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UTILITY PATENT APPLICATION TRANSMITTAL

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

Attorney Docket No.	085199-0996
First Named 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** (PTO/SB/17 or equivalent)
2. [ ] **Applicant asserts small entity status.** See 37 CFR 1.27
3. [ ] **Applicant certifies micro entity status.** See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
4. [X] **Specification** [*Total Pages* 56]
   Both the claims and abstract must start on a new page.
   (See MPEP § 608.01(a) for information on the preferred arrangement)
5. [X] **Drawing(s)** *(35 U.S.C. 113)* [*Total Sheets* 10]
6. **Inventor's Oath or Declaration** [*Total Pages*]
   (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))
   a. [ ] Newly executed (original or copy)
   b. [ ] A copy from a prior application (37 CFR 1.63(d))
7. [X] **Application Data Sheet** **See note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
8. [ ] **CD-ROM or CD-R** In duplicate, large table, or Computer Program *(Appendix)*
   [ ] Landscape Table on CD
9. **Nucleotide and/or Amino Acid Sequence Submission** *(if applicable, items a. – c. are required)*
   a. [ ] Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. [ ] CD-ROM or CD-R (2 copies); or ii. [ ] Paper
   c. [ ] Statements verifying identity of above copies

ADDRESS TO: **Commissioner for Patents**
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Alexandria, VA 22313-1450

ACCOMPANYING APPLICATION PARTS

10. [ ] **Assignment Papers** (cover sheet & document(s))
    Name of Assignee
11. [ ] **37 CFR 3.73(c) Statement** *(when there is an assignee)* [ ] **Power of Attorney**
12. [ ] **English Translation Document** *(if applicable)*
13. [ ] **Information Disclosure Statement** (PTO/SB/08 or PTO-1449)
    [ ] Copies of citations attached
14. [X] **Preliminary Amendment**
15. [ ] **Return Receipt Postcard** *(MPEP § 503) (Should be specifically itemized)*
16. [ ] **Certified Copy of Priority Document(s)** *(if foreign priority is claimed)*
17. [ ] **Nonpublication Request** Under 35 U.S.C.122 (b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
18. [ ] Other:

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

18. CORRESPONDENCE ADDRESS

[X] The address associated with Customer Number: 20277 ***OR*** [ ] Correspondence address below

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Address					
City		State		Zip Code	
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Signature	/Paul M. Zagar/	Date	September 26, 2014
Name (Print/Type)	Paul M. Zagar	Registration No. (Attorney/Agent)	52,392

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Dated: September 26, 2014 Signature: /Hiroko Lavietes/

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DRAFT 9/26/14

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Filer:	Paul Michael Zagar/Hiroko Lavietes
Attorney Docket Number:	085199-0996

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Late Filing Fee for Oath or Declaration	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1740**

Electronic Acknowledgement Receipt	
EFS ID:	20258571
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	20277
Filer:	Paul Michael Zagar/Hiroko Lavietes
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Attorney Docket Number:	085199-0996
Receipt Date:	26-SEP-2014
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Payment was successfully received in RAM	$1740
RAM confirmation Number	2084
Deposit Account	500417
Authorized User	

File Listing:

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

1		Specification_1.PDF	2605299 365f84993411bc88d98259bf882ccb35957e9689	yes	56

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	47
Claims	48	55
Abstract	56	56

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Information:

2		Amendment_2.PDF	27427 881171b3614e010935b1f3798bf444da84aba9fc	yes	4

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Specification	2	2
Claims	3	3
Applicant Arguments/Remarks Made in an Amendment	4	4

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Information:

3	Application Data Sheet	Application_Data_Sheet_Fillable_PDF_3.PDF	1503257 fe2d4ae264cf1c29244818d33a183433f085c717	no	7

Warnings:

Information:

4	Drawings-only black and white line drawings	Drawings_4.PDF	483078 0b17d27d5818f2da5ae4dd2732ca0560e555bc58	no	10

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Information:

5	Transmittal of New Application	Transmittal_5.PDF	33972 2d25fbde5474e900ca43e26ea655e3b52bb38e8e	no	1
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	36766 432514a1d67edac27f5c3345d872f9921644904d	no	2
Warnings:					
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			Total Files Size (in bytes):	4689799	

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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.

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.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: September 26, 2014 Signature: /Hiroko Lavietes/

Docket No.: 085199-0996
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Amir SHOJAEI et al.	:	Customer Number: 20277
Application No.: Not Yet Assigned	:	Confirmation No.: N/A
Filed: Concurrently Herewith	:	Art Unit: N/A
For: CONTROLLED DOSE DRUG DELIVERY SYSTEM	:	Examiner: Not Yet Assigned

FIRST PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

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

Madam:

INTRODUCTORY COMMENTS

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

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE SPECIFICATION

On page 1 of the specification, after the title of the invention, please insert the paragraph as follows:

CROSS REFERENCE TO PRIOR APPLICATIONS

This application is a continuation of U.S. Patent Application No. 11/383,066, filed May 12, 2006, which is herein incorporated by reference.

AMENDMENTS TO THE 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. – 58. (Cancelled)

REMARKS

The specification has been amended in accordance with 37 CFR §1.78 to incorporate by reference the U.S. priority application.

Claims 2 – 58 have been cancelled without prejudice.

No new matter has been added by the amendment.

Entry of the above amendments is respectfully requested.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-0417, under Order No. 085199-0996 from which the undersigned is authorized to draw.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

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PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085199-0996
	Application Number	
Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085199-0996
	Application Number	
Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM	

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All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	20277		
Email Address	mweipdocket@mwe.com	Add Email	Remove Email

Application Information:

Title of the Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM		
Attorney Docket Number	085199-0996	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	10	Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085199-0996
	Application Number	
Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	20277		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
	Continuation of	11383066	2006-05-12	8846100	2014-09-30

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [i] (if applicable)

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085199-0996
	Application Number	
Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

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Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085199-0996
	Application Number	
Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	Shire LLC		
Mailing Address Information:			
Address 1	9200 Brookfield Court		
Address 2			
City	Florence	**State/Province**	KY
Country [i]	US	Postal Code	41042
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Non-Applicant Assignee Information:

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Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	085199-0996
	Application Number	
Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM	

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information:

Address 1	
Address 2	

City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

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Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/Paul M. Zagar/			Date (YYYY-MM-DD)	2014-09-26
First Name	Paul	Last Name	Zagar	Registration Number	52392

Additional Signature may be generated within this form by selecting the Add button. Add

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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.

FIG. 1

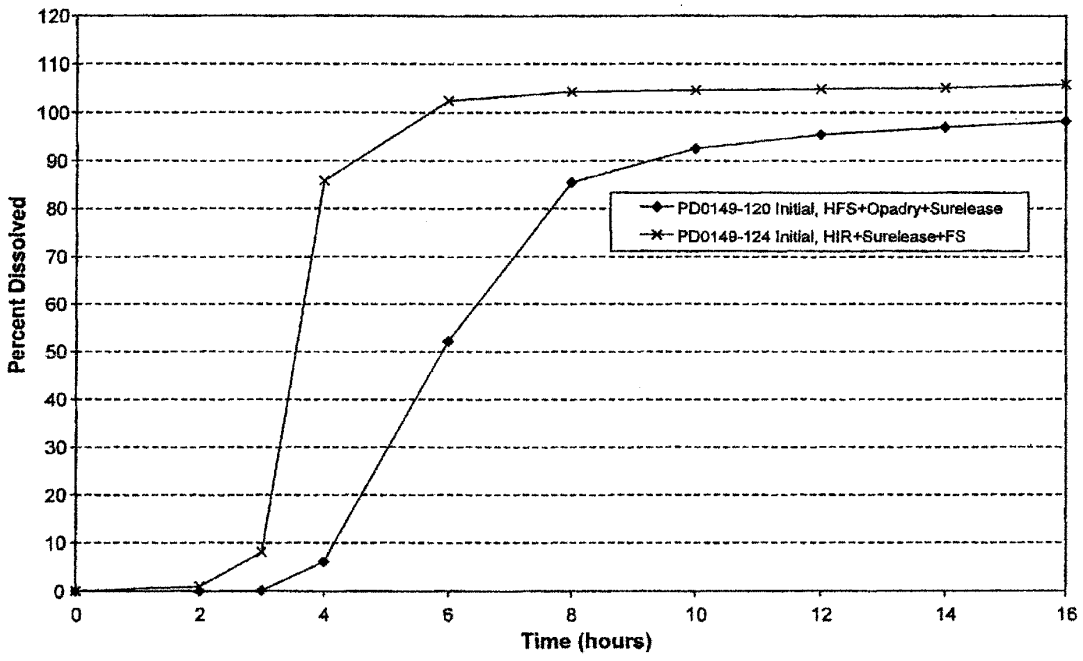

120
110
100
90
80
70
60
50
40
30
20
10
0
Percent Dissolved
0
2
4
6
8
10
12
14
16
Time (hours)
PD0149-120 Initial, HFS+Opadry+Surelease
PD0149-124 Initial, HIR+Surelease+FS

FIG. 2

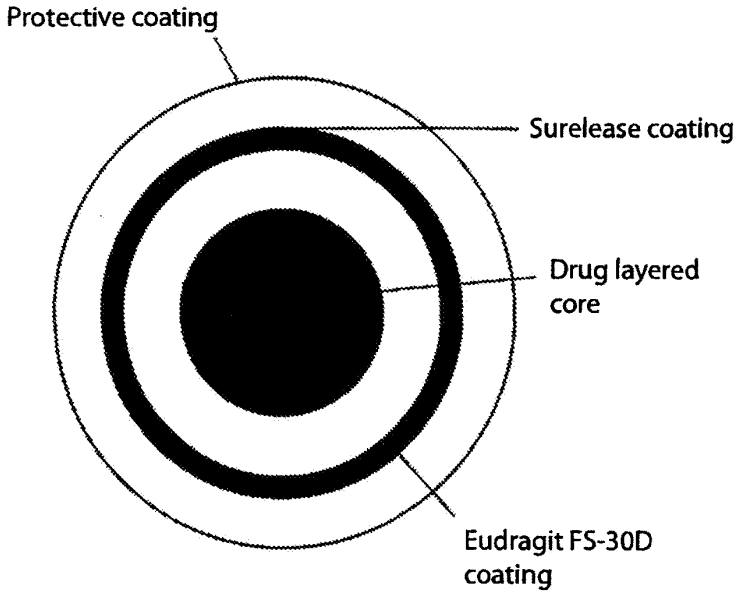


FIG. 3

SPD465 Sustained Release Capsule

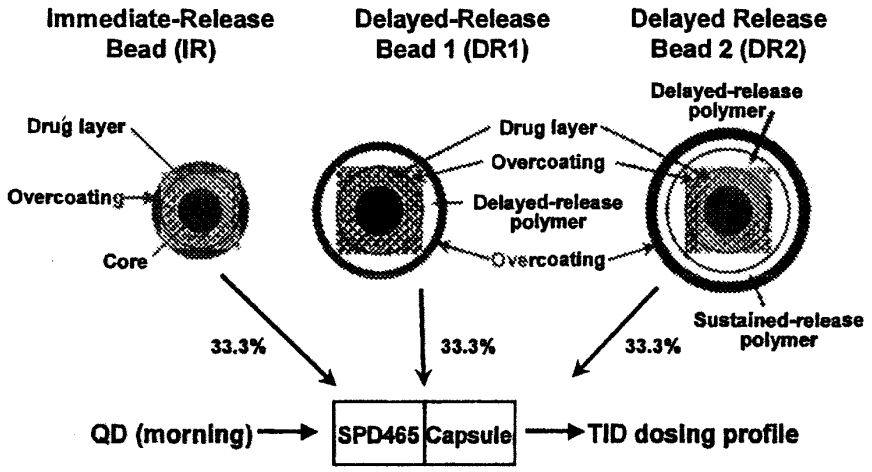


FIG. 4

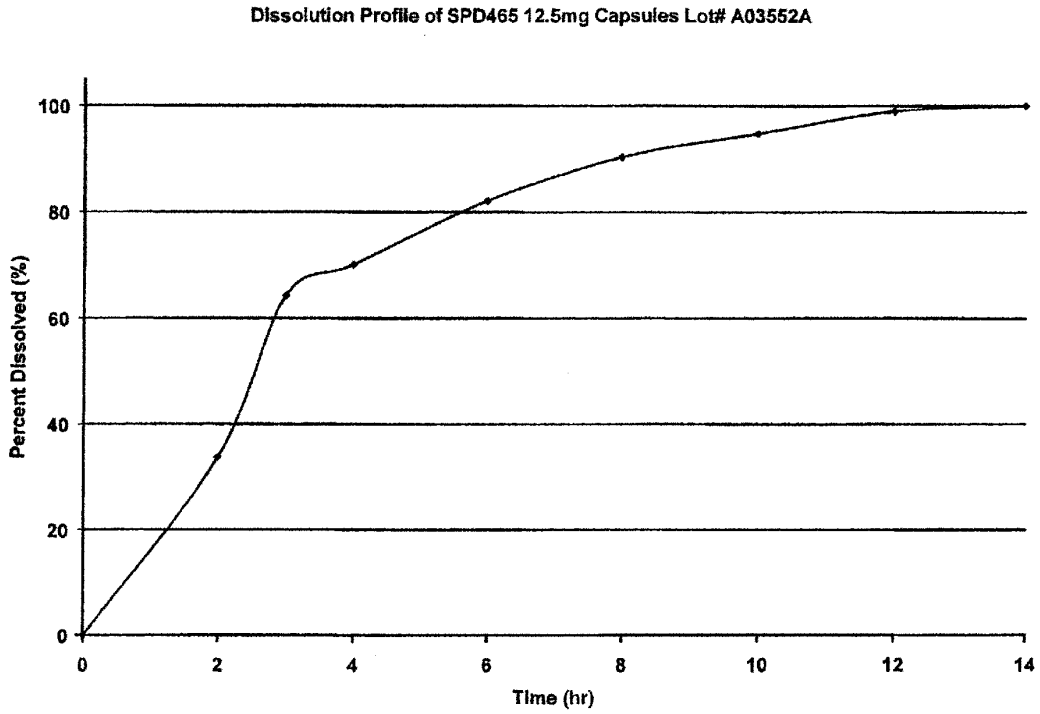

Dissolution Profile of SPD465 12.5mg Capsules Lot# A03552A
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 5

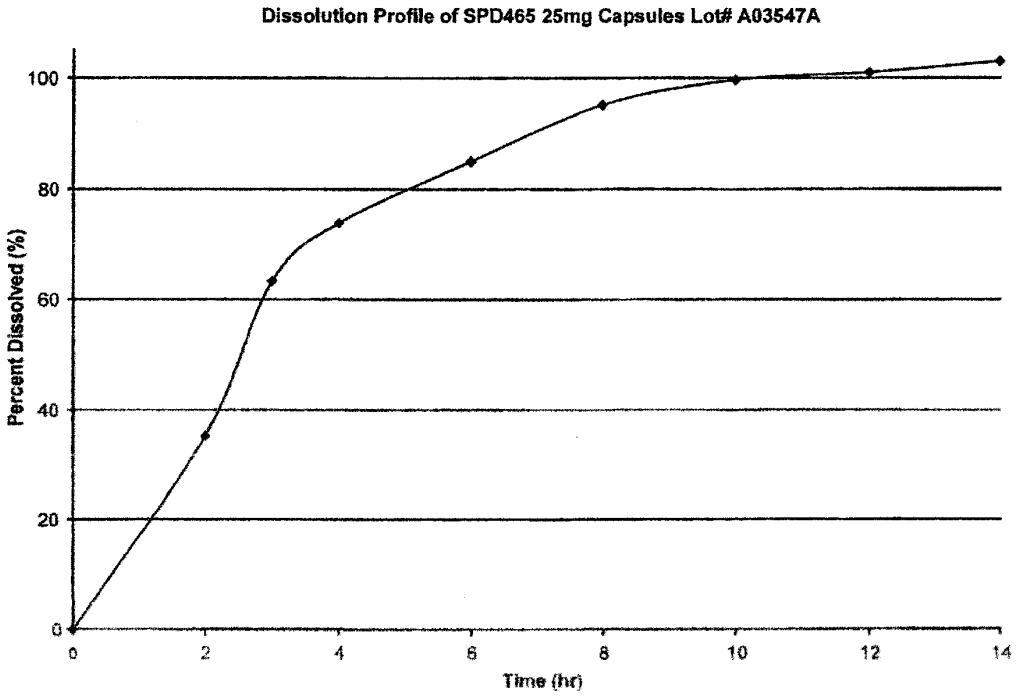

Dissolution Profile of SPD465 25mg Capsules Lot# A03547A
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 6

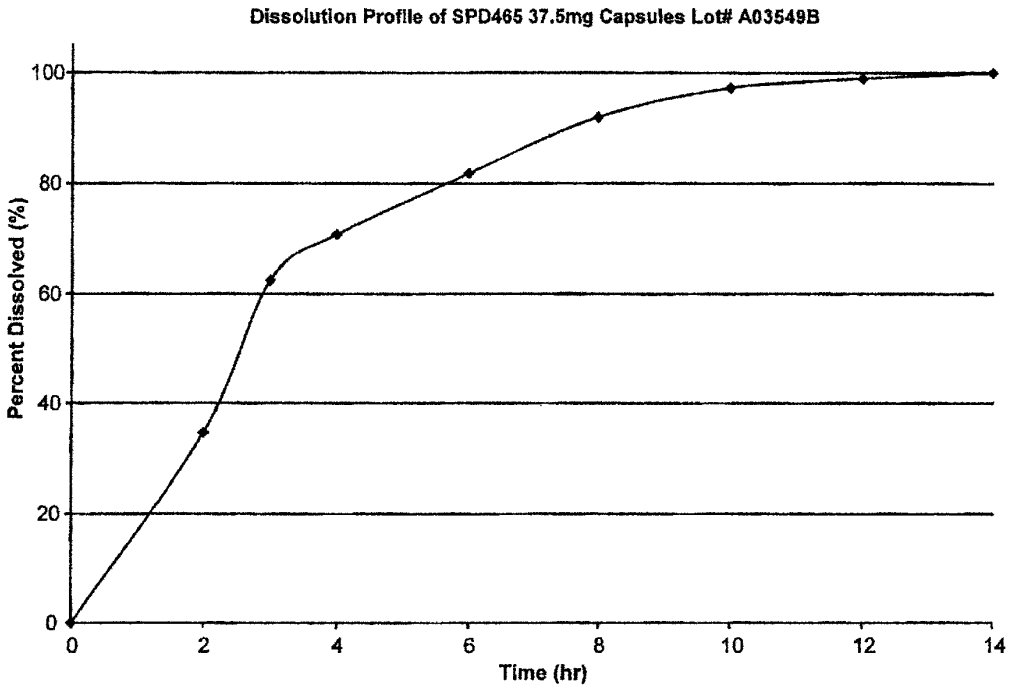

Dissolution Profile of SPD465 37.5mg Capsules Lot# A03549B
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 7

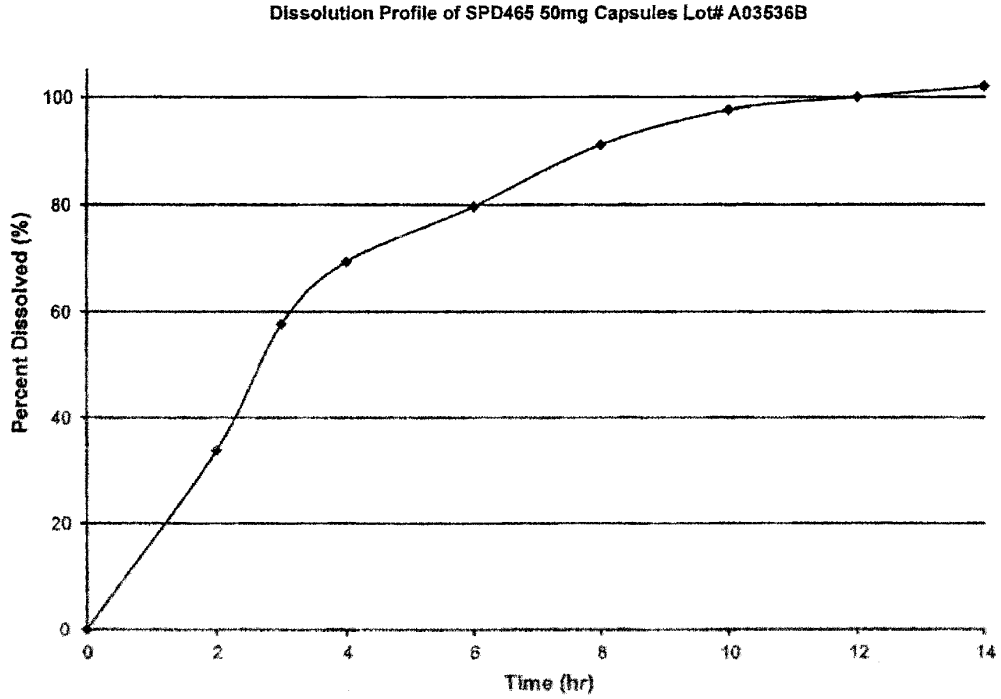

Dissolution Profile of SPD465 50mg Capsules Lot# A03536B
Percent Dissolved (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
Time (hr)

FIG. 8

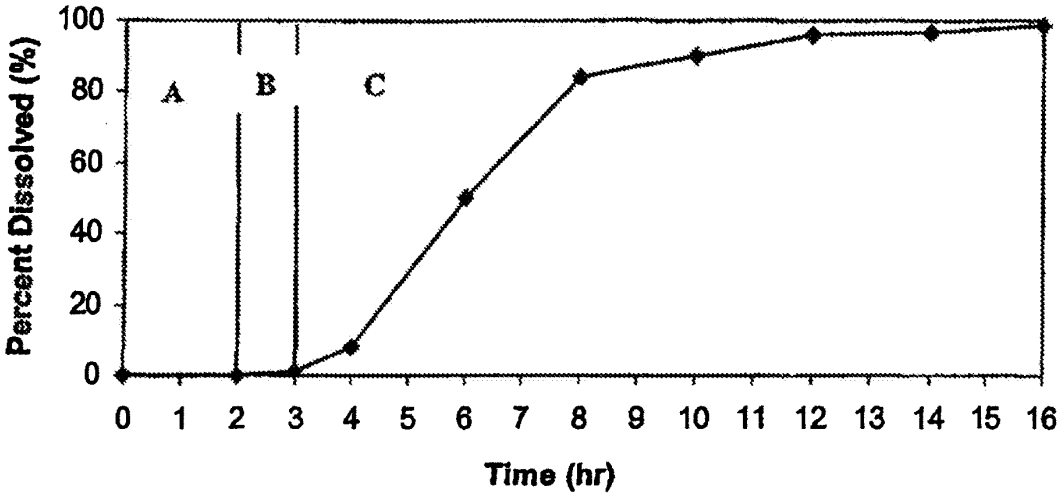

Percent Dissolved (%)
100
80
60
40
20
0
A
B
C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Time (hr)

FIG. 9

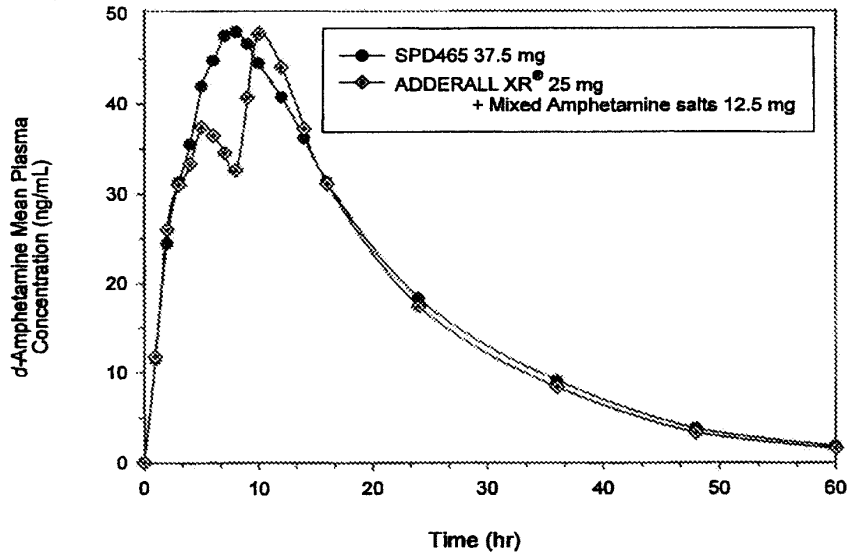

d-Amphetamine Mean Plasma Concentration (ng/mL)
50
40
30
20
10
0
SPD465 37.5 mg
ADDERALL XR® 25 mg
+ Mixed Amphetamine salts 12.5 mg
0 10 20 30 40 50 60
Time (hr)

FIG. 10

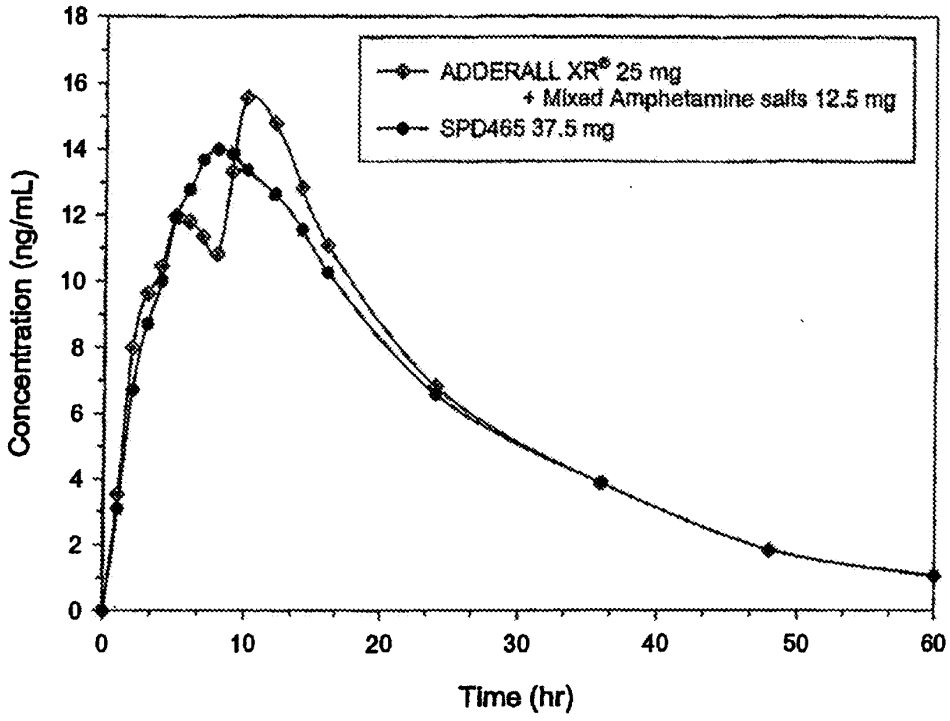

ADDERALL XR® 25 mg
+ Mixed Amphetamine salts 12.5 mg
SPD465 37.5 mg
Concentration (ng/mL)
Time (hr)
0
2
4
6
8
10
12
14
16
18
0
10
20
30
40
50
60

FIG. 11

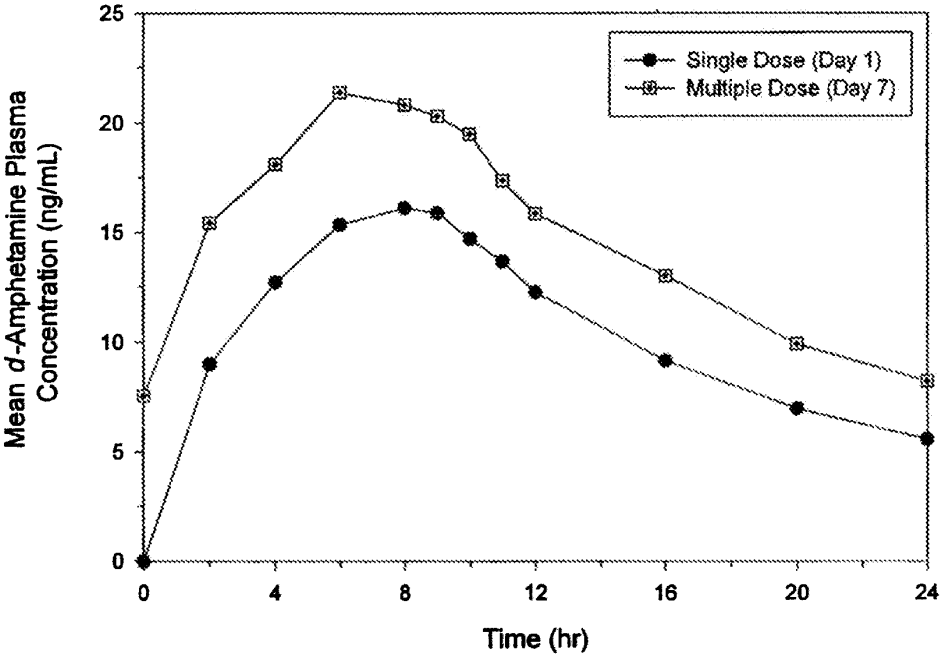

Single Dose (Day 1)
Multiple Dose (Day 7)
Mean d-Amphetamine Plasma Concentration (ng/mL)
Time (hr)
0
5
10
15
20
25
0
4
8
12
16
20
24

FIG. 12

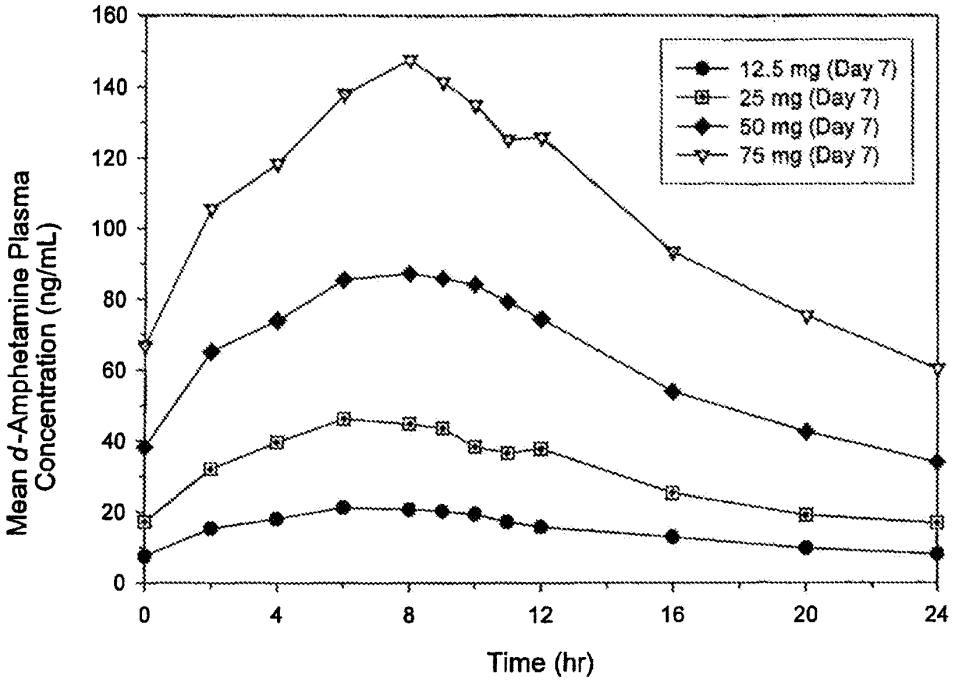

Mean d-Amphetamine Plasma Concentration (ng/mL)
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
Time (hr)
12.5 mg (Day 7)
25 mg (Day 7)
50 mg (Day 7)
75 mg (Day 7)

FIG. 13

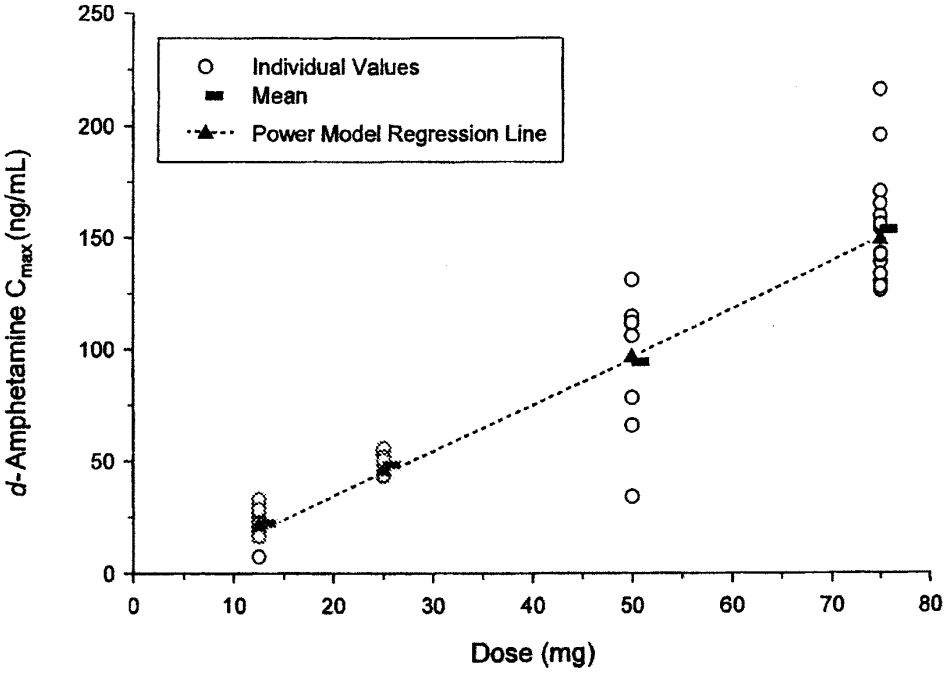

d-Amphetamine C_{max} (ng/mL)
250
200
150
100
50
0
0
10
20
30
40
50
60
70
80
Dose (mg)
Individual Values
Mean
Power Model Regression Line

FIG. 14

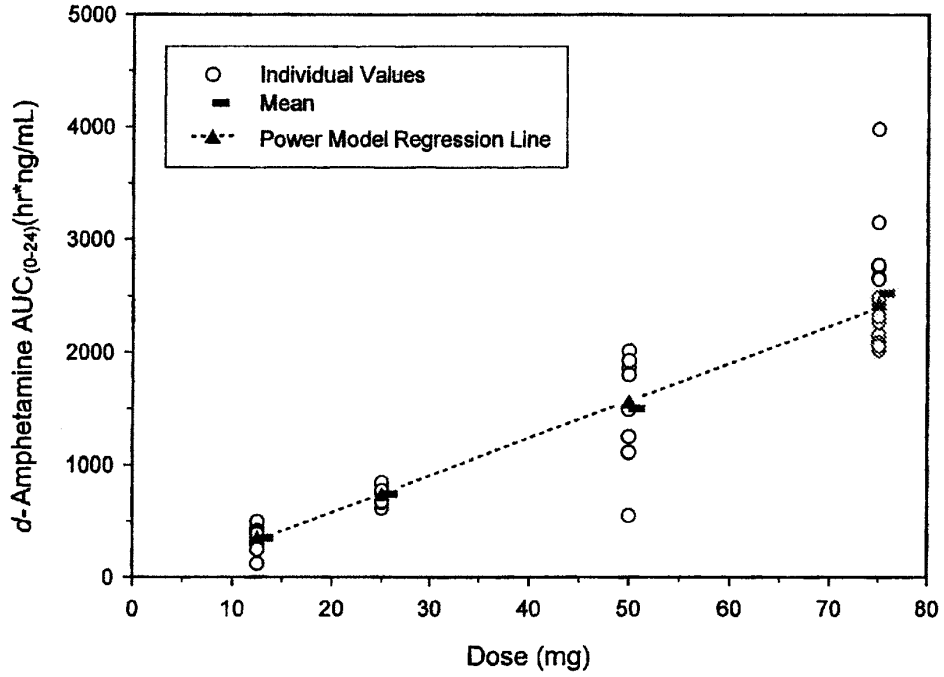

Individual Values
Mean
Power Model Regression Line
d-Amphetamine AUC(0-24)(hr*ng/mL)
Dose (mg)
0
1000
2000
3000
4000
5000
0
10
20
30
40
50
60
70
80

FIG. 15

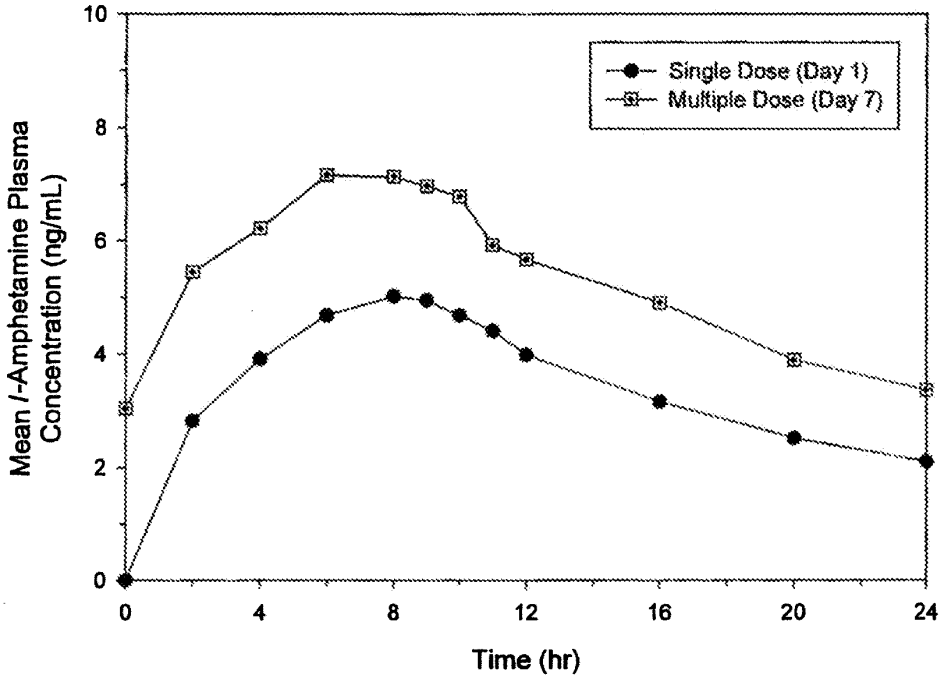

Single Dose (Day 1)
Multiple Dose (Day 7)
Mean l-Amphetamine Plasma Concentration (ng/mL)
Time (hr)
0
2
4
6
8
10
0
4
8
12
16
20
24

FIG. 16

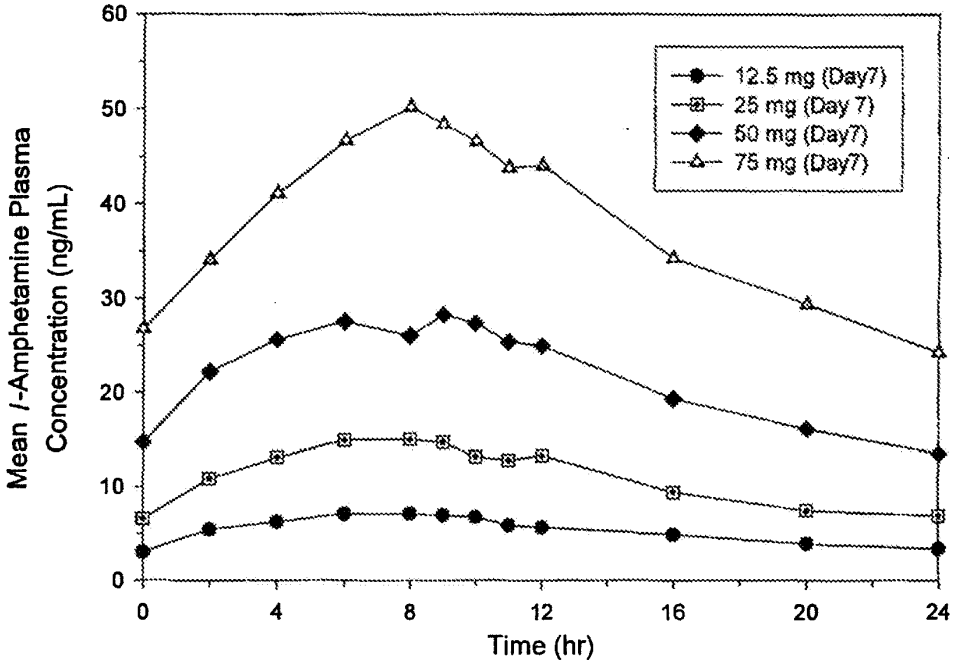

Mean l-Amphetamine Plasma Concentration (ng/mL)
Time (hr)
12.5 mg (Day7)
25 mg (Day 7)
50 mg (Day7)
75 mg (Day7)
0
10
20
30
40
50
60
0
4
8
12
16
20
24

FIG. 17

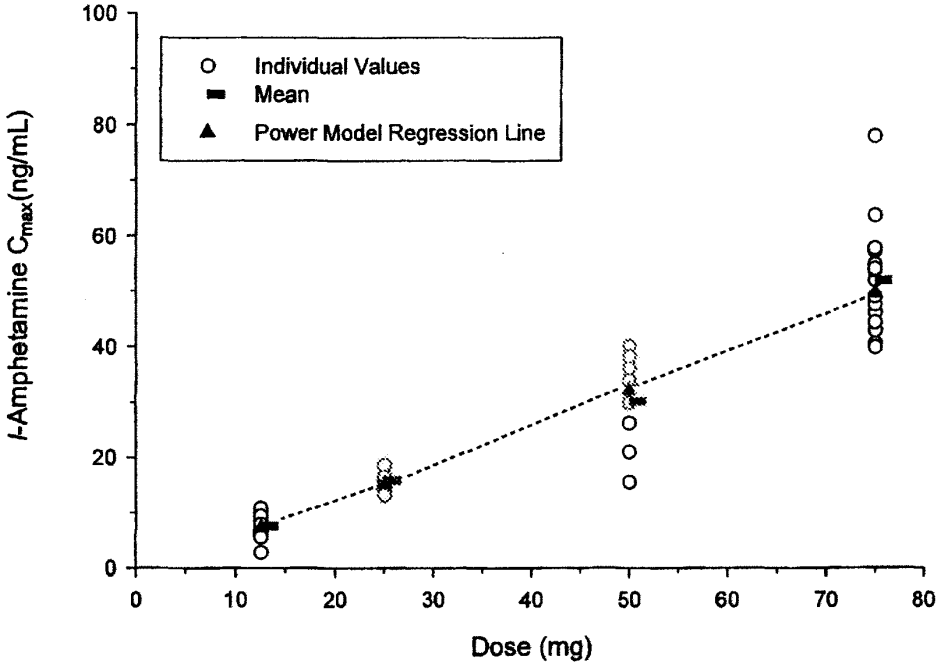
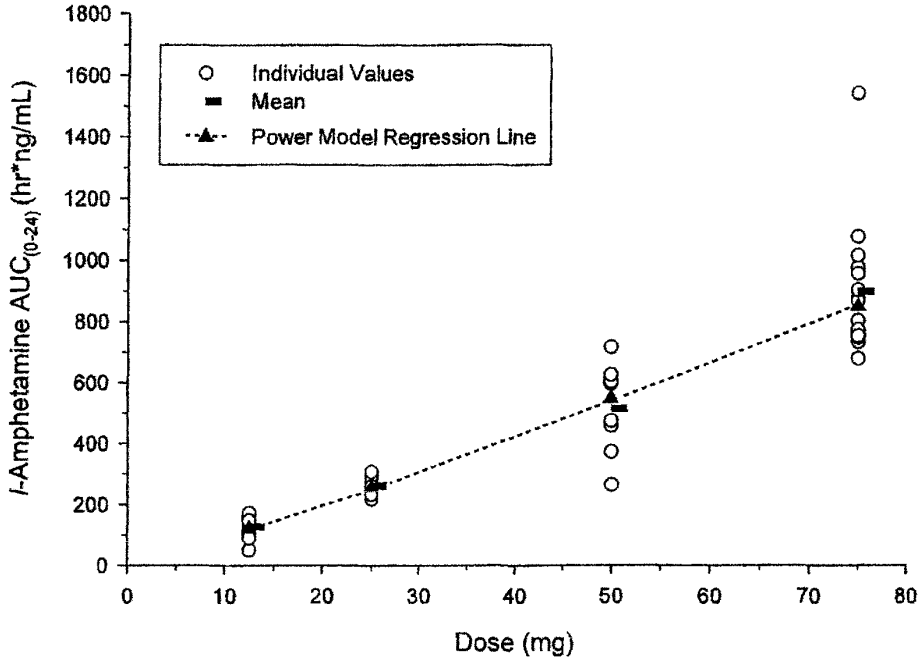

l-Amphetamine C_{max}(ng/mL)
Dose (mg)
Individual Values
Mean
Power Model Regression Line
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80

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

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/498,130	Filing Date 09/26/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	09/26/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 1	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L 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.

LIE
/CHERYL CLARK/

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996

CONFIRMATION NO. 5887

20277
MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, N.W.
WASHINGTON, DC 20001

FORMALITIES LETTER

OC000000071110636

Date Mailed: 10/03/2014

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. 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 required item(s) identified below must be timely submitted to avoid abandonment:

- A substitute specification in compliance with 37 CFR 1.52, 1.121(b)(3), and 1.125, is required. The substitute specification must be submitted with markings and be accompanied by a clean version (without markings) as set forth in 37 CFR 1.125(c) and a statement that the substitute specification contains no new matter (see 37 CFR 1.125(b)). The specification, claims, and/or abstract page(s) submitted is not acceptable and cannot be scanned or properly stored because:
  - The line spacing on the specification, claims, and/or abstract is not 1½ or double spaced (see 37 CFR 1.52(b)).

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Amir SHOJAEI
  Stephanie READ
  Richard A. COUCH
  Paul HODGKINS

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/tmekuria/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/498,130	09/26/2014	1615	1740	085199-0996	1	1

CONFIRMATION NO. 5887

20277
MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, N.W.
WASHINGTON, DC 20001

FILING RECEIPT

OC000000071110635

Date Mailed: 10/03/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Amir SHOJAEI, Phoenixville, PA;
Stephanie READ, Philadelphia, PA;
Richard A. COUCH, Bryn Mawr, PA;
Paul HODGKINS, Exton, PA;

Applicant(s)

Shire LLC, Florence, KY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 11/383,066 05/12/2006 PAT 8846100

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 10/01/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/498,130**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No

Title

CONTROLLED DOSE DRUG DELIVERY SYSTEM

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/498,130

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L 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 found in the appropriate box in column 1.

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with 37 CFR § 1.6(a)(4).

Dated: December 2, 2014 Signature: /Hiroko Lavietes/

Docket No.: 085199-0996
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Amir SHOJAEI et al.	:	Customer Number: 20277
Application No.: 14/498,130	:	Confirmation No.: 5887
Filed: September 26, 2014	:	Art Unit: 1615
For: CONTROLLED DOSE DRUG DELIVERY SYSTEM	:	Examiner: Not Yet Assigned

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS

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

Madam:

In response to the Notice to File Corrected Application Papers – Filing Date Granted mailed October 3, 2014, Applicants respectfully resubmit the Specification as filed previously.

Applicants believe that the line spacing of the Specification is 1 ½ spaced, and that no correction is required. Applicants respectfully request that the Notice be withdrawn and that this application be formally accorded a filing date.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0417, under Order No. 085199-0996.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

/Paul M. Zagar/

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Date: December 2, 2014

Please recognize our Customer No. 20277 as our correspondence address.

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.

Electronic Acknowledgement Receipt

EFS ID:	20845211
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	20277
Filer:	Paul Michael Zagar/Hiroko Lavietes
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	085199-0996
Receipt Date:	02-DEC-2014
Filing Date:	26-SEP-2014
Time Stamp:	17:08:17
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	Applicant Response to Pre-Exam Formalities Notice	Response.PDF	22528 2ad0eff8191e1081fed5bc535362a01acf0b1a11	no	2

Warnings:	
Information:	

2		Specification.PDF	2605299 365f84993411bc88d98259bf882ccb35957e9689	yes	56

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	47
	Claims	48	55
	Abstract	56	56

Warnings:

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Total Files Size (in bytes):	2627827

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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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/498,130

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L 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 found in the appropriate box in column 1.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996

CONFIRMATION NO. 5887

20277
MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, N.W.
WASHINGTON, DC 20001

NOTICE

OC000000072212273

Date Mailed: 12/08/2014

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Amir SHOJAEI
  Stephanie READ
  Richard A. COUCH
  Paul HODGKINS

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/498,130	09/26/2014	1615	1740	085199-0996	1	1

CONFIRMATION NO. 5887

UPDATED FILING RECEIPT

20277
MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, N.W.
WASHINGTON, DC 20001

OC000000072212272

Date Mailed: 12/08/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Amir SHOJAEI, Phoenixville, PA;
Stephanie READ, Philadelphia, PA;
Richard A. COUCH, Bryn Mawr, PA;
Paul HODGKINS, Exton, PA;

Applicant(s)

Shire LLC, Florence, KY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 11/383,066 05/12/2006 PAT 8846100

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 10/01/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/498,130**

Projected Publication Date: 03/19/2015

Non-Publication Request: No

Early Publication Request: No

Title

CONTROLLED DOSE DRUG DELIVERY SYSTEM

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996	5887

20277 7590 01/16/2015

MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, N.W.
WASHINGTON, DC 20001

EXAMINER
YOUNG, MICAH PAUL

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
01/16/2015	ELECTRONIC

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.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mweipdocket@mwe.com

Office Action Summary	Application No. 14/498,130	Applicant(s) SHOJAEI ET AL.	
	Examiner MICAH-PAUL YOUNG	Art Unit 1618	AIA (First Inventor to File) Status No

-- 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 MONTHS 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 _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) 1 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) 1 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what

form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claim 1 is rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of U.S. Patent No. 8,846,100. Although the claims at issue are not identical, they are not patentably distinct from each other because both claims are drawn to a pharmaceutical composition comprising an immediate release bead, a first and second delayed release bead where the first bead provides a sustained release profile and the second bead provides a pulsed release. The claims differ in that the 100 claim specifies the coating arrangement for the first and second beads. The instant claim is of a broader scope with the 100 being a species of the instant genus. However, the scope of the claims overlap. This overlap in scope forecloses the claims being allowed together.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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 pre-AIA 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.

Claim 1 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over the combined disclosures of Percel et al (US 2003/0157173 hereafter '173) in view of Odidi et al (US 2003/0050620 hereafter '620).

The 173 patent discloses a timed pulse release system comprising an immediate release bead comprising an active agent, a delayed release bead comprising the drug and a coating and a sustained release bead comprising the drug, a delayed release coating and a sustained release coating over the delayed release sustained [0014-0016]. The delayed release coatings can comprise enteric polymers, pH dependent coatings [0028]. The beads are collected into capsules or compressed into tablets [0031].

The reference discloses a pharmaceutical composition comprising an immediate release bead, a first delayed release bead and second delayed are disclosed that provides a sustained release effect. The formulation discloses a different drug for differential release however. The use of various active agents in a differential release formulation are well known as seen in the '620 publication.

The 620 publication discloses a controlled release formulation where various active agents are differentially released including propranolol and amphetamine salts are delivered to a patient [abstract, 0030]. The formulation comprises coated beads coated with release controlling polymers [0037]. The granules or beads are collected into capsules of compressed into tablets

[Examples]. It would have been obvious to substitute the amphetamine of the 620 for the propranolol of the 173 publication as they are both used for differential release of active agents.

With these aspects in mind it would have been obvious to combine the prior art with an expected result of a stable drug useful in maintaining wakefulness. It would have been obvious to substitute the active agents from the 620 into the 173 publication since they solve the same problem of differential drug release, and can be used in similar controlled release formulations. One of ordinary skill in the art would have been motivated to combine the prior art with an expected result of a stable drug formulation.

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-Thursday 7:00-5:30; every 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.

/MICAH-PAUL YOUNG/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 14/498,130	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-2003/0050620	03-2003	Odidi et al.	604/890.1
*	B	US-2003/0157173	08-2003	Percel et al.	424/473
	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
	14498130	SHOJAEI ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	489-502	1/10/15	MPY

SEARCH NOTES		
Search Notes	Date	Examiner

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

/MICAH-PAUL YOUNG/ Examiner.Art Unit 1618	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14498130	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	01/10/2015								
	1	✓								

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996

CONFIRMATION NO. 5887

20277
MCDERMOTT WILL & EMERY LLP
The McDermott Building
500 North Capitol Street, N.W.
WASHINGTON, DC 20001

PUBLICATION NOTICE

Title:CONTROLLED DOSE DRUG DELIVERY SYSTEM

Publication No.US-2015-0080474-A1
Publication Date:03/19/2015

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	14498130
Filing Date	2014-09-26
First Named Inventor	Amir SHOJAEI
Art Unit	1618
Examiner Name	Not Yet Assigned
Attorney Docket Number	085199-0996

U.S.PATENTS Remove

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	Millman	
	2	6322819		2001-11-27	Burnside et al.	
	3	6605300		2003-08-12	Burnside et al.	
	4	RE41148		2010-02-23	Burnside et al.	
	5	5496561		1996-03-05	Okada et al.	
	6	5328697		1994-07-12	Raman et al.	
	7	6005027		1999-12-21	Guillet et al.	
	8	6913768		2005-07-05	Couch et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

	9	6764696		2004-07-20	Pather et al.	
	10	6749867		2004-06-15	Robinson et al.	
	11	5846568		1998-12-08	Olinger et al.	
	12	5773031		1998-06-30	Shah et al.	
	13	5733575		1998-03-31	Mehra et al.	
	14	5618559		1997-04-08	Desai et al.	
	15	5501861		1996-03-26	Makino et al.	
	16	5422121		1995-06-06	Lehmann et al.	
	17	5411745		1995-05-02	Oshlack et al.	
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	46	Deposition of Transcript of Charlotte M. McGuiness, dated 8/6/04	☐
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	1	Response to Office Action filed May 2, 2006 in U.S. Patent Application No. 11/091/010	☐
	2	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed February 3, 2006	☐
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	34	Shire Laboratories Inc.'s Opposition to Barr Laboratories' Motion to Amend Its Answers and Counterclaims, September 15, 2004	☐
	35	Slattum, et al., Compararision of Methods for the Assessment of Central Nervous System Stimulant Response after Dextroamphetamine Administration to Healthy Male Volunteers, J.clin Pharmacal (1996) 36,1039-1050	☐
	36	Sprowls' American Pharmacy: An Introduction to Pharmaceutical Techniques and Dosage Forms, 7th Ed. (1974), 387-388	☐
	37	Sriamornsak, et al., Development of Sustained Release Theophylline Pellets Coated with Calcium Pectinate, Journal of Controlled Release 47 (1997) 221-232	☐
	38	Stevens, et al., Controlled, Multidose, Pharmacokinetic Evaluation of Two Extended-Release Carbamazepine Formulations (carbatrol and Tegretoi-XR), Journal of Pharmaceutical Sciences Vol. 87, No. 12, December 1998, 1531-1S34	☐
	39	Teva Notice letter dated February 21, 200S	☐
	40	Teva Notice letter dated June 1, 2005	☐
	41	The Merck Index: Amphetamine, 12th Ed., 620	☐
	42	The Merck Index: Amphetamine, 13th Ed. (2001), 97, 1089	☐
	43	The United States Pharmacopeia 23, National Formulary 18 {1995) pp. 1791-1799	☐
	44	The United States Pharmacopeia 26, National Formulary 21 {2003) pp. 2157-2165	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
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	45	The United States Pharmacopeia 27, National Formulary 22(2004) pp. 2302-2312	☐
	46	Treatise on Controlled Drug Delivery, pp. 185-199 (Agis Kydonieus ed. 1992)	☐
	47	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 Va:. 22, No. 11, (2002), 140S-141S	☐
	48	Vasilevska, et al., Preparation and Dissolution Characteristics of Controlled Release Diltiazem Pellets, Drug Development and Industrial Pharmacy, 18(15), 1649-1661 (1992)	☐
	49	Watano, et al., Evaluation of aqueous Enteric Coated Granules Prepared by Moisture Control Method in Tumbling Fluidized Bed Process, Chern. Pharm. Bull. 42(3) 663-667 (1994)	☐
	50	Wesdyk, et al., Factors affecting differences in film thickness of beads coated in fluidized bed units, International Journal of Pharmaceutics, 93, 101-109, (1993)	☐

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Signature	/Paul M. Zagar/	Date (YYYY-MM-DD)	2015-04-02
Name/Print	Paul M. Zagar	Registration Number	52392

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First Named Inventor	Amir SHOJAEI
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Examiner Name	Not Yet Assigned
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	1	Deposition of Transcript of Richard Rong-Kun Chang, dated 1/20/05	☐
	2	Deposition of Transcript of Richard A. Couch, dated 9/14/04	☐
	3	Deposition of Transcript of Robert Schaffer, dated August 17, 2005	☐
	4	Deposition of Transcript of Xiaodi Guo, dated 1/24/05	☐
	5	Deposition of Transcript of Xiaodi Guo, dated 7/26/04	☐
	6	Deposition transcript of Honorable Gerald J. Mossinghoff and exhibits thereto, dated June 8, 2005	☐
	7	Deposition Transcript of Richard Chang, dated 9/8/04	☐
	8	Edward Stempel, Prolonged Drug Action, HUSA's Pharmaceutical Dispensing, Sixth Edition, 1996, 464, 481-485	☐
	9	Expert Report of Dr. Joseph R. Robinson, expert for Barr Laboratories and exhibits thereto, February 28, 2005	☐
	10	Expert Report of the Honorable Gerald J. Mossinghoff, expert for Barr Laboratories, Inc. and exhibits thereto, March 16, 2005	☐
	11	Freedom of Information Request Results for- Dexadrine (SmithKiine Beecham): 5/20/1976 Disclosable Approval Information	☐

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	12	Fukumori, Coating of Multiparticulates Using Polymeric Dispersions, Multiparticulate Oral Drug Delivery (Swarbrick and Selassie eds. 1994),79-110	☐
	13	Garnett et al., Pharmacokinetic Evaluation of Twice-Daily Extended-Release	☐
	14	Carbamazepine(CBZ) and Four-Times- Daily Immediate-Release CBZ in Patients with Epilepsy, Epilepsia 39(3): 274-279, 1998	☐
	15	Glatt, The World of the Fluid Bed, Fluid Bed Systems, 1-19	☐
	16	Goodhart et al., An evaluation of Aqueous Film-forming Dispersions for Conrolled Release, Pharmaceutical Technology, April1984, 64-71	☐
	17	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	☐
	18	Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (1997)	☐
	19	Guidance for Industry: Food- Effect Bioavailability and Fed Bioequivalence Studies (2002)	☐
	20	Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms (1997)	☐
	21	Hall HS and Pendell RE, Controlled Release Technologies: Methods, Theory, and Applications, pp. 133-154 (Agis F. Kydonieus ed. 1980)	☐
	22	Handbook of Pharmaceutical Excipients: Ethycellulose, Polymethacrylates, 4th ed. (2003), 237-240, 462-468	☐

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	23	Handbook of Pharmaceutical Excipients: Polymethacrylates, 2nd Ed. (1994), 361-366	☐
	24	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	☐
	25	Harris, et al., Aqueous Polymeric Coating for Modified-Release Pellets, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms (McGinity ed., 1989), 63-79	☐
	26	Hawley's Condensed Chemical Dictionary 13th Ed. 1997, 584, 981	☐
	27	Holt, Bioequivalence Studies of Ketoprofen: Product formulation, Pharmacokinetics, Deconvolution, and In Vitro- In Vivo correlations, Thesis submitted to Oregon State University, August20, 1997(1997)	☐
	28	Husson et al., Influence of Size Polydispersity on Drug Release from Coated Pellets, International Journal of Pharmaceutics, 86 (1992) 113-121, 1992	☐
	29	Impax Laboratories Answer And Affirmative Defenses Shire Laboratories, Inc. v. Impax Laboratories, Inc., Civil Action No. 03-CV-01164-GMS	☐
	30	Impax Laboratories, Inc.'s First Supplemental Responses to Shire Laboratories Inc.'s First Set of Interrogatories (Nos. 11-12) dated 3/28/05	☐
	31	Impax Laboratories, Inc.'s Memorandum in Support of the Motion to Amend Its Answer dated 2/25/05 and exhibits thereto	☐
	32	Impax Laboratories, Inc.'s Reply Memorandum in Support of the Motion to Amend Its Answer dated 3/18/05 and exhibits thereto	☐
	33	Impax Laboratories, Inc's First Amended Answer and Affirmative Defenses, dated May 2, 2005	☐

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	34	Ishibashi et al., Design and Evaluation of a New Capsule-type Dosage Form for Colontargeted Delivery of Drugs, International Journal of Pharmaceutics 168, (1998) 31-40	☐
	35	J. Sjogren, Controlled Release Oral Formulation technology, Rate Control in Drug Therapy, (1985) 38-47	☐
	36	Jarowski, The Pharmaceutical Pilot Plant, Pharmaceutical Dosage Forms: Tablets, Vol. 3, 2nd Ed. (1990), 303-367	☐
	37	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	☐
	38	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)	☐
	39	Klaus Lehmann, Coating of Multiparticulates Using Polymeric Solutions, Multi particulate Oral Drug Delivery {Swarbrick and Sellassie ed., 1994f 51-78	☐
	40	Krowczynski & Brozyna, Extended-Release Dosage Forms, pp. 123-131 (1987)	☐
	41	Leon Lachman, Herbert A. Liebeman, Joseph L. Kanig, The Theory and Practice of Industrial Pharmacy, Second Edition (1976) 371-373	☐
	42	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	☐
	43	Lin & Cheng, In-vitro Dissolution Behaviour of Spansule-type Micropellets Prepared by Pan Coating Method, Pharm. Ind. 51 No.5 (1989) 528-531	☐
	44	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)	☐

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	45	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	☐
	46	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)	☐
	47	McGough, et al., Pharmacokinetics of SL 1381 (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	☐
	48	McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed. (1994), 97,972	☐
	49	Mehta, et al., Evaluation of Fluid-bed Processes for Enteric Coating Systems, Pharmaceutical Technology, April1986, 46-56	☐
	50	Meller, 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	☐

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	1	Wouessidjewe, Aqueous polymethacrylate Dispersions as Coating Materials for Sustained and Enteric Release Systems, S.T.P. Pharma Sciences 7(6) 469-475 (1997)	☐
	2	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	☐
	3	Court Docket for Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated January 8, 2007	☐
	4	Complaint in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., and exhibits thereto, Case No. 2:06 -cv-00952-SD dated March 2, 2006	☐
	5	Answer and Counterclaims in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated July 24, 2006	☐
	6	Reply To Counterclaims in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated August 16, 2006	☐
	7	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	☐
	8	Defendants' Responses to Plaintiffs 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	☐
	9	Plaintiffs 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	☐
	10	Plaintiffs 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	☐
	11	Defendants' Responses to Plaintiffs 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	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

	12	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	☐
	13	Petition Under Section 8 and exhibits thereto, submitted to the Canadian Patent Office on December 4, 2006	☐
	14	Office Action in U.S. Patent Application Serial No. 11/091 ,011, mailed December 1, 2006	☐
	15	Response to Non-Final Office Action filed January 10, 2007 in U.S. Patent Application No. 11/091,011	☐
	16	Response to Non-Final Office Action filed January 10, 2007 in U.S. Patent Application No. 11/091,010	☐
	17	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), papes 2067-2079, XP009092848, ISSN: 0363-9045	☐
	18	Patrick et al., Pharmacology of Methylphenidate, Amphetamine Enantiomers and pemoline in Attention- Deficit Hyperactivity Disorder, Human Psychopharmacology, vol. 12, pp. 527-546 (1997)	☐
	19	Chaumeil et al., Enrobages gastro-resistants a l'acetophtalate de cellulose, Annales Pharmaceutiques Francaises 1973, no. 5, pp. 375-384	☐
	20	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	☐
	21	Communication pursuant to Article 96(2) EPC dated June 21, 2006 for corresponding application No EP99 970 594.0.	☐
If you wish to add additional non-patent literature document citation information please click the Add button Add			

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

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	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

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.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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	/Paul M. Zagar/	Date (YYYY-MM-DD)	2015-04-02
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.**

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.

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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.

Docket No.: 085199-0996
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Amir SHOJAEI et al.	:	Customer Number: 20277
Application No.: 14/498,130	:	Confirmation No.: 5887
Filed: September 26, 2014	:	Art Unit: 1618
For: CONTROLLED DOSE DRUG DELIVERY SYSTEM	:	Examiner: MICAH PAUL YOUNG

INFORMATION DISCLOSURE STATEMENT (IDS)

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

Madam:

Pursuant to 37 C.F.R. § 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the U.S. filing date AND after the mailing date of the first Office Action on the merits, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 C.F.R. § 1.97(c)) or an action that otherwise closes prosecution in the application.

The documents cited in the attached form PTO/SB/08 are not supplied because they were previously cited by or submitted to the Office in prior application number 11/383,0666 filed May 12, 2006 and relied upon in this application for an earlier filing date under 35 U.S.C. § 120.

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 C.F.R. § 1.56(a) exists. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98 and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 50-0417 in the amount of $180.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0417, under Order No. 085199-0996.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

//Paul M. Zagar//

Paul M. Zagar
Registration No. 52,392

Please recognize our Customer No. 20277 as our correspondence address.

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Phone: (212) 547-5767 PMZ:jc
Facsimile: (212) 547-5444
Date: April 2, 2015

Electronic Patent Application Fee Transmittal

Application Number:	14498130
Filing Date:	26-Sep-2014
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Filer:	Bernard P. Codd/Joanna Chacon
Attorney Docket Number:	085199-0996

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	21954305
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	20277
Filer:	Bernard P. Codd/Joanna Chacon
Filer Authorized By:	Bernard P. Codd
Attorney Docket Number:	085199-0996
Receipt Date:	02-APR-2015
Filing Date:	26-SEP-2014
Time Stamp:	17:41:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

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5	Transmittal Letter	TransmittalforIDS.pdf	20792 4ba2f2565122a2a72fc902891ac8ee6a4bffe2f0	no	2
Warnings:					
Information:					

6	Fee Worksheet (SB06)	fee-info.pdf	30853 76beb9e3831a75eabee9c0c7830eb4023e68785c	no	2
Warnings:					
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			Total Files Size (in bytes):	2512918	

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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.: 085199-0996
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Amir SHOJAEI et al.	:	Customer Number: 20277
Application No.: 14/498,130	:	Confirmation No.: 5887
Filed: September 26, 2014	:	Art Unit: 1615
For: CONTROLLED DOSE DRUG DELIVERY SYSTEM	:	Examiner: Micah Paul YOUNG

RESPONSE TO NON-FINAL OFFICE ACTION

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

Madam:

This is in response to the January 16, 2015 non-final Office Action. A request for a two-month extension of time accompanies this response.

Amendments to the claims begin on page 2.

Remarks begin on page 6.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-0417, under Order No. 085199-0996.

Listing of the claims

1-58. (Canceled)

59. (New) A method for treating attention deficit hyperactivity disorder (ADHD) which comprises:

administering to a patient 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;

wherein the second delayed release bead comprises at least one amphetamine salt layered onto or incorporated into a core; a delayed release coating layered onto the amphetamine core; and a sustained release coating layered onto the delayed release coating, wherein the sustained release coating is pH-independent; and

wherein the first delayed release bead and the second delayed release bead comprise an enteric coating.

60. (New) The method of claim 59, wherein the enteric coating is pH dependent.

61. (New) The method of claim 59, wherein the first delayed release bead and the second delayed release bead comprise different enteric coatings.

62. (New) The method of claim 59, wherein the first delayed release bead and the second delayed release bead comprise the same enteric coating.

63. (New) The method of claim 59, 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.

64. (New) The method of claim 59, 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 nghr/ml.

65. (New) The method of claim 59, 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 nghr/ml.

66. (New) The method of claim 59, 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.

67. (New) The method of claim 59, 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.

68. (New) The method of claim 59, 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 nghr/ml.

69. (New) The method of claim 59, wherein the 1-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 nghr/ml.

70. (New) The method of claim 59, wherein the 1-amphetamine T_{max} is about 8.4 hours after administration of a 37.5 mg dose of the pharmaceutical composition to a human patient.

71. (New) The method of claim 59, wherein the immediate release bead and at least one delayed release bead are present on a single core.

72, (New) The method of claim 59, wherein the immediate release bead and at least one delayed release bead are present on different cores.

73. (New) The method of claim 59, wherein the at least one amphetamine salt is coated onto a core.

74. (New) The method of claim 59, wherein the at least one amphetamine salt is incorporated into a core.

75. (New) The method of claim 59, which further comprises a protective layer over at least one enteric coating.

76. (New) The method of claim 59, which further comprises a protective layer between the amphetamine salt and at least one enteric coating.

77. (New) The method of claim 59, 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.

78. (New) The method of claim 77, wherein the at least one amphetamine salt is a mixture of dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate, and amphetamine sulfate.

79. (New) The method of claim 59, wherein the composition does not exhibit a food effect.

80. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 12.5 mg.

81. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 18.75 mg.

82. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 25 mg.

83. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 31.25 mg.

84. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 37.5 mg.

85. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 43.75 mg.

86. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 50 mg.

87. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 62.5 mg.

88. (New) The method of claim 59, wherein the amount of at least one amphetamine salt is about 75 mg.

89. (New) The method of claim 59, wherein a protective coating is layered between the delayed release coating and the sustained release coating.

Remarks

Claims 1-58 have been canceled. New claims 59-89 have been added. The new claims are method of treatment claims comprising the administration of the pharmaceutical composition claimed in the parent patent, No. 8,846,100.

Rejection for obviousness-type double patenting

Claim 1 has been rejected for obviousness-type double patenting over claim 1 of U.S. Patent No. 8,846,100. This rejection is rendered moot in view of the cancellation of claim 1.

Rejection under 35 USC 103

Claim 1 has been rejected under 35 USC 103(a) as obvious over U.S. Publication No. 2003/0157173 (Percel) in view of U.S. Publication No. 2003/0050620 (Odidi). This rejection is rendered moot in view of the cancellation of claim 1. New claims 59-89 are non-obvious over Percel and Odidi because the pharmaceutical composition, claimed in U.S. Patent No. 8,866,100 is non-obvious over these references. According, claims reciting a method of treating comprising administering the pharmaceutical compound are also non-obvious over Percel and Odidi. The following documents from the prosecution of the parent, U.S. Patent No. 8,866,100, are included in the accompanying IDS, and show that the claimed pharmaceutical composition is non-obvious over the references cited in the instant rejection:

April 30, 2014 Office Action in U.S. Application No. 11/383,066 (now U.S. Patent No. 8,866,100);

June 3, 2014 Amendment in U.S. Application No. 11/383,066; and

July 7, 2014 Notice of Allowance and Interview Summary in U.S. Application No. 11/383,066.

For the reasons stated above, applicants respectfully request that this rejection be withdrawn.

Conclusion

This application is believed to be in condition for allowance. If any issues remain which may be addressed by a supplemental or Examiner's amendment, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

/Paul M. Zagar/

Paul M. Zagar
Registration No. 52,392

Please recognize our Customer No. 20277 as our correspondence address.

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New York, NY 10173
Phone: (212) 547-5767
Facsimile: (212) 547-5444
Date: May 20, 2015

Electronic Patent Application Fee Transmittal

Application Number:	14498130
Filing Date:	26-Sep-2014
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Filer:	Bernard P. Codd/Lynn Cruz
Attorney Docket Number:	085199-0996

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	600	600
Miscellaneous:				
		Total in USD ($)		**600**

Electronic Acknowledgement Receipt	
EFS ID:	22406769
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	20277
Filer:	Bernard P. Codd/Lynn Cruz
Filer Authorized By:	Bernard P. Codd
Attorney Docket Number:	085199-0996
Receipt Date:	20-MAY-2015
Filing Date:	26-SEP-2014
Time Stamp:	18:01:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$600
RAM confirmation Number	4821
Deposit Account	500417
Authorized User	ZAGAR, PAUL M.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		085199-0996_Amendment.pdf	27139 b0e46a7d685c5d7e643a5bf09cc41ea6675a64d8	yes	7

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	7

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	31024 add4f36cb0bacf236e91ca5501252cc914d82f2d	no	2

Warnings:

Information:

Total Files Size (in bytes):	58163

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.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1615
	Examiner Name	Micah Paul Young
	Attorney Docket Number	085199-0996

U.S.PATENTS						Remove
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					
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

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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
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FOREIGN PATENT DOCUMENTS							Remove	
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							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button							Add	

NON-PATENT LITERATURE DOCUMENTS			Remove
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	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1615
	Examiner Name	Micah Paul Young
	Attorney Docket Number	085199-0996

	1	April 30, 2014 Office Action in U.S. Application No. 11/383,066 (now U.S. Patent No. 8,866,100)	☐
	2	June 3, 2014 Amendment in U.S. Application No. 11/383,066	☐
	3	July 7, 2014 Notice of Allowance and Interview Summary in U.S. Application No. 11/383,066	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

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	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1615
	Examiner Name	Micah Paul Young
	Attorney Docket Number	085199-0996

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.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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	/Paul M. Zagar/	Date (YYYY-MM-DD)	2015-05-20
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.**

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 Patent Application Fee Transmittal

Application Number:	14498130
Filing Date:	26-Sep-2014
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Filer:	Bernard P. Codd/Lynn Cruz
Attorney Docket Number:	085199-0996

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt	
EFS ID:	22407369
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	20277
Filer:	Bernard P. Codd/Lynn Cruz
Filer Authorized By:	Bernard P. Codd
Attorney Docket Number:	085199-0996
Receipt Date:	20-MAY-2015
Filing Date:	26-SEP-2014
Time Stamp:	18:44:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	5405
Deposit Account	500417
Authorized User	ZAGAR, PAUL M.
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	085199-0996_IDS.pdf	612225 f02bc790336076e7debad84e24244c33d956dfaf	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Non Patent Literature	NPL1.pdf	462698 7c67d13b5d37c1190354a8b94ca18b94c81f7ce5	no	12
Warnings:					
Information:					
3	Non Patent Literature	NPL2.pdf	609345 3593172efa21bb9d931da0f01021d8cd9a298db0	no	16
Warnings:					
Information:					
4	Non Patent Literature	NPL3.pdf	461942 3e3ca1b6224287189030c600f4a221b05141c09d	no	8
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	30849 d9abd2998b5564bb06441b848c122d7f94405d06	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2177059		

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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.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/498,130	Filing Date 09/26/2014	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/20/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 31	Minus	** 20	= 11	X $80 =	880
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**880**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L 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.

LIE
/CORALIA BETANCOURT/

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 05/26/2015

CBETANCO SALE #00000003 Mailroom Dt: 05/20/2015 500417 14498130
01 FC : 1202 880.00 DA

PTO/AIA/26 (04-14)
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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 085199-0996

In re Application of: Amir SHOJAEI et al.

Application No.: 14/498,130-Conf. #5887

Filed: September 26, 2014

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM

The applicant, Shire LLC, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8846100 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 52,392

/Paul M. Zagar/ — Signature
June 11, 2015 — Date

Paul M. Zagar. M.D. — Typed or printed name

Agent of Record — Title
212-885-5290 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

999998.05404/100511726v.1

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Shire LLC

Application No./Patent No.: 14/498,130 Filed/Issue Date: September 26, 2014

Titled: CONTROLLED DOSE DRUG DELIVERY SYSTEM

Shire LLC (Name of Assignee) , a Corporation (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. [X] The assignee of the entire right, title, and interest.

2. [ ] An assignee of less than the entire right, title, and interest (check applicable box):

   [ ] The extent (by percentage) of its ownership interest is _____ %). Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   [ ] There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. [ ] The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. [ ] The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____
      The document was recorded in the United States Patent and Trademark Office at
      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____
      The document was recorded in the United States Patent and Trademark Office at
      Reel _____, Frame _____, or for which a copy thereof is attached.

140891.02600/100512398v.1

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	Date: 15 JUN 2015
Printed or Typed Name: MIKE CHAPMAN	Title or Registration Number: PRESIDENT

140891.02600/100512398v.1

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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 displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
14/498,130	September 26, 2014

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

[X] I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 14296

OR

[ ] I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

[X] The address associated with the above-mentioned Customer Number

OR

[ ] The address associated with Customer Number: 14296

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Shire LLC

[ ] Inventor or Joint Inventor (title not required below)

[ ] Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

[X] Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

[ ] Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Mike Chapman	Date (Optional)	15 JUN 2015
Name	MIKE CHAPMAN		
Title	PRESIDENT		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

[ ] Total of 1 forms are submitted.

999998.05404/100511656v.1

Electronic Acknowledgement Receipt

EFS ID:	22649089
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	20277
Filer:	Paul Michael Zagar/Judy Yeddo
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	085199-0996
Receipt Date:	16-JUN-2015
Filing Date:	26-SEP-2014
Time Stamp:	16:50:41
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	Terminal Disclaimer Filed	Terminal_Disclaimer.pdf	19875 29c0172a68dbb00369ad7d1b6d08656efb633623	no	1

Warnings:	
Information:	

2		373_POA.pdf	111067 bbc9b919270f2b6352b523d4a9a53383e2372c05	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Assignee showing of ownership per 37 CFR 3.73	1	2
	Power of Attorney	3	3

Warnings:	
Information:	
Total Files Size (in bytes):	130942

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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/498,130	SHOJAEI ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☐ APPROVED	☒ DISAPPROVED
Date Filed : 6/16/15	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

The disclaimer fee under 37 CFR 1.20(d) in the amount of $160.00 has not been submitted, nor is there any pre authorization in the application to charge to a deposit account. (See FP 14.24 and 14.26.07.)
Jean Proctor

U.S. Patent and Trademark Office

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	ATTY. DOCKET NO./TITLE
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996

CONFIRMATION NO. 5887

14296
Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

POA ACCEPTANCE LETTER

OC000000075819588

Date Mailed: 06/18/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/16/2015.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/zabraha/

PTO/AIA/26 (04-14)
Approved for use through 07/31/2016. 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 displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 085199-0996

In re Application of: Amir SHOJAEI et al.

Application No.: 14/498,130-Conf. #5887

Filed: September 26, 2014

For: CONTROLLED DOSE DRUG DELIVERY SYSTEM

The applicant, Shire LLC, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8846100 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 52,392

/Paul M. Zagar/ — Signature
June 11, 2015 — Date

Paul M. Zagar. M.D. — Typed or printed name

Agent of Record — Title
212-885-5290 — Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

999998.05404/100511726v.1

Electronic Patent Application Fee Transmittal

Application Number:	14498130
Filing Date:	26-Sep-2014
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Filer:	Paul Michael Zagar/Judy Yeddo
Attorney Docket Number:	085199-0996

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Statutory or Terminal Disclaimer	1814	1	160	160

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**160**

Electronic Acknowledgement Receipt	
EFS ID:	22687795
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	14296
Filer:	Paul Michael Zagar/Judy Yeddo
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	085199-0996
Receipt Date:	19-JUN-2015
Filing Date:	26-SEP-2014
Time Stamp:	16:19:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$160
RAM confirmation Number	2951
Deposit Account	022555
Authorized User	YEDDO, JUDY
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer Filed	TD.PDF	48652 00783bf70efd6b56403f0d3be0d8f70acf29f79c	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30566 5bdca65b5cf7cc68366d2d307fede491dca01df2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	79218		

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.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/498,130	SHOJAEI ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 6/19/15	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

jean proctor

U.S. Patent and Trademark Office

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

14296 7590 06/26/2015

Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

EXAMINER
YOUNG, MICAH PAUL

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 06/26/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996	5887

TITLE OF INVENTION: CONTROLLED DOSE DRUG DELIVERY SYSTEM

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

14296 7590 06/26/2015
Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996	5887

TITLE OF INVENTION: CONTROLLED DOSE DRUG DELIVERY SYSTEM

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
YOUNG, MICAH PAUL	1618	424-490000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996	5887

14296 7590 06/26/2015

Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

EXAMINER	
YOUNG, MICAH PAUL	

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 06/26/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice Requiring Inventor's Oath or Declaration	Application No. 14/498,130	Applicant(s) Amir SHOJAEI	
	Examiner YOUNG, MICAH PAUL	Art Unit 1618	

This notice is an attachment to the Notice of Allowability (PTOL-37), or the Notice of Allowability For A Design Application (PTOL-37D).

An inventor's oath or declaration in compliance with 37 CFR 1.63 or 1.64 executed by or with respect to each inventor has not yet been submitted.

An oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each inventor (for any inventor for which a compliant oath, declaration, or substitute statement has not yet been submitted) MUST be filed no later than the date on which the issue fee is paid. See 35 U.S.C. 115(f). Failure to timely comply will result in ABANDONMENT of this application.

A properly executed inventor's oath to declaration has not been received for the following inventor(s):

If applicant previously filed one or more oaths, declarations, or substitute statements, applicant may have received an informational notice regarding deficiencies therein.

The following deficiencies are noted:

INFORMAL ACTION PROBLEMS

- A properly executed inventor's oath or declaration has not been received for the following inventor(s): **Amir SHOJAEI**, **Stephanie READ**, **Richard A. COUCH**, and **Paul HODGKINS**.
  Applicant may submit the inventor's oath or declaration at any time before the Notice of Allowance and Fee(s) Due, PTOL-85, is mailed.

Questions relating to this Notice should be directed to the Application Assistance Unit at 571-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 12 minutes 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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 disclosure of these records is required by the Freedom of Information Act.
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 inspection 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.

Notice of Allowability	Application No. 14/498,130	Applicant(s) SHOJAEI ET AL.	
	Examiner MICAH-PAUL YOUNG	Art Unit 1618	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *response dated 5/20/15*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *59-70,73-89*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
      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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 4/02/15, 5/20/15
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☒ Other *bib data sheet*.

/MICAH-PAUL YOUNG/ Examiner, Art Unit 1618	/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Paul M. Zagar on 6/15/16.

The application has been amended as follows:

Amend claim 59 as follows:

In line 3 of the claim insert in need thereof, between "patient" and "a pharmaceutical composition".

Cancel claims 71 and 72.

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-Thursday 7:00-5:30; every 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.

/MICAH-PAUL YOUNG/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	14498130
Filing Date	2014-09-26
First Named Inventor	Amir SHOJAEI
Art Unit	1615
Examiner Name	Micah Paul Young
Attorney Docket Number	085199-0996

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	Examiner Name	Micah Paul Young
	Attorney Docket Number	085199-0996

/M.Y./	1	April 30, 2014 Office Action in U.S. Application No. 11/383,066 (now U.S. Patent No. 8,866,100)	☐
/M.Y./	2	June 3, 2014 Amendment in U.S. Application No. 11/383,066	☐
/M.Y./	3	July 7, 2014 Notice of Allowance and Interview Summary in U.S. Application No. 11/383,066	☐

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EXAMINER SIGNATURE

Examiner Signature	/Micah Paul Young/ (06/22/2015)	Date Considered	06/22/2015

*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.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Application Number	14498130
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	1	2881113		1959-04-07	Millman	
	2	6322819		2001-11-27	Burnside et al.	
	3	6605300		2003-08-12	Burnside et al.	
	4	RE41148		2010-02-23	Burnside et al.	
	5	5496561		1996-03-05	Okada et al.	
	6	5328697		1994-07-12	Raman et al.	
	7	6005027		1999-12-21	Guillet et al.	
	8	6913768		2005-07-05	Couch et al.	

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	9	6764696		2004-07-20	Pather et al.	
	10	6749867		2004-06-15	Robinson et al.	
	11	5846568		1998-12-08	Olinger et al.	
	12	5773031		1998-06-30	Shah et al.	
	13	5733575		1998-03-31	Mehra et al.	
	14	5618559		1997-04-08	Desai et al.	
	15	5501861		1996-03-26	Makino et al.	
	16	5422121		1995-06-06	Lehmann et al.	
	17	5411745		1995-05-02	Oshlack et al.	
	18	5202159		1993-04-13	Chen et al.	
	19	5137733		1992-08-11	Noda et al.	

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	Attorney Docket Number	085199-0996

	20	4794001		1988-12-27	Mehta et al.	
	21	3979349		1976-09-07	Fink et al.	
	22	3365365		1968-01-23	J.A. Butler et al.	
	23	3066075		1962-11-27	Deutsch Marshalle	
	24	3048526		1962-08-07	C.L. Boswell	
	25	2738303		1956-03-13	R.H. Blythe	
	26	2099402		1937-11-16	J.W. Keller	
	27	6475493		2002-11-05	Mulye	
	28	6228398		2001-05-08	Devane et al.	

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	1	20030050620	A1	2003-03-13	Odidi et al.	
	2	20030157173	A1	2003-08-21	Percel et al.	

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	1	1987/000441	WO	A1	1987-01-15	The Upjohn Company		☐
	2	2004028509	WO	A1	2004-04-08	Shire Laboratories, Inc,		☐
	3	109,438	AU		1940-01-11	I. Lipowski		☐
	4	59-082311	JP		1984-05-12	Shionogi & Co Ltd		☐
	5	07-061922	JP		1995-03-07	SS Pharmaceut Co Ltd		☐
	6	10-081634	JP		1998-03-31	Taisho Pharmaceut Co Ltd		☐
	7	09237035	JP		1997-10-14	Kanegafuchi Chemical Ind Co Ltd		☐

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	8	03-148215	JP		1991-06-25	Nippon Shinyaku Co Ltd		☐
	9	09-249557	JP		1997-09-22	Shionogi & Co		☐
	10	98/14168	WO	A2	1998-04-09	Alza Corp		☐
	11	97/03673	WO	A1	1997-02-06	Chiroscience Ltd		☐
	12	00/35450	WO	A1	2000-06-22	Paul D Goldenheim		☐
	13	0640337	EP	A2	1995-03-01	Ss Pharmaceutical Co., Ltd		☐
	14	99/03471	WO	A1	1999-01-28	Mehta, Atul		☐
	15	00/25752	WO	A1	2000-05-11	John G Devane		☐

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	1	International Search Report dated November 21, 2006 issued for corresponding International Application No. PCT/US06/18453.	☐

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	2	Conte et al., "Press-coated tablets for time-programmed release of drugs," Biomaterials, Vol. 14, No. 13, pp.1017-1023 (1993).	☐
	3	Gazzaniga et al., "Oral Chronotopic Drug Delivery Systems: Achievement of Time and/or Site Specificity," Eur J Pharm Biopharm, Vol. 40, No. 4, pp. 246-250 (1994).	☐
	4	Theeuwes, "Oros Osmotic System Development," Drug Dev Ind Pharm, Vol. 9, No. 7, pp. 1331-1357 (1983).	☐
	5	Walia et al., "Preliminary Evaluation of an Aqueous Wax Emulsion for Controlled-Release Coating," Pharm Dev Tech, Vol. 3, No. 1, pp. 103-113 (1998).	☐
	6	Xu et al., Programmable Drug Delivery from an Erodible Association Polymer System," Pharm Res, Vol. 10, No. 8, pp. 1144-1152 (1993).	☐
	7	Office Action dated February 18, 2014, which is issued during the prosecution of Mexican Patent Applicaion No. MX/a/2008/014455, which is related to the present application together with a letter from a foreign agent re. the Office Action in English.	☐
	8	Office Action in Japanese Application No. 2008-159637 dated September 11, 2012 (Original Japanes and English Translation attached).	☐
	9	U.S. Application No. 11/091,011: Final Office Action dated November 13, 2009, including Form PTO-892 and the references cited therein (10 pages).	☐
	10	Adderall XR Package Inset, Sept. (2004)	☐
	11	Agyilirah GA and Banker SB, Polymers for Enteric Coating applications, Polymers for Controlled Drug Delivery (Peter J. Tarcha ed. 1991) 39-66	☐
	12	American Chemcial Society, Polymer Preprints, pp. 633-634, Vol. 34, No. 1, March 1993 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.Y./	☐

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	13	Ansel, et al., Rate Controlled Dosage Forms and Drug Delivery Systems, Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. (1995), 213-222.	☐
	14	Answering Expert Report of Dr. Alexander M. Klibanov, expert for Shire Laboratories, Inc., April 25, 2005.	☐
	15	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.	☐
	16	Barr Laboratories' Objections and Responses to Plaintiff Shire Laboratores Inc's Fifth Set of Interrogatories (No. 17), dated September 3, 2004.	☐
	17	Barr Laboratories' Amended Answer, Affirmative Defenses And Counterclaims Shire Laboratories, Inc. v. Barr Laboratories, Inc., Civil Action No. 03-CV-1219-PKC	☐
	18	Barr Laboratories' Answer, Affirmative Defenses, and Counterclaims, dated September 25, 2003	☐
	19	Barr Laboratories Inc.'s Objections and Responses to Shire Laboratories Inc.'s Second Set of Interrogatores (Nos. 8-11), dated February 18, 2004.	☐
	20	Barr Laboratories Inc.'s Objections and Responses to Shire Laboratories Inc.'s Fourth Set of Interrogatories (Nos.15-16), dated July 9, 2004	☐
	21	Barr Laboratories' Memorandum in Support of Its Motion to Amend Its Pleadings and exhibits thereto, dated September 10, 2004	☐
	22	Barr Laboratories' Memorandum in Support of Its Motion to Compel Production, dated September 13, 2004	☐
	23	Barr Laboratories' Supplemental Objections and Responses to Plaintiff Shire Laboratories Inc.'s Third Set of Interrogatories (Nos. 12-14)(Redacted), dated August 27 2004 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.Y./	☐

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	24	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. §3550)(2)(B)(ii) and 21 C.F.R. § 314.95)	☐
	25	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. §355fj)(2)(B)(ii) and 21 C.F.R. § 314.95)	☐
	26	Bauer, et al., Cellulose Acetate Phthalate (CAP) and Trimellitate (CAT), Coated Pharmaceutical Dosage Forms (1998), 102-104	☐
	27	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	☐
	28	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	☐
	29	Brown et al., Plasma Levels of d-Amphetamine in Hyperactive Children, Psychopharmacology 62, 133-140, 1979	☐
	30	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	☐
	31	C. Lin et al., Bioavailability of d-pseudoephedrine and Azatadine from a Repeat Action Tablet Formulation, J Int Med Res (1982), 122-125	☐
	32	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) 10,126-128	☐
	33	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	☐
	34	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	☐

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	35	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	☐
	36	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	☐
	37	Civil Docket For Case #: 1 :03-cv-01164-GMS Shire Laboratories, Inc. v. Impax Laboratories, Inc., Civil Action No. 03-CV-01164-GMS	☐
	38	Civil Docket For Case#: 1:03-cv-01219-PKC-DFE Shire Laboratories, Inc. v. Baff Laboratories, Inc., Civil Action No. 03-CV-1219-PKC	☐
	39	Civil Docket For Case#: 1 :03-cv-06632-VM-DFE Shire Laboratories, Inc. v. Barr Laboratories, Inc., Civil Action No. 03-CV-6632-PKC	☐
	40	Civil Docket For Case#: 1 :05-cv-00020-GMS Shire Laboratories, Inc. v. Impax Laboratories, Inc., Civil Action No. 05-20-GMS	☐
	41	Cody et al., Amphetamine Enantiomer Excretion Profile Following Administration of Adderall, Journal of Analytical Toxicology, Vol. 2, October 2003, 485-492	☐
	42	Complaint for Declaratory Judgment, Impax Laboratories, Inc. v. Shire International Laboratories, Inc. (Civ. Action No. 05772) and Exhibits attached thereto	☐
	43	Daynes, Treatment of Noctural Enuresis with Enteric-Coated Amphetamine, The Practitioner, No. 1037, Vol. 173, November 1954	☐
	44	Deposition of Transcript of Beth Burnside, dated 2/2/05	☐
	45	Deposition of Transcript of Beth Burnside, dated 2/3/05 ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.Y./	☐

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	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

	46	Deposition of Transcript of Charlotte M. McGuiness, dated 8/6/04	☐
	47	Deposition of Transcript of Donald John Treacy, Jr., dated 8/31/04	☐
	48	Deposition of Transcript of Edward Rudnic, dated 7/28/04	☐
	49	Deposition of Transcript of James J. Harrington, dated July 27, 2005	☐
	50	Deposition of Transcript of Kimberly Fiske, dated 9/17/04	☐

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Examiner Signature	/Micah Paul Young/ (06/22/2015)	Date Considered	06/22/2015

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14498130
	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

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.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

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	/Paul M. Zagar/	Date (YYYY-MM-DD)	2015-04-02
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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Attorney Docket Number	085199-0996

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/M.Y./	1	Response to Office Action filed May 2, 2006 in U.S. Patent Application No. 11/091/010	☐
/M.Y./	2	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed February 3, 2006	☐
/M.Y./	3	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed July 13, 2006	☐
/M.Y./	4	Response to Office Action filed July 18, 2006 in U.S. Patent Application No. 11/091,010	☐
/M.Y./	5	Office Action in U.S. Patent Application Serial No. 11/091,010, mailed October 10,2006	☐
/M.Y./	6	Office Action mailed March 2, 2005 in European Patent Ap_plication No. 99 970594.0-2123	☐
/M.Y./	7	Opening Expert Report of Dr. Michael Mayersohn, expert for Impax Laboratories Inc. and exhibits thereto, March 12, 2005	☐
/M.Y./	8	Opening Expert Report of Dr. Walter Chambliss, expert for Impax Laboratories, Inc. and exhibits thereto, March 15, 2005	☐
/M.Y./	9	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	☐
/M.Y./	10	PDR Drug information for Ritalin LA Capsules, April (2004)	☐
/M.Y./	11	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	☐

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/M.Y./	12	Physicians' Desk Reference: Adderall, 51st Ed. (1997)	☐
/M.Y./	13	Physicians' Desk Reference: Adderall, 56th Ed. (2002)	☐
/M.Y./	14	Physicians' Desk Reference: Dexedrine, 56th ed. (2002)	☐
/M.Y./	15	Physicians' Desk Reference: Ritalin, 56th Ed. (2002)	☐
/M.Y./	16	Porter and Bruno, Coating of Pharmaceutical Solid-Dosage Forms, 77-160	☐
/M.Y./	17	Prescribing Information: Dexedrine, brand of dextroamphetamine sulfate (2001)	☐
/M.Y./	18	R. Bianchini & C. Vecchio, Oral Controlled Release Optimization of Pellets Prepared by Extrusion- Spheronization Processing, IL Farmaco 44(6), 645-654, 1989	☐
/M.Y./	19	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	☐
/M.Y./	20	Remington: The Science and Practice of Pharmacy, Basic Phar::acokinetics, 16th Ed. (1980), 693	☐
/M.Y./	21	Remington: The Science and Practice of Pharmacy, Elutriation, 20th Ed.(2000), 690	☐
/M.Y./	22	Remington's Pharmaceutical Sciences, Fifteenth Edition (1975) 1624-1625	☐

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/M.Y./	23	Remington's Pharmaceutical Sciences, RPS XIV, 1700-1714	☐
/M.Y./	24	Reply to Barr Laboratories Inc.'s Amended Answer, Affirmatice Defenses And Counterclaims Shire Laboratories, Inc. v. Ba" Laboratories, Inc., Civil Action No. 03-CV-1219-PKC	☐
/M.Y./	25	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	☐
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/M.Y./	30	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	☐
/M.Y./	31	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	☐
/M.Y./	32	Shargel; Pharmacokinetics of Oral Absorption, Applied Biopharmaceutics & Pharmacokinetics. 5th Ed. {225}, 164-166	☐
/M.Y./	33	Sheen et al., Aqueous Film Coating Studies of Sustained Release Nicotinic Acid Pellets: An In-Vitro Evaluation, Drug Development and Industrial Pharmacy, 18(8), 8S1-860 (1992)	☐

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/M.Y./	34	Shire Laboratories Inc.'s Opposition to Barr Laboratories' Motion to Amend Its Answers and Counterclaims, September 15, 2004	☐
/M.Y./	35	Slattum, et al., Compararision of Methods for the Assessment of Central Nervous System Stimulant Response after Dextroamphetamine Administration to Healthy Male Volunteers, J.clin Pharmacal (1996) 36,1039-1050	☐
/M.Y./	36	Sprowls' American Pharmacy: An Introduction to Pharmaceutical Techniques and Dosage Forms, 7th Ed. (1974), 387-388	☐
/M.Y./	37	Sriamornsak, et al., Development of Sustained Release Theophylline Pellets Coated with Calcium Pectinate, Journal of Controlled Release 47 (1997) 221-232	☐
/M.Y./	38	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, 1531-1S34	☐
/M.Y./	39	Teva Notice letter dated February 21, 200S	☐
/M.Y./	40	Teva Notice letter dated June 1, 2005	☐
/M.Y./	41	The Merck Index: Amphetamine, 12th Ed., 620	☐
/M.Y./	42	The Merck Index: Amphetamine, 13th Ed. (2001), 97, 1089	☐
/M.Y./	43	The United States Pharmacopeia 23, National Formulary 18 {1995) pp. 1791-1799	☐
/M.Y./	44	The United States Pharmacopeia 26, National Formulary 21 {2003) pp. 2157-2165	☐

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/M.Y./	45	The United States Pharmacopeia 27, National Formulary 22(2004) pp. 2302-2312	☐
/M.Y./	46	Treatise on Controlled Drug Delivery, pp. 185-199 (Agis Kydonieus ed. 1992)	☐
/M.Y./	47	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 Va:. 22, No. 11, (2002), 140S-141S	☐
/M.Y./	48	Vasilevska, et al., Preparation and Dissolution Characteristics of Controlled Release Diltiazem Pellets, Drug Development and Industrial Pharmacy, 18(15), 1649-1661 (1992)	☐
/M.Y./	49	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)	☐
/M.Y./	50	Wesdyk, et al., Factors affecting differences in film thickness of beads coated in fluidized bed units, International Journal of Pharmaceutics, 93, 101-109, (1993)	☐

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Examiner Signature	/Micah Paul Young/ (06/22/2015)	Date Considered	06/22/2015

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/M.Y./	1	Deposition of Transcript of Richard Rong-Kun Chang, dated 1/20/05	☐
/M.Y./	2	Deposition of Transcript of Richard A. Couch, dated 9/14/04	☐
/M.Y./	3	Deposition of Transcript of Robert Schaffer, dated August 17, 2005	☐
/M.Y./	4	Deposition of Transcript of Xiaodi Guo, dated 1/24/05	☐
/M.Y./	5	Deposition of Transcript of Xiaodi Guo, dated 7/26/04	☐
/M.Y./	6	Deposition transcript of Honorable Gerald J. Mossinghoff and exhibits thereto, dated June 8, 2005	☐
/M.Y./	7	Deposition Transcript of Richard Chang, dated 9/8/04	☐
/M.Y./	8	Edward Stempel, Prolonged Drug Action, HUSA's Pharmaceutical Dispensing, Sixth Edition, 1996, 464, 481-485	☐
/M.Y./	9	Expert Report of Dr. Joseph R. Robinson, expert for Barr Laboratories and exhibits thereto, February 28, 2005	☐
/M.Y./	10	Expert Report of the Honorable Gerald J. Mossinghoff, expert for Barr Laboratories, Inc. and exhibits thereto, March 16, 2005	☐
/M.Y./	11	Freedom of Information Request Results for- Dexadrine (SmithKiine Beecham): 5/20/1976 Disclosable Approval Information	☐

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/M.Y./	12	Fukumori, Coating of Multiparticulates Using Polymeric Dispersions, Multiparticulate Oral Drug Delivery (Swarbrick and Selassie eds. 1994),79-110	☐
/M.Y./	13	Garnett et al., Pharmacokinetic Evaluation of Twice-Daily Extended-Release	☐
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/M.Y./	15	Glatt, The World of the Fluid Bed, Fluid Bed Systems, 1-19	☐
/M.Y./	16	Goodhart et al., An evaluation of Aqueous Film-forming Dispersions for Conrolled Release, Pharmaceutical Technology, April1984, 64-71	☐
/M.Y./	17	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	☐
/M.Y./	18	Guidance for Industry: Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (1997)	☐
/M.Y./	19	Guidance for Industry: Food- Effect Bioavailability and Fed Bioequivalence Studies (2002)	☐
/M.Y./	20	Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms (1997)	☐
/M.Y./	21	Hall HS and Pendell RE, Controlled Release Technologies: Methods, Theory, and Applications, pp. 133-154 (Agis F. Kydonieus ed. 1980)	☐
/M.Y./	22	Handbook of Pharmaceutical Excipients: Ethycellulose, Polymethacrylates, 4th ed. (2003), 237-240, 462-468	☐

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	Filing Date	2014-09-26
	First Named Inventor	Amir SHOJAEI
	Art Unit	1618
	Examiner Name	Not Yet Assigned
	Attorney Docket Number	085199-0996

/M.Y./	23	Handbook of Pharmaceutical Excipients: Polymethacrylates, 2nd Ed. (1994), 361-366	☐
/M.Y./	24	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	☐
/M.Y./	25	Harris, et al., Aqueous Polymeric Coating for Modified-Release Pellets, Aqueous Polymeric Coating for Pharmaceutical Dosage Forms (McGinity ed., 1989), 63-79	☐
/M.Y./	26	Hawley's Condensed Chemical Dictionary 13th Ed. 1997, 584, 981	☐
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/M.Y./	29	Impax Laboratories Answer And Affirmative Defenses Shire Laboratories, Inc. v. Impax Laboratories, Inc., Civil Action No. 03-CV-01164-GMS	☐
/M.Y./	30	Impax Laboratories, Inc.'s First Supplemental Responses to Shire Laboratories Inc.'s First Set of Interrogatories (Nos. 11-12) dated 3/28/05	☐
/M.Y./	31	Impax Laboratories, Inc.'s Memorandum in Support of the Motion to Amend Its Answer dated 2/25/05 and exhibits thereto	☐
/M.Y./	32	Impax Laboratories, Inc.'s Reply Memorandum in Support of the Motion to Amend Its Answer dated 3/18/05 and exhibits thereto	☐
/M.Y./	33	Impax Laboratories, Inc's First Amended Answer and Affirmative Defenses, dated May 2, 2005	☐

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/M.Y./	34	Ishibashi et al., Design and Evaluation of a New Capsule-type Dosage Form for Colontargeted Delivery of Drugs, International Journal of Pharmaceutics 168, (1998) 31-40	☐
/M.Y./	35	J. Sjogren, Controlled Release Oral Formulation technology, Rate Control in Drug Therapy, (1985) 38-47	☐
/M.Y./	36	Jarowski, The Pharmaceutical Pilot Plant, Pharmaceutical Dosage Forms: Tablets, Vol. 3, 2nd Ed. (1990), 303-367	☐
/M.Y./	37	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	☐
/M.Y./	38	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)	☐
/M.Y./	39	Klaus Lehmann, Coating of Multiparticulates Using Polymeric Solutions, Multi particulate Oral Drug Delivery {Swarbrick and Sellassie ed., 1994f 51-78	☐
/M.Y./	40	Krowczynski & Brozyna, Extended-Release Dosage Forms, pp. 123-131 (1987)	☐
/M.Y./	41	Leon Lachman, Herbert A. Liebeman, Joseph L. Kanig, The Theory and Practice of Industrial Pharmacy, Second Edition (1976) 371-373	☐
/M.Y./	42	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	☐
/M.Y./	43	Lin & Cheng, In-vitro Dissolution Behaviour of Spansule-type Micropellets Prepared by Pan Coating Method, Pharm. Ind. 51 No.5 (1989) 528-531	☐
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/M.Y./	45	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	☐
/M.Y./	46	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)	☐
/M.Y./	47	McGough, et al., Pharmacokinetics of SL 1381 (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	☐
/M.Y./	48	McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed. (1994), 97,972	☐
/M.Y./	49	Mehta, et al., Evaluation of Fluid-bed Processes for Enteric Coating Systems, Pharmaceutical Technology, April1986, 46-56	☐
/M.Y./	50	Meller, 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	☐

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Examiner Signature	/Micah Paul Young/ (06/22/2015)	Date Considered	06/22/2015

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Signature	/Paul M. Zagar/	Date (YYYY-MM-DD)	2015-04-02
Name/Print	Paul M. Zagar	Registration Number	52392

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Application Number	14498130
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First Named Inventor	Amir SHOJAEI
Art Unit	1618
Examiner Name	Not Yet Assigned
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/M.Y./	1	Wouessidjewe, Aqueous polymethacrylate Dispersions as Coating Materials for Sustained and Enteric Release Systems, S.T.P. Pharma Sciences 7(6) 469-475 (1997)	☐
/M.Y./	2	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	☐
/M.Y./	3	Court Docket for Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated January 8, 2007	☐
/M.Y./	4	Complaint in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., and exhibits thereto, Case No. 2:06 - cv-00952-SD dated March 2, 2006	☐
/M.Y./	5	Answer and Counterclaims in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated July 24, 2006	☐
/M.Y./	6	Reply To Counterclaims in Shire Laboratories Inc. v. Teva Pharmaceutical Industries Ltd., Case No. 2:06-cv-00952-SD dated August 16, 2006	☐
/M.Y./	7	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	☐
/M.Y./	8	Defendants' Responses to Plaintiffs 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	☐
/M.Y./	9	Plaintiffs 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	☐
/M.Y./	10	Plaintiffs 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	☐
/M.Y./	11	Defendants' Responses to Plaintiffs 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	☐

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/M.Y./	12	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	☐
/M.Y./	13	Petition Under Section 8 and exhibits thereto, submitted to the Canadian Patent Office on December 4, 2006	☐
/M.Y./	14	Office Action in U.S. Patent Application Serial No. 11/091 ,011, mailed December 1, 2006	☐
/M.Y./	15	Response to Non-Final Office Action filed January 10, 2007 in U.S. Patent Application No. 11/091,011	☐
/M.Y./	16	Response to Non-Final Office Action filed January 10, 2007 in U.S. Patent Application No. 11/091,010	☐
/M.Y./	17	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), papes 2067-2079, XP009092848, ISSN: 0363-9045	☐
/M.Y./	18	Patrick et al., Pharmacology of Methylphenidate, Amphetamine Enantiomers and pemoline in Attention- Deficit Hyperactivity Disorder, Human Psychopharmacology, vol. 12, pp. 527-546 (1997)	☐
/M.Y./	19	Chaumeil et al., Enrobages gastro-resistants a l'acetophtalate de cellulose, Annales Pharmaceutiques Francaises 1973, no. 5, pp. 375-384	☐
/M.Y./	20	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	☐
/M.Y./	21	Communication pursuant to Article 96(2) EPC dated June 21, 2006 for corresponding application No EP99 970 594.0.	☐

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	MICAH-PAUL YOUNG	1618

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A61K		9	/	1676	I	2013-01-01
A61K		9	/	4808	I	2013-01-01
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	Examiner	**Art Unit**
	MICAH-PAUL YOUNG	1618

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
424	490	A	6	1	K	9 / 16 (2006.0)						
CROSS REFERENCE(S)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											
424	463	493										

/MICAH-PAUL YOUNG/ Examiner.Art Unit 1618	06/22/2015	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/MICHAEL G HARTLEY/ Supervisory Patent Examiner.Art Unit 1618	06/22/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14498130	SHOJAEI ET AL.
	Examiner	**Art Unit**
	MICAH-PAUL YOUNG	1618

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/MICAH-PAUL YOUNG/ Examiner.Art Unit 1618	06/22/2015	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	29	
/MICHAEL G HARTLEY/ Supervisory Patent Examiner.Art Unit 1618	06/22/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office Part of Paper No. 20150622-A

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14498130	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	01/10/2015	06/22/2015							
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	36		-							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14498130	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

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14498130	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								
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	88		=							
	89		=							
	1	✓								

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

BIB DATA SHEET

CONFIRMATION NO. 5887

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/498,130	09/26/2014	424	1618	085199-0996

APPLICANTS
Shire LLC, Florence, KY;

INVENTORS
Amir SHOJAEI, Phoenixville, PA;
Stephanie READ, Philadelphia, PA;
Richard A. COUCH, Bryn Mawr, PA;
Paul HODGKINS, Exton, PA;

**** CONTINUING DATA ***************************
This application is a CON of 11/383,066 05/12/2006 PAT 8846100

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
10/01/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /MICAH-PAUL YOUNG/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA	10	1	1

ADDRESS

Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037
UNITED STATES

TITLE

CONTROLLED DOSE DRUG DELIVERY SYSTEM

FILING FEE RECEIVED		
2620	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14498130	SHOJAEI ET AL.
	Examiner	Art Unit
	MICAH-PAUL YOUNG	1618

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 9/1676, 28, 2806, 284, 2866, 2886	6/22/15	MPY

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	489-502	1/10/15	MPY
above	to date	6/22/15	MPY

SEARCH NOTES		
Search Notes	Date	Examiner
east brs search, odp with parent possible, td filed and approved	6/22/15	MPY

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
424/A61K	489, 490/ 9/2806, 2833, 2866,	6/22/15	MPY

/MICAH-PAUL YOUNG/ Examiner.Art Unit 1618	

POWER OF ATTORNEY AND

STATEMENT OF OWNERSHIP UNDER 37 C.F.R. 3.73(b)

Shire LLC, located at 9200 BROOKFIELD COURT, FLORENCE, KENTUCKY 41042, is the owner of the entire right, title, and interest in the patent applications and patents identified in Appendix A, by virtue of the recorded assignments identified in Appendix A.

I am authorized to act on behalf of Shire, LLC in connection with these patent applications and patents.

I hereby revoke all previous powers of attorney given in the patent applications and patents identified on the attached Appendix A.

I hereby appoint all practitioners associated with Customer Number **14296** and all of Blank Rome LLP, The Chrysler Building, 405 Lexington Ave., New York, New York 10174-0208, jointly, and each of them severally, my attorneys at law and patent agents, with full power of substitution, delegation and revocation, to prosecute these patent applications and patents, 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.

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from Shire, LLC Technologies, Inc. as to any action to be taken in the United States Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

Please mail all correspondence to

Address associated with Customer Number:

14296

Please direct telephone calls to: Paul M. Zagar, M.D. at (212) 885-5290.

Please direct facsimiles to: Paul M. Zagar, M.D. at (917) 332-3063.

Signature: _____ Date: 22 JUL 2015

Name: MIKE CHAPMAN

Title: PRESIDENT

APPENDIX A

Blank Rome Reference	Application Number	Filing Date	Patent Number	Issue Date	Owner Name
134389.01413	09/176542	21-Oct-98	6322819	27-Nov-01	SHIRE, LLC
134389.01414	09/807462	19-Jul-01	6605300	12-Aug-03	SHIRE, LLC
134389.01415	11/091011	24-Mar-05	RE42096	1-Feb-11	SHIRE, LLC
134389.01416	11/091010	24-Mar-05	RE41148	23-Feb-10	SHIRE, LLC
134389.01500	11/383066	12-May-06	8846100	30-Sep-14	SHIRE, LLC
134389.01723	10/353073	29-Jan-03	6913768	5-Jul-05	SHIRE, LLC
134389.01800	09/611098	6-Jul-00	6384020	7-May-02	SHIRE, LLC
134389.01947	10/857619	1-Jun-04	7223735	29-May-07	SHIRE, LLC
134389.02003	11/400304	10-Apr-06	7700561	20-Apr-10	SHIRE, LLC
134389.02004	12/131923	2-Jun-08	7659253	9-Feb-10	SHIRE, LLC
134389.02004	12/201739	29-Aug-08	7678770	16-Mar-10	SHIRE, LLC
134389.02005	12/201586	29-Aug-08	7659254	9-Feb-10	SHIRE, LLC
134389.02006	12/201760	29-Aug-08	7655630	2-Feb-10	SHIRE, LLC
134389.02007	12/201794	29-Aug-08	7687466	30-Mar-10	SHIRE, LLC
134389.02008	12/201866	29-Aug-08	7662788	16-Feb-10	SHIRE, LLC

APPENDIX A

Blank Rome Reference	Application Number	Filing Date	Patent Number	Issue Date	Owner Name
134389.02009	12/201907	29-Aug-08	7713936	11-May-10	SHIRE, LLC
134389.02010	12/201950	29-Aug-08	7671030	2-Mar-10	SHIRE, LLC
134389.02011	12/201982	29-Aug-08	7674774	9-Mar-10	SHIRE, LLC
134389.02012	12/202003	29-Aug-08	7723305	25-May-10	SHIRE, LLC
134389.02013	12/202096	29-Aug-08	7718619	18-May-10	SHIRE, LLC
134389.02014	12/202146	29-Aug-08	7678771	16-Mar-10	SHIRE, LLC
134389.02015	12/202159	29-Aug-08	7671031	2-Mar-10	SHIRE, LLC
134389.02016	12/202067	29-Aug-08	7687467	30-Mar-10	SHIRE, LLC
134389.02108	09/642820	22-Aug-00	6716452	6-Apr-04	SHIRE, LLC
134389.02109	10/136433	2-May-02	7163918	16-Jan-07	SHIRE, LLC
134389.02110	10/156527	29-May-02	7060708	13-Jun-06	SHIRE, LLC
134389.02111	10/923088	23-Aug-04	7427600	23-Sep-08	SHIRE, LLC
134389.02112	10/953116	30-Sep-04	7375082	20-May-08	SHIRE, LLC
134389.02113	12/169389	8-Jul-08	8394813	12-Mar-13	SHIRE LLC
134389.02200	10/885878	8-Jul-04	7438900	21-Oct-08	SHIRE, LLC

APPENDIX A

Blank Rome Reference	Application Number	Filing Date	Patent Number	Issue Date	Owner Name
134389.02300	08/347104	22-Nov-94	5767227	16-Jun-98	SHIRE, LLC
134389.02301	08/917098	25-Aug-97	5910569	8-Jun-99	SHIRE, LLC
134389.02500	09/440635	16-Nov-99	6627660	30-Sep-03	SHIRE, LLC
134389.02607	10/858526	1-Jun-04	7105486	12-Sep-06	SHIRE, LLC
134389.02608	10/923257	23-Aug-04	7622441	24-Nov-09	SHIRE, LLC
134389.02707	11/179801	13-Jul-05	8133881	13-Mar-12	SHIRE, LLC
134389.02810	10/953119	30-Sep-04	7375083	20-May-08	SHIRE, LLC
134389.02811	10/953110	30-Sep-04	7338939	4-Mar-08	SHIRE, LLC
134389.02812	10/955006	30-Sep-04	7169752	30-Jan-07	SHIRE, LLC
134389.02813	11/635788	8-Dec-06	8106016	31-Jan-12	SHIRE, LLC
134389.03101	09/986426	8-Nov-01	7018654	28-Mar-06	SHIRE, LLC
134389.03500	61/936678	6-Feb-14			SHIRE, LLC
134389.03600	14/498130	26-Sep-14			SHIRE, LLC

Electronic Acknowledgement Receipt

EFS ID:	22994546
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	14296
Filer:	Paul Michael Zagar/Judy Yeddo
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	085199-0996
Receipt Date:	22-JUL-2015
Filing Date:	26-SEP-2014
Time Stamp:	17:09:41
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	Power of Attorney	Shire_POA.pdf	305251 a9e8a4ed792fa231eaed6198a662fe9e095757cf	no	5

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):	305251

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996

CONFIRMATION NO. 5887

14296
Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

POA ACCEPTANCE LETTER

OC000000076591026

Date Mailed: 07/30/2015

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/22/2015.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/ytdemisse/

Doc code: Oath
Document Description: Oath or declaration filed

PTO/AIA/02 (07-13)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

SUBSTITUTE STATEMENT IN LIEU OF AN OATH OR DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (35 U.S.C. 115(d) AND 37 CFR 1.64)

Title of Invention	CONTROLLED DOSE DRUG DELIVERY SYSTEM

This statement is directed to:

[ ] The attached application,

OR

[x] United States application or PCT international application number 14/498,130 filed on 09/26/2014.

LEGAL NAME of inventor to whom this substitute statement applies:

(*E.g.*, Given Name (first and middle (if any)) and Family Name or Surname)

Paul HODGKINS

Residence (except for a deceased or legally incapacitated inventor):

City	PA State	United States of America Country

Mailing Address (except for a deceased or legally incapacitated inventor):

15 Landon Way

Exton City	PA State	19341 Zip	United States of America Country

I believe the above-named inventor or joint inventor to be the original inventor or an original joint inventor of a claimed invention in the application.

The above-identified application was made or authorized to be made by me.

I hereby acknowledge that any willful false statement made in this statement is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

Relationship to the inventor to whom this substitute statement applies:

[ ] Legal Representative (for deceased or legally incapacitated inventor only),

[ ] Assignee,

[x] Person to whom the inventor is under an obligation to assign,

[ ] Person who otherwise shows a sufficient proprietary interest in the matter (petition under 37 CFR 1.46 is required), or

[ ] Joint Inventor.

134389.03600/101321696v.1

PTO/SB/AIA/02 (07-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

SUBSTITUTE STATEMENT

Circumstances permitting execution of this substitute statement:

- [ ] Inventor is deceased,
- [ ] Inventor is under legal incapacity,
- [x] Inventor cannot be found or reached after diligent effort, or
- [ ] Inventor has refused to execute the oath or declaration under 37 CFR 1.63.

If there are joint inventors, please check the appropriate box below:

- [x] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) naming the entire inventive entity has been or is currently submitted.

OR

- [ ] An application data sheet under 37 CFR 1.76 (PTO/AIA/14 or equivalent) has not been submitted. Thus, a Substitute Statement Supplemental Sheet (PTO/AIA/11 or equivalent) naming the entire inventive entity and providing inventor information is attached. See 37 CFR 1.64(b).

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

Name: MIKE CHAPMAN | Date (Optional): 24 AUG 2015

Signature: Mike Chapman

APPLICANT NAME AND TITLE OF PERSON EXECUTING THIS SUBSTITUTE STATEMENT:

If the applicant is a juristic entity, list the applicant name and the title of the signer:

Applicant Name:

Title of Person Executing This Substitute Statement:

The signer, whose title is supplied above, is authorized to act on behalf of the applicant.

Residence of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent):

City	State	Country

Mailing Address of the signer (unless provided in an application data sheet, PTO/AIA/14 or equivalent)

City	State	Zip	Country

Note: Use an additional PTO/AIA/02 form for each inventor who is deceased, legally incapacitated, cannot be found or reached after diligent effort, or has refused to execute the oath or declaration under 37 CFR 1.63.

Electronic Acknowledgement Receipt

EFS ID:	23444105
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	14296
Filer:	Paul Michael Zagar/Judy Yeddo
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	134389.03600
Receipt Date:	09-SEP-2015
Filing Date:	26-SEP-2014
Time Stamp:	16:29:50
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	Oath or Declaration filed	SubstituteStatement.pdf	638029 f28a70e0646c49958b9cf8d01fd8116d04c8c66d	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	638029

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.

COMBINED ASSIGNMENT & DECLARATION
FOR UTILITY OR DESIGN PATENT APPLICATIONS

ASSIGNMENT

THIS ASSIGNMENT, made by **Amir SHOJAEI; Stephanie READ; Richard A. COUCH**; and **Paul HODGKINS** (hereinafter referred to as Assignors), residing at 241 Rivercrest Drive, Phoenixville, PA 19460; 237 Gay Street, Philadelphia, PA 19128; 777 Woodleave Road, Bryn Mawr, PA 19010; and 15 Landon Way, Exton, PA 19341, respectively;

WHEREAS, Assignors have invented certain new and useful improvements in **CONTROLLED DOSE DRUG DELIVERY SYSTEM**, set forth in a Patent application for Letters Patent of the United States, already filed on **September 26, 2014** as U.S. Application No. **14/498,130**; and

WHEREAS, **Shire LLC**, a corporation organized under and pursuant to the laws of Kentucky having its principal place of business at **9200 Brookfield Court, Florence, KY 41042** (hereinafter referred to as Assignee), is desirous of acquiring the entire right, title and interest in and to said inventions and said Application for Letters Patent of the United States, and in and to any Letters Patent of the United States to be obtained therefore and thereon.

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and sufficient consideration, the receipt of which is hereby acknowledged, Assignors have sold, assigned, transferred and set over, and by these presents do sell, assign, transfer and set over, unto Assignee, its successors, legal representatives and assigns, the entire right, title and interest in and to the above-mentioned inventions and application for Letters Patent, and in and to any and all direct and indirect divisions, continuations and continuations-in-part of said application, and any and all Letters Patent in the United States which may be granted therefore and thereon, and reissues, reexaminations and extensions of said Letters Patent, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by Assignee, for its own use and benefit and the use and benefit of its successors, legal representatives and assigns, to the full end of the term or terms for which Letters Patent

may be granted and/or extended, as fully and entirely as the same would have been held and enjoyed by Assignors, had this sale and assignment not been made.

AND for the same consideration, Assignors hereby represent and warrant to Assignee, its successors, legal representatives and assigns, that, at the time of execution and delivery of these presents, except for any rights, titles and/or interests that have arisen to Assignee under law or that have already been transferred to Assignee, Assignors are the sole and lawful owners of the entire right, title and interest in and to the said inventions and application for Letters Patent above-mentioned, and that the same are unencumbered and that Assignors have good and full right and lawful authority to sell and convey the same in the manner herein set forth.

AND for the same consideration, Assignors hereby covenant and agree to and with Assignee, its successors, legal representatives and assigns, that Assignors will sign all papers and documents, take all lawful oaths and do all acts necessary or required to be done for the procurement, maintenance, enforcement and defense of any Letters Patent and applications for Letters Patent for said inventions, without charge to Assignee, its successors, legal representatives and assigns, whenever counsel of Assignee, or counsel of its successors, legal representatives and assigns, shall advise: that any proceeding in connection with said inventions, or said Patent application for Letters Patent, or any proceeding in connection with any Letters Patent or applications for Letters Patent for said inventions including but not limited to interference proceedings, is lawful and desirable; or, that any division, continuation or continuation-in-part of any application for Letters Patent, or any reissue, reexamination or extension of any Letters Patent, to be obtained thereon, is lawful and desirable.

AND Assignors hereby request the Commissioner for Patents and Trademarks to issue said Letters Patent of the United States to Assignee, as Assignee of said inventions and the Letters Patent to be issued thereon, for the sole use and benefit of Assignee, its successors, legal representatives and assigns.

AND Assignors acknowledge an obligation of assignment of this invention to Assignee at the time the invention was made.

DECLARATION

As a below named inventor, I hereby declare that:

This declaration is directed to the patent application entitled:

CONTROLLED DOSE DRUG DELIVERY SYSTEM

the specification of which was filed on **September 26, 2014** as Application No. **14/498,130**.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I have reviewed and understand the contents of the above-identified application.

I am aware of the duty to disclose to the Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56.

I hereby acknowledge that any willful false statement made in this Declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

In the event that the filing date and/or Application No. are not entered above at the time I execute this document, and if such information is deemed necessary, I hereby authorize and request the attorneys/agent(s) at McDermott Will & Emery LLP to insert the filing date and/ or Application No. of said application into this document.

Date: _____ Signature: _____
Amir Shojaei

Date: _____ Signature: _____
Stephanie Read

Date: _____ Signature: _____
Richard A. Couch

Date: _____ Signature: _____
Paul Hodgkins

In the event that the filing date and/or Application No. are not entered above at the time I execute this document, and if such information is deemed necessary, I hereby authorize and request the attorneys/agent(s) at McDermott Will & Emery LLP to insert the filing date and/ or Application No. of said application into this document.

Date: _____ Signature: _____
Amir Shojaei

Date: _____ Signature: _____
Stephanie Read

Date: 25 Mai 2015 Signature: Richard A. Couch
Richard A. Couch

Date: _____ Signature: _____
Paul Hodgkins

In the event that the filing date and/or Application No. are not entered above at the time I execute this document, and if such information is deemed necessary, I hereby authorize and request the attorneys/agent(s) at McDermott Will & Emery LLP to insert the filing date and/ or Application No. of said application into this document.

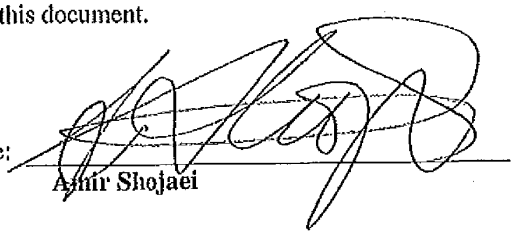
Date: _____ Signature: _____
Amir Shojaei

Date: 11 Apr 2015 Signature: _____
Stephanie Read

Date: _____ Signature: _____
Richard A. Couch

Date: _____ Signature: _____
Paul Hodgkins

In the event that the filing date and/or Application No. are not entered above at the time I execute this document, and if such information is deemed necessary, I hereby authorize and request the attorneys/agent(s) at McDermott Will & Emery LLP to insert the filing date and/ or Application No. of said application into this document.

Date: Apr 1 2015 Signature: 

Amir Shojaei

Date: _____ Signature: _____

Stephanie Read

Date: _____ Signature: _____

Richard A. Couch

Date: _____ Signature: _____

Paul Hodgkins

Electronic Acknowledgement Receipt

EFS ID:	23592791
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	14296
Filer:	Paul Michael Zagar/Judy Yeddo
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	134389.03600
Receipt Date:	24-SEP-2015
Filing Date:	26-SEP-2014
Time Stamp:	15:13:44
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	Oath or Declaration filed	Declaration.pdf	134118 44480d2266131977ddf2220e99404af49d8700fa	no	7
Warnings:					
Information:					

Total Files Size (in bytes):	134118

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.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

14296 7590 06/26/2015
Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/498,130	09/26/2014	Amir SHOJAEI	085199-0996	5887

TITLE OF INVENTION: CONTROLLED DOSE DRUG DELIVERY SYSTEM

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	09/28/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
YOUNG, MICAH PAUL	1618	424-490000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Blank Rome LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
Shire LLC	Florence, KY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 022555 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date 9-25-2015
Typed or printed name Paul M. Zagar, MD Registration No. 52,392

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	14498130
Filing Date:	26-Sep-2014
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Filer:	Paul Michael Zagar/Judy Yeddo
Attorney Docket Number:	134389.03600

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt	
EFS ID:	23611663
Application Number:	14498130
International Application Number:	
Confirmation Number:	5887
Title of Invention:	CONTROLLED DOSE DRUG DELIVERY SYSTEM
First Named Inventor/Applicant Name:	Amir SHOJAEI
Customer Number:	14296
Filer:	Paul Michael Zagar/Judy Yeddo
Filer Authorized By:	Paul Michael Zagar
Attorney Docket Number:	134389.03600
Receipt Date:	25-SEP-2015
Filing Date:	26-SEP-2014
Time Stamp:	17:35:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	4873
Deposit Account	022555
Authorized User	ZAGAR, PAUL
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IssueFee.pdf	90342 c4cfcd609846cdd482f72a6280457691712c5006	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30710 b03f5f96f6fcbffcc8ed3826a5168d542df04a23	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	121052		

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
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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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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.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/498,130	11/03/2015	9173857	134389.03600	5887

14296 7590 10/14/2015

Blank Rome LLP (NY)
c/o Blank Rome LLP
Attn: Patent Docketing
600 New Hampshire Avenue, NW
Washington, DC 20037

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Amir SHOJAEI, Phoenixville, PA;
Shire LLC, Florence, KY;
Stephanie READ, Philadelphia, PA;
Richard A. COUCH, Bryn Mawr, PA;
Paul HODGKINS, Exton, PA;