクロスカルボキシルメチルセルロースのアルカリ金属塩からなる群より選ばれる１種または２種以上、ならびに（Ｂ）マグネシウムを含有する水溶性のアルカリ物質からなる基剤である。

【００１２】

【発明の実施の形態】本発明において「マグネシウムを含有する水溶性のアルカリ物質」とは、医薬品添加物と

して使用可能な、マグネシウムを含有する水に可溶のアルカリ物質であり、溶解遅延効果の点から好ましいものとして、酸化マグネシウム、水酸化マグネシウムおよび炭酸マグネシウムをあげることができる。また、それらを２種以上併用することも可能である。

【００１３】本発明のアルカリ金属塩とは、ナトリウム、リチウム、カリウムなどのアルカリ金属との塩であるが、最も好ましいものとしてナトリウム塩をあげることができる。

【００１４】本発明における各成分の配合量は、カルボキシメチルセルロースのアルカリ金属塩、カルボキシメチルスターチのアルカリ金属塩およびクロスカルボキシルメチルセルロースのアルカリ金属塩からなる群より選ばれる１種または２種以上を１重量部に対して、マグネシウムを含有する水溶性のアルカリ物質を０．２～５重量部となる量を配合することが好ましい。

【００１５】薬物放出パターンの調節は基剤の添加量、構成、その比率などの組合せで達成することが可能であり、具体的な方法として時限放出型製剤に用いるには、薬物を含有する中心錠の周囲を本発明の基剤により被覆し外殻層を設ければよい。製造法としては、薬物、賦形剤、崩壊剤、結合剤などを混合して、常法により造粒、整粒して得られた造粒物に滑沢剤などを添加して得られた中心錠に、本発明の基剤を圧縮被覆する方法、または、常法により製造した薬物を含む中心顆粒または錠剤に、本発明の基剤、賦形剤、結合剤などを水などに溶解または懸濁したものを、スプレー被覆する方法などにより、時限放出型製剤が得られる。

【００１６】本発明の基剤を徐放化製剤として用いるには、薬物および本発明の基剤を混合し造粒すれば得られる。該徐放化製剤は徐々に溶解する基剤と共に、薬物も長時間放出され続ける。製造法は、本発明の基剤と薬物、必要で有れば賦形剤、崩壊剤、結合剤などの通常必要な物質を混合して、常法により造粒、整粒することによって得られるが、造粒物をそのまま用いるだけでなく、適当な滑沢剤、賦形剤、薬物の速放顆粒などを添加したものを、カプセルに詰めてカプセル剤にしたり、圧縮成形することで錠剤とすることもできる。

【００１７】本発明の基剤を用いた時限放出型製剤では、薬剤層、外殻層を繰り返すことにより１回の服用で、定期的に数回の薬剤投与を行ったのと同様の効果を得ることも可能である。また、本発明の基剤を用いた徐放化製剤の外殻をさらに本発明の基剤で被覆すれば、特定の部位（大腸など）のみに薬物を徐々に投与することも可能である。なお、本発明の基剤を用いた製剤は製造方法、製造順序については特に制限はなく、一般に医薬品製造法として用いられる製造機器や手法を用いて製造することができる。

【００１８】本発明の基剤を用いた製剤は、消炎剤、血管拡張剤、中枢神経系薬物、向精神剤、抗そう鬱剤、抗ヒスタミン剤、緩下剤、鎮痛剤、ビタミン剤、制酸剤、高血圧防止剤、抗血小板凝集剤、解熱剤、鎮咳剤、去たん剤、鎮痙剤、利尿剤、喘息防止薬、栄養添加物、抗ガン剤、ペプチド性薬剤、駆虫薬、抗生物質などの経口投与可能な薬物に使用可能である。

【００１９】本発明の基剤を用いて製剤とするときは、その効果を損なわない範囲で、医薬品添加物として使用可能な他の基剤、賦形剤、滑沢剤、矯味剤、コーティング剤、糖衣剤、結合剤（ヒドロキシプロピルセルロース（ＨＰＣ）、ヒドロキシプロピルメチルセルロース（ＨＰＭＣ）、ポリビニルピロリドン（ＰＶＰ）など）などの通常使用される成分が使用可能である。

【００２０】また、製剤の崩壊性の調節、顆粒強度の向上、粉体流動性の改善など製造効率の改善のために、賦形剤、崩壊剤など一般に医薬品添加物として使用が可能なものを添加することができ、必要に応じて薬物放出を調節、薬物の苦味マスキング、光による分解防止などを目的として、腸溶性皮膜、フィルムコート、疎水性皮膜または糖衣層などを施すこともできる。

【００２１】

【実施例】以下、実施例および試験例により、本発明を詳細に説明する。

【００２２】実施例１：時限放出型製剤

カルボキシメチルセルロースナトリウム（ＣＭＣ－Ｎａ）低粘度　１５０ｇ、酸化マグネシウム軽質（協和化学）　１５０ｇ、ニュウトウ　２００ｇ、トウモロコシデンプン　５０ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後、ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターにより水を用いて造粒し、造粒物を乾燥後、スピードミルで粗砕、篩過し、ステアリン酸マグネシウム　５ｇを加え外殻層構成物を得た。

【００２３】テオフィリン　５０ｍｇを含有する６ｍｍ径錠剤（錠剤重量　８５ｍｇ）を中心錠とし、上記で得られた外殻層構成物約２８０ｍｇを９ｍｍ径普通面の杵で圧縮被覆し時限放出型錠剤を得た。

【００２４】実施例２：時限放出型製剤

ＣＭＣ－Ｎａ低粘度　２００ｇ、酸化マグネシウム軽質　２００ｇ、ニュウトウ　１６ｇ、トウモロコシデンプン　２０ｇ、結晶セルロース　８０ｇ、軽質無水ケイ酸　２４ｇ、ヒドロキシプロピルセルロース　５６ｇをビニール袋で混合し、サンプルミルで粉砕した後、ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターにより水を用いて造粒した。造粒物を乾燥後、スピードミルで粗砕、篩過し、ステアリン酸マグネシウム　４ｇを加え外殻層構成物を得た。

【００２５】テオフィリン　５０ｍｇを含有する６ｍｍ径錠剤（錠剤重量　８５ｍｇ）を中心錠とし、上記で得られた外殻層構成物約２８０ｍｇを９ｍｍ径普通面の杵

で圧縮被覆し時限放出型錠剤を得た。

【００２６】対照例１

実施例１の「酸化マグネシウム軽質」に変えて「トウモロコシデンプン」を増量した処方（トウモロコシデンプン　２００ｇ）で実施例１と同様の方法で対照用錠剤を得た。

【００２７】実施例３：時限放出型製剤

クロスカルボキシメチルセルロースナトリウム　１２０ｇ、酸化マグネシウム軽質　１２０ｇ、ニュウトウ　１００ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース　８０ｇ、軽質無水ケイ酸　２４ｇ、ヒドロキシプロピルセルロース　５２ｇをビニール袋で混合し、サンプルミルで粉砕した後、ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターにより水を用いて造粒した。造粒物を乾燥後、スピードミルで粗砕、篩過し、ステアリン酸マグネシウム　５ｇを加え外殻層構成物を得た。

【００２８】テオフィリン　５０ｍｇを含有する６ｍｍ径錠剤（錠剤重量　８５ｍｇ）を中心錠とし、上記で得られた外殻層構成物約２８０ｍｇを９ｍｍ径普通面の杵で圧縮被覆し時限放出型錠剤を得た。

【００２９】対照例２

実施例３の「酸化マグネシウム軽質」に変えて「ニュウトウ」および「トウモロコシデンプン」をそれぞれ６０ｇずつ増加した処方（ニュウトウ　１６０ｇ、トウモロコシデンプン　１６０ｇ）で実施例３と同様にして対照用錠剤を得た。

【００３０】実施例４：徐放化製剤

酸性薬物のイブプロフェン　２００ｇ、ＣＭＣ－Ｎａ低粘度　１５０ｇ、酸化マグネシウム軽質　１５０ｇ、トウモロコシデンプン　５０ｇ、結晶セルロース１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後、ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターにより水を用いて造粒した。造粒物を乾燥後、スピードミルで粗砕、篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７ｍｍ径普通面の杵を用い、１５０ｍｇの粉体に対して１．０ton／cm^{2}の圧力で圧縮成形し錠剤を得た。

【００３１】対照例３

実施例４の「酸化マグネシウム軽質」を「炭酸水素ナトリウム」に変えた処方で実施例４と同様の方法で対照用錠剤を得た。

【００３２】対照例４

実施例４の「酸化マグネシウム軽質」を「ニュウトウ」に変えた処方で実施例４と同様の方法で対照用錠剤を得た。

【００３３】実施例５：徐放化製剤

酸性薬物のイブプロフェン　２００ｇ、クロスカルメロースナトリウム　１５０ｇ、酸化マグネシウム軽質　７５ｇ、炭酸水素ナトリウム　７５ｇ、トウモロコシデンプン　５０ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７ｍｍ径普通面の杵を用い１．０ton／cm^{2}の圧力で圧縮成形し錠剤を得た。

【００３４】対照例５

酸性薬物のイブプロフェン　１６０ｇ、クロスカルメロースナトリウム　１２０ｇ、ニュウトウ　６０ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース８０ｇ、軽質無水ケイ酸　２４ｇ、ヒドロキシプロピルセルロース　５２ｇをビニール袋で混合し、サンプルミルで粉砕した後、ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターにより水を用いて造粒した。造粒物を乾燥後、スピードミルで粗砕、篩過し、ステアリン酸マグネシウム　４ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７ｍｍ径普通面の杵を用い、１５０ｍｇの粉体に対して１．０ton／cm^{2}の圧力で圧縮成形し錠剤を得た。

【００３５】実施例６：徐放化製剤

塩基性薬物のメトクロプラミド　５ｇ、カルボキシメチルスターチナトリウム（木村産業）　１５０ｇ、酸化マグネシウム軽質（協和化学）　１５０ｇ、Ｄ－マンニトール　１００ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７ｍｍ径普通面の杵を用い１．０ton／cm^{2}の圧力で圧縮成形し錠剤を得た。

【００３６】実施例７：徐放化製剤

塩基性薬物のメトクロプラミド　５ｇ、ＣＭＣ－Ｎａ　１５０ｇ、酸化マグネシウム軽質　１５０ｇ、Ｄ－マンニトール　１００ｇ、トウモロコシデンプン１００ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７ｍｍ径普通面の杵を用い１．０ton／cm^{2}の圧力で圧縮成形し錠剤を得た。

【００３７】実施例８：徐放化製剤

塩基性薬物のメトクロプラミド　５ｇ、ＣＭＣ－Ｎａ　１５０ｇ、合成ヒドロタルサイト（協和化学工業）　１５０ｇ、Ｄ－マンニトール　１００ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７㎜径普通面の杵を用い１．０ton／cm^2の圧力で圧縮成形し錠剤を得た。

【００３８】実施例９：徐放化製剤

塩基性薬物のメトクロプラミド　５ｇ、ＣＭＣ－Ｎａ　１５０ｇ、水酸化マグネシウム　１５０ｇ、Ｄ－マンニトール　１００ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７㎜径普通面の杵を用い１．０ton／cm^2の圧力で圧縮成形し錠剤を得た。

【００３９】実施例１０：徐放化製剤

塩基性薬物のメトクロプラミド　５ｇ、ＣＭＣ－Ｎａ　１５０ｇ、炭酸マグネシウム　１５０ｇ、Ｄ－マンニトール　１００ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７㎜径普通面の杵を用い１．０ton／cm^2の圧力で圧縮成形し錠剤を得た。

【００４０】実施例１１：徐放化製剤

塩基性薬物のメトクロプラミド　５ｇ、ＣＭＣ－Ｎａ　１５０ｇ、メタケイ酸アルミン酸マグネシウム　１５０ｇ、Ｄ－マンニトール　１００ｇ、トウモロコシデンプン　１００ｇ、結晶セルロース　１００ｇ、軽質無水ケイ酸　３０ｇ、ヒドロキシプロピルセルロース　６５ｇをビニール袋で混合し、サンプルミルで粉砕した後再度ビニール袋で混合し合剤を得た。この合剤をバーチカルグラニュレーターで水を用いて造粒し、乾燥、スピードミルで篩過し、ステアリン酸マグネシウム　５ｇを加えた後、コレクト１２打錠機（菊水製作所）で、７㎜径普通面の杵を用い１．０ton／cm^2の圧力で圧縮成形し錠剤を得た。

【００４１】対照例６

実施例６の「酸化マグネシウム軽質」に変えて「Ｄ－マンニトール」および「トウモロコシデンプン」を７５ｇずつ増量した処方（Ｄ－マンニトール　１７５ｇ、トウモロコシデンプン　１７５ｇ）で実施例６と同様にして対照用錠剤を得た。

【００４２】対照例７

実施例７の「酸化マグネシウム軽質」に変えて「Ｄ－マンニトール」および「トウモロコシデンプン」を７５ｇずつ増量した処方（Ｄ－マンニトール　１７５ｇ、トウモロコシデンプン　１７５ｇ）で実施例７と同様にして対照用錠剤を得た。

【００４３】試験例１

実施例１および対照例１の錠剤について、第１２改正日本薬局方溶出試験法第２法（試験液として、ｐＨ１．２の日局１液に浸漬し、適時試料を採取してテオフィリンの溶出量をＨＰＬＣ法により測定）により、テオフィリンの溶出量を測定した。経時的な薬物溶出量の結果を図１に示した。

【００４４】試験例２

実施例２および対照例１の錠剤について、第１２改正日本薬局方溶出試験法第２法（試験液として、ｐＨ６．５の日局リン酸塩緩衝液を用い、適時試料を採取してテオフィリンの溶出量をＨＰＬＣ法により測定）により、テオフィリンの溶出量を測定した。経時的な薬物溶出量の結果を図２に示した。

試験例３

実施例３および対照例２の錠剤について、試験例２と同様の試験により、テオフィリンの溶出量を測定した。経時的な薬物溶出量の結果を図３に示した。

【００４５】試験例４

実施例４ならびに対照例３および４の錠剤について、第１２改正日本薬局方溶出試験法第２法（試験液として、ｐＨ１．２の日局１液を用い、適時試料を採取してイブプロフェンの溶出量をＨＰＬＣ法により測定）により、イブプロフェンの溶出性を調べた。経時的な薬物溶出量の結果を図４に示した。

【００４６】試験例５

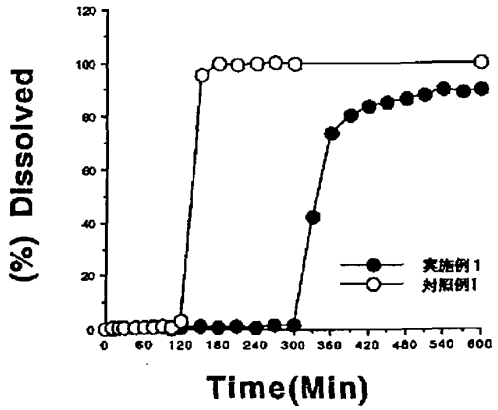
実施例５および対照例５の錠剤について、第１２改正日本薬局方溶出試験法第２法（試験液として、ｐＨ７．２の日局リン酸塩緩衝液を用い、適時試料を採取してイブプロフェンの溶出量をＨＰＬＣ法により測定）により、イブプロフェンの溶出性を調べた。経時的な薬物溶出量の結果を図５に示した。

【００４７】試験例６

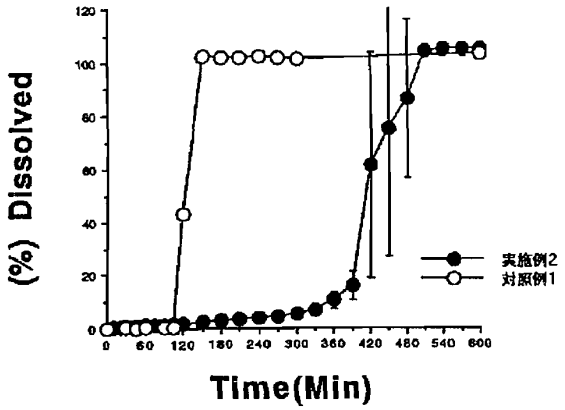
実施例６および対照例６の錠剤について、第１２改正日本薬局方溶出試験法第２法（試験液として、ｐＨ６．５の日局リン酸塩緩衝液を用い、適時試料を採取してメトクロプラミドの溶出量を測定）により、メトクロプラミドの溶出性を調べた。経時的な薬物溶出量の結果を図６に示した。

【００４８】試験例７
実施例７～１１および対照例７の錠剤について、第１２改正日本薬局方溶出試験法第２法（試験液として、ｐＨ６．５の日局リン酸塩緩衝液を用い、適時試料を採取してメトクロプラミドの溶出量をＨＰＬＣ法により測定）により、メトクロプラミドの溶出性を調べた。経時的な薬物溶出量の結果を図７に示した。
【００４９】
【発明の効果】本発明により、製造が容易で、かつ、全く新しい発想の時限放出型製剤、徐放化製剤などが提供可能になった。
【図面の簡単な説明】
【図１】　実施例１および対照例１のｐＨ１．２でのテオフィリンの溶出量の経時変化を示した図である。
＊【図２】　実施例２および対照例１のｐＨ６．５でのテオフィリンの溶出量の経時変化を示した図である。
【図３】　実施例３および対照例２のｐＨ６．５でのテオフィリンの溶出量の経時変化を示した図である。
【図４】　実施例４、対照例３および対照例４のｐＨ１．２でのイブプロフェンの溶出量の経時変化を示した図である。
【図５】　実施例５および対照例５のｐＨ７．２でのイブプロフェンの溶出量の経時変化である。
【図６】　実施例６と対照例６のｐＨ６．５でのメトクロプラミドの溶出量の経時変化を示した図である。
【図７】　実施例７～１１および対照例７のｐＨ６．５でのメトクロプラミドの溶出量の経時変化を示した図である。

【図１】



【図２】



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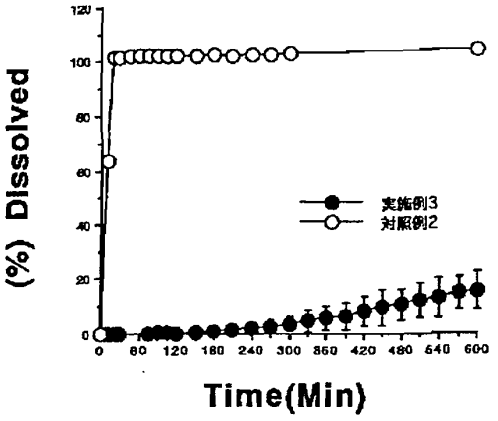
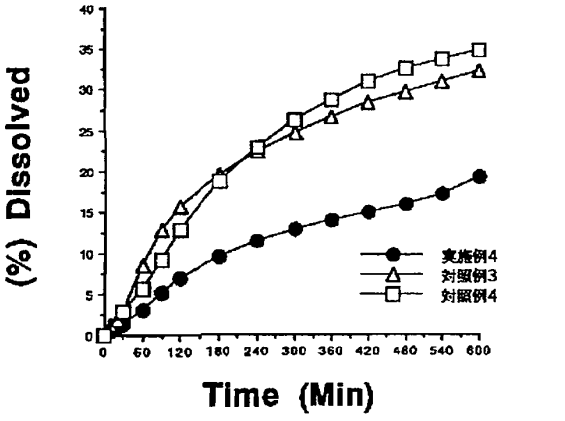


【図４】



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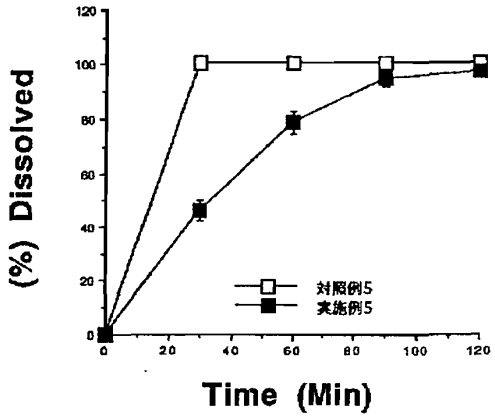

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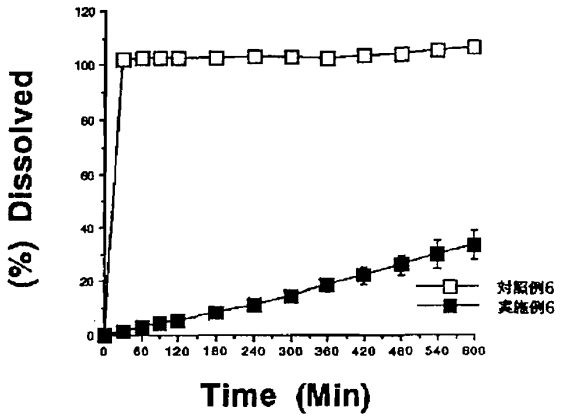
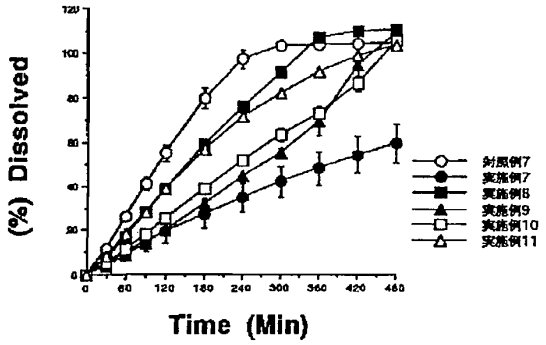


【図７】



フロントページの続き

(51)Int.Cl.[6]	識別記号	庁内整理番号	F I		技術表示箇所
Ａ６１Ｋ　47/36			Ａ６１Ｋ　47/36		D
47/38			47/38		D
					C

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/445	A1	(11) International Publication Number: WO 97/03673
		(43) International Publication Date: 6 February 1997 (06.02.97)

(21) International Application Number: PCT/GB96/01690

(22) International Filing Date: 15 July 1996 (15.07.96)

(30) Priority Data:
9514451.5 14 July 1995 (14.07.95) GB

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(81) Designated States: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SUSTAINED-RELEASE FORMULATION OF D-THREO-METHYLPHENIDATE

(57) Abstract

A sustained-release formulation of *d-threo*-methylphenidate (dtmp).

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SUSTAINED RELEASE FORMULATION OF D-THREO-METHYLPHENIDATE

Field of the Invention

This invention relates to a sustained-release formulation of methylphenidate.

Background of the Invention

Methylphenidate is a known drug. It is used primarily to treat hyperactive children. It is a controlled substance.

Methylphenidate is a chiral molecule. The properties of the enantiomers have been investigated to some extent, although the drug is still administered as the racemate. It is generally thought that *d-threo*-methylphenidate (abbreviated herein as dtmp) is the active material, and that its antipode (ltmp) is metabolised more rapidly.

Methylphenidate is often administered in a sustained-release formulation. For example, a coated tablet comprising racemic methylphenidate is administered, with a view to maintaining a therapeutically-effective level of the drug in circulation. This formulation does not provide satisfactory or reproducible dosing.

Srinivas *et al*, Pharmaceutical Research 10(1):14 (1993), disclose a further disadvantage of known methylphenidate sustained-release formulations, i.e. that serum levels of the drug are increased by chewing. Many children chew tablets, and are therefore liable to receive an unnecessarily high dose of a controlled substance.

Patrick *et al*, Biopharmaceutics and Drug Disposition 10:165-171 (1989), describe the absorption of sustained-release methylphenidate formulations compared to an immediate-release formulation. It is suggested that the optimum dosage of methylphenidate for children is 0.5-0.7 mg/kg/day.

Summary of the Invention

The present invention is based on an appreciation of the fact that, although it is possible to provide a model of chiral drug distribution, and measure the concentration of individual enantiomers and their breakdown products in

a subject, over time, this is a poor model for understanding the effectiveness of the enantiomers. Since, after an initial period, the sustained-release formulation should ideally release the active material as evenly as possible, the administration of a racemate, i.e. of two related compounds, takes no account of interaction between the enantiomers. According to this invention, it has surprisingly been found both that there is considerable interaction, and that dtmp provides relatively linear kinetics within the clinically effective dose range in a suitable model, and is therefore suitable for incorporation in a sustained-release formulation. The experiments and data on which this discovery is based are given below.

Description of the Invention

The dtmp that is used in this invention is substantially free of its antipode (ltmp), e.g. in an enantiomeric excess (ee) of at least 70%, preferably at least 90%, and more preferably at least 95%. The dtmp may be substantially enantiopure. It may be used in the form of any suitable salt, e.g. the hydrochloride.

The dtmp may be administered by the same means as is known for racemic methylphenidate, in a sustained-release formulation, e.g. a coated tablet. It may be administered in any other conventional sustained-release formulation, via any suitable route of administration. Conventional dosing parameters may be adopted, i.e. those which are known to or adapted to the practice of those skilled in the art.

Compositions of the invention may be administered for known purposes, e.g. the treatment of attention-deficient hyperactivity disorder (ADHD; this term is used herein to encompass attention-deficit disorder) in pre-pubertal children and in adults, as a stimulant in cancer patients treated with narcotic analgesics, and also for the treatment of depression (e.g. in AIDS patients), compulsive shopping disorder, narcolepsy and hypersomnia. By contrast to known formulations of methylphenidate, the present

invention may have any or all of the following advantages: linear kinetics within the clinically effective dose range, the reduction of exposure to a controlled substance, reduced side-effects (which include anorexia, insomnia, stomach ache and headache), reduced abuse potential, reduced C_{max}, a reduced level of active material even when chewed, reduced patient variability, reduced interaction with ltmp or other drugs, and less variability between fed and fasted subjects.

By controlling the nature of the formulation, it is possible to control dissolution *in vitro*, and thus match or exceed the US National Formulary (NF) drug release profile for methylphenidate hydrochloride. Further, when administered to a healthy subject, a serum level of dtmp can be attained that is at least 50% of C_{max}, over a period of at least 8 hours, e.g. 8-16, 8-12 or 8-10 hours. Thus, for example, a shorter release period may be preferred or a different period before the serum level drops below a different proportion of C_{max}.

The serum level may be also controlled so that it remains high during the day, after taking a dosage in the morning, and is reduced in the evening, before it can have any undesirable effect on sleeping patterns. Preferably, the serum level is at least 50% C_{max} after 8 hours and less than 25% C_{max} after 12 to 16 hours.

A formulation of the invention may be a unit dosage such as a tablet, capsule or suspension. It may be in matrix, coating, reservoir, osmotic, ion-exchange or density exchange form. It may comprise a soluble polymer coating which is dissolved or eroded, after administration. Alternatively, there may be an insoluble coating, e.g. of a polymer, through which the active ingredient permeates, as from a reservoir, diffuses, e.g. through a porous matrix, or undergoes osmotic exchange. A further option for a sustained-release formulation involves density exchange, e.g. in the case where the formulation alters on administration, e.g. from microparticles to a gel, so that

the active ingredient diffuses or permeates out. Ion-based resins may also be used, the active component being released by ionic exchange, and wherein the rate of release can be controlled by using cationic or anionic forms of the drug.

It is preferred to use a formulation in this invention that is resistant to chewing, e.g. micronised particles that are individually coated and which do not immediately release the active component on chewing, or possibly even actively discourage chewing by their consistency. The various effects etc may be due to the use of dtmp and/or the absence of ltmp.

Comparative Pharmacodynamics of *d-threo*-methylphenidate and Racemate

The study design was based on that described by Aoyama *et al*, J. Pharmacobio-Dyn. 13:647-652 (1990). Male Wistar rats were dosed with methylphenidate hydrochloride or its d-isomer at nominal dose levels of

racemate: 1.5, 3, 4.5 or 6 mg base/kg body weight
d-isomer: 0.75, 1.5, 2.25 or 3 mg base/kg body weight

Blood samples were taken pre-dose, and 7 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4.5 h, 6 h, 8 h post-dose. The samples were centrifuged to separate the plasma. Plasma samples were assayed for dtmp, by liquid chromatography mass spectrometry.

The results are shown in the accompanying drawing. Figure 1 gives a comparison of the AUC (area under the curve) for values, obtained from plasma concentration of dtmp, versus time, for dtmp and methylphenidate (at equivalent dtmp quantities) dosed at a range of dtmp concentrations. Both curves show non-linear kinetics, evident as a point of disjunction in each curve. As the doses administered are increased, the quantity absorbed (i.e. AUC) increases in a linear fashion, until the disjunction, when the absorbed quantity is dramatically

increased. This disjunction occurs within the clinically-relevant range (16-140 mg.h/ml in humans) for racemate dosing, but, surprisingly, is outside of this range for dtmp dosing.

This means that conventional dosing of the racemate, which involves increasing amounts of the drug, cannot be satisfactorily controlled. The possibility exists that a dosage will be given that is unnecessarily high.

Administration of dtmp has a surprising beneficial effect, in that a relatively linear dtmp AUC level in serum (lower curve) is achieved within the clinically-relevant range. The point of disjunction occurs outside the clinically-relevant range and, therefore, the flux of drug into and out of the circulatory system is more controllable. This makes dtmp suitable for incorporation in a sustained release formulation.

CLAIMS

1. A sustained-release formulation of *d-threo*-methylphenidate (dtmp).

2. A formulation according to claim 1, which meets, or exceeds in terms of slower dissolution, the NF drug release profile for methylphenidate hydrochloride.

3. A formulation according to claim 1 or claim 2, which comprises less than 20 mg dtmp per unit dosage.

4. A formulation according to claim 3, which comprises less than 15 mg dtmp per unit dosage.

5. A formulation according to any of claims 1 to 4, selected from those comprising a soluble, erodable or otherwise modified coating, and those having an insoluble coating through which the dtmp passes, in use.

6. A formulation according to any of claims 1 to 5, in which the dtmp is micronised.

7. A formulation according to any of claims 1 to 6, which (on average) when administered to (a sample of) healthy subjects, exhibits a serum level of dtmp of at least 50% C_{max}, over a period of at least 8 hours.

8. A formulation according to claim 7, wherein the period is 8 to 12 hours.

9. A formulation according to claim 7 or claim 8, wherein the serum level is less than 25% C_{max} after 12 to 16 hours.

10. A formulation according to any of claims 1 to 9, which on administration to a healthy subject, exhibits C_{max} of 2 to 20 ng/ml at a dosage of at least 2 mg.

11. A formulation according to any of claims 7 to 10, wherein C_{max} is substantially unaffected by chewing.

12. A method for treating a subject having a disorder capable of treatment using methylphenidate, which comprises administering to said subject a sustained-release formulation comprising dtmp in an amount sufficient to maintain a serum level of at least 50% of the maximum level, for at least 8 hours.

13. A method according to claim 12, wherein at least the initial dosage is less than 15 mg dtmp per day.

14. A method according to claim 12 or 13, wherein the subject is adult and the disorder is compulsive shopping disorder, narcolepsy or hypersomnia.

15. A method according to claim 12 or 13, wherein the disorder is attention-deficit hyperactivity disorder.

16. A method according to claim 12, wherein said amount is less than 1 mg/kg/day.

17. A method according to claim 12, wherein said amount is less than 0.5 mg/kg/day.

Chart 1

Comparison of AUC for d-isomer; d-isomer vs racemate dosing

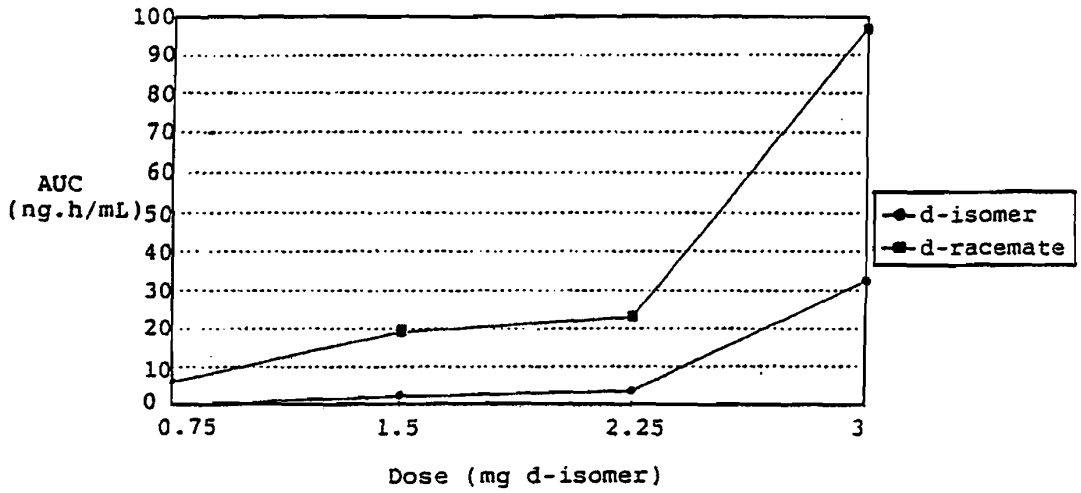

FIG. 1

INTERNATIONAL SEARCH REPORT

Intern ·al Application No
PCT/GB 96/01690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J. PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 241, no. 1, April 1987, USA, pages 152-158, XP000612231 PATRICK ET AL.: "Pharmacology of the Enantiomers of threo-Methylphenidate" see the whole document ---	1-17
A	PHARMACOLOGY, BIOCHEMISTRY AND BEHAVIOR, vol. 40, no. 4, December 1991, USA, pages 875-880, XP000612226 ECKERMAN ET AL.: "Enantioselective Behavioral Effects of threo -Methylphenidate in Rats" see the whole document -----	1-17

☐ Further documents are listed in the continuation of box C.

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3 December 1996	17.12.96

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 09-249557

(43)Date of publication of application : 22.09.1997

(51)Int.Cl. A61K 31/265
A61K 31/265
A61K 9/00
A61K 9/48
A61K 9/52
A61K 47/14
A61K 47/26
A61K 47/32
A61K 47/34
A61K 47/38

(21)Application number : 08-058114

(22)Date of filing : 14.03.1996

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(72)Inventor : TSUKADA TAKAYUKI
FUJII TOSHIROU
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OGURA TOSHIHIRO

(54) SUSTAINED RELEASE PREPARATION OF SLIGHTLY WATER-SOLUBLE MEDICINE

(57)Abstract:

PROBLEM TO BE SOLVED: To prepare a sustained release preparation capable of gradually releasing slightly water-soluble medicines to sustain their activities by combining a slow soluble part and a quickly releasing part with each other which contain slightly water-soluble medicines treated with wetness-improving agents, respectively.

SOLUTION: This sustained release preparation comprises a quickly releasing part containing a slightly water-soluble medicine (e.g. ecadotril) treated with a wetness- improving agent and a slow soluble part comprising a core granule containing a slightly water-soluble medicine treated with a wetness-improving agent and coated with an enteric layer. The slow soluble part and the quickly releasing part separately exist as an enteric granule and a quickly releasing granule, and one or more water-soluble, inactive separation layers are disposed between the core granule and the enteric layer in the slow soluble part and/or between the enteric layer and the quickly releasing part. Even when a highly plastic, slightly water-soluble medicine having a high melting point is used, a function for controlling the release of the medicines can thereby be stabilized. The wetness-improving agents are used for improving the granule surface wetness and dissolution speeds of the granules containing the slightly water-soluble medicines, respectively, and includes hydroxypropylcellulose.

LEGAL STATUS

[Date of request for examination] 29.01.2003

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] The sustained release drug characterized by consisting of a fast-discharging part containing the difficulty water solubility drug which was damp and was processed by the improvement agent, and ****** to which coating of the core granulation containing the difficulty water solubility drug which was damp and was processed by the improvement agent was carried out in the enteric layer.
[Claim 2] The sustained release drug according to claim 1 with which ****** and a fast-discharging part exist as granulation, respectively.
[Claim 3] The sustained release drug containing the compound granulation with which it comes to carry out coating of the fast-discharging part to the perimeter of ****** according to claim 1.

[Claim 4] A sustained release drug given in either of claims 1-3 which has the water-soluble 1st isolation layer between core granulation and an enteric layer.
[Claim 5] A sustained release drug given in the claim which has the water-soluble 2nd isolation layer between ****** and a fast-discharging part 3 or 4.
[Claim 6] The sustained release drug according to claim 5 which contains in core granulation the compound granulation with which it comes to carry out coating of the water-soluble 1st isolation layer, an enteric layer, the water-soluble 2nd isolation layer, and the fast-discharging part to order.
[Claim 7] A sustained release drug given in either of claims 4-6 in which the 1st isolation layer contains a water soluble polymer and a saccharide.
[Claim 8] A sustained release drug given in either of claims 4-6 in which the 2nd isolation layer contains a water soluble polymer and a saccharide.
[Claim 9] A sustained release drug given in either of claims 1-8 whose difficulty water solubility drug is EKADO tolyl.
[Claim 10] A sustained release drug given in either of claims 1-9 which is capsule pharmaceutical preparation.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the sustained release drug containing the drug of difficulty water solubility.
[0002]
[Description of the Prior Art] In order to maintain the effectiveness of a drug, sustained-release-drug-izing combining a fast-discharging part and ****** is known (for example, JP,61-13683,B and JP,62-32166,B). However, each of these is restricted when using a soluble high drug comparatively. Since the remarkable decline in an absorption coefficient is generally seen when it is going to gradual-release-ize the drug of difficulty water solubility by these approaches, gradual release-ization by such approach is made difficult. Especially drug effect continuation according to gradual-release-izing when it is difficulty water solubility like EKADO tolyl and the disappearance half-life in blood is a short drug for example, becomes more difficult.
[0003]
[Problem(s) to be Solved by the Invention] The purpose of this invention is offering the sustained release drug which drug effect's maintains by releasing the drug of difficulty water solubility gradually. It is offering the pharmaceutical preparation which the drug effect of a drug with the short disappearance half-life in difficulty water solubility like EKADO tolyl and blood maintains especially.
[0004]
[Means for Solving the Problem] The sustained release drug of this invention consists of a fast-discharging part containing the difficulty water solubility drug which was damp and was processed by the improvement agent, and ****** to which coating of the core granulation containing the difficulty water solubility drug which was damp and was processed by the improvement agent was carried out in the enteric layer.
[0005] In a suitable embodiment, said ****** and fast-discharging part exist as granulation, respectively.
[0006] In a suitable embodiment, the sustained release drug of this invention contains the compound granulation with which it comes to carry out coating of said fast-discharging part to the perimeter of said ******.
[0007] In a suitable embodiment, the sustained release drug of this invention has the water-soluble 1st isolation layer between said core granulation and said enteric layers.
[0008] In a suitable embodiment, the sustained release drug of this invention has the water-soluble 2nd isolation layer between said ****** and said fast-discharging parts.
[0009] In a suitable embodiment, the sustained release drug of this invention contains in the core granulation containing a difficulty water solubility drug the compound granulation with which it comes to carry out coating of the water-soluble 1st isolation layer, an enteric layer, the water-soluble 2nd isolation layer, and the fast-discharging part to order.
[0010] In a suitable embodiment, a difficulty water solubility drug is EKADO tolyl.
[0011] In a suitable embodiment, the sustained release drug of this invention is capsule pharmaceutical preparation.

[0012]
[Embodiment of the Invention] In order that a fast-discharging part may emit a drug in the stomach and ****** may subsequently emit a drug in intestines, as for the sustained release drug of this invention, continuous drug effect is obtained. This pharmaceutical preparation may be the 1st and 2nd following pharmaceutical preparation typically.
[0013] In the 1st sustained release drug of this invention, ****** and a fast-discharging part exist separately as enteric granulation and immediate-release granulation respectively. Coating of the core granulation containing the difficulty water solubility drug which this enteric granulation was damp and was processed by the improvement agent is carried out in the enteric layer. Immediate-release granulation is homogeneous on the core granulation and the essential target of enteric granulation, and is obtained on them. That is, it is granulation which does not have an enteric layer, including the difficulty water solubility drug which was damp and was processed by the improvement agent. By mixing these enteric granulation and immediate-release granulation at a desired rate, the 1st sustained release drug of this invention is obtained.
[0014] In the 2nd sustained release drug of this invention, ****** and a fast-discharging part exist as compound granulation with which coating of the perimeter of ****** was carried out by the fast-discharging part and which contains both ****** and a fast-discharging part in the same granulation. Coating of the core granulation containing the difficulty water solubility drug which ****** got wet like the case of the 1st pharmaceutical preparation of the above, and was processed by the improvement agent is carried out in the enteric layer here.
[0015] The amount of solvents required for the drug of difficulty water solubility contained in the core granulation of ****** meaning the drug equivalent to "it being hard to melt", "it being very hard to melt", or "hardly melting" in the 1st and 2nd pharmaceutical preparation of the above, and melting 1g of solutes and 1ml may be the drug of the arbitration which is 100ml or more (20 degrees C). [which is defined by the Japanese pharmacopoeia] As such a difficulty water solubility drug, EKADO tolyl, nifedipine, a griseofulvin, phenytoin, SURUFISOKISAZARU, aminopyrine, secobarbital, prednisolone, indomethacin, a phenacetin, phenobarbital, tolbutamide, etc. are mentioned. EKADO tolyl is used suitably. EKADO tolyl (N-[(S)-alpha-(acetyl thiomethyl) hydronalium cinnamoyl] glycine benzyl ester; N-[(S)-alpha-(mercaptomethyl) hydrocinnamoyl] glycine, benzyl ester, and acetate (ester) are enkephalinase inhibitors used as a hypotensive agent and a cardiac insufficiency remedy, and about 33microg [ml] (37 degrees C) /, the melting point of 70-74 degrees C, and the in-the-living-body disappearance half-life of the solubility to water are the drugs of 1 or less hour.)
[0016] Since a dissolution rate becomes high so that it is small as much as possible, it is advantageous, and the particle size of the above-mentioned difficulty water solubility drug contained in the core granulation of ****** in the 1st and 2nd pharmaceutical preparation of the above is 10 micrometers. It is 3 micrometers or less preferably hereafter. When a detailed drug particle is not obtained in a crystallization phase, in order to aim at an improvement of a dissolution rate, a grinder etc. is used with a conventional method, it grinds, and surface area of a substantial drug is enlarged. as a grinder, a jet mill, a ball mill, a hammer mill, a pressurization mold homogenizer, a colloid mill, a nano mizer, a roller mill, etc. use, for example -- having -- a drug -- the mixed stock of independent or a drug, and an additive -- dry grinding -- or wet grinding is carried out. When grinding a drug with the low melting point, the small grinding approach of generation of heat is desirable. The content of the difficulty water solubility drug in core granulation is 45 - 65 % of the weight preferably 30 to 80% of the weight to core granulation.

[0017] It gets wet the account of a top, and it is used in order for an improvement agent to improve **** on the front face of a particle of a difficulty water solubility drug and to improve a dissolution rate. That is, if a thin coat is formed in the front face of a bad damp drug (hydrophobicity and water-repellent drug with the large contact angle over water) and the ease of getting wet is improved, the property which crawls the water of a drug can weaken and it will become easy to distribute in water. That is, the solubility of a drug improves. such -- getting wet -- as an improvement agent -- hydroxypropylcellulose (HPC) -- The hydroxypropyl methylcellulose (HPMC), methyl cellulose, Water soluble polymers, such as povidone, poly vinyl

alcohol, and gelatin, Sodium lauryl sulfate, a monostearin acid polyethylene glycol, Glyceryl monostearate, polyoxyethylene RORUBITAN fatty acid ester, Surfactants, such as polyoxyethylene hydrogenated castor oil and a polyoxyethylene polyoxypropylene glycol, etc. are mentioned, and hydroxypropylcellulose and the hydroxypropyl methylcellulose are desirable especially. It gets wet, and an improvement agent is the form where it adheres to the particle front face of a difficulty water solubility drug, and is contained in core granulation together with a difficulty water solubility drug. It gets wet and the content in the core granulation of an improvement agent is 3 - 6 weight section preferably [it is desirable and] to 2 - 10 weight section and a pan below 20 weight sections to the difficulty water solubility drug 100 weight section.

[0018] The core granulation of ****** may contain the above-mentioned difficulty water solubility drug and the additive which is damp and is permitted on the galenical pharmacy of disintegrator, an excipient, a binder, a coloring agent, an aromatizing agent, a stabilizing agent, etc. in addition to an improvement agent.

[0019] The above-mentioned disintegrator is drugs which give collapsibility to pharmaceutical preparation, and it is used in order to distribute a difficulty water solubility drug promptly. Disintegrator is matter which is excellent in compatibility with water although it does not dissolve in water, swells by contact in water, and helps contact in a drug and water. As such disintegrator, carboxy-methyl-starch sodium, cross carmellose sodium, crystalline cellulose, cross povidone, etc. are raised whenever [carmellose calcium (CMC-calcium), hydroxypropylcellulose partial alpha-ized starch, carboxy-methyl-starch sodium, and low permutation], and carmellose calcium, hydroxypropylcellulose, cross carmellose sodium, cross povidone, etc. are desirable especially. the content of the disintegrator in core granulation -- the difficulty water solubility drug 100 weight section -- receiving -- below 20 weight sections -- desirable -- 5 - 15 weight section -- it is 7 - 12 weight section more preferably.

[0020] The above-mentioned excipient is used in order to give predetermined magnitude and weight to pharmaceutical preparation. The excipient used for this invention is the mixture of the pulverized water-soluble excipient or a water-soluble excipient, and a hydrophilic excipient preferably. As a water-soluble excipient, a lactose, white soft sugar, a mannitol, etc. are mentioned, for example. As a hydrophilic excipient, mineral, such as starches, such as corn starch, potatostarch, and hydroxypropyl starch, a silicic acid anhydride, and anhydrous dibasic calcium phosphate, is mentioned, for example.

[0021] The above-mentioned binder is used in order to give bonding strength to the mixture of component powder and to ** stable granulation. As such a binder, for example, methyl cellulose, povidone, hydroxypropylcellulose, the hydroxypropyl methylcellulose, fusibility alpha-ized starch, poly vinyl alcohol, gelatin, a dextrin, etc. are mentioned, and especially, since it gets wet and also has an improvement effect, hydroxypropylcellulose and the hydroxypropyl methylcellulose are desirable.

[0022] Various kinds of perfume may be used as the above-mentioned aromatizing agent for which an iron oxide and lake coloring matter may be used as the above-mentioned coloring agent. A sodium hydrogensulfite etc. may be used as the above-mentioned stabilizing agent.

[0023] The content of the above-mentioned additive is respectively adjusted suitably depending on the class of drug, the purpose of using pharmaceutical preparation, the magnitude of dosage forms, the manufacture approach, the class of other additives, an amount, etc.

[0024] In the 1st and 2nd pharmaceutical preparation of the above, the enteric layer by which coating is carried out to the core granulation of the above-mentioned ****** is a layer containing an enteric macromolecule, by the stomach, is insoluble and is dissolved in intestines. It is gradually emitted as the drug in core granulation is not emitted within the stomach by existence of an enteric layer but pharmaceutical preparation shifts to intestines from the stomach by it. As the above-mentioned enteric macromolecule, OIDORAGITTOL (methacrylic acid copolymer (rhe MUFAMA)) and L30D (methacrylic acid copolymer LD (rhe MUFAMA)), hydroxypropylmethylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), hydroxypropyl-methylcellulose acetate succinate (HPMCAS), carboxy methyl ethyl cellulose (CMEC), a macromolecule similar to these, etc. are mentioned. Since an enteric layer is formed

by preparing coating liquid using such an enteric giant molecule, and coating core granulation, its enteric giant molecules (for example, HPMCAS etc.) which can be used with the solvent of a drainage system from a viewpoint of safety and a residual solvent are desirable.
[0025] An enteric layer may contain a plasticizer, lubricant, etc., in order to secure the stability other than the above-mentioned enteric giant molecule, and in order to make coating actuation easy. As a plasticizer, citric-acid triethyl, a triacetin, a glycerine fatty acid ester, succinic-acid dibutyl, macro gall, a plasticizer similar to these, etc. are mentioned. As lubricant, talc, magnesium stearate, SUARIN acid monoglyceride, etc. are mentioned. The amount of coatings of an enteric layer is 20 - 40 weight section preferably to 15 - 50 weight section and a pan in dryness to the core granulation 100 weight section, although it is dependent on the magnitude of core granulation, a configuration, etc.
[0026] While hydrophobicity is difficulty water solubility strongly, when pharmaceutical-preparation-izing a low-melt point point and the drug of the Takayoshi plasticity like EKADO tolyl especially, it is desirable to prepare a further water-soluble and inactive isolation layer (the 1st isolation layer) between the above-mentioned core granulation and an enteric layer. It is because a drug dissolves into an enteric layer, a drug deposits on an enteric layer front face gradually, when the granulation containing the drug of such difficulty water solubility and a low-melt point point is coated with a direct enteric layer, so it becomes difficult to control emission of a drug. the desiccation process after such a deposit phenomenon especially performs coating of an enteric layer, or warming of pharmaceutical preparation -- it generates notably at the time of an accelerated test. By preparing the above-mentioned 1st isolation layer between core granulation and an enteric layer, it becomes possible to prevent the dissolution of the drug to such an enteric layer, and the drug release of pharmaceutical preparation can be controlled to stability.
[0027] The above-mentioned 1st isolation layer usually coats core granulation with the liquid containing a water soluble polymer and a saccharide, and is formed. As a water soluble polymer, hydroxypropylcellulose (HPC), the hydroxypropyl methylcellulose (HPMC), povidone (PVP), etc. are mentioned. White soft sugar, a lactose, etc. are mentioned as a saccharide. An isolation layer may contain lubricant, such as talc, further. Coating of the 1st isolation layer is preferably carried out to 5 - 30 weight section and a pan at a rate of 10 - 20 weight section by dryness to the core granulation 100 weight section.
[0028] The fast-discharging part contained in the sustained release drug of this invention existed apart from enteric granulation as immediate-release granulation by the 1st pharmaceutical preparation of this invention as mentioned above, and has coated the perimeter of ****** with the 2nd pharmaceutical preparation of this invention. This fast-discharging part contains the difficulty water solubility drug contained in the above-mentioned ******, and a drug of the same kind. Like [the difficulty water solubility drug contained in a fast-discharging part] the case of ******, since a dissolution rate becomes high, it is desirable, and 10 micrometers or less of particle size are 3 micrometers or less preferably, so that particle size is small. Therefore, as for the difficulty water solubility drug of a fast-discharging part as well as the case of ******, being ground and used is desirable. The content of the difficulty water solubility drug in a fast-discharging part is usually 40 - 60 % of the weight preferably 30 to 80% of the weight to a fast-discharging part. The dissolution rate is raised, the difficulty water solubility drug of a fast-discharging part is also damp in order to promote prompt emission and absorption of a drug, and it is processed by the improvement agent. It gets wet in a fast-discharging part, and the content of an improvement agent is 20 - 50 weight section preferably [it is desirable and] to the 10 - 100 weight section and a pan below the 120 weight sections to the difficulty water solubility drug 100 weight section in a fast-discharging part.
[0029] A fast-discharging part may contain further the additive permitted on the galenical pharmacy of disintegrator, an excipient, a binder, lubricant, an antistatic agent, a coloring agent, an aromatizing agent, a stabilizing agent, etc. The thing same as these additives as the additive which may be used by the above-mentioned ****** may be used. The content is respectively adjusted suitably depending on the class of drug, the purpose of using pharmaceutical preparation, the magnitude of dosage forms, the manufacture approach, the class of other

additives, an amount, etc. As for a fast-discharging part, it is desirable to contain an excipient, in order to secure the content homogeneity of a difficulty water solubility drug. Although especially the content of the excipient in a fast-discharging part is not restricted, it is usually the 70 - 100 weight section preferably [it is desirable and] to the 50 - 200 weight section and a pan below the 250 weight sections to the difficulty water solubility drug 100 weight section in a fast-discharging part.

[0030] While hydrophobicity is difficulty water solubility strongly, when pharmaceutical-preparation-izing a low-melt point point and the drug of the Takayoshi plasticity like EKADO tolyl especially in the case of the 2nd pharmaceutical preparation of this invention, it is desirable to prepare a water-soluble and inactive isolation layer (the 2nd isolation layer) between the above-mentioned ****** and a fast-discharging part. By arranging this 2nd isolation layer, the dissolution of the drug from a fast-discharging part to an enteric layer is prevented, and emission of a drug can be controlled to stability. The 2nd isolation layer has the same presentation as the 1st isolation layer, and coating is carried out by the same approach. Coating of the 2nd isolation layer is preferably carried out to 5 - 30 weight section and a pan at a rate of 10 - 20 weight section by dryness to the ****** 100 weight section.

[0031] The dosage forms of the sustained release drug of this invention are a capsule or a granule preferably. In the case of the 1st pharmaceutical preparation, according to a conventional method, the sustained release drug of this invention of the dosage forms of arbitration, such as a capsule and a granule, may be obtained, using enteric granulation and immediate-release granulation the specified quantity every respectively. As for the case of the 2nd pharmaceutical preparation, the sustained release drug of this invention of the dosage forms of arbitration may be obtained in compound granulation like the case of **** for the specified quantity, and the 1st pharmaceutical preparation of the above.

[0032] Thus, as for the sustained release drug of obtained this invention, a fast-discharging part is first eluted with the stomach, and the concentration of a drug in the living body reaches to effective concentration promptly. ****** does not change at this time. After being gradually discharged from the stomach, since an enteric layer begins to melt, ****** emits a drug. Therefore, drug effect carries out long duration continuation.

[0033] (The manufacture approach) The typical manufacture approach of the sustained release drug of this invention is explained hereafter.

[0034] 1. Manufacture approach 1.1 of the 1st pharmaceutical preparation The method-of-preparation enteric granulation of enteric granulation is obtained by coating the core granulation containing a difficulty water solubility drug with the 1st isolation layer at arbitration, and coating an enteric layer further.

[0035] 1.1.1. The crystal front face gets wet the difficulty water solubility drug made detailed with means, such as grinding, as mentioned above, and the formation core granulation of core granulation may be manufactured by corning getting wet the account of a top and improving a property by the improvement agent. The art may be performed by the granulation approach of arbitration in the limitation by which the ease of getting wet is improved. Some examples of the approach are given to below. When the content of a difficulty water solubility drug is large, the following methods of kneading 1 are simple and the most effective.

[0036] 1) Carry out wet kneading of the kneading method difficulty water solubility drug powder and the mixture which is damp and consists of additives (an excipient, disintegrator, binder, etc.) of arbitration by the improvement agent, water, and request using a kneading machine. By this, it gets wet on the crystal front face of a difficulty water solubility drug, and an improvement agent will be in the condition that surface treatment was given and carried out. As a kneading facility, a high speed mixer, a REDIGE mixer, a ribbon blender, a monopodium, or a double compound kneading machine is used. The obtained kneaded object is ******(ed), and is corned by approaches, such as law and a grain method made from extrusion, and core granulation is obtained through desiccation and refining.

[0037] As an option, it gets wet to the unsettled poorly soluble drug which has not been pulverized, optimum dose addition of the water solution or water of an improvement agent is carried out, and the water suspension liquid which pulverized this by the wet-grinding method is

prepared, and this water suspension liquid may be added to the additive of arbitration, and wet kneading may be carried out as mentioned above, and you may corn it. This water suspension liquid may contain an excipient (water-soluble desirable excipient) further.
[0038] 2) Use an agitation granulation method blade rotation mold mixer or a high share mixer, and they are agitation granulation and a method of drying and refining and obtaining chief remedy granulation like the method of kneading the above 1. Or in addition to the additive powder of a desired class, or the end of mixing, agitation granulation of a poorly soluble drug and the water suspension liquid which is damp and contains an excipient by the improvement agent and request and by which wet grinding was carried out can be carried out like the case of the above 1.
[0039] 3) Use the fluid bed corning method fluid bed granulating machine, and corn, carrying out a spray after the additive powder of the class of request which made a difficulty water solubility drug and the water suspension liquid which is damp and contains an excipient by the improvement agent and request, and by which wet grinding was carried out flow, or mixing. As a spray method, both a top spray a side spray and a tangential spray can be used. By the usual approach of adding after mixing, making a poorly soluble drug flow, getting wet in this, and carrying out the spray of a water solution or water, such as an improvement agent and a binder, since the water repellence of a drug is high, a granulation is difficult.
[0040] 4) Use the coating corning method fluid bed granulating machine, a revolution mold fluid bed granulating machine, or the Wurster mold granulating machine, and it is the approach of carrying out the spray of a difficulty water solubility drug and the water suspension liquid which is damp and contains an excipient by the improvement agent and request and by which wet grinding was carried out to a nuclear particle, and carrying out coating granulation. A nuclear particle may be a particle of arbitration with a particle size of several 10 micrometers - about 300 micrometers, and are a D-mannitol crystal, Nonpareil, a crystalline cellulose grain, granulated sugar, a spray dry lactose, etc. preferably.
[0041] 5) It is the approach of using the spray-drying method spray dryer and carrying out spray drying of a difficulty water solubility drug and the water suspension liquid which is damp and contains an excipient by the improvement agent and request and by which wet grinding was carried out.
[0042] 1.1.2. Form an isolation layer between core granulation and an enteric layer by giving the core granulation which used the fluid bed coating machine, the aeration type coating machine, the rolling flow coating machine, etc., and was obtained [coating machine] by above-mentioned 1.1.1. in the coating liquid containing the formation water soluble polymer and saccharide of the 1st isolation layer. A fluid bed coating machine is used preferably because of uniform coating.
[0043] 1.1.3. On the 1st isolation layer obtained by the core granulation or above-mentioned 1.1.2. obtained by formation above-mentioned 1.1.1. of an enteric layer, the coating liquid containing a plasticizer, lubricant, etc. is given, it dries at an enteric giant molecule and arbitration, and enteric granulation is obtained by forming an enteric layer. The above-mentioned coating liquid is preferably obtained by making an enteric giant molecule and arbitration distribute a plasticizer, lubricant, etc. with the emulsion method, a particle suspension method, a neutralization process, etc. by the aqueous intermediation system.
[0044] 1.2. The preparation immediate-release granulation of immediate-release granulation may be prepared like the core granulation of above-mentioned 1.1.1.
[0045] 2. Preparation 2.1 of the 2nd pharmaceutical preparation ****** of the 2nd pharmaceutical preparation of formation this invention of ****** can be formed like the enteric granulation of the 1st pharmaceutical preparation of the above. That is, ****** is obtained by forming the 1st isolation layer in the perimeter of core granulation at arbitration, and forming an enteric layer further.
[0046] 2.2 In preparing the 2nd isolation layer between formation ****** of the 2nd isolation layer, and a fast-discharging part, it coats with the coating liquid containing the same water soluble polymer and same saccharide as the above-mentioned 1st isolation layer ****** obtained by the above 2.1 by the same approach as the 1st isolation layer.
[0047] 2.3 Prepare the difficulty water solubility drug processed by the formation **** improvement agent of a fast-discharging part, and the coating liquid which contains additives,

such as an excipient, disintegrator, a binder, and lubricant, if needed. Compound granulation is obtained by using and giving a fluid bed coating machine, an aeration type coating machine, a rolling flow coating machine, etc. on the 2nd isolation layer obtained in this coating liquid by ****** obtained by the above 2.1, or the above 2.2. A fluid bed coating machine is used preferably because of uniform coating.

[0048] in preparing the sustained release drug of this invention as a granule, after carrying out each specified quantity weighing capacity of the enteric granulation and immediate-release granulation which were prepared separately as mentioned above in the case of the 1st pharmaceutical preparation, or a request coming out of enteric granulation and immediate-release granulation comparatively and mixing, specified quantity weighing capacity is carried out and it packages separately. In the case of the 2nd pharmaceutical preparation, specified quantity weighing capacity of the compound granulation obtained as mentioned above is carried out, and it is packaged separately.

[0049] When preparing the sustained release drug of this invention as a capsule, after in the case of the 1st pharmaceutical preparation carrying out specified quantity weighing capacity of enteric granulation and the immediate-release granulation, and filling these up with a desired ratio into a capsule or mixing enteric granulation and immediate-release granulation at a desired rate, specified quantity weighing capacity is carried out and a capsule is filled up. In the case of the 2nd pharmaceutical preparation, a specified quantity capsule is filled up with compound granulation. Furthermore, the strip package package (SP package) of this capsule may be carried out.

[0050] In case it prepares in the case of the 1st pharmaceutical preparation (for example, a capsule), since it is difficult, specified quantity weighing capacity of each granulation is carried out separately, and mixing these granulation at an exact rate and filling up a capsule is usually filled up with it in many cases. However, in order to perform capacity weighing capacity, it is tended to change the weighing capacity precision of little direction, when there is little one capacity. Therefore, in such a case, it dilutes with an additive etc., and capacity is made to increase to it so that the active-ingredient (namely, difficulty water solubility drug) concentration of the granulation of an approach with little capacity may become low. However, the fill to a capsule must be increased in this case, as a result, capsule size may become large, and difficulty may be caused to recipe. Since what is necessary is just to carry out weighing capacity of one kind of granulation, there is no fluctuation in capacity precision, the restoration to a capsule is easy, since it is not necessary to make the fill to a capsule increase still as mentioned above, in the case of the 2nd pharmaceutical preparation which prepares the compound granulation which unified ****** and a fast-discharging part, the miniaturization of a capsule can be attained, and it is easy to take. It is also the same as when using as a granule. Therefore, when it is the drug with which it has set to mixing with ****** and a fast-discharging part, and few one [a gap or] amounts of active ingredients are wanted for there to be compared with another side, the 2nd pharmaceutical preparation of this invention is desirable.

[0051] the curve obtained by the optimal ratio of ****** and a fast-discharging part measuring the blood drug concentration of the active ingredient when prescribing enteric granulation and immediate-release granulation for the patient independently, respectively, and performing a curve fitting to each blood-drug-concentration-time amount plot -- compounding -- various mixing ratios -- it can determine by asking for the time amount which maintains the effective blood drug concentration in the case of a rate, the time amount which reaches effective blood drug concentration, and maximum drug concentration. For example, when using EKADO tolyl for a difficulty water solubility drug and a ratio with the EKADO tolyl in ****** and a fast-discharging part is 80:20, blood drug concentration continues for about 8 hours, and the sustained release drug of the durability in which bis die administration is possible is obtained. As a result of preparing such pharmaceutical preparation and medicating a healthy adult, blood-drug-concentration transition was in agreement with a prediction curve and fitness.

[0052]

[Example] Although an example is shown below and this invention is explained to it still more concretely, this invention is not limited to this. Hereafter, the section expresses the weight

section in this example.
[0053] (Example 1)
1) EKADO tolyl was ground using the grinding jet mill grinder of EKADO tolyl, and the grinding end of 3 micrometers of average particles was obtained.
[0054] 2) Mix the grinding EKADO tolyl 80 section obtained by the manufacture above 1 of core granulation, the mannitol 25 section, the corn-starch 15 section, and the carmellose-calcium (CMC-calcium) 5 section. while mixing this end of mixing with a monopodium kneading machine -- 5% water solution of hydroxypropylcellulose (HPC) -- ** -- carrying out — the two sections -- in addition, it kneaded. The obtained kneaded object was corned and refined [dried and] through the grain machine made from a cylinder with a diameter of 7mm, and cylinder-like core granulation was obtained.
[0055] 3) The core granulation 100 above-mentioned section obtained by the coating above 2 of the 1st isolation layer was taught to the fluid bed coating machine, and spray coating of the 15% water solution containing the hydroxypropyl-methylcellulose (HPMC, TC-5E (Shin-etsu chemistry)) 1 section, the white-soft-sugar 5 section, and the talc 8 section was carried out to the 14 sections (solid content) to the core granulation 100 section.
[0056] 4) The ammonia of optimum dose was added in 15% drainage system coating liquid of the coating hydroxypropyl-methylcellulose acetate succinate (HPMCAS) (A quart (Shin-etsu chemistry)) 40 section of an enteric layer, the citric-acid triethyl 5 section, and the talc 10 section, and HPMCAS was neutralized. The 20 sections (solid content conversion) were coated for this coating liquid using the fluid bed coating machine to the granulation 100 section which was obtained by the 3rd above-mentioned term and which carries out the 1st isolation ****.
[0057] 5) To the coating above-mentioned ****** 100 section of the 2nd isolation layer, the liquid 14 section (solid content conversion) of the same presentation ratio as the 1st isolation layer coating liquid was coated using the fluid bed coating machine, and the 2nd isolation layer was formed.
[0058] 6) 10% water solution which contains the grinding EKADO tolyl 20 section obtained by the 1st above-mentioned term, the mannitol 20 section, and the hydroxypropyl-methylcellulose (HPMC-E) 5 section in the granulation which coated the 2nd isolation layer of the coating above of a fast-discharging part was prepared. To the granulation 100 section which coated the above-mentioned 2nd isolation layer, this water-solution 22.7 section (solid content conversion) was coated using the fluid bed coating machine, the fast-discharging part was formed, and the single compound granulation with which coating of the four layers was carried out to core granulation was obtained.
[0059] 7) The No. 3 capsule was filled up with the above-mentioned compound granulation of 100mg considerable amount as encapsulation EKADO tolyl, and capsule pharmaceutical preparation was obtained.
[0060] (Example 2) The EKADO tolyl durability capsule was obtained by the same approach as an example 1 except having carried out 35 section (solid content conversion) coating of the 15% drainage system coating liquid containing the 35 sections of OIDORAGITTO L30D (solid content conversion), the citric-acid triethyl 3.5 section, and the talc 15 section using the Wurster mold fluid bed coating machine to the granulation 100 section which coated the 1st isolation layer obtained by the 3rd term of an example 1, and having formed the enteric layer.
[0061] (Example 3) The grinding EKADO tolyl 80 section obtained by the 1st term of an example 1 was suspended in the HPMC water solution 5%, and spray liquid was prepared. The white-soft-sugar starch spherical granulation (Nonpareil -101) (Freund Industrial) 100 section was taught to CF centrifugal tumbling granulator, the spray of the above-mentioned spray liquid was carried out, sprinkling the mixed end of the lactose 20 section and the cross povidone 3 section, and globular form core granulation was obtained. The EKADO tolyl durability capsule was obtained by the same approach as an example 1 except this.
[0062] (Example 4) The EKADO tolyl durability capsule was prepared by the same approach as an example 1 except using OIDORAGIDDO L55 as a coating basis of an enteric layer.
[0063] (Example 1 of reference) The 1st isolation layer was not given to the core granulation containing the EKADO tolyl obtained by 1 of an example 1, but the direct enteric layer was

coated, and enteric granulation was obtained.
[0064] (Evaluation) After saving the enteric granulation obtained by the 4th term of an example 1, and the enteric granulation obtained in the example 1 of reference for seven days at 60 degrees C, the acid-proof trial of the method convention of a station was performed using the 1st liquid (pH 1.2) of collapse test fluid of the 12th amendment Japanese pharmacopoeia. A result is shown in drawing 1 . With the enteric granulation of an example 1, the rate of elution of 2 hours after was 0%. With the granulation of the example 1 of reference, the rate of elution of 2 hours after was 6%.
[0065] The electron microscope photograph on the front face of granulation when saving these granulation for five days at 60 degrees C is shown in drawing 2 . In the case of the granulation (example 1 of reference) which does not have an isolation layer, drawing 2 shows that EKADO tolyl dissolves and deposits in the enteric layer.
[0066] It was shown that a drug dissolving in an enteric layer and depositing by preparing the 1st isolation layer between core granulation and an enteric layer is prevented, and a good drug release control function is maintained from the above-mentioned result when sustained-release-drug-izing the drug of difficulty water-soluble like especially EKADO tolyl, and a low-melt point point and Takayoshi plastic.
[0067] Furthermore, it checked acid resistance and enteric using the capsule obtained in the example 4. A result is shown in drawing 3 .
[0068]
[Effect of the Invention] According to this invention, the sustained release drug which releases a difficulty water solubility drug gradually and drug effect maintains is offered by combining ****** and the fast-discharging part containing the difficulty water solubility drug which was damp and was processed by the improvement agent. According to this invention, even when a drug with the short disappearance half-life in difficulty water solubility and blood is used, it is possible to make the drug effect maintain. Furthermore, by arranging a water-soluble and inactive isolation layer between the core granulation of **** circles, and an enteric layer, and/or between an enteric layer and a fast-discharging part, even when a low-melt point point and the difficulty water solubility drug of the Takayoshi plasticity are used, a drug release control function is stabilized.

[Translation done.]

(19)日本国特許庁（ＪＰ）　(12) **公開特許公報（A）**　(11)特許出願公開番号

特開平9－249557

(43)公開日　平成9年(1997)9月22日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ		技術表示箇所
Ａ６１Ｋ 31/265	ＡＢＮ		Ａ６１Ｋ 31/265	ＡＢＮ	
	ＡＢＵ			ＡＢＵ	
9/00			9/00	Ｄ	
9/48			9/48	Ｃ	
				Ｆ	

審査請求　未請求　請求項の数10　ＯＬ　（全 8 頁）　最終頁に続く

(21)出願番号　特願平8－58114

(22)出願日　平成8年(1996)3月14日

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(54)【発明の名称】　**難水溶性薬物の徐放性製剤**

(57)【要約】
【課題】　難水溶性薬物の徐放性製剤を提供すること。
【解決手段】　濡れ改善剤で処理された難水溶性薬物を含む速放部、および濡れ改善剤で処理された難水溶性薬物を含有するコア顆粒が腸溶層でコーティングされた遅溶部からなることを特徴とする、徐放性製剤。

1

【特許請求の範囲】

【請求項１】　濡れ改善剤で処理された難水溶性薬物を含む速放部、および濡れ改善剤で処理された難水溶性薬物を含有するコア顆粒が腸溶層でコーティングされた遅溶部からなることを特徴とする、徐放性製剤。

【請求項２】　遅溶部および速放部がそれぞれ顆粒として存在する、請求項１に記載の徐放性製剤。

【請求項３】　遅溶部の周囲に速放部がコーティングされてなる複合顆粒を含む、請求項１に記載の徐放性製剤。

【請求項４】　コア顆粒と腸溶層との間に、水溶性の第１隔離層を有する、請求項１から３のいずれかに記載の徐放性製剤。

【請求項５】　遅溶部と速放部との間に、水溶性の第２隔離層を有する、請求項に３または４に記載の徐放性製剤。

【請求項６】　コア顆粒に、水溶性の第１隔離層、腸溶層、水溶性の第２隔離層、および速放部が順にコーティングされてなる複合顆粒を含む、請求項５に記載の徐放性製剤。

【請求項７】　第１隔離層が、水溶性高分子および糖類を含有する、請求項４から６のいずれかに記載の徐放性製剤。

【請求項８】　第２隔離層が、水溶性高分子および糖類を含有する、請求項４から６のいずれかに記載の徐放性製剤。

【請求項９】　難水溶性薬物が、エカドトリルである、請求項１から８のいずれかに記載の徐放性製剤。

【請求項１０】　カプセル製剤である、請求項１から９のいずれかに記載の徐放性製剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、難水溶性の薬物を含有する徐放性製剤に関する。

【０００２】

【従来の技術】薬物の効果を持続するために、速放部と遅溶部とを組み合わせて徐放性製剤化することが知られている（例えば、特公昭61-13683号公報および特公昭62-32166号公報）。しかし、これらはいずれも、比較的溶解性の高い薬物を使用する場合に限られる。難水溶性の薬物は、これらの方法で徐放化しようとする場合、一般に著しい吸収率の低下がみられるために、このような方法での徐放化は困難であるとされている。特に例えば、エカドトリルのように難水溶性でありかつ血中の消失半減期が短い薬物の場合、徐放化による薬効持続はより困難となる。

【０００３】

【発明が解決しようとする課題】本発明の目的は、難水溶性の薬物を徐放することにより薬効が持続する徐放性製剤を提供することである。特に、エカドトリルのような難水溶性かつ血中の消失半減期が短い薬物の薬効が持続する製剤を提供することである。

2

【０００４】

【課題を解決するための手段】本発明の徐放性製剤は、濡れ改善剤で処理された難水溶性薬物を含む速放部、および濡れ改善剤で処理された難水溶性薬物を含有するコア顆粒が腸溶層でコーティングされた遅溶部からなる。

【０００５】好適な実施態様においては、前記遅溶部および速放部はそれぞれ顆粒として存在する。

【０００６】好適な実施態様においては、本発明の徐放性製剤は、前記遅溶部の周囲に前記速放部がコーティングされてなる複合顆粒を含む。

【０００７】好適な実施態様においては、本発明の徐放性製剤は、前記コア顆粒と前記腸溶層との間に、水溶性の第１隔離層を有する。

【０００８】好適な実施態様においては、本発明の徐放性製剤は、前記遅溶部と前記速放部との間に、水溶性の第２隔離層を有する。

【０００９】好適な実施態様においては、本発明の徐放性製剤は、難水溶性薬物を含有するコア顆粒に、水溶性の第１隔離層、腸溶層、水溶性の第２隔離層、および速放部が順にコーティングされてなる複合顆粒を含む。

【００１０】好適な実施態様においては、難水溶性薬物は、エカドトリルである。

【００１１】好適な実施態様においては、本発明の徐放性製剤は、カプセル製剤である。

【００１２】

【発明の実施の形態】本発明の徐放性製剤は速放部が胃において薬物を放出し、次いで遅溶部が腸で薬物を放出するため、持続的な薬効が得られる。この製剤は、代表的には次の第１および第２の製剤であり得る。

【００１３】本発明の第１の徐放性製剤においては、遅溶部と速放部は各々、腸溶性顆粒と速放性顆粒として別々に存在する。この腸溶性顆粒は、濡れ改善剤で処理された難水溶性薬物を含むコア顆粒が、腸溶層でコーティングされている。速放性顆粒は、腸溶性顆粒のコア顆粒と本質的に同質であり得る。すなわち、濡れ改善剤で処理された難水溶性薬物を含み、かつ腸溶層を有さない顆粒である。これらの腸溶性顆粒と速放性顆粒を所望の割合で混合することによって、本発明の第１の徐放性製剤が得られる。

【００１４】本発明の第２の徐放性製剤においては、遅溶部および速放部は、遅溶部の周囲が速放部によってコーティングされた、同一顆粒中に遅溶部と速放部の両方を含む複合顆粒として存在する。ここで遅溶部は上記第１の製剤の場合と同様に、濡れ改善剤で処理された難水溶性薬物を含むコア顆粒が腸溶層でコーティングされている。

【００１５】上記第１および第２の製剤において、遅溶部のコア顆粒に含まれる難水溶性の薬物とは、日本薬局

方で定義される「溶けにくい」、「極めて溶けにくい」または「ほとんど溶けない」に相当する薬物を意味し、溶質1gまたは1mlを溶かすに要する溶媒量が100ml以上（20℃）である任意の薬物であり得る。このような難水溶性薬物としては、エカドトリル、ニフェジピン、グリセオフルビン、フェニトイン、スルフィソキサザール、アミノピリン、セコバルビタール、プレドニゾロン、インドメタシン、フェナセチン、フェノバルビタール、トルブタミドなどが挙げられる。好適にはエカドトリルが用いられる。エカドトリル(N-[(S)-α-(アセチルチオメチル)ヒドロシンナモイル]グリシンベンジルエステル；N-[(S)-α-(mercaptomethyl)hydrocinnamoyl] glycine, benzyl ester, acetate(ester)は、降圧薬および心不全治療薬として利用されるエンケファリナーゼ阻害剤であり、水に対する溶解度は約33μg/ml(37℃)、融点70～74℃、体内消失半減期は1時間以下の薬物である。

【００１６】上記第1および第2の製剤において、遅溶部のコア顆粒に含まれる上記難水溶性薬物の粒径は、できるだけ小さい程溶解速度が高くなるため有利であり、10μm 以下、好ましくは3μm以下である。微細な薬物粒子が晶析段階で得られない場合には、溶解速度の改善を図るために、常法により粉砕機などを用いて粉砕し、実質的な薬物の表面積を大きくする。粉砕機としては、例えば、ジェットミル、ボールミル、ハンマーミル、加圧型ホモジェナイザー、コロイドミル、ナノマイザー、ローラーミルなどが用いられ、薬物単独または薬物と添加剤との混合系で乾式粉砕または湿式粉砕する。融点の低い薬物を粉砕する場合は発熱の小さい粉砕方法が好ましい。コア顆粒中の難水溶性薬物の含量は、コア顆粒に対して30～80重量%、好ましくは45～65重量%である。

【００１７】上記濡れ改善剤は、難水溶性薬物の粒子表面の濡れを改善して、溶解速度を向上するために用いられる。すなわち、濡れの悪い薬物（水に対する接触角が大きく、疎水性かつ撥水性の薬物）の表面に薄い皮膜が形成され、濡れ易さが改善されると、薬物の水をはじく性質が弱められ、水に分散しやすくなる。すなわち、薬物の溶解性が向上する。このような濡れ改善剤としては、ヒドロキシプロピルセルロース（HPC）、ヒドロキシプロピルメチルセルロース(HPMC)、メチルセルロース、ポビドン、ポリビニールアルコール、ゼラチンなどの水溶性高分子、ラウリル硫酸ナトリウム、モノステアリン酸ポリエチレングリコール、モノステアリン酸グリセリン、ポリオキシエチレンロルビタン脂肪酸エステル、ポリオキシエチレン硬化ヒマシ油、ポリオキシエチレンポリオキシプロピレングリコールなどの界面活性剤などが挙げられ、なかでもヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロースが好ましい。濡れ改善剤は、難水溶性薬物の粒子表面に付着する形で、難水溶性薬物と一緒にコア顆粒中に含まれる。濡れ改善剤のコア顆粒中の含有量は、難水溶性薬物100重量部に対して20重量部以下、好ましくは2～10重量部、さらに好ましくは3～6重量部である。

【００１８】遅溶部のコア顆粒は上記難水溶性薬物および濡れ改善剤に加えて、崩壊剤、賦形剤、結合剤、着色剤、着香剤、安定化剤などの製剤学上許容される添加剤を含有し得る。

【００１９】上記崩壊剤は製剤に崩壊性を与える薬剤であって、難水溶性薬物を速やかに分散するために用いられる。崩壊剤は、水には溶解しないが水との親和性に優れ、水との接触により膨潤し、薬物と水との接触を助ける物質である。このような崩壊剤としては、カルメロースカルシウム（CMC-Ca）、低置換度ヒドロキシプロピルセルロース、部分アルファー化デンプン、カルボキシメチルスターチナトリウム、低置換度カルボキシメチルスターチナトリウム、クロスカルメロースナトリウム、結晶セルロース、クロスポビドンなどがあげられ、なかでもカルメロースカルシウム、低置換度ヒドロキシプロピルセルロース、クロスカルメロースナトリウム、およびクロスポビドンなどが好ましい。コア顆粒中の崩壊剤の含有量は難水溶性薬物100重量部に対して20重量部以下、好ましくは5～15重量部、より好ましくは7～12重量部である。

【００２０】上記賦形剤は、製剤に所定の大きさと重量を与えるために用いられる。本発明に使用される賦形剤は、好ましくは、微粉砕した水溶性賦形剤、または水溶性賦形剤と親水性賦形剤との混合物である。水溶性賦形剤としては、例えば、乳糖、白糖、マンニトールなどが挙げられる。親水性賦形剤としては、例えば、トウモロコシデンプン、バレイショデンプン、ヒドロキシプロピルスターチなどのデンプン類、無水ケイ酸、無水リン酸水素カルシウムなどの無機塩類が挙げられる。

【００２１】上記結合剤は、成分粉末の混合物に結合力を与え安定な顆粒を製するために用いられる。このような結合剤としては、例えば、メチルセルロース、ポビドン、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、可溶性アルファー化デンプン、ポリビニールアルコール、ゼラチン、デキストリンなどが挙げられ、なかでもヒドロキシプロピルセルロース、およびヒドロキシプロピルメチルセルロースは、濡れ改善効果も合わせ持つために好ましい。

【００２２】上記着色剤としては酸化鉄、レーキ色素類などが用いられ得る、上記着香剤としては各種の香料が用いられ得る。上記安定化剤としては亜硫酸水素ナトリウムなどが用いられ得る。

【００２３】上記添加剤の含有量は、薬物の種類、製剤の使用目的、剤形の大きさ、製造方法、他の添加剤の種類および量などに依存して、各々適宜調節される。

【００２４】上記第1および第2の製剤において、上記遅溶部のコア顆粒にコーティングされる腸溶層は腸溶性

高分子を含む層であり、胃では不溶で腸で溶解する。腸溶層の存在により、コア顆粒内の薬物は胃内で放出されず、製剤が胃から腸に移行するに従って徐々に放出される。上記腸溶性高分子としては、オイドラギットL（メタアクリル酸コポリマー（レームファーマ社））およびL30D（メタアクリル酸コポリマーLD（レームファーマ社））、ヒドロキシプロピルメチルセルロースフタレート（HPMCP）、セルロースアセテートフタレート（CAP）、ヒドロキシプロピルメチルセルロースアセテートサクシネート（HPMCAS）、カルボキシメチルエチルセルロース（CMEC）、およびこれらに類似する高分子などが挙げられる。腸溶層は、このような腸溶性高分子を用いてコーティング液を調製し、コア顆粒をコーティングすることによって形成されるので、安全性および残留溶媒の観点から、水系の溶媒と共に使用できる腸溶性高分子（例えば、HPMCASなど）が好ましい。

【００２５】腸溶層は、上記腸溶性高分子の他に、安定性を確保するため、およびコーティング操作を容易にするために、可塑剤、滑沢剤などを含有し得る。可塑剤としては、クエン酸トリエチル、トリアセチン、グリセリン脂肪酸エステル、コハク酸ジブチル、マクロゴール、およびこれらに類似の可塑剤などが挙げられる。滑沢剤としては、タルク、ステアリン酸マグネシウム、ステアリン酸モノグリセライドなどが挙げられる。腸溶層のコーティング量は、コア顆粒の大きさ、形状などに依存するが、好ましくは、コア顆粒100重量部に対して乾燥状態で15～50重量部、さらに好ましくは20～40重量部である。

【００２６】特に、エカドトリルのように疎水性が強く難水溶性であると共に低融点、高可塑性の薬物を製剤化する場合、上記コア顆粒と腸溶層との間に、さらに、水溶性で不活性の隔離層（第１隔離層）を設けることが好ましい。このような難水溶性かつ低融点の薬物を含有する顆粒に直接腸溶層をコーティングした場合、腸溶層中に薬物が溶解し、徐々に腸溶層表面に薬物が析出するため、薬物の放出を制御することが困難になるからである。このような析出現象は、特に、腸溶層のコーティングを行った後の乾燥工程、あるいは製剤の加温加速試験時に顕著に発生する。上記の第１隔離層をコア顆粒と腸溶層との間に設けることによって、このような腸溶層への薬物の溶解を防止することが可能となり、製剤の薬物放出を安定に制御し得る。

【００２７】上記第１隔離層は、通常、水溶性高分子および糖類を含有する液をコア顆粒にコーティングして形成される。水溶性高分子としては、ヒドロキシプロピルセルロース（HPC）、ヒドロキシプロピルメチルセルロース（HPMC）、ポビドン（PVP）などが挙げられる。糖類としては白糖、乳糖などが挙げられる。隔離層はさらにタルクなどの滑沢剤を含み得る。第１隔離層は、好ましくは、コア顆粒100重量部に対して、乾燥状態で５～30重量部、さらに好ましくは10～20重量部の割合でコーティングされる。

【００２８】本発明の徐放性製剤に含まれる速放部は、上記のように、本発明の第１の製剤では速放性顆粒として腸溶性顆粒とは別に存在し、そして本発明の第２の製剤では遅溶部の周囲をコーティングしている。この速放部は、上記遅溶部に含有される難水溶性薬物と同種の薬物を含有する。速放部に含まれる難水溶性薬物も、遅溶部の場合と同様、粒径が小さい程、溶解速度が高くなるため好ましく、粒径は10μm以下、好ましくは３μm以下である。従って、速放部の難水溶性薬物も遅溶部の場合と同様に、粉砕して用いられることが好ましい。速放部中の難水溶性薬物の含有量は速放部に対して通常30～80重量%、好ましくは40～60重量%である。速放部の難水溶性薬物も、その溶解速度を向上させ、薬物の速やかな放出および吸収を促進するために濡れ改善剤で処理されている。速放部中の濡れ改善剤の含有量は速放部中の難水溶性薬物100重量部に対して120重量部以下、好ましくは10～100重量部、さらに好ましくは20～50重量部である。

【００２９】速放部はさらに、崩壊剤、賦形剤、結合剤、滑沢剤、帯電防止剤、着色剤、着香剤、安定化剤などの製剤学上許容される添加剤を含有し得る。これらの添加剤としては、上記遅溶部で使用され得る添加剤と同様のものが使用され得る。その含有量は、薬物の種類、製剤の使用目的、剤形の大きさ、製造方法、他の添加剤の種類および量などに依存して、各々適宜調節される。難水溶性薬物の含量均一性を確保するために速放部は賦形剤を含有することが好ましい。速放部中の賦形剤の含有量は特に制限されないが通常、速放部中の難水溶性薬物100重量部に対して250重量部以下、好ましくは50～200重量部、さらに好ましくは70～100重量部である。

【００３０】本発明の第２の製剤の場合、特に、エカドトリルのように疎水性が強く難水溶性であると共に低融点、高可塑性の薬物を製剤化する場合、上記遅溶部と速放部との間には、水溶性で不活性の隔離層（第２隔離層）を設けることが好ましい。この第２隔離層を配置することによって、速放部から腸溶層への薬物の溶解が防止され、薬物の放出を安定に制御し得る。第２隔離層は第１隔離層と同様の組成を有し、同様の方法によりコーティングされる。第２隔離層は、好ましくは、遅溶部100重量部に対して、乾燥状態で５～30重量部、さらに好ましくは10～20重量部の割合でコーティングされる。

【００３１】本発明の徐放性製剤の剤形は、好ましくは、カプセル剤または顆粒剤である。第１の製剤の場合、腸溶性顆粒と速放性顆粒とを各々所定量づつ用いて、常法に従って、カプセル剤、顆粒剤などの任意の剤形の本発明の徐放性製剤が得られ得る。第２の製剤の場合は複合顆粒を所定量用いて、上記第１の製剤の場合と同様に任意の剤形の本発明の徐放性製剤が得られ得る。

【００３２】このようにして得られた本発明の徐放性製剤は、まず、胃で速放部が溶出し、薬物の体内濃度は速やかに有効濃度まで達する。このとき、遅溶部は変化しない。遅溶部は、胃から徐々に排出された後、腸溶層が溶け出してから薬物を放出する。従って、薬効が長時間持続する。

【００３３】（製造方法）以下、本発明の徐放性製剤の代表的な製造方法について説明する。

【００３４】１．第１の製剤の製造方法

1.1　腸溶性顆粒の調製法

腸溶性顆粒は、難水溶性薬物を含有するコア顆粒に任意に第１隔離層をコーティングし、さらに腸溶層をコーティングすることにより得られる。

【００３５】1.1.1.　コア顆粒の形成

コア顆粒は、上記のように粉砕などの手段で微細化された難水溶性薬物を、その結晶表面の濡れ特性を上記濡れ改善剤で改善しながら造粒することによって製造され得る。その処理方法は、濡れ易さが改善される限りにおいては任意の造粒方法によって行われ得る。以下にその方法のいくつかの例を挙げる。難水溶性薬物の含量が大きい場合には以下の１）の混練法が最も簡便かつ有効である。

【００３６】１）混練法

難水溶性薬物粉末、濡れ改善剤、水および所望により任意の添加剤（賦形剤、崩壊剤、結合剤など）からなる混合物を、練合機を用いて湿式練合する。このことにより、難水溶性薬物の結晶表面に濡れ改善剤が付与されて表面処理された状態となる。練合設備としては、ハイスピードミキサー、レディゲミキサー、リボンブレンダー、単軸または複軸練合機などを使用する。得られた練合物を、篩ほぐし法、押し出し製粒法などの方法で造粒し、乾燥、調粒を経てコア顆粒を得る。

【００３７】別の方法として、微粉砕していない未処理の難溶性薬物に濡れ改善剤の水溶液または水を適量添加し、これを湿式粉砕法によって微粉砕した水懸濁液を調製し、この水懸濁液を任意の添加剤に加えて、上記のように湿式練合して造粒してもよい。この水懸濁液は、さらに賦形剤（好ましくは水溶性の賦形剤）を含有し得る。

【００３８】２）撹拌造粒法

ブレード回転型ミキサーまたはハイシェアミキサーを使用し、上記１の混練法と同様に、撹拌造粒、乾燥、調粒して主薬顆粒を得る方法である。あるいは上記１の場合と同様に難溶性薬物、濡れ改善剤および所望により賦形剤を含有する、湿式粉砕された水懸濁液を所望の種類の添加剤粉末または混合末に加えて撹拌造粒し得る。

【００３９】３）流動層造粒法

流動層造粒機を使用し、難水溶性薬物、濡れ改善剤および所望により賦形剤を含有する、湿式粉砕された水懸濁液を、流動させた所望の種類の添加剤粉末または混合末にスプレーしながら造粒する。スプレー方式としては、トップスプレー、サイドスプレー、タンジェンシャルスプレーのいずれをも用い得る。難溶性薬物を混合末に添加して流動させ、これに濡れ改善剤、結合剤などの水溶液または水をスプレーする通常の方法では、薬物の撥水性が高いために、造粒が困難である。

【００４０】４）コーティング造粒法

流動層造粒機、旋回型流動層造粒機、またはワースター型造粒機を使用し、難水溶性薬物、濡れ改善剤および所望により賦形剤を含有する、湿式粉砕された水懸濁液を、核粒子にスプレーしてコーティング造粒する方法である。核粒子は、数10μm～300μm程度の粒径の任意の粒子であり得、好ましくは、D-マンニトール結晶、ノンパレル、結晶セルロース粒、グラニュー糖、スプレードライ乳糖などである。

【００４１】５）スプレードライ法

スプレードライヤーを使用し、難水溶性薬物、濡れ改善剤および所望により賦形剤を含有する湿式粉砕された水懸濁液を噴霧乾燥する方法である。

【００４２】1.1.2.　第１隔離層の形成

水溶性高分子および糖類を含有するコーティング液を、流動層コーティング機、通気式コーティング機、転動流動コーティング機などを使用して、上記1.1.1.で得られたコア顆粒に付与することによりコア顆粒と腸溶層との間に隔離層を形成する。均一なコーティングのために好ましくは流動層コーティング機が使用される。

【００４３】1.1.3.　腸溶層の形成

上記1.1.1.で得られるコア顆粒または上記1.1.2.で得られる第１隔離層上に、腸溶性高分子と任意に可塑剤、滑沢剤などを含有するコーティング液を付与して乾燥し、腸溶層を形成することにより腸溶性顆粒がえられる。上記コーティング液は、好ましくは、腸溶性高分子および任意に可塑剤、滑沢剤などを水溶媒系でエマルジョン法、微粒子懸濁法、中和法などにより分散させることにより得られる。

【００４４】1.2.　速放性顆粒の調製

速放性顆粒は、上記1.1.1.のコア顆粒と同様に調製され得る。

【００４５】２．第２の製剤の調製

2.1　遅溶部の形成

本発明の第２の製剤の遅溶部は、上記第１の製剤の腸溶性顆粒と同様に形成し得る。すなわち、コア顆粒の周囲に任意に第１の隔離層を形成し、さらに腸溶層を形成することによって遅溶部が得られる。

【００４６】2.2　第２隔離層の形成

遅溶部と速放部との間に第２隔離層を設ける場合には、上記2.1で得られる遅溶部に、上記第１隔離層と同様の水溶性高分子および糖類を含有するコーティング液を、第１隔離層と同様の方法によってコーティングする。

【００４７】2.3　速放部の形成

濡れ改善剤で処理された難水溶性薬物と、必要に応じて賦形剤、崩壊剤、結合剤、滑沢剤などの添加剤とを含有するコーティング液を調製する。このコーティング液を、上記2.1で得られる遅溶部または上記2.2で得られる第２隔離層上に、流動層コーティング機、通気式コーティング機、転動流動コーティング機などを使用して、付与することによって複合顆粒が得られる。均一なコーティングのために好ましくは流動層コーティング機が使用される。

【００４８】本発明の徐放性製剤を顆粒剤として調製する場合には、第１の製剤の場合、上記のように別々に調製した腸溶性顆粒および速放性顆粒を各々所定量秤量するか、あるいは腸溶性顆粒と速放性顆粒とを所望の割合で混合した後、所定量秤量し、分包する。第２の製剤の場合、上記のようにして得られた複合顆粒を所定量秤量し、分包する。

【００４９】本発明の徐放性製剤をカプセル剤として調製する場合は、第１の製剤の場合、腸溶性顆粒および速放性顆粒を所定量秤量し、これらを所望の比でカプセルに充填するか、あるいは腸溶性顆粒と速放性顆粒を所望の割合で混合した後、所定量秤量し、カプセルに充填する。第２の製剤の場合、複合顆粒を所定量カプセルに充填する。さらに、このカプセル剤をストリップパッケージ包装（ＳＰ包装）してもよい。

【００５０】第１の製剤の場合、例えばカプセル剤を調製する際には、これらの顆粒を正確な割合で混合してカプセルに充填することは通常、困難であるため、各顆粒を別々に所定量秤量して充填することが多い。しかし、容量秤量を行うため一方の容量が少ない場合には、少ない方の秤量精度が変動しやすい。従って、このような場合には、容量の少ない方法の顆粒の活性成分（すなわち難水溶性薬物）濃度が低くなるように添加剤などで希釈して容量を増加させる。しかし、この場合カプセルへの充填量を増加しなければならず、その結果カプセルサイズが大きくなって服用に困難をきたすことがある。遅溶部と速放部とを一体化した複合顆粒を調製する第２の製剤の場合は、一種類の顆粒を秤量すればよいので容量精度に変動がなく、カプセルへの充填が容易であり、さらに上記のようにカプセルへの充填量を増加させる必要がないので、カプセルの小型化が図れ、服用が容易である。顆粒剤として用いる場合も同様である。従って、遅溶部と速放部との混合においていずれか一方の活性成分量が他方に比べて少ないことが望まれるような薬物の場合には、本発明の第２の製剤が好ましい。

【００５１】遅溶部と速放部との最適な比率は、腸溶性顆粒と速放性顆粒をそれぞれ単独に投与したときの活性成分の血中濃度を測定し、それぞれの血中濃度－時間プロットに対してカーブフィッティングを行い、得られた曲線を合成して、種々の混合比率の場合の、有効血中濃度を持続する時間、有効血中濃度に到達する時間、および最高血中濃度を求めることによって決定し得る。例えば、難水溶性薬物にエカドトリルを使用する場合、遅溶部中と速放部中のエカドトリルとの比率が80：20のとき、血中濃度が約８時間持続し、１日２回投与が可能な持続性の徐放性製剤が得られる。このような製剤を調製し、健常な成人に投与した結果、血中濃度推移は、予測カーブと良好に一致した。

【００５２】

【実施例】以下に実施例を示して本発明をさらに具体的に説明するが、本発明はこれに限定されるものではない。以下、本実施例中で部は重量部を表す。

【００５３】（実施例１）

１）　エカドトリルの粉砕

ジェットミル粉砕機を用いてエカドトリルを粉砕し、平均粒子3μmの粉砕末を得た。

【００５４】２）　コア顆粒の製造

上記１）で得られた粉砕エカドトリル80部、マンニトール25部、コーンスターチ15部、およびカルメロースーカルシウム（CMC-Ca）５部を混合する。この混合末を単軸練合機で混合しながら、ヒドロキシプロピルセルロース（HPC）の５％水溶液をとして２部加えて混練した。得られた練合物を直径7mmの円筒製粒機を通して造粒し、乾燥、調粒して円柱状のコア顆粒を得た。

【００５５】３）　第１隔離層のコーティング

上記２）で得られた上記コア顆粒100部を流動層コーティング機に仕込み、ヒドロキシプロピルメチルセルロース（HPMC、TC-5E(信越化学)）１部、白糖５部、およびタルク８部を含む15％水溶液をコア顆粒100部に対して14部（固形分）までスプレーコーティングした。

【００５６】４）　腸溶層のコーティング

ヒドロキシプロピルメチルセルロースアセテートサクシネート（HPMCAS）（Aコート（信越化学））40部、クエン酸トリエチル5部、およびタルク10部の15％水系コーティング液に適量のアンモニアを添加してHPMCASを中和した。上記３項で得られた第１隔離層有する顆粒100部に対し、このコーティング液を20部（固形分換算）を流動層コーティング機を用いてコーティングした。

【００５７】５）　第２隔離層のコーティング

上記遅溶部100部に対し、第１隔離層コーティング液と同一組成比の液14部（固形分換算）を流動層コーティング機を用いてコーティングし、第２隔離層を形成した。

【００５８】６）　速放部のコーティング

上記第２隔離層をコーティングした顆粒に、上記１項で得られた粉砕エカドトリル20部、マンニトール20部、ヒドロキシプロピルメチルセルロース(HPMC-E)５部を含む10%水溶液を調製した。上記第２隔離層をコーティングした顆粒100部に対し、この水溶液22.7部（固形分換算）を流動層コーティング機を用いてコーティングし、速放部を形成し、コア顆粒に対して４層がコーティングされた単一の複合顆粒を得た。

【００５９】７）　カプセル充填
エカドトリルとして100mg相当量の上記複合顆粒を３号カプセルに充填し、カプセル製剤を得た。

【００６０】（実施例２）実施例１の３項で得られた第１隔離層をコーティングした顆粒100部に対し、オイドラギットL30D（固形分換算）の35部、クエン酸トリエチル3.5部、およびタルク15部を含む15％水系コーティング液をワースター型流動層コーティング機を用いて35部（固形分換算）コーティングして腸溶層を形成したこと以外は、実施例１と同様の方法でエカドトリル持続性カプセル剤を得た。

【００６１】（実施例３）実施例１の１項で得られた粉砕エカドトリル80部を５％HPMC水溶液に懸濁し、スプレー液を調製した。CF遠心転動造粒機に白糖デンプン球状顆粒（ノンパレル-101）（フロイント産業）100部を仕込み、乳糖20部およびクロスポビドン３部の混合末を散布しながら上記スプレー液をスプレーし、球形のコア顆粒を得た。このこと以外は、実施例１と同様の方法でエカドトリル持続性カプセル剤を得た。

【００６２】（実施例４）腸溶層のコーティング基剤としてオイドラギッドL55を使用する以外は、実施例１と同様の方法によってエカドトリル持続性カプセル剤を調製した。

【００６３】（参考例１）実施例１の１）で得られたエカドトリルを含有するコア顆粒に第１隔離層を付与せず、直接腸溶層をコーティングし、腸溶性顆粒を得た。

【００６４】（評価）実施例１の４項で得られた腸溶性顆粒、および参考例１で得られた腸溶性顆粒を60℃で７日間保存した後、第１２改正日本薬局方の崩壊試験液第１液（pH 1.2）を用いて局方規定の耐酸性試験を行った。結果を図１に示す。実施例１の腸溶性顆粒では、２時間後の溶出率は０％であった。参考例１の顆粒では、＊２時間後の溶出率は６％であった。

【００６５】これらの顆粒を60℃で５日間保存したときの顆粒表面の電子顕微鏡写真を図２に示す。図２から、隔離層を有さない顆粒（参考例１）の場合、エカドトリルが腸溶層に溶解および析出しているのが分かる。

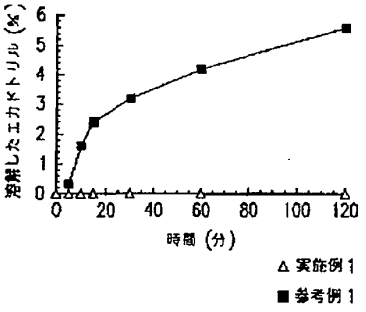
【００６６】上記の結果から、特にエカドトリルのような難水溶性かつ低融点・高可塑性の薬物を徐放性製剤化する場合には、コア顆粒と腸溶層との間に第１隔離層を設けることによって、薬物が腸溶層に溶解して析出されることが防止され、良好な薬物放出制御機能が維持されることが示された。

【００６７】さらに、実施例４で得られたカプセル剤を用いて、耐酸性および腸溶性を確認した。結果を図３に示す。

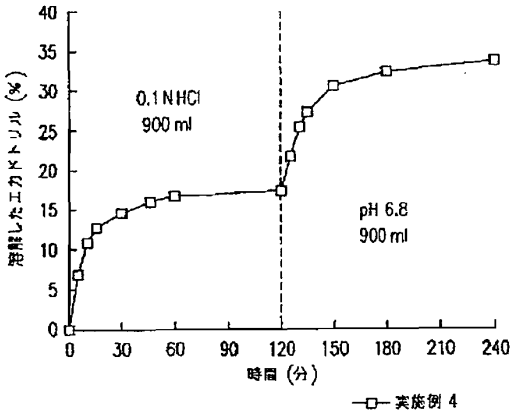
【００６８】
【発明の効果】本発明によれば、濡れ改善剤により処理された難水溶性薬物を含む、遅溶部と速放部とを組み合わせることにより、難水溶性薬物を徐放して薬効が持続する徐放性製剤が提供される。本発明によれば、難水溶性かつ血中の消失半減期が短い薬物を用いた場合でも、その薬効を持続させることが可能である。さらに、遅溶部内のコア顆粒と腸溶層との間および／または腸溶層と速放部との間に水溶性で不活性の隔離層を配置することにより、低融点、高可塑性の難水溶性薬物を用いた場合でも薬物放出制御機能は安定化される。

【図面の簡単な説明】
【図１】第１隔離層を有する腸溶性顆粒、および第１隔離層を有さない腸溶性顆粒の溶出曲線である。
【図２】第１隔離層を有する腸溶性顆粒、および第１隔離層を有さない腸溶性顆粒を60℃で５日間保存した後の、顆粒表面の電子顕微鏡写真である。
【図３】本発明の徐放性製剤の溶出曲線である。

【図１】

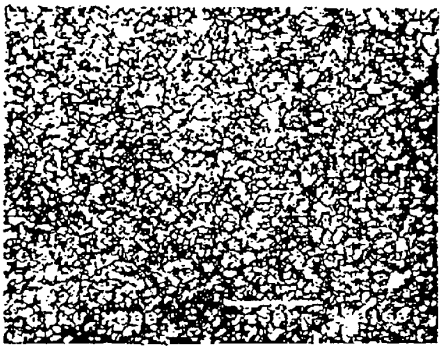


【図３】



【図２】

参考例　１



実施例　１

フロントページの続き

(51)Int.Cl.[6]		識別記号	庁内整理番号	FI		技術表示箇所
Ａ６１Ｋ	9/52			Ａ６１Ｋ	9/52	Ａ
						Ｊ
						Ｎ
	47/14				47/14	Ｄ
	47/26	ＡＥＤ			47/26	ＡＥＤＤ
	47/32				47/32	Ｄ
	47/34				47/34	Ｄ
	47/38				47/38	Ｄ

Electronic Acknowledgement Receipt

EFS ID:	2102034
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Jay Philip Lessler/Lillian Garcia
Filer Authorized By:	Jay Philip Lessler
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	20-AUG-2007
Filing Date:	12-MAY-2006
Time Stamp:	17:22:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		01209479.pdf	1152990 f4dd8a180503cbfbc5de89bf07ef079f240e6259	yes	24

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Information Disclosure Statement Letter	1	4
	Information Disclosure Statement (IDS) Filed	5	8
	NPL Documents	9	24

Warnings:					
Information:					
2	Foreign Reference	01209426.pdf	266796 88f341ed8f0745da19ad2db893a7ae1f189888ca	no	6
Warnings:					
Information:					
3	Foreign Reference	01209444.pdf	436204 1a3c07924268e3a196d0d36217579ef8efa78898	no	10
Warnings:					
Information:					
4	Foreign Reference	01209432.pdf	861660 05afc85d8a2fa1e24a1a3bc3b58522b51f8e856d	no	14
Warnings:					
Information:					
5	Foreign Reference	01209423.pdf	214698 e41e8edbcfe88327bc4027306694425d0fd611d0	no	6
Warnings:					
Information:					
6	Foreign Reference	01209443.pdf	1028217 555a17896ce91c31d5fd6d0a05829111f57acde2	no	14
Warnings:					
Information:					
7	Foreign Reference	01209438.pdf	570620 4fab43b14c8967d7a275bd1f85d224fa5d7d91ff	no	9
Warnings:					
Information:					
8	Foreign Reference	01209424.pdf	434417 9bb63bd838ce7bdd11b5948dd36f74a7ff52b89c	no	11
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Information:					
9	Foreign Reference	01209447.pdf	1615626 a8127a8f666bea3e85f68e2c47e1e2dfee0c5956	no	20
Warnings:					
Information:					
			Total Files Size (in bytes):	6581228	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 | Confirmation No.: 7083

Filed: May 12, 2006 | Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. Payment in the amount of the fee set forth in 1. 17(p), presently believed to be $180, is enclosed.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(p) payment in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[x] A. Pursuant to the Notice issued by the United States Patent and Trademark Office dated August 5, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the U.S. Patent(s) and/or U.S. Patent Application Publication(s) on PTO/SB/08 is/are not being submitted.

[ ] B. Document(s) _____ is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[ ] 3. Cite Nos. _____ are not in the English language. In accordance with 1.98(c), Applicant states:

[ ] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application , or English-language abstract (or claim) is enclosed.

[ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

[x] 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

[ ] 5. Other information being provided for the examiner's consideration follows:

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

No fee is believed to be due for the filing of this Information Disclosure Statement. The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: January 10, 2008

Respectfully submitted,

By /FB/ Flynn Barrison (53,970)
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Attorneys/Agents For Applicant

PTO/SB/08a (05-07)
Approved for use through 11/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99**)		
	Application Number	11383066
	Filing Date	2006-05-12
	First Named Inventor	Amir Shojaei
	Art Unit	1615
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	20342/1202653-US8

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	2881113		1959-04-07		

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11383066
	Filing Date	2006-05-12
	First Named Inventor	Amir Shojaei
	Art Unit	1615
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	20342/1202653-US8

	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11383066
	Filing Date	2006-05-12
	First Named Inventor	Amir Shojaei
	Art Unit	1615
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	20342/1202653-US8

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/FB/ Flynn Barrison (53,970)	Date (YYYY-MM-DD)	2008-01-10
Name/Print	Thomas H. Burrows, Jr.	Registration Number	60463

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	2696896
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	7278
Filer:	Jay Philip Lessler/Lillian Garcia
Filer Authorized By:	Jay Philip Lessler
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	10-JAN-2008
Filing Date:	12-MAY-2006
Time Stamp:	12:24:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1		01379531.PDF	167587 8659b1201bca75edcbd50ae50be127bad1420a58	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Information Disclosure Statement Letter	1	4
	Information Disclosure Statement (IDS) Filed	5	8
Warnings:			
Information:			
	Total Files Size (in bytes):	167587	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 | Confirmation No.: 7083

Filed: May 12, 2006 | Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [X] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. Payment in the amount of the fee set forth in 1. 17(p), presently believed to be $180, is enclosed.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(p) payment in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

☐ A. Pursuant to the Notice issued by the United States Patent and Trademark Office dated August 5, 2003 waiving the requirements of 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the U.S. Patent(s) and/or U.S. Patent Application Publication(s) on PTO/SB/08 is/are not being submitted.

☐ B. Document(s) _____ is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

☐ C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

☒ 3. Cite Nos. CC are not in the English language. In accordance with 1.98(c), Applicant states:

☐ An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application , or English-language abstract (or claim) is enclosed.

☒ The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

☐ A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

☐ A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

☐ A concise explanation of document(s) _____ can be found on the attached sheet.

☐ 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

☒ 5. Other information being provided for the examiner's consideration follows: **EP Search Report, dated August 21, 2008.**

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of' the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: September 18, 2008

Respectfully submitted,

By /Flynn Barrison 53,970/
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New York, New York 10008-0770
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Attorneys/Agents For Applicant

PTO/SB/08a (08-08)
Approved for use through 09/30/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	11/383,066-Conf. #7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	20342/1202653-US8

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (08-08)
Approved for use through 09/30/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	**11/383,066-Conf.** #7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	20342/1202653-US8

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Neville et al., *Disintegration of Dextran Sulfate Tablet Products: Effect of Physicochemical Properties,* Drug Development and Industrial Pharmacy, New York, NY, vol. 18, no. 19, 1 January 1992 (1992-01-01), pages 2067-2079, XP009092848, ISSN: 0363-9045	
		Patrick et al., *Pharmacology of Methylphenidate, Amphetamine Enantiomers and pemoline in Attention-Deficit Hyperactivity Disorder,* Human Psychopharmacology, vol. 12, pp. 527-546 (1997)	
		Chaumeil et al., *Enrobages gastro-resistants a l'acetophtalate de cellulose,* Annales Pharmaceutiques Francaises, 1973, no. 5, pp. 375-384	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	3968163
Application Number:	11383066
International Application Number:	
Confirmation Number:	7083
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir Shojaei
Customer Number:	07278
Filer:	Marie Louise Collazo/Judy Yeddo
Filer Authorized By:	Marie Louise Collazo
Attorney Docket Number:	20342/1202653-US8
Receipt Date:	18-SEP-2008
Filing Date:	12-MAY-2006
Time Stamp:	18:01:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		IDS_SBO8.PDF	63046 2fc4b3c5d5a05ec71e3c3651094cf08754d07174	yes	6

	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Information Disclosure Statement Letter		1	4	
	Information Disclosure Statement (IDS) Filed (SB/08)		5	6	
Warnings:					
Information:					
2	NPL Documents	XP009092848_Neville_Disintegration_of_Dextran.PDF	783613 9a5124bf906234f33372db580fc1b14e624f84f2	no	13
Warnings:					
Information:					
3	NPL Documents	XP008031884_Patrick_Pharmacology_of_Methylphenidate.PDF	2217015 ed5b8e78f3f4d0dbfde80298ef697d7dc75b18e9	no	20
Warnings:					
Information:					
4	NPL Documents	XP0009092849_Chaumeil_Enrobages_gastro_resistants.PDF	670328 26c6acc79aaf0263957fed557e1fc50f5af38f1c	no	10
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	EP_SEARCH_REPORT.PDF	644120 2ed9a0db5497a3d1acd0f14250d8eb025f87e151	no	11
Warnings:					
Information:					
		Total Files Size (in bytes):	4378122		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/383,066	05/12/2006	Amir Shojaei	20342/1202653-US8	7083

7278 7590 10/02/2009

DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
YOUNG, MICAH PAUL	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
10/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/383,066	SHOJAEI ET AL.	
	Examiner	Art Unit	
	MICAH-PAUL YOUNG	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 59-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/26/07, 12/7/07, 1/9/07, 3/30/07, 8/20/07, 1/10/08, 9/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/26/07, 12/7/07, 1/9/07, 3/30/07, 8/20/07, 1/10/08 and 9/1/08 were filed in a timely fashion. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6 and 59-61 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 59-61 contain the trademark/trade name ADDERALL XL. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe a commercially available mixture of amphetamine salts used in treating ADHD and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-23, 25, 26 and 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Burnside et al (USPN 6,605,300 hereafter '300).

The '300 patent teaches an oral pulsed release formulation comprising a combination of immediate release and delayed release amphetamine beads (abstract). The formulation can comprise a coated core comprising an immediate release portion of the amphetamine salts, along with an enterically coated delayed release bead (claim 1). The enteric polymers include pH dependent enteric polymers (col. 8, lin. 43-68). The formulation further comprises a protective coating to the core between the drug layers, or at the enteric layer (col. 8, lin. 10-30). The amphetamine is coated to an inert seed material (Example 1). This coated seed is then coated with various polymers, forming a core with the amphetamine incorporated (Examples 2 and 3). The formulation can comprise multiple coated delayed core comprises different enteric polymers or the same polymers such as Eudragit L or 4110D (Examples 1-4). The formulation comprises a combination of immediate release beads and controlled release beads (Example 4). The formulation can comprise up to 20 mg of a mixture of amphetamine salts including dextroamphetamine saccharate and amphetamine sulfate (claim 1). A single immediate release bead can be coated with a delayed release bead coating solution and combined with a second

delayed release formulation so that the immediate and delayed release portions are present in the same bead and on different beads (Example 4).

Regarding the bioequivalence of the formulation to that of ADDERALL XL, and the other physiological effects of the instant dosage form (food, Tmax, AUC and Cmax values) it is the position of the Examiner that these limitations are merely functional limitations that are the result of the instant compositional components. These functional limitations are inherent properties of the composition and are dependent from the composition components, since a compound and its properties cannot be separated. The same compositions, comprising the same components and compounds must have the same properties. As such, since the formulation of the '300 patent comprises the same immediate release and delayed release beads, comprising the same polymers and arrangement the formulation of the '300 patent must also have the same bioequivalence, and blood plasma concentrations.

Further specifically regarding the potential Tmax, Cmax and AUC of a 37.5 mg dose, it is the position of the Examiner that these limitation merely recite a future intended use for the composition. These values are based on a theoretical future dosage form that has the same fundamental structure and components as the '300 formulation. As such if the same components are applied to the theoretical model they would inherently result in the same in vivo results.

For these reasons the claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-32 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over the disclosures of Burnside et al (USPN 6,605,300 hereafter '300).

As discussed above the '300 patent discloses a controlled release dosage form comprising immediate release bead sand delayed release beads where the delayed release beads comprise enter polymers and protective coating. The beads comprise a mixture of amphetamine salts and are disclosed at a concentration of at least 20 mg (claims). The reference is silent to a higher dosage, however concentration however increasing the dosage of a well known pharmaceutical dependent on the patient is well within the limits of one of ordinary skill and would be an obvious modification. Since dosing concentrations are based on patient need an increase or decrease in the potency of a dosage form would be an obvious modification to provide the result effective variable to increase or decrease the effectiveness of the dosage form. The general conditions of the claim have been met, namely a pharmaceutical dosage form comprising immediate release and sustained release beads coated with enteric polymers. Applicant is reminded that where the general conditions of a claim are disclosed in the prior art, it is not

inventive to discover the optimum or workable ranges by routine experimentation. *See* In re Aller, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Furthermore the claims differ from the reference by reciting various concentrations of the active ingredient(s). However, the preparation of various pharmaceutical compositions having various amounts of the active is within the level of skill of one having ordinary skill in the art at the time of the invention. It has also been held that the mere selection of proportions and ranges is not patentable absent a showing of criticality. *See* In re Russell, 439 F.2d 1228 169 USPQ 426 (CCPA 1971).

With these things in mind it would have been obvious to modify the concentration of the active amphetamine salt mixture in order to accommodate each individual patient. It would have been obvious to adjust the dosage in order to provide more precise care for the patient. One of ordinary skill in the art would have been motivated to optimize and modify the concentrations of the active components with an expected result of tailored dosage form useful in treating ADHD.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICAH-PAUL YOUNG whose telephone number is (571)272-0608. The examiner can normally be reached on Monday-Friday 8:00-5:30; every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/MICAH-PAUL YOUNG/
Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 11/383,066	Applicant(s)/Patent Under Reexamination SHOJAEI ET AL.	
	Examiner MICAH-PAUL YOUNG	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,605,300	08-2003	Burnside et al.	424/452
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11383066	SHOJAEI ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

SEARCHED			
Class	Subclass	Date	Examiner
424	489-502	9/29/09	MPY

SEARCH NOTES		
Search Notes	Date	Examiner
east brs search, inventor search	9/29/09	MPY

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/MICAH-PAUL YOUNG/ Examiner.Art Unit 1618	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11383066	SHOJAEI ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/29/2009								
	1	✓								
	2	✓								
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	4	✓								
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	35	-								
	36	-								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11383066	SHOJAEI ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/29/2009								
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04-02-07 IFW

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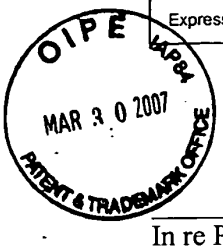

Docket No.: 20342/1202653-US8
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Amir Shojaei et al.

Application No.: 11/383,066 Confirmation No.: 7083

Filed: May 12, 2006 Art Unit: 1615

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM Examiner: Not Yet Assigned

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Information Disclosure Statement is submitted in accordance with 37 C.F.R. 1.97, 1.98, and it is requested that the information set forth in this statement and in the listed documents be considered during the pendency of the above-identified application, and any other application relying on the filing date of the above-identified application or cross-referencing it as a related application.

1. This IDS should be considered, in accordance with 37 C.F.R. 1.97, as it is filed: (Check one of the boxes A-D)

- [ ] A. within three months of the filing date of the above-identified national application or within three months of the entry into the national stage of the above identified national application
- [x] B. before the mailing date of a first office action on the merits, or a first office action after filing a request for continued examination.
- [ ] C. after (A) and (B) above, but before final rejection or allowance, and Applicants have made the necessary statement in box "i" below or paid the necessary fee in box "ii" below.

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(check one of the boxes "i" and "ii" below:)

☐ i. Counsel states that, upon information and belief, each item of information listed herein was (check one of boxes (a) or (b))

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

☐ ii. Payment in the amount of the fee set forth in 1.17(p), presently believed to be $180, is indicated below.

☐ D. after (A), (B) and (C) above, but before payment of the issue fee: Applicant petitions under 37 C.F.R. 1.97(d) for the consideration of this IDS. Under 37 CFR 1.17(i) a check in the amount of $180.00 is enclosed. Counsel certifies that, upon information and belief, each item of information listed herein was

(check one of the boxes "a" and "b" below:)

☐ (a) first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

☐ (b) was not cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of undersigned after making reasonable inquiry, was not known to any individual designated in 1.56(c) more than three months prior to the filing of this IDS.

2. In accordance with 37 C.F.R. 1.98, this IDS includes a list (e.g., form PTO/SB/08) of all patents, publications, or other information submitted for consideration by the office, either incorporated into this IDS or as an attachment hereto. A copy of each document listed is attached, except as explained below.

(check boxes A, B and/or C and fill in blanks, if appropriate.)

[x] A. Pursuant to the 37 C.F.R. § 1.98(a)(2)(ii), a copy/copies of the **U.S. Patent(s) and/or U.S. Patent Application Publication(s)** on PTO/SB08 is/are not being submitted.

[ ] B. Document(s) _____ is (are) deemed substantially cumulative to document(s) _____ , and, in accordance with 1.98(c), only a copy of each of the latter documents is enclosed.

[ ] C. Certain documents were previously cited by or submitted to the Office in the following prior applications, which are relied upon under 35 U.S.C. 120:

<<INSERT SERIAL NO. & FILING DATE>>

Applicant identifies these documents by attaching hereto copies of the forms PTO-892, PTO-1449 and/or PTO/SB/08 from the files of the prior application(s) or a fresh PTO/SB/08 listing these documents, and request that they be considered and made of record in accordance with 1.98(d). Per 37 CFR 1.98(d), copies of these documents need not be filed in this application.

[ ] 3. Cite No(s). _____ are not in the English language. In accordance with 1.98(c), Applicant states:

[ ] An English translation of each document (or of the pertinent portions thereof), or a copy of each corresponding English-language patent or application , or English-language abstract (or claim) is enclosed.

[ ] The requirement for a concise explanation of the relevance of any foreign language document is satisfied by the attached search report; citation of the documents cited in the search report shall not be construed as an admission that they are or are considered to be, material to patentability of the subject matter claimed herein (See MPEP §609).

[ ] A concise explanation of the relevance of document(s) _____ is set forth as follows: [Insert concise explanation of relevance]

[ ] A concise explanation of the relevance of document(s) _____ can be found on page(s) _____ of the specification.

[ ] A concise explanation of document(s) _____ can be found on the attached sheet.

[x] 4. No explanation of relevance is necessary for documents in the English language (see reply to Comments 67 in the preamble to the final rules; 1135 OG 13 at 20).

[ ] 5. Other information being provided for the examiner's consideration follows:

[A/An _____ Search Report, dated_____, which issued during the prosecution of _____Application No._____ which corresponds to the present application.]

6. In accordance with 37 C.F.R. 1.97(g) and (h), the filing of this IDS should not be construed as a representation that a search has been made or that information cited is, or is considered to be, material to patentability as defined in §1.56 (b), or that any cited document listed or attached is (or constitutes) prior art. Unless other-wise indicated, the date of publication indicated for an item is taken from the face of the item and Applicant reserves the right to prove that the date of publication is in fact different.

Early and favorable consideration is earnestly solicited.

The Commissioner is authorized to charge any deficiency of up to $300.00 or credit any excess in this fee to Deposit Account No. 04-0100.

Dated: March 30, 2007

Respectfully submitted,

By _____

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New York, New York 10150-5257
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Attorneys/Agents For Applicant

PTO/SB/08a/b (07-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449A/B/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/M.Y./	AA	US-6,913,768	07-05-2005	Couch et al.	
	AB	US-6,764,696	07-20-2004	Pather et al.	
	AC	US-6,749,867	06-15-2004	Robinson et al.	
	AD	US-5,846,568	12-08-1998	Olinger et al.	
	AE	US-5,773,031	06-30-1998	Shah et al.	
	AF	US-5,733,575	03-31-1998	Mehra, et al.	
	AG	US-5,618,559	04-08-1997	Desai, et al.	
	AH	US-5,501,861	03-26-1996	Makino et al.	
	AI	US-5,422,121	06-06-1995	Lehmann et al.	
	AJ	US-5,411,745	05-02-1995	Oshlack et al.	
	AK	US-5,202,159	04-13-1993	Chen et al.	
	AL	US-5,137,733	08-11-1992	Noda et al.	
	AM	US-4,794,001	12-27-1988	Mehta et al.	
	AN	US-3,979,349	09-07-1976	H. Fink	
	AO	US-3,365,365	01-23-1968	J.A. Butler et al.	
	AP	US-3,066,075	11-27-1962	DEUTSCH MARSHALL E	
	AQ	US-3,048,526	08-07-1962	C. L. Boswell	
	AR	US-2,738,303	03-13-1956	R. H. Blythe	
/M.Y./	AS	US-2,099,402	11-16-1937	J. W. Keller	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
/M.Y./	BA	AU-109,438	01-11-1940	I. Lipowski		

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Examiner's signature	/Micah Paul Young/ (09/29/2009)	Date Considered	09/29/2009

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/M.Y./	CA	Adderall XR Package Inset, Sept. (2004)	
/M.Y./	CB	Agyilirah GA and Banker SB, Polymers for Enteric Coating applications, Polymers for Controlled Drug Delivery (Peter J. Tarcha ed. 1991) 39-66	
/M.Y./	CC	American Chemical Society, Polymer Preprints, pp. 633-634, Vol. 34, No. 1, March 1993	
/M.Y./	CD	Ansel, et al., Rate Controlled Dosage Forms and Drug Delivery Systems, Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. (1995), 213-222	
/M.Y./	CE	Answering Expert Report of Dr. Alexander M. Klibanov, expert for Shire Laboratories, Inc., April 25, 2005	
/M.Y./	CF	Answering Expert Report of Robert Langer, Sc. D. Regarding United States Patent Nos. 6,322,819 and 6,605,300, expert for Shire Laboratories Inc., dated April 25, 2005	
/M.Y./	CG	Barr Laboratories' Objections and Responses to Plaintiff Shire Laboratories Inc.'s Fifth Set of Interrogatories (No. 17), dated September 3, 2004	
/M.Y./	CH	Barr Laboratories' Amended Answer, Affirmative Defenses And Counterclaims *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-1219-PKC	
/M.Y./	CI	Barr Laboratories' Answer, Affirmative Defenses, and Counterclaims, dated September 25, 2003	
/M.Y./	CJ	Barr Laboratories Inc.'s Objections and Responses to Shire Laboratories Inc.'s Second Set of Interrogatories (Nos. 8-11), dated February 18, 2004	
/M.Y./	CK	Barr Laboratories Inc.'s Objections and Responses to Shire Laboratories Inc.'s Fourth Set of Interrogatories (Nos.15-16), dated July 9, 2004	
/M.Y./	CL	Barr Laboratories' Memorandum in Support of Its Motion to Amend Its Pleadings and exhibits thereto, dated September 10, 2004	
/M.Y./	CM	Barr Laboratories' Memorandum in Support of Its Motion to Compel Production, dated September 13, 2004	
/M.Y./	CN	Barr Laboratories' Supplemental Objections and Responses to Plaintiff Shire Laboratories Inc.'s Third Set of Interrogatories (Nos. 12-14)(Redacted), dated August 27, 2004	
/M.Y./	CO	Barr Laboratories, Inc.'s '300 Notification Pursuant to §505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)(2)(B)(ii) and 21 C.F.R. § 314.95)	
/M.Y./	CP	Barr Laboratories, Inc.'s '819 Notification Pursuant to §505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)(2)(B)(ii) and 21 C.F.R. § 314.95)	
/M.Y./	CQ	Bauer, et al., Cellulose Acetate Phthalate (CAP) and Trimellitate (CAT), Coated Pharmaceutical Dosage Forms (1998), 102-104	
/M.Y./	CR	Bodmeier et al., the Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Catinoc Polymer Dispersions, Eudragit RS, RL 30D, Pharmaceutical Research Vol. 13, No. 1, 1996, 52-56	
/M.Y./	CS	Brown et al., Behavior and Motor Activity Response in Hyperactive Children and Plasma Amphetamine Levels Following a Sustained Release Preparation, Journal of the American Academy of Child Psychiatry, 19:225-239, 1980	
/M.Y./	CT	Brown et al., Plasma Levels of d-Amphetamine in Hyperactive Children, Psychopharmacology 62, 133-140, 1979	
/M.Y./	CU	Burns et al., A study of Enteric-coated Liquid-filled Hard Gelatin Capsules with Biphasic Release Characteristics, International Journal of Pharmaceutics 110 (1994) 291-296	
/M.Y./	CV	C. Lin et al., Bioavailability of d-pseudoephedrine and Azatadine from a Repeat Action Tablet Formulation, J Int Med Res (1982), 122-125	
/M.Y./	CW	C. Lin et al., Comparative Bioavailability of d-Pseudoephedrine from a Conventional d-Pseudoephedrine Sulfate Tablet and from a Repeat Action Tablet, J Int Med Res (1982) 10,	

Examiner's signature	/Micah Paul Young/ (09/29/2009)	Date Considered	09/29/2009

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

		126-128	
/M.Y./	CX	Chan, Materials Used for Effective Sustained-Release Products, Proceedings of the International Symposium held on 29th to 31st of January 1987 (The Bombay College of Pharmacy 1988), 69-84	
/M.Y./	CY	Chan, New Polymers for Controlled Products, Controlled Release Dosage Forms Proceedings of the International Symposium held on 29th to 31st of January 1987 (The Bombay College of Pharmacy 1988) 59-67	
/M.Y./	CZ	Chang et al., Preparation and Evaluation of Shellac Pseudolatex as an Aqueous Enteric Coating Systems for Pellets, International Journal of Pharmaceuticals, 60 (1990) 171-173	
/M.Y./	CA1	Charles S. L. Chlao and Joseph R. Robinson, Sustained-Release Drug Delivery Systems, Remington: The Science and Pratice of Pharmacy, Tenth Edition (1995) 1660-1675	
/M.Y./	CB1	Civil Docket For Case #: 1:03-cv-01164-GMS *Shire Laboratories, Inc. v. Impax Laboratories, Inc.*, Civil Action No. 03-CV-01164-GMS	
/M.Y./	CC1	Civil Docket For Case #: 1:03-cv-01219-PKC-DFE *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-1219-PKC	
/M.Y./	CD1	Civil Docket For Case #: 1:03-cv-06632-VM-DFE *Shire Laboratories, Inc. v. Barr Laboratories, Inc.*, Civil Action No. 03-CV-6632-PKC	
/M.Y./	CE1	Civil Docket For Case #: 1:05-cv-00020-GMS *Shire Laboratories, Inc. v. Impax Laboratories, Inc.*, Civil Action No. 05-20-GMS	
/M.Y./	CF1	Cody et al., Amphetamine Enantiomer Excretion Profile Following Administration of Adderall, Journal of Analytical Toxicology, Vol. 2, October 2003, 485-492	
/M.Y./	CG1	Complaint for Declaratory Judgment, Impax Laboratories, Inc. v. Shire International Laboratories, Inc. (Civ. Action No. 05772) and Exhibits attached thereto	
/M.Y./	CH1	Daynes, Treatment of Noctural Enuresis with Enteric-Coated Amphetamine, The Practitioner, No. 1037, Vol. 173, November 1954	
	CI1	Deposition of Transcript of Beth Burnside, dated 2/2/05	
	CJ1	Deposition of Transcript of Beth Burnside, dated 2/3/05	
	CK1	Deposition of Transcript of Charlotte M. McGuiness, dated 8/6/04	
	CL1	Deposition of Transcript of Donald John Treacy, Jr., dated 8/31/04	
	CM1	Deposition of Transcript of Edward Rudnic, dated 7/28/04	
	CN1	Deposition of Transcript of James J. Harrington, dated July 27, 2005	
	CO1	Deposition of Transcript of Kimberly Fiske, dated 9/17/04	
	CP1	Deposition of Transcript of Richard Rong-Kun Chang, dated 1/20/05	
	CQ1	Deposition of Transcript of Richard A. Couch, dated 9/14/04	
	CR1	Deposition of Transcript of Robert Schaffer, dated August 17, 2005	
	CS1	Deposition of Transcript of Xiaodi Guo, dated 1/24/05	
	CT1	Deposition of Transcript of Xiaodi Guo, dated 7/26/04	
/M.Y./	CU1	Deposition transcript of Honorable Gerald J. Mossinghoff and exhibits thereto, dated June 8, 2005	
	CV1	Deposition Transcript of Richard Chang, dated 9/8/04	
	CW1	Edward Stempel, Prolonged Drug Action, HUSA's Pharmaceutical Dispensing, Sixth Edition, 1996, 464, 481-485	
	CX1	Expert Report of Dr. Joseph R. Robinson, expert for Barr Laboratories and exhibits thereto, February 28, 2005	
	CY1	Expert Report of the Honorable Gerald J. Mossinghoff, expert for Barr Laboratories, Inc. and exhibits thereto, March 16, 2005	
	CZ1	Freedom of Information Request Results for - Dexadrine (SmithKline Beecham): 5/20/1976 Disclosable Approval Information	
	CA2	Fukumori, Coating of Multiparticulates Using Polymeric Dispersions, Multiparticulate Oral Drug Delivery (Swarbrick and Selassie eds. 1994),79-110	
/M.Y./	CB2	Garnett et al., Pharmacokinetic Evaluation of Twice-Daily Extended-Release	

Examiner's signature	/Micah Paul Young/ (09/29/2009)	Date Considered	09/29/2009

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 4 of 7

Complete if Known	
Application Number	11/383,066-Conf.#7083
Filing Date	May 12, 2006
First Named Inventor	Amir Shojaei
Art Unit	1615
Examiner Name	M. Young
Attorney Docket Number	20342/1202653-US8

/M.Y./		Carbamazepine(CBZ) and Four-Times- Daily Immediate-Release CBZ in Patients with Epilepsy, Epilepsia 39(3): 274-279, 1998	
/M.Y./	CC2	Glatt, The World of the Fluid Bed, Fluid Bed Systems, 1-19	
	CD2	Goodhart et al., An evaluation of Aqueous Film-forming Dispersions for Conrolled Release, Pharmaceutical Technology, April 1984, 64-71	
	CE2	Greenhill et al., A Pharmacokinetic/Pharmacodynamic Study Comparing a Single Morning Dose of Adderall to Twice-Daily Dosing in Children with ADHD. J. Am. Acad. Adolesc. Psychiatry, 42:10, October 2003	
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	CS2	Impax Laboratories, Inc.'s Memorandum in Support of the Motion to Amend Its Answer dated 2/25/05 and exhibits thereto	
	CT2	Impax Laboratories, Inc.'s Reply Memorandum in Support of the Motion to Amend Its Answer dated 3/18/05 and exhibits thereto	
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Examiner's signature	/Micah Paul Young/ (09/29/2009)	Date Considered	09/29/2009