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(54) **Title:**

**METHODS AND COMPOSITIONS FOR TREATMENT OF  
ATTENTION DEFICIT DISORDER**

(57) **Abstract:**

Therapeutic compositions and methods for treatment of attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) include dosage forms that deliver a therapeutic amount of active drug in a delayed and controlled release formulation. The dosage form can be administered at night and drug release is delayed for from 3 to 8 hours, followed by an ascending release rate..



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(54) Title: METHODS AND COMPOSITIONS FOR TREATMENT OF ATTENTION DEFICIT DISORDER

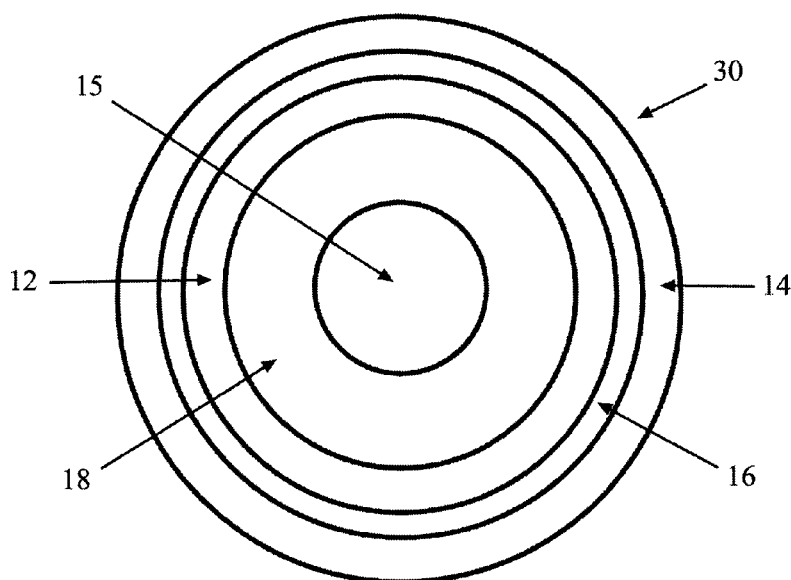


FIG. 3

(57) Abstract: Therapeutic compositions and methods for treatment of attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD) include dosage forms that deliver a therapeutic amount of active drug in a delayed and controlled release formulation. The dosage form can be administered at night and drug release is delayed for from 3 to 8 hours, followed by an ascending release rate..

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Methods and Compositions for Treatment of Attention Deficit Disorder

Cross-References To Related Applications

**[0001]** This application claims benefit of priority to US Provisional Application No. 61/591,129, filed January 26, 2012, US Provisional Application No. 61/561,763, filed November 18, 2011 and US Provisional No. 61/466,684, filed March 23, 2011, the contents of all of which are incorporated herein by reference in their entirety for all purposes.

Background of The Invention

**[0002]** Attention disorder- hyperactivity disorder (ADHD) is a developmental disorder characterized by symptoms such as impulsiveness, hyperactivity and/or inattentiveness. Hyperactivity is common among children with ADHD but tends to disappear during adulthood. However, over half of children with ADHD continue to have some symptoms of inattention throughout their lives.

**[0003]** Stimulant medications are widely used as a pharmacological treatment for ADHD. Stimulants, in the short term, have been found to be safe in the appropriately selected patient and appear well tolerated over five years of treatment. Active pharmaceutical agents now approved in the USA for use in treatment of ADHD or ADD are primarily affectors of the dopamine or norepinephrin neural pathways. Approved agents include salts and isomers of amphetamine and methylphenidate, the dextroamphetamine prodrug, lisdexamfetamine dimesylate, and atomoxetine.

**[0004]** One of the challenges of treating ADHD and other CNS stimulant responsive conditions is delivering and maintaining an effective concentration in patients throughout the day and in particular, in the morning hours when cognitive abilities and concentration are needed for school or work and in the late afternoon or evening when students often do homework. Early formulations relied on a twice daily administration of an immediate release formulation, causing problems with compliance. Various long-acting formulations were developed and are now available that have been shown in clinical trials to be effective for from 8-14 hours (Brams et al., *Current Medical Research and Opinion*, vol. 26 no. 8, pgs 1809-1825, August 2010).

Summary

**[0005]** The compositions and methods of the present disclosure provide novel formulations and methods for treating diseases or conditions that are responsive to central nervous system stimulants. Such conditions include but are not limited to attention deficit disorder, attention deficit hyperactivity disorder, narcolepsy, excessive daytime sleepiness, major depressive disorder, bipolar depression, negative symptoms in schizophrenia, chronic fatigue, fatigue associated with chemotherapy or binge eating disorder. The compositions and methods are effective for treating the adult, pediatric and adolescent populations that are in need of such treatment.

**[0006]** The disclosed compositions and methods provide a convenient method of administration in that a single dose can be taken typically in the evening prior to going to bed, or at whatever time of day one retires for an extended period of sleep and the release of the drug is delayed for from 4 to 12 hours in some examples and then released in a controlled or sustained manner. In certain embodiments, the compositions are water soluble capsules that contain coated particles such as beads or minitables. These particles are coated with an outer, delayed release coating and an inner, sustained release coating over a drug containing core. The delayed release allows the subject to sleep, and as the outer layer of the composition dissolves and the sustained release layer begins to lose some of its integrity, the drug starts to slowly release. This results in a low, but therapeutic level of drug in the serum of the patient when that patient would normally wake up and prepare for the day. Subsequent to this slow release, the drug release rate increases over a period of about eight to ten hours or more, to continue to provide a therapeutic amount during the typically active part of the day. The compositions and methods disclosed herein thus provide a single dose that is conveniently taken prior to sleeping and that provides a therapeutic effect from the time a subject normally awakes and through the productive portion of the day.

**[0007]** Although the present compositions are described as effective as a once a day dosage, it is understood that additional doses can be administered as needed at the direction of a physician. The description herein is primarily directed to treatment of persons with a typical schedule of going to sleep from around 9 P.M. to about midnight.

for example, and sleeping for 6 to 9 hours. It is understood, however, that the use and efficacy of the compositions and methods is not limited to such a schedule, but can be adopted for use with different daily schedules, such as night workers, or people with longer, shorter or more variable sleep patterns.

**[0008]** In certain embodiments, the compositions disclosed herein include, but are not limited to tablets, minitables or beads contained in a water soluble capsule. The minitables or beads can include a drug containing core or a drug coated inert bead core in which the drug core or drug layer can also contain an optional disintegrant, osmagent or pore forming agent. In certain embodiments the disintegrant can be a superdisintegrant. In certain embodiments the drug layer or core is enclosed by a sustained release layer that can include a water insoluble and water permeable polymer layer that controls the rate of absorption of water and release of the drug. The outer, delayed release layer is coated on the sustained release layer. The delayed release layer may contain a plasticizer or solubility is pH dependent. The delayed release layer can thus be a pH dependent layer that is insoluble in aqueous solution at a pH below 5.0 and soluble at the higher pH in the ileum or colon, or it can be a pH independent layer. In certain embodiments, an outer, pH dependent layer dissolves in the higher pH of the ileum or colon. As the sustained release layer then loses integrity the sustained release layer ruptures and releases the remaining drug in the core.

**[0009]** The active ingredients include central nervous system stimulants that are effective to treat ADD and ADHD or other conditions associated with dopamine or norepinephrin neural pathways. The active ingredients include, but are not limited to the active isomers of amphetamines and amphetamine salts including salts of dextroamphetamine, and methylphenidate and its active salts, all of which can be used as racemic mixtures or pure isomers such as d-threo methylphenidate. The disclosed compositions can also include one or more prodrug of central nervous system stimulants, including but not limited to amino acid conjugated active ingredients such as l-lysine-d-amphetamine, for example.

**[00010]** The compositions and methods of the present disclosure can be described in certain embodiments, therefore, as a solid, oral pharmaceutical composition including a core comprising a therapeutic amount of a central nervous system stimulant, at least one

pharmaceutically acceptable excipient and optionally a disintegrant, osmagent, or a pore forming agent; a sustained release layer coating the core; and a delayed release layer enclosing the sustained release layer, wherein the combination of the sustained release and delayed release layers provide a three to eight, ten or even twelve to thirteen hour delay during which no more than 10% of the central nervous system stimulant is released when the composition is placed in a simulated gastric environment. The term simulated gastric environment is intended to be used herein to convey its ordinary meaning as understood in the art, and is understood in a broad sense to mean an aqueous environment of low pH, 1-5 for example, followed after a period of up to about 2 hours with immersion in a higher pH aqueous environment, such as pH 6.8, for example, or a three stage environment in which the low pH is followed by an intermediate pH of about 6 wherein the environments are maintained at about 37.0°C. Alternatively, for certain embodiments a simulated gastric environment is described as the USP Apparatus I (Baskets) with agitation in which the composition is placed in 700 ml aqueous solution of 0.1N HCl pH 1.1, v for up to 2 hours followed by 2-6hr in sodium phosphate buffer at pH 6.0; followed by 6-20 hr in sodium phosphate buffer, pH 7.2, adding NaOH to adjust pH to 7.2.

**[00011]** Any of the solid oral pharmaceutical compositions disclosed herein can be in the form of coated beads, or they can be compressed into tablet or minitabket form. The beads or minitabkets can then be apportioned in single dose amounts into water soluble gelatin capsules, or into a liquid or gel suspension for administration.

**[00012]** An aspect of the compositions and methods of the present disclosure can also be described as a solid, oral pharmaceutical composition including a core comprising a therapeutic amount of a central nervous system stimulant and at least one pharmaceutically acceptable excipient wherein the core is substantially free of a disintegrant, osmagent, or a pore forming agent; a sustained release layer coating the core; and a delayed release layer enclosing the sustained release layer, wherein the combination of the sustained release and delayed release layers provide a three to twelve hour delay during which no more than 10% of the central nervous system stimulant is released when the composition is placed in a simulated gastric environment.

**[00013]** A solid, oral pharmaceutical composition of the disclosure can be described as a formulation in which the in vitro dissolution rate of the dosage form when measured by the USP Apparatus I (Baskets) with agitation in which the composition is placed in 700 ml aqueous solution of 0.1N HCl pH 1.1, v for up to 2 hours followed by 2-6hr in sodium phosphate buffer at pH 6.0; followed by 6-20 hr in sodium phosphate buffer, pH 7.2, adding NaOH to adjust pH to 7.2 at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  is between 0 and about 20% drug released after 8 hours, between about 2 and about 30% released after 10 hours, between about 10 and about 65% released after 12 hours and between 45% and 95% released after 15 hours, and wherein the amount of active ingredient released per each hour increases from the period between 20% released and 65% released. The compositions and methods of the present disclosure can also be described as a solid, oral pharmaceutical composition in which the in vitro dissolution rate of the dosage form when measured by the USP Apparatus I (Baskets) with agitation in which the composition is placed in 700 ml aqueous solution of 0.1N HCl pH 1.1, v for up to 2 hours followed by 2-6 hr in sodium phosphate buffer at pH 6.0; followed by 6-20 hr in sodium phosphate buffer, pH 7.2, adding NaOH to adjust pH to 7.2 at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  is between 0 and about 10% drug released after 6 hours, between about 15 and about 28% released after 10 hours, between about 40 and about 60% released after 12 hours and between about 80% and about 95% released after 15 hours, and wherein the amount of active ingredient released per each hour increases from the period between 20% released and 65% released, or as a solid, oral pharmaceutical composition as described when measured by the USP Apparatus I (Baskets) with agitation in which the composition is placed 700 ml aqueous solution of 0.1N HCl pH 1.1, for up to 2 hours followed by 2-6hr in sodium phosphate buffer at pH 6.0; followed by 6-20 hr in sodium phosphate buffer, pH 7.2, adding NaOH to adjust pH to 7.2 at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ , no more than about 10% of the agent is released within 6 hours and no more than about 50% of the agent is released within 12 hours, and wherein, when the composition is administered to a human, a plot of plasma concentration versus time after administration exhibits a single maximum between 12 and 20 hours after administration.

**[00014]** The solid oral pharmaceutical compositions of the present disclosure can also include a plurality of core pellets that in certain embodiments are substantially



spherical beads. The core can consist essentially of a central nervous system stimulant and one or more excipients, or the core can consist essentially of the stimulant and one or more excipients coated on an inert non-pareil bead. These cores are then coated with two or more release control layers to produce a population of particles for drug delivery. It is an aspect of the compositions and methods of the present disclosure, however, that it is advantageous to provide a smooth spherical core to the extent possible in order to obtain a more consistent coating and a reproducible release profile of the active ingredient from the populations of particles.

**[00015]** The solid oral pharmaceutical compositions of the present disclosure also include a central nervous system stimulant which can be generally defined as a chemical entity that affects the dopamine or norepinephrine neural pathways. Preferred pharmaceutically active ingredients include, but are not limited to amphetamine, dextroamphetamine, the active isomers of amphetamines and amphetamine salts including salts of dextroamphetamine, methylphenidate and its active salts, or combinations thereof, all of which can be used as racemic mixtures or pure isomers such as d-threo methylphenidate, or a prodrug or pharmaceutical salt, or mixed pharmaceutical salts of any thereof alone or in combination. The disclosed compositions can also include a prodrug, including but not limited to amino acid conjugated active ingredients such as l-lysine-d-amphetamine. Suitable excipients in the core of the pharmaceutical composition can include polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, lactose, sucrose, microcrystalline cellulose or combinations of any thereof.

**[00016]** It is an aspect of the disclosed compositions that the delayed release layer can include a pH dependent polymer or copolymer that is insoluble in aqueous medium at pH lower than 5.5. Such a delayed release layer can include, but is not limited to cellulose acetate phthalate, cellulose acetate triacetate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, acrylic polymers, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, shellac, methacrylic acid copolymers, Eudragit L30D, Eudragit L100, Eudragit FS30D, Eudragit S100 or combinations of any thereof. The delayed release layer can also include a plasticizer, or in certain embodiments the delayed release layer can include methacrylic acid copolymer Type B, mono- and diglycerides, dibutyl sebacate and polysorbate 80.

**[00017]** In certain embodiments of the disclosed solid oral pharmaceutical compositions, the sustained release layer includes a water-insoluble and water-permeable polymer and can further include a water soluble polymer. In certain embodiments, the sustained release layer includes, but is not limited to a cellulose ether derivative, an acrylic resin, a copolymer of acrylic acid and methacrylic acid esters with quaternary ammonium groups, a copolymer of acrylic acid and methacrylic acid esters or a combination of any thereof, or it can include ethyl cellulose, hydroxypropyl cellulose, dibutyl sebacate and magnesium stearate.

**[00018]** In certain embodiments the core can include a disintegrant and can include corn starch, potato starch, a pre-gelatinized starch, a modified starch, a sweetener, a clay, bentonite, microcrystalline cellulose, carboxymethylcellulose calcium, croscarmellose sodium, alginic acid, sodium alginate, cellulose polyacrilin potassium, an alginate, sodium starch glycolate, a gum, agar, guar, locust bean, karaya, pectin, tragacanth, crospovidone or low substituted hydroxypropyl cellulose. The compositions can also include a disintegrant, osmagent, or a pore forming agent, which can be a salt, an acid, a base, a chelating agent, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, polyol, mannitol, sulfatol, xylitol, a carbohydrate, a carbonate, a bicarbonate, electrolyte, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, alpha-hydroxy acids, citric acid, ascorbic acid, or a combination of any thereof. It is a further aspect of the disclosure that the disclosed formulations can include an abuse deterrent agent that can be a nasal irritant such as a capsaicinoid or sodium lauryl sulfate.

**[00019]** In certain embodiments the optional disintegrant, osmagent, or pore forming agent constitutes from 0 to about 75% of the core by weight. The compositions can also include a swellable layer or a sealing layer disposed between the core and the sustained release layer. The swellable layer can include a superdisintegrant, an osmotic agent, or a combination thereof, and in certain embodiments includes a hydrophilic polymer such as polyethylene oxide and a binder and can further include a drug containing layer between the swellable layer and the sustained release layer and can include a seal between the swellable layer and the drug containing layer.

**[00020]** In certain embodiments the compositions and methods of the present disclosure can be described as a method of treating a condition in a subject with a disorder or condition responsive to the administration of a central nervous system stimulant, comprising orally administering the disclosed solid, oral pharmaceutical compositions. The method of treatment can include administering a single dosage form or two per day depending on the need of a particular patient. It is an aspect of the compositions and methods of the present disclosure that the administration of the dosage form on a once-a-day basis provides a delayed release of from about 4 to about 12 hours, followed by an increasing plasma concentration profile, which for a 24 hour period commencing with an administration of the dosage form results in a single maximum serum concentration (C<sub>max</sub>) which occurs at least 12 hours, at least 14 hours, or at least 15 hours after administration.

**[00021]** The compositions and methods of the present disclosure can also be described in certain embodiments as a solid, oral pharmaceutical composition including a therapeutic amount of a central nervous system stimulant wherein the composition, when orally administered to a human, provides a delayed release of from 4 to 12 hours, an ascending serum concentration of central nervous system stimulant for a period of from 7 to 12 hours and a maximum serum concentration (C<sub>max</sub>) from 10 to 16 hours after administration. In certain embodiments, the serum concentration exhibits a single maximum.

**[00022]** The compositions and methods of the present disclosure can also be described in certain embodiments as a solid, oral pharmaceutical composition comprising a core comprising a therapeutic amount of a central nervous system stimulant and at least one pharmaceutically acceptable excipient wherein the core is substantially free of a disintegrant, osmagent, or a pore forming agent; a sustained release layer coating the core; and a delayed release layer enclosing the sustained release layer, wherein when the composition is placed in a simulated gastric environment, the combination of the sustained release and delayed release layers provide: a mean three to twelve hour delay during which no more than 10% of the central nervous system stimulant is released and a mean ascending release of central nervous system agent from 8 to 16 hours after being placed in the simulated gastric environment.

**[00023]** Conditions or disorders that can be treated include, but are not limited to attention deficit disorder, attention deficit hyperactivity disorder, excessive daytime sleepiness, major depressive disorder, bipolar depression, negative symptoms in schizophrenia, chronic fatigue, fatigue associated with chemotherapy or binge eating disorder. Attention deficit disorders are characterized by hyperactive, impulsive or inattentive symptoms that cause impairment in social, academic, or occupational functioning, and are often present in two or more settings, school (or work) and at home, for example. For the Inattentive Type, at least 6 of the following symptoms have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; and forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn, and intrusive. The combined type includes both inattentive and hyperactive-impulsive behaviors.

**[00024]** It is understood that the term treatment as used herein is not limited to the cure or elimination of any condition or disorder nor is that term limited to the achievement of certain milestones or improvement criteria in a particular subject, but includes the administration of an agent for the purpose of achieving positive effects in terms of cognitive or behavioral function, reduction of symptoms or side effects. All such activities are considered to be treatment whether or not any improvement is immediately observable or measureable.

**[00025]** It is well known, for example, that certain side effects may occur in conjunction with administration of CNS stimulants. These side effects can include, but are not limited to headache, nausea, dizziness, hot flush, decreased appetite, insomnia, abdominal discomfort (stomach ache), dry mouth, fast heartbeat, nervousness, mood swings, irritability, weight loss, or complaints of just not feeling good. It is contemplated that treatment with the disclosed formulations will result in reduced incidence or severity of side effects relative to treatments in which the active agent is rapidly released in the stomach. As such, treatment would encompass not only reduction of symptoms of the condition or disorder but also reduction in side effects.

**[00026]** The compositions and active agents of this disclosure are administered in an "effective amount," "effective dose," or "therapeutically effective amount or dose." By an "effective" amount or a "therapeutically effective amount" or dose of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect. In the current disclosure, an "effective amount" is the amount of that composition or active agent that is effective to improve, ameliorate or prevent one or more symptoms of the condition being treated. The amount that is "effective" will vary from subject to subject, depending on the age and general condition of the individual, or the particular active agent. A therapeutic or effective dose or amount is determined by a physician and is often based on empirical data obtained by administering increasing doses until the best balance of benefit vs. side effects is reached.

**[00027]** An effective dose in the compositions of the present disclosure, particular for treatment of ADHD include doses shown to be effective in the treatment of those conditions by oral dosage, including but not limited to 5, 9, 10, 15, 18, 20, 25, 27, 30, 35, 36, 45 or 54 mg once or twice daily. It is also understood that other dosage ranges may be effective for conditions or symptoms other than ADHD and as such, the therapeutically effective drug concentration in the disclosed compositions can be from 0.1 to 1000 mg inclusive of any particular concentration within that range.

**[00028]** As used herein, the term "pharmaceutically acceptable salt" refers to non-toxic pharmaceutically acceptable salts as described (Ref. International J. Pharm., 1986, 33, 201-217; J. Pharm. Sci., 1997 (January), 86, 1, 1). Other salts well known to those in the art may, however, be useful in the preparation of compositions of the disclosure including, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

**[00029]** The compositions and methods of the present disclosure can also be described in certain embodiments as a solid, oral pharmaceutical composition comprising a therapeutic amount of a central nervous system stimulant wherein the composition, when orally administered to a human, provides a delayed release of from 3 to 8 hours, an ascending rate of release of central nervous system stimulant for a period of from 7 to 12 hours and a serum concentration C<sub>max</sub> from 10 to 16 hours after administration, and wherein a plot of the serum concentration versus time after release exhibits a single maximum. The solid oral pharmaceutical can be further defined as one in which no more than 10% of the central nervous system stimulant is released within 6 hours after administration.

**[00030]** In certain embodiments the compositions and methods of the present disclosure can be defined as a solid, oral pharmaceutical composition comprising: a core comprising a therapeutic amount of a central nervous system stimulant and at least one pharmaceutically acceptable excipient a sustained release layer coating the core; and a delayed release layer enclosing the sustained release layer, wherein the core is substantially free of a disintegrant, osmagent, or a pore forming agent; wherein when the composition is administered to a human, the combination of the sustained release and delayed release layers provide: a mean three to eight hour delay during which no more than 10% of the central nervous system stimulant is released; a mean ascending serum concentration of central nervous system agent from the onset of absorbance to a period of from 12 to 16 hours after administration and in which the serum concentration exhibits a single maximum.

#### Brief Description of the Drawings

**[00031]** The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present inventions. The disclosure can be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

**[00032]** FIG. 1A is a schematic representation of a bead pharmaceutical composition with a drug containing core surrounded by a sustained release layer and a delayed release layer. FIG. 1B a composition as in 1A with an added swellable layer disposed between the sustained release layer and the delayed release layer.

**[00033]** Fig. 2A is a schematic representation of a minitabket pharmaceutical composition with a drug containing core surrounded by a sustained release layer and a delayed release layer. FIG. 2B a composition as in 2A with an added swellable layer disposed between the sustained release layer and the delayed release layer.

**[00034]** Fig. 3 is a schematic representation of a bead pharmaceutical composition that includes a core surrounded by 4 layers, an inert inner core, a swelling polymer, a drug layer, a sustained release layer and an enteric layer.

**[00035]** Fig. 4 is a graph of dissolution profiles of DOE 1-8.

**[00036]** Fig. 5 is a graph of dissolution profiles of DOE 9, 10, 11, 3, 4.

**[00037]** Fig. 6 is a graph of stability dissolution profile of DOE 4.

**[00038]** Fig. 7 is a graph of stability dissolution profile of DOE 3.

**[00039]** Fig. 8 is a graph of enteric coating on DOE 3 (3-Stage) dissolution profile.

**[00040]** Fig. 9 is a graph of dissolution of DOE 3 coatings.

**[00041]** Fig. 10 is a graph of dissolution profile of Lot 2009-138-45 (30 % Weight Gain).

**[00042]** Fig. 11 is a graph of two-week stability dissolution profile.

**[00043]** Fig. 12 is a graph of dissolution profile of DOE 3 (Lot 2009-138-45) cured at 50°C.

**[00044]** Fig. 13 is a graph of dissolution profile DOE 3 (Lot 2009-138-45) cured at 55°C.

**[00045]** Fig. 14 is a graph of dissolution profile of DOE 3 (Lot 2009-138-45) cured at 55°C on stability.

**[00046]** Fig. 15 is a graph of dissolution profile of DOE 3 (Lot 2009-138-45) 8 month stability.

**[00047]** Fig. 16 is a graph of the dissolution profiles of the formulations described in Examples 14-18.

**[00048]** Fig. 17 is a graph of the serum concentration of healthy volunteers after ingesting the formulations of Examples 14-18.

**[00049]** Fig. 18 is a comparison of the data of Fig. 17 with commercially available formulations.

#### Detailed Description of the Invention

**[00050]** The present disclosure provides therapeutic compositions and methods for treatment of attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) or other conditions or disorders responsive to central nervous system stimulants by providing dosage forms that deliver a therapeutic amount of active drug in a delayed and controlled release pattern in order to maintain a therapeutic amount of drug through the active portion of the day. For pediatric patients including adolescents and also for adults, a therapeutic amount is desirable upon arising and throughout the morning, as well as through the afternoon hours in which work or homework needs to be done.

**[00051]** The disclosed formulations can provide a therapeutic amount of drug during extended periods of the day with a single administration. The dosage forms provide a delayed release such that the dosage form can be administered conveniently prior to the patient's sleeping. A small percentage of the drug can be released over the first 6 to 8 hours after administration such that the patient has already received a minimal therapeutic dose at the normal awakening time. The patient thus does not need to be awakened, given a pill, and then required to have breakfast and prepare for their day prior to experiencing a therapeutic effect.

**[00052]** The formulations disclosed herein also provide an ascending release of the drug over the next 8 to 16 hours or so after the delay period, or up to 16 hours after administration of the dosage forms. The dosage forms thus can provide a delayed release followed by a sigmoidal release curve as shown in the accompanying drawings, Figs. 3 and 5.

#### Central Nervous System Stimulants

**[00053]** Stimulant medications (e.g., methylphenidate and amphetamines and prodrugs) are often prescribed to treat individuals diagnosed with attention-deficit hyperactivity disorder (ADHD). According to the National Institute of Health, all stimulants work by increasing dopamine levels in the brain. Dopamine is a brain chemical (or neurotransmitter) associated with pleasure, movement, and attention. The therapeutic effect of stimulants is achieved by slow and steady increases of dopamine, which are similar to the natural production by the brain. The doses prescribed by physicians start low and increase gradually until a therapeutic effect is reached.



**[00054]** Treatment of ADHD with stimulants, often in conjunction with psychotherapy, helps to improve the symptoms of ADHD, as well as the self-esteem, cognition, and social and family interactions of the patient. The most commonly prescribed medications include amphetamines and methylphenidate. These medications have a paradoxically calming and “focusing” effect on individuals with ADHD. Researchers speculate that because methylphenidate amplifies the release of dopamine, it can improve attention and focus in individuals who have dopamine signals that are weak.

**[00055]** Amphetamines that are useful in the disclosed formulations and methods include amphetamine and its isomers such as dextroamphetamine, d,l amphetamines and their pharmaceutically acceptable salts, such as sulfate, saccharate, and aspartate salts, for example. Amphetamines are non-catecholamine, sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevations of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

**[00056]** Dextroamphetamine is the dextro isomer of the compound d,l - amphetamine sulfate, a sympathomimetic amine of the amphetamine group. Chemically, dextroamphetamine is d-alpha-methylphenethylamine. Dextroamphetamine can be used in the practice of the present disclosure, or various pharmaceutically acceptable salts of dextroamphetamine can be used.

Methylphenidate

**[00057]** Methylphenidate is another central nervous system (CNS) stimulant that has been used since the 1960's in the treatment of ADD, ADHD, fatigue, and narcolepsy. Methylphenidate can be prescribed in a racemic mix of *dextro* and *levo* conformations or as the pure *dextro* isomer. Methylphenidate has two chiral centers in the molecule and thus can also be further refined to enrich the *d threo* isomer. The use of pharmaceutically acceptable salts of methylphenidate, such as methylphenidate hydrochloride are also contemplated by the present disclosure.

**[00058]** It is understood that the active pharmaceutical ingredients of the present disclosure can be present as prodrugs that are activated in the body of a user. One form of prodrug has an amino acid conjugated to the active ingredient. When the amino acid is enzymatically cleaved, the active drug is released. Prodrugs comprising a lysyl, isoleucyl

or aspartyl conjugate are contemplated to be useful in the practice of the present disclosure.

#### Formulations

**[00059]** The formulations of the disclosure are designed to provide novel release and serum profiles that include a first lag phase followed by a sigmoidal release phase. By providing this profile, the dosage forms provide a timed, prolonged therapeutic effect when taken once a day. Based on the release characteristics, in which the dosage form passes through the stomach prior to release, the formulations disclosed herein are expected to provide at least the following further advantages, low variability in gastric emptying, low dependence on nutrition state (fed or fasting), low risk of sudden dose dumping, and low intra- and inter-individual variability.

**[00060]** A first example of a dosage form is a single population of beads that can be administered in a capsule or a liquid or gel suspension containing the beads. An example of a bead structure **10** is shown in schematic form in Fig. 1A-B. In Fig. 1A, the inner circle represents a drug containing core, which includes the active ingredient or pro-drug, the appropriate excipients and optionally a superdisintegrant or osmagent. A core can include, for example, an active agent, a disintegrant, osmagent, or pore forming agent, and a binder. An exemplary core includes about 20-25% active agent, about 45-60% microcrystalline cellulose, about 10-30% potassium chloride and about 3-5% binder such as polyvinyl pyrrolidone or hydroxypropyl cellulose, for example. The drug containing core can be made by a variety of processes known in the art, including wet granulation, extrusion, and spheronization. In this embodiment, two layers cover the core. The first layer is a sustained release layer and the outer layer is a delayed release layer that is optionally pH dependent. In certain embodiments, the core as shown in Fig. 1A can be an inert non-pareil bead. The inner core is a bead of sugar and starch or it can be composed of microcrystalline cellulose. Any spherical bead that is suitable for forming the core bead and is pharmaceutically acceptable can be used. In such embodiments, the drug and excipients of the core are layered onto the core bead, providing a three layer formulation.

**[00061]** The outermost layer **14** is a delayed release or an enteric coating. In certain embodiments this layer comprises a water soluble polymer. a water insoluble

polymer, a plasticizer and a lubricant. The time of delay of drug release is controlled by the ratio of water soluble and insoluble polymers, the plasticizer concentration, amount of lubricant, and the coating weight gain, which can be up to 35-45%. Alternatively this layer is a pH dependent polymer that dissolves at pH above 5.0.

**[00062]** A sustained release layer **16** is designed to provide a slower initial rate of release that increases over a period of up to 8-10 hours after the layer is exposed to an aqueous environment. The increasing drug profile can be achieved by a membrane that becomes more permeable over time. An example of a sustained release layer includes a water soluble polymer, a water insoluble polymer, a plasticizer and a lubricant. The rate of drug release can be controlled or sustained by varying the ratio of water soluble and water insoluble polymers and by varying the coating thickness up to 15-45% weight gain.

**[00063]** An alternative embodiment is shown in Fig. 1B. In this figure, a swellable layer **18**, including a superdisintegrant or osmotic agent is disposed between the core and the sustained release layer.

**[00064]** In certain embodiments, the compositions and methods of the present disclosure include a formulation of 4 layers **30** as shown in Fig. 3. This formulation can include an inner core **15** of a non-pareil bead and 4 concentric layers from inner to outer described as, a swelling polymer layer **18**, drug layer **12**, a sustained release layer **16** and a pH dependent delayed release layer **14**, which can be a pH dependent layer.

**[00065]** In certain embodiments, the 4 layer composition can be made in a step-wise fashion. In the first step, a hydrophilic polymer suspended in ethanol with a binder is coated onto nonpareil beads to a 30-50% weight gain. In certain embodiments PolyOx Coagulant SFP (PEO) marketed by the Dow Chemical Company is the hydrophilic polymer and hydroxypropyl cellulose (HPC LF) is added as the binder. The PolyOx layer is then sealed with a hydroxypropyl cellulose such as Klucel<sup>®</sup> EF to a 10% weight gain. The API is then suspended in ethanol with a binder and coated onto the layered bead and the sustained release and delayed release coatings are applied as described herein.

**[00066]** Figs. 2A-B represent embodiments in which the core is a minitab<sup>®</sup>let **20** rather than a bead. The core and layers in Figs. 2A and B are functionally the same as the like numbered layers on the beads in Fig. 1A-B. except there is no optional inert core.

**[00067]** Various water soluble polymers can be used in the disclosed formulations. Such polymers include, but are not limited to polyethylene oxide (PEO), ethylene oxide-propylene oxide co-polymers, polyethylene-polypropylene glycol (*e.g.* poloxamer), carbomer, polycarbophil, chitosan, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), hydroxyalkyl celluloses such as hydroxypropyl cellulose (HPC), hydroxyethyl cellulose, hydroxymethyl cellulose and hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, polyacrylates such as carbomer, polyacrylamides, polymethacrylamides, polyphosphazines, polyoxazolidines, polyhydroxyalkylcarboxylic acids, alginic acid and its derivatives such as carrageenate alginates, ammonium alginate and sodium alginate, starch and starch derivatives, polysaccharides, carboxypolymethylene, polyethylene glycol, natural gums such as gum guar, gum acacia, gum tragacanth, karaya gum and gum xanthan, povidone, gelatin or the like.

**[00068]** In certain embodiments, at least the delayed release layer includes one or more polymers such as an acrylic polymer, acrylic copolymer, methacrylic polymer or methacrylic copolymer, including but not limited to Eudragit® L100, Eudragit® L100-55, Eudragit® L 30 D-55, Eudragit® S100, Eudragit® 4135F, Eudragit® RS, acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, polyacrylic acid, polymethacrylic acid, methacrylic acid alkylamine copolymer, polymethyl methacrylate, polymethacrylic acid anhydride, polymethacrylate, polyacrylamide, polymethacrylic acid anhydride and glycidyl methacrylate copolymers, an alkylcellulose such as ethylcellulose, methylcellulose, calcium carboxymethyl cellulose, certain substituted cellulose polymers such as hydroxypropyl methylcellulose phthalate, and hydroxypropyl methylcellulose acetate succinate, cellulose acetate butyrate, cellulose acetate phthalate, and cellulose acetate trimaleate, polyvinyl acetate phthalate, polyester, waxes, shellac, zein, or the like.

**[00069]** Eudragits are well known polymers and copolymers useful for controlled release applications. The EUDRAGIT® grades for enteric coatings are based on anionic polymers of methacrylic acid and methacrylates. They contain –COOH as a functional group. They dissolve at ranges from pH 5.5 to pH 7. EUDRAGIT® FS 30 D is the

aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid. It is insoluble in acidic media, but dissolves by salt formation above pH 7.0. Eudragit L100-55 and L30-55 dissolve at pH above 5.5. Eudragit L100 and S100 dissolve at pH above 6.0.

**[00070]** Sustained-release EUDRAGIT<sup>®</sup> formulations are employed for many oral dosage forms to enable time-controlled release of active ingredients. Drug delivery can be controlled throughout the whole gastro-intestinal tract for increased therapeutic effect and patient compliance. Different polymer combinations of EUDRAGIT<sup>®</sup> RL (readily permeable) and RS (sparingly permeable) grades allow custom-tailored release profiles and enable a wide range of alternatives to achieve the desired drug delivery performance. The EUDRAGIT<sup>®</sup> NE polymer is a neutral ester dispersion which requires no plasticizer and is particularly suitable for granulation processes in the manufacture of matrix tablets and sustained release coatings.

**[00071]** Exemplary osmagents or osmotic agents include organic and inorganic compounds such as salts, acids, bases, chelating agents, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, combinations thereof and other similar or equivalent materials which are widely known in the art.

**[00072]** As used herein, the term “disintegrant” is intended to mean a compound used in solid dosage forms to promote the disruption of a solid mass (layer) into smaller particles that are more readily dispersed or dissolved. Exemplary disintegrants include, by way of example and without limitation, starches such as corn starch, potato starch, pre-gelatinized and modified starches thereof, sweeteners, clays, bentonite, microcrystalline cellulose (e.g., Avicel<sup>™</sup>), carboxymethylcellulose calcium, croscarmellose sodium, alginic acid, sodium alginate, cellulose polyacrilin potassium (e.g., Amberlite<sup>™</sup>), alginates, sodium starch glycolate, gums, agar, guar, locust bean, karaya, pectin, tragacanth, crospovidone and other materials known to one of ordinary skill in the art. A superdisintegrant is a rapidly acting disintegrant. Exemplary superdisintegrants include crospovidone and low substituted HPC.

**[00073]** In preferred embodiments, a plasticizer is also included in the oral dosage form. Plasticizers suitable for use in the present invention include, but are not limited to, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers, triacetin, propylene glycol and glycerin. Such plasticizers can also include ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutyl sebacate, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate.

**[00074]** It is an aspect of the compositions and methods of the present disclosure that the formulations or dosage forms can also incorporate one or more ingredients that discourage or prevent abuse of the active ingredients by crushing and inhaling a powdered form of the formulations. As such, a nasal irritant can be included, either as a separate layer, or incorporated into an outer layer, a sustained release layer or the core of the dosage forms. Exemplary irritants include, but are not limited to sodium lauryl sulfate, which is also called sodium dodecyl sulfate or capsaicinoids including capsaicin and synthetic capsaicins. In certain embodiments, the dosage forms include from 1 to 10% sodium lauryl sulfate.

**[00075]** The compositions of the present disclosure can also include one or more functional excipients such as lubricants, thermal lubricants, antioxidants, buffering agents, alkalizing agents, binders, diluents, sweeteners, chelating agents, colorants, flavorants, surfactants, solubilizers, wetting agents, stabilizers, hydrophilic polymers, hydrophobic polymers, waxes, lipophilic materials, absorption enhancers, preservatives, absorbents, cross-linking agents, bioadhesive polymers, retardants, pore formers, and fragrance.

**[00076]** Lubricants or thermal lubricants useful in the present invention include, but are not limited to fatty esters, glyceryl monooleate, glyceryl monostearate, wax, carnauba wax, beeswax, vitamin E succinate, and a combination thereof.

**[00077]** As used herein, the term “antioxidant” is intended to mean an agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by oxidation due to the presence of oxygen free radicals or free metals in the composition. Such compounds include, by way of example and without limitation, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), hypophosphorous acid, monothioglycerol, sodium ascorbate, sodium formaldehyde sulfoxylate and sodium metabisulfite and others known to those of ordinary skill in the art. Other suitable antioxidants include, for example, vitamin C, sodium bisulfite, vitamin E and its derivatives, propyl gallate or a sulfite derivative.

**[00078]** Binders suitable for use in the present invention include beeswax, carnauba wax, cetyl palmitate, glycerol behenate, glyceryl monostearate, glyceryl palmitostearate, glyceryl stearate, hydrogenated castor oil, microcrystalline wax, paraffin wax, stearic acid, stearic alcohol, stearate 6000 WL1644, gelucire 50/13, poloxamer 188, and polyethylene glycol (PEG) 2000, 3000, 6000, 8000, 10000 or 20000.

**[00079]** A buffering agent is used to resist change in pH upon dilution or addition of acid or alkali. Such compounds include, by way of example and without limitation, potassium metaphosphate, potassium phosphate, monobasic sodium acetate and sodium citrate anhydrous and dihydrate, salts of inorganic or organic acids, salts of inorganic or organic bases, and others known to those of ordinary skill in the art,

**[00080]** As used herein, the term “alkalizing agent” is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, by way of example and without limitation, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, triethanolamine, and triethylamine and others known to those of ordinary skill in the art.

**[00081]** Exemplary binders include: polyethylene oxide; polypropylene oxide; polyvinylpyrrolidone; polyvinylpyrrolidone-co-vinylacetate; acrylate and methacrylate copolymers; polyethylene; polycaprolactone; polyethylene-co-polypropylene;

alkylcelluloses and cellulosic derivatives such as low substituted HPC (L-HPC), methylcellulose; hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxybutylcellulose; hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose; starches, pectins; PLA and PLGA, polyesters (shellac), wax such as carnauba wax, beeswax; polysaccharides such as cellulose, tragacanth, gum arabic, guar gum, and xanthan gum.

**[00082]** Exemplary chelating agents include EDTA and its salts, alphahydroxy acids such as citric acid, polycarboxylic acids, polyamines, derivatives thereof, and others known to those of ordinary skill in the art.

**[00083]** As used herein, the term "colorant" is intended to mean a compound used to impart color to solid (*e.g.*, tablets) pharmaceutical preparations. Such compounds include, by way of example and without limitation, FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel, and ferric oxide, red, other F.D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and other materials known to one of ordinary skill in the art. The amount of coloring agent used will vary as desired.

**[00084]** As used herein, the term "flavorant" is intended to mean a compound used to impart a pleasant flavor and often odor to a pharmaceutical preparation. Exemplary flavoring agents or flavorants include synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants, leaves, flowers, fruits and so forth and combinations thereof. These may also include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leave oil, oil of nutmeg, oil of sage, oil of bitter almonds and cassia oil. Other useful flavors include vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. Flavors that have been found to be particularly useful include commercially available orange, grape, cherry and bubble gum flavors and mixtures thereof. The amount of flavoring may depend on a number of factors, including the organoleptic effect desired. Flavors will be



present in any amount as desired by those of ordinary skill in the art. Particular flavors are the grape and cherry flavors and citrus flavors such as orange.

**[00085]** Suitable surfactants include Polysorbate 80, sorbitan monooleate, polyoxymer, sodium lauryl sulfate or others known in the art. Soaps and synthetic detergents may be employed as surfactants. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts. Suitable detergents include cationic detergents, for example, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene) copolymers; and amphoteric detergents, for example, alkyl  $\beta$ -aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

**[00086]** A wetting agent is an agent that decreases the surface tension of a liquid. Wetting agents would include alcohols, glycerin, proteins, peptides water miscible solvents such as glycols, hydrophilic polymers Polysorbate 80, sorbitan monooleate, sodium lauryl sulfate, fatty acid alkali metal, ammonium, and triethanolamine salts, dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl and olefin sulfonates, alkyl, olefin, ether and monoglyceride sulfates, and sulfosuccinates; nonionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene)-*block*-poly(oxypropylene) copolymers; and amphoteric detergents, for example, alkyl  $\beta$ -aminopropionates and 2-alkylimidazoline quaternary ammonium salts; and mixtures thereof.

**[00087]** Solubilizers include cyclodextrins, povidone, combinations thereof, and others known to those of ordinary skill in the art.

**[00088]** Exemplary waxes include carnauba wax, beeswax, microcrystalline wax and others known to one of ordinary skill in the art.

**[00089]** Exemplary absorption enhancers include dimethyl sulfoxide, Vitamin E PGS, sodium cholate and others known to one of ordinary skill in the art.

**[00090]** Preservatives include compounds used to prevent the growth of microorganisms. Suitable preservatives include, by way of example and without

limitation, benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal and others known to those of ordinary skill in the art.

**[00091]** Examples of absorbents include sodium starch glycolate (Explotab™, Primojel™) and croscarmellose sodium (Ac-Di-Sol™), cross-linked PVP (Polyplasdone™ XL 10), veegum, clays, alginates, PVP, alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose (e.g., Avicel™), polacrillin potassium (e.g., Amberlite™), sodium alginate, corn starch, potato starch, pregelatinized starch, modified starch, cellulosic agents, montmorillonite clays (e.g., bentonite), gums, agar, locust bean gum, gum karaya, pectin, tragacanth, and other disintegrants known in to those of ordinary skill in the art.

**[00092]** A cross-linking agent is defined as any compound that will form cross-links between the moieties of the polymer. A cross-linking agent can include, by way of example and without limitation, an organic acid, an alpha-hydroxy acid, a beta-hydroxy acid. Suitable cross-linking agents include tartaric acid, citric acid, fumaric acid, succinic acid and others known to those of ordinary skill in the art.

**[00093]** Bioadhesive polymers include polyethylene oxide, KLUCEL (hydroxypropylcellulose), CARBOPOL, polycarbophil, GANTREZ, Poloxamer, and combinations thereof, and others known to one of ordinary skill in the art.

**[00094]** Retardants are agents that are insoluble or slightly soluble polymers with a glass transition temperature (T<sub>g</sub>) above 45°C, or above 50°C before being plasticized by other agents in the formulation including other polymers and other excipients needed for processing. The excipients include waxes, acrylics, cellulose, lipids, proteins, glycols, and the like.

**[00095]** Exemplary pore formers include water soluble polymers such as polyethylene glycol, propylene glycol, polaxamer and povidone; binders such as lactose, calcium sulfate, calcium phosphate and the like; salts such as sodium chloride, magnesium chloride and the like; combinations thereof and other similar or equivalent materials which are widely known in the art.

**[00096]** As used herein, the term "sweetening agent" is intended to mean a compound used to impart sweetness to a preparation. Such compounds include, by way

of example and without limitation, aspartame, dextrose, glycerin, mannitol, saccharin sodium, sorbitol, sucrose, fructose and other such materials known to those of ordinary skill in the art.

**[00097]** It should be understood that compounds used in the art of pharmaceutical formulation generally serve a variety of functions or purposes. Thus, if a compound named herein is mentioned only once or is used to define more than one term herein, its purpose or function should not be construed as being limited solely to that named purpose(s) or function(s).

**[00098]** It is an aspect of the compositions and methods of the present disclosure that the disclosed pharmaceutical formulations provide novel release profiles in vivo and when orally administered to a human. The formulations provide a lag time of from 4-12 hours in certain embodiments followed by release of 85% of the drug over the following 9 hours in an ascending dose.

**[00099]** The dissolution profile is performed in conditions designed to mimic the gastric environment, or the environment that is encountered by an oral composition that is swallowed by a human. Although residence time in the stomach varies, a typical test places the composition in the low pH solution of 0.1N HCl for two hours to mimic the residence time in stomach acid. The composition is then placed in a higher pH aqueous solution, about pH 6 for 2-6 hours followed by typically pH 6.8 to mimic the environment of the ileum and colon. As used herein, simulated gastric conditions encompasses both the acidic first stage and the subsequent higher pH stages of a normal human gastrointestinal tract.

**[000100]** Following the delay period, the serum concentration increases over approximately 9 to 10 hours to reach a maximum serum concentration ( $C_{max}$ ). Based on this release profile, a dose taken at 9:00 P.M. with a 6 hour delay begins to release the drug at about 3 A.M. and the maximum serum concentration is reached about 16 hours later. At that point, the drug is cleared from the system at essentially the same rate at which it is absorbed.

**[000101]** It is a further aspect of the compositions and methods of the present disclosure that the drug can begin to be slowly released during the lag time. This release is determined by the composition of the delayed release layer as described herein. Some

examples of a small release during the lag time are those in which no more than about 10% of the drug is released during the 3 to 12 hour lag. It is also understood that a greater percentage, 12%, 15%, 18% or even 20%, can be released as the delayed release layer becomes more permeable.

**[000102]** Disclosed herein, therefore, are pharmaceutical preparations for once daily administration of a central nervous system stimulant for treatment of conditions that respond to such drugs, such as ADD, ADHD, bipolar depression, narcolepsy, sleeping disorders, and fatigue. The dosage is formulated to be taken prior to going bed and starts to release after a lag of several hours so the patient has absorbed a sufficient amount of drug to have a therapeutic effect while awakening and preparing to leave for work or school. It is a further aspect of the formulations that the drug is released in an ascending dose through the day to overcome any acute tolerance effect and maintain a therapeutic level of drug.

**[000103]** An embodiment of the compositions and methods of the present disclosure is a dosage form that includes a capsule enclosing a single population of beads or minitablets that include a core and 2 or more coatings surrounding the core. The inner core is a bead or minitabulet containing an active pharmaceutical ingredient (API) and one or more excipients. The core is enclosed in a sustained release layer, and an outer, delayed release layer.

**[000104]** In certain embodiments the sustained release layer includes a combination of water soluble polymers and water insoluble polymers. The sustained release coating can contain a combination of polyethylene oxide and an ethylcellulose, for example, or a hydroxypropylmethyl cellulose and ethylcellulose. An ethylcellulose product that can be used in the disclosed dosage forms is Ethocel™, marketed under a trade mark of The Dow Chemical Company. The rate of dissolution of the sustained release layer can be controlled by adjusting the ratio of water soluble polymer to water insoluble polymer in the coating or layer. The weight ratio of water insoluble to water soluble polymers can be adjusted, for example, from 90:10 to 10:90, from 80:20 to 20:80, from 75:25 to 25:75, from 70:30 to 30:70, from 67.5:33.5 to 33.5:67.5 from 60:40 to 40:60, from 56:44 to 44:56, or to 50:50.

**[000105]** The sustained release coating can also contain plasticizers such as triethyl citrate (TEC) at levels of from 3% to 50% of the combined weight of the polymers. Other additives to the coating can include titanium dioxide, talc, colloidal silicone dioxide or citric acid.

**[000106]** Some examples of sustained release layers are shown in the following table. The various formulations include those in which the ratios of water insoluble to water soluble polymers are varied and one in which the ratios are reversed. Citric acid was added to a formula keep the micro environment pH in the film low to inhibit the dissolution of HPMCAS-LF, which dissolves at  $\geq$  pH5.5 thus creating a lag at the beginning of the dissolution curve. In certain embodiments, the active ingredient, or API can be included in the sustained release layer. In initial testing, a model drug, metronidazole was micronized and added to the formulation as a suspension. Any of the appropriate disclosed API's can be added to the sustained release layer, however.

Table 1 Exemplary Sustained Release Layers

Component	A (% w/w)	B (% w/w)	C (% w/w)	D (% w/w)	E (% w/w)	F (%w/w)
Ethocel	51.0	34.9	34.5	34.4	60.2	36.1
API				47.2		
PEO					36.1	60.2
HPMC E5 P	17.0	13.1				
HPMCAS-LF			27.6	11.5		
Talc	3.6	2.8	3.6	2.4		
Titanium Dioxide	24.0	18.5	24.0			
Citric acid			6.9			
Colloidal silicon dioxide	0.4					
TEC	4.0	26.2	3.4	4.6	3.6	3.6
Totals	100.0	100.0	100.0	100.0	100.0	

**[000107]** An exemplary core was synthesized as shown in Table 2. In this example, an osmotic agent is added to the core.

Table 2

Component	Pellet Core (% w/w)
API	20.0
Avicell PH101	47.0
Potassium chloride	30.0
Klucell EF	3.0
Totals	100.0

**[000108]** A sustained release layer with the formula shown in the right hand column (F) of Table 1 was synthesized on an API containing bead. The formula was designated 2009-043-10A when the sustained release layer provided a 25% wt gain and 2009-043-10 when the sustained release layer provided a 35% gain. Additional layers were synthesized as shown in columns A and B of Table 1. In column B, the formula of column A was modified such that the colloidal silicon dioxide was removed and the plasticizer was increased to 50% w/w of the polymer level. All of the other ratios as shown in column A were maintained.

**[000109]** The formula of column A was also modified to produce the sustained release layer of column C of Table 1. In this formula, the colloidal silicon dioxide was removed and citric acid was added. The ratio of Ethocel:HPMCAS was decreased from 75:25 to 56:44. This formula was expected to provide a lower pH in the microenvironment to increase the lag time. A sample layered to produce a 25% wt gain and another sample with a 45% wt gain were subjected to dissolution testing.

**[000110]** Another embodiment of a sustained release layer was produced in which the drug or API was included in the sustained release layer. This layer is described in column D of Table 1. In this formula, the ratio between Ethocel and HPMCAS was 75:25. A micronized drug was added to the formula as a suspension. A sample with a 25% wt gain was subjected to dissolution testing.

**[000111]** Core tablets as described in Table 2 were coated with a sustained release layer formulated as in column A of Table 1. This formulation exhibited an initial slow drug release (3% in the first 3 hours).

**[000112]** Another embodiment of a sustained release coating was designed with polyethyleneoxide (PEO) to ethyl cellulose ratio of 37.5:62.5. Talc was also added to one sample at 10% to improve the coating process. The presence of talc did not affect drug release. The release profiles for these formulations processed with a 25% wt gain and a 40% wt gain were also determined. The formulations exhibited a 1 hour lag and the drug was substantially completely released within 9 hours.

**[000113]** While the disclosed compositions of a capsule containing a single population of beads or minitables with a sustained release layer and an outer, delayed release layer are shown here in to be an effective delivery system with novel release characteristics and surprisingly low variability in absorbance when administered to humans, it is understood that alternative compositions can be used in light of the present disclosure.

**[000114]** In certain embodiments a drug containing core bead or minitabket is coated with a delayed release layer that includes one or more water insoluble polymers, one or more water soluble polymers and a silicone oil to achieve a desired delay or lag time prior to release as in the present disclosure. Lag time and release are controlled by the proportion of the two types of polymers and the thickness of the layer. In such embodiments, the delayed release layer can include, but is not limited to cellulose acetate phthalate, cellulose acetate trimaleate, hydroxyl propyl methylcellulose phthalate, polyvinyl acetate phthalate, acrylic polymers, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, shellac, methacrylic acid copolymers, Eudragit L30D, Eudragit L100, Eudragit FS30D, Eudragit S100 or combinations of any thereof. The delayed release layer can also include a plasticizer, or in certain embodiments the delayed release layer can include methacrylic acid copolymer Type B, mono- and diglycerides, dibutyl sebacate and polysorbate 80. The delayed release layer can also include a cellulose ether derivative, an acrylic resin, a copolymer of acrylic acid and methacrylic acid esters with quaternary ammonium groups, a copolymer of acrylic acid and methacrylic acid esters or a combination of any thereof.

The layer can further include a powder component such as talc as a carrier for the silicone oil.

**[000115]** In certain embodiments of the invention, a central nervous system stimulant can be contained in a delayed and/or controlled release capsule. In such embodiments a water insoluble capsule contains one or more compartments in which the drug or active agent is held. Additionally one or more absorbents, superabsorbents or osmagents are included in the drug containing compartments. The capsules also include one more apertures plugged with a water soluble polymer, at least one in fluid communication with each compartment and a delayed release layer enclosing the entire capsule.

**[000116]** In such embodiments the length of initial delay can be controlled by the composition and thickness of the outer, delayed release layer. This layer can be a pH dependent layer or a pH independent layer as disclosed herein. When the capsule is administered to a human, the delayed release layer begins to lose integrity as the capsule passes through the GI tract. When the water soluble plugs are exposed and dissolve, aqueous fluid enters the drug containing compartment(s) and is absorbed by the absorbent or osmagent, thus driving the active agent from the capsule through the aperture. The release profile can be controlled by the concentration and absorbance characteristics of the absorbent or osmagent to obtain the desired profile.

#### Sustained Release Coatings on Dextroamphetamine Sulfate Pellets

**[000117]** Formulations of the disclosure are made in which hydrophobic excipients are introduced to give an added delay in the drug release. The plasticizer level is kept at 7.26 % of the Ethocel<sup>TM</sup> level. The formulations are described in Table 3.

**Table 3: Sustained Release Formulations**

Lot Number	2009-066-51	2009-066-53	2009-066-59	2009-066-64	2009-066-67	2009-066-69	2009-066-72	2009-066-75	2009-066-78
Component	% W/W								
Ethocel <sup>TM</sup> Std. 10	35.8	35.8	38.5	43.0	45.4	55.9	53.2	50.7	45.4
Klucel <sup>TM</sup> (EF)	8.9	8.9	6.1	1.3	11.3		2.9	5.6	11.3



Triethyl Citrate	2.6	2.6	2.8	3.1	3.3				
Imperial Talc 500	52.6								
Dibutyl Sebacate						4.1	3.9	3.7	3.3
Magnesium Stearate		52.6	52.6	52.6	40.0	40.0	40.0	40.0	40.0

**[000118]** These formulations were coated to a 30 % weight gain level and samples were submitted for testing at 10 mg free base capsule dose. The dissolution testing took place in pH 7.0 buffer with a paddle speed of 75 rpm.

**[000119]** Lot 2009-066-51 has a water insoluble to water-soluble ratio of 80:20. This results in a significantly faster release profile. The API releases 25 % in the first hour. In further formulations talc was removed and replaced with magnesium stearate.

**[000120]** In Lot 2009-066-53, which contained magnesium stearate, the initial release was significantly slower. Further changes included increasing the Ethocel™ level in Lot -59 and -64 while decreasing the Klucel® level. The ratio of Ethocel™ to Klucel® in Lot -59 and -64 respectfully is 86:14 and 97:3. This change was expected to slow the release from Lot 53, but the dissolution release time actually increased. Lot -67 included a decrease of the magnesium stearate and decrease in the Ethocel™ to Klucel® ratio (back to 80:20). This resulted in a release faster than the model profile.

**[000121]** Replacement of the hydrophilic plasticizer TEC with dibutyl sebacate (DBS), a hydrophobic plasticizer resulted in a significantly longer delay prior to initial release. Lot 2009-066-69 was the first lot utilizing DBS as a plasticizer. With the addition of DBS and the removal of Klucel®, the initial drug release was less than 2 % over 8 hours.

**[000122]** Klucel® was added back into the formulation in Lot 2009-066-72. The ratio of Ethocel™ to Klucel® was 95:5. The dissolution profile was similar to Lot 2009-066-69. In Lot 2009-066-75, the ratio of Ethocel™ to Klucel® decreased from 95:5 to 90:10. This change did not result in a different release profile compared to the two previous formulations.

**[000123]** For Lot 2009-066-78, the ratio of Ethocel™ to Klucel® was decreased to 80:20, for a higher level of water-soluble polymer. Formulation 2009-066-78 exhibited a 20 % drug release over 4 hours followed by an increasing release until over 80% release.

#### DOE Sustained Release Coatings

**[000124]** A design of experiment (DOE) was set up with three ratios of Ethocel™ to Klucel® ratios: 70:30, 75:25, and 80:20. The coatings were applied in the GPCG2 with a 1.0 mm spray nozzle. For a DOE coating run 650.0 g of pellets were used. The pellets consisted of 80 % w/w placebo pellets and 20 % Dextroamphetamine sulfate pellets. The pellets were diluted to conserve the D-amphetamine sulfate pellets. The DOE formulations are shown in Table 4. Each coating formulation contained 12 % solids w/w. The solvents consisted of ethanol to DI water at a ratio of 95:5.

**Table 4 DOE Formulations**

Lot Number	2009-104-13	2009-104-17	2009-104-44	2009-104-48	2009-104-52	2009-104-55	2009-104-58	2009-104-61	2009-104-81	2009-138-12	2009-138-29
DOE Run	1	2	3	4	5	6	7	8	9	10	11
Component	% W/W										
Ethocel™ Std. 10	41.18	36.64	49.15	39.29	34.84	43.30	41.59	46.43	41.86	57.58	44.08
Klucel® (EF)	17.65	15.70	12.29	9.82	14.93	18.56	10.40	11.61	13.95	14.39	11.02
Dibutyl Sebacate	6.18	2.66	3.56	5.89	5.23	3.14	3.02	6.96	4.19	3.03	4.91
Magnesium Stearate	35.00	45.00	35.00	45.00	45.00	35.00	45.00	35.00	40.00	25.00	40.00

**[000125]** Each of the DOE formulations was coated to 30 % weight gain, then samples were loaded into capsules at 13.6 mg dose (equivalent to 10.0 mg free base dose), and submitted for dissolution testing in pH 7.2 phosphate buffer with a paddle speed of 75 rpm (this was the paddle speed for all of the dissolution testing).

**[000126]** A standard mixing procedure was developed for the sustained released coating preparations as follows. Charge the ethanol into an appropriate sized beaker. Place the beaker under a lab mixer with a Cowles blade attached. Create a vortex by increasing the mixing speed and charge the Ethocel™, Klucel®, and DBS into the ethanol. The speed of the mixer is turned down so there is no vortex and the excipients mixed until dissolved. Once the excipients dissolve, a vortex can be created for the addition of the magnesium stearate. The magnesium stearate is mixed for a minimum of 30 minutes

or until no agglomerates are present. Adding the DI water to the mixing dispersion is the last step of the process. The first eight DOE dissolution profiles are shown in Fig. 4.

**[000127]** As shown in Fig. 5, DOE 9 had an Ethocel™ to Klucel® ratio of 75:25 and produced a faster dissolution release. In DOE 10 the Ethocel™ to Klucel® ratio was 80:20 and the magnesium stearate level was decreased from 40 % w/w/ to 25 % w/w. By making these changes, the dissolution profile shifts to the right far beyond the model profile. The DOE 11 formulation is similar to Lot 2009-066-78 (see Table 3 and Table 4 for formulations). DOE 11, 3, and 4 have release profiles that are close to the model profile. All three have an Ethocel™ to Klucel® ratio of 80:20, but differ in percent w/w of the hydrophobic excipients. The DOE 3 coating was the closest profile to the model.

#### Stability of DOE 3 and DOE 4

**[000128]** For a stability study, 13.6 mg (equivalent to 10.0 mg free base dose) dose capsules were loaded into HDPE bottles and loaded into the following stability chambers for the study: 40°C/75 % RH, 25°C/60 % RH, and 30°C/65 % RH. Pellets were also loaded into HDPE bottles with no capsules at 40°C/75 % RH for an open container study. After 2 and 4 weeks for the open container study at 40°C/ 75 % RH dissolution testing of the pellets took place in pH 7.2 phosphate buffer. The dissolution results are shown in Fig. 6 and Fig. 7.

**[000129]** All of the dissolution profiles from the different stability time points had similar drug release profiles, demonstrating that the sustained release coatings are stable. The next step in the development was to add a pH dependent coating on top of the sustained release coating.

#### pH Dependent Coatings

**[000130]** For the pH dependent coatings studies, the DOE 3 pellets were used. Samples of 13.6 mg dose (10.0 mg free base dose) were loaded into capsules. The dissolution testing took place for 2 hours (T=0-2 hour) in 0.1N HCl, then in pH 6.0 phosphate buffer for 4 hours (T=2-6 hour), and finally in pH 7.0 phosphate buffer for the remaining time. The formulations are shown in Table 5.

**Table 5: pH dependent Formulations**

Lot Number	2009-104-76	2009-104-78	2009-104-92 <sup>1</sup>	2009-138-22	2009-138-25
Component	% W/W				
Eudragit® S 100	60.6		60.0	76.9	80.6
Eudragit® FS 30 D		64.5			
Triethyl Citrate	9.1	3.2	9.1		
Dibutyl Sebacate				7.7	8.1
Magnesium Stearate				15.4	
ImperialTalc 500	30.3	32.3	30.3		
Imwitor® 900 K					8.1
Tween® 80					3.2

<sup>1</sup> Same formulation as Lot 2009-104-76, but coated at a product temperature 4°C higher.

**[000131]** The S 100 coatings are made with alcohol/DI water as the solvent at 94.4 % w/w to 5.6 % w/w and the FS 30 D coating is aqueous only. The dissolution profiles are shown in Fig. 8.

**[000132]** Lot 2009-104-78 exhibited a delay of 6 hours followed by a fast release. The S 100 formulation with GMS (Imwitor 900 K) at 10% w/w was then coated on the DOE 3 pellets. Lot 2009-138-25B exhibits a delay at the start of the drug release followed by a release curve that is similar to the model profile.

#### pH Dependent/SR Coated DOE 3 Pellets

**[000133]** The study with a pH dependent coating on the DOE 3 SR coating was repeated with a 100 % active core pellet batch (no placebo pellets). The coating parameters are shown in Table 6.

**Table 6: Lot 2009-138-32 Coating Parameters**

Parameters	Ranges
Product Temperature	32.0-33.0°C
Inlet Temperature	48.4-54.1°C
Exhaust Temperature	29.3-30°C
Process Air	40-53 m <sup>3</sup> /h
Atomization Air	2.0 Bar
Spray Time	126.75 min
Spray Rate	12.8 g/min

**[000134]** The dissolution profiles of the active and placebo diluted pellets of the DOE 3 coatings are shown in Fig. 9.

**[000135]** The pH dependent coating (Lot 2009-138-45) containing GMS was then coated on the sustained release DOE 3 coating. The pellets were coated to a 30 % weight

gain with a sample pulled at 25 % weight gain. The pellets were dosed into 13.6 mg capsules (10.0 mg freebase) and tested in the 3-stage dissolution study. The coating parameters are in Table 7 and the dissolution profiles are shown in Fig. 10.

**Table 7: Lot 2009-138-45 Coating Parameters**

Parameters	Ranges
Product Temperature	32.0-33.0°C
Inlet Temperature	48.4-54.1°C
Exhaust Temperature	29.3-30°C
Process Air	40-53 m <sup>3</sup> /h
Atomization Air	2.0 Bar
Spray Time	126.75 min
Spray Rate	12.8 g/min

**[000136]** At the 10-hour time point, DOE 3 had released 20 % of the drug, closely matching the target profile. A portion of the pellets from DOE 3 (Lot 2009-138-45) were encapsulated to 13.6 mg dose (equivalent to 10 mg free base dose) in gelatin capsules and placed on stability. Bottles were filled with 16 capsules and placed in the following conditions: 4 bottles at 40°C/75 % relative humidity, 4 bottles at 30°C/65 % relative humidity, 1 bottle at 25°C/60 % relative humidity. Two bottles just containing pellets equivalent to 16 capsules placed in 40°C/ 75 % relative humidity for an open dish accelerated study. After being in stability for two weeks samples were pulled from open container, 30°C/ 65 % relative humidity, and 40°C/ 75 % relative humidity. The dissolution profiles for these samples are shown in Fig. 11.

**[000137]** The two-week open container pellets started to release the drug at the 4-hour time point. The initial pellets and the other closed container samples did not start drug release until after the 6-hour time point. The two closed container samples released the drug slower than the initial release. It was presumed that pellets were absorbing moisture causing the GMS (Imwitor<sup>®</sup>) to become unstable and releasing the drug faster in the open container study. To try to stabilize the GMS, samples from Lot 2009-138-45 were placed in an oven and cured for 12 hours, 24 hours, and 48 hours at 50°C. The dissolution results are located in Fig. 12.

**[000138]** At 50°C, the curing time did not affect the drug release. Another curing study was set up with the oven set at 55°C. Samples from Lot 2009-138-45 (DOE 3) were cured for 24, 48, and 108 hours (4.5 days). The dissolution profiles are shown in Fig. 13.

**[000139]** The release of drug after curing the pellets at 55°C was not directly dependent on time. For the samples cured at 55°C, the pellets were dosed (13.6 mg /10.0 mg free base dose) into gelatin and HPMC capsules. The HPMC capsules contain a one-gram desiccant in each bottle to absorb any excess moisture. The samples were cured at 50°C dosed only in the HPMC capsules with the one-gram desiccant in each bottle. Sixteen capsules were loaded into each bottle. The stability conditions are shown in Table 8.

**Table 8 Stability Conditions for Cured Pellets**

Stability Conditions	40°C/75 % Relative Humidity	30°C/65 % Relative Humidity	25°C/60 % Relative Humidity	40°C/75 % Relative Humidity (Pellets only Open Container)
<b>Capsule Type</b>	<b>Number of Bottles per Condition</b>			
HPMC at 55°C	4	4	1	2
Gelatin at 55°C	4	4	1	
HPMC at 50°C	4	4	1	2

**[000140]** After 2 and 4 weeks, the samples cured at 55°C were pulled and dissolution testing performed on them. The dissolution results for the stability samples are shown in Fig. 14.

**[000141]** For pellets cured at 55°C loaded into the HPMC capsules the dissolution profile for the initial, 2-week, and 4-week samples gave similar results. This demonstrates product stability under those conditions. The gelatin-loaded capsules produced a dissolution profile a little slower than the initial release at 2 and 4 week samples.

**[000142]** Lot 2009-138-45 (DOE 3, SR and pH Coated) containing HPMC capsules with desiccant was left on stability 40°C/75 % RH (closed container) for 8 months. Samples were pulled at 2, 3, and 8 months for dissolution testing. The dissolution profiles for the HPMC capsules containing the D-amphetamine sulfate pellets are shown in Fig. 15.

**[000143]** After 8 months in accelerated stability, the D-amphetamine sulfate has a similar profile to the initial release profile (T=0). The only difference is a slower release between hours 7-10.

## Example 1

**[000144]** An example of a core pellet as described herein contains the following components as produced in a 5 kg batch.

**[000145]** Batch size 5,000 grams

**[000146]** Granulation Medium Solids 6%

Component	mg/1mg pellet	% w/w	g/batch
Dextroamphetamine Sulfate, USP	22.0	22.0	1100.0
Avicel PH-101	65.0	65.0	3250.0
Starch 1500	10.0	10.0	500.0
Methocel E5 P LV <sup>I</sup>	3.0	3.0	150.0
Total	10.0	100.0	5000.0
DI Water	removed during processing		2356.0

**[000147]** In processing the extra water is added into the granulation medium. Water is 47.12% of the dry blend batch size. The granulation medium is 2506.0 grams and the spray rate is  $418 \pm 20$  g/min.

## Example 2

**[000148]** An example of a sustained release coating to be applied to the core pellet is prepared with the following components.

**[000149]** Core batch size - 1100.0 g

**[000150]** Coating wt. gain – 30%

**[000151]** Solids – 12.0 %

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
Ethocel S 10	14.75		49.15	162.2
Klucel EF	3.69		12.29	40.6
Dibutyl Sebacate	1.07		3.56	11.7
Mag Stearate 2257	10.50		35.00	115.5
			100.00	330.0

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
Ethanol		95		2299.0
DI Water		5		121.0
Theoretical amount of coated pellets (g)		1430		

## Example 3

**[000152]** An S100 pH dependent coating formulated for a 30% weight gain is formulated with the following components.

**[000153]** Coating wt gain – 30%

**[000154]** Solids – 10.0%

**[000155]** Batch size - 715 g

**[000156]** Core pellet amount – 550 g

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
Eudragit S100	24.18		80.6	133.0
Imwitor 900K	2.43		8.1	13.4
Dibutyl Sebacate	2.43		8.1	13.4
Tween 80	0.96		3.2	5.3
Ethanol		94.4		1402.5
DI Water		5.6		82.5
			100.0	1650.0
Theoretical amount of coated pellets (g)		880.0		

## Example 4

**[000157]** An S100 pH dependent coating formulated for a 50% weight gain contains the following components.

**[000158]** Coating wt gain – 50.0%

**[000159]** Solids – 10.0%

**[000160]** Batch size - 715 g

**[000161]** Core pellet amount – 550 g

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
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Eudragit S100	40.30		80.6	221.7
Imwitor 900K	4.05		8.1	22.3
Dibutyl Sebacate	4.05		8.1	22.3
Tween 80	1.60		3.2	8.8
Ethanol		94.4		2337.5
DI Water		5.6		137.5
			100.0	2750.0
Theoretical amount of coated pellets (g)		990.0		

## Example 5

**[000162]** A formulation was made with a pellet core as in Example 1, a sustained release coating as in Example 2 and a pH dependent coating with a 30% weight gain as in Example 3.

Component	mg/1g pellet	%w/w
Dextroamphetamine Sulfate USP	22.00	13.75
Avicel PH-101	65.00	40.63
Starch 1500	10.00	6.25
Methocel E5 P LV <sup>1</sup>	3.00	1.88
Ethocel Std 10	14.75	9.22
Klucel EF	3.69	2.30
Dibutyl Sebacate	1.07	0.67
Mag Stearate 2257	10.50	6.56
Eudragit S100	24.18	15.11
Imwitor 900K	2.43	1.52
Dibutyl Sebacate	2.43	1.52
Tween 80	0.96	0.60
	160.00	100.00

## Example 6

**[000163]** A formulation was made with a pellet core as in Example 1, a sustained release coating as in Example 2 and a pH dependent coating with a 50% weight gain as in Example 3.

Component	mg/1g pellet	%w/w
Dextroamphetamine Sulfate USP	22.00	12.22
Avicel PH-101	65.00	36.11
Starch 1500	10.00	5.56
Methocel E5 P LV <sup>1</sup>	3.00	1.67
Ethocel Std 10	14.75	8.19
Klucel EF	3.69	2.05
Dibutyl Sebacate	1.07	0.59
Mag Stearate 2257	10.50	5.83
Eudragit S100	40.30	22.39
Imwitor 900K	4.05	2.25
Dibutyl Sebacate	4.05	2.25
Tween 80	1.60	0.89
	180.00	100.00

#### Example 7

**[000164]** An example of a sustained release coating with an alternate ratio of water soluble (Klucel) to water insoluble polymer (Ethocel) is prepared with the following components to obtain a faster release profile.

**[000165]** Core batch size - 1100.0 g

**[000166]** Coating wt. gain – 30%

**[000167]** Solids – 12.0 %

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
Ethocel Std 10	12.48		41.59	137.2
Klucel EF	3.12		10.40	34.3
Dibutyl Sebacate	0.90		3.01	9.9
Mag Stearate 2257	13.50		45.00	148.5

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
				330.0
Ethanol		95		2299.0
DI Water		5		121.0
			100.00	2750.0
Theoretical amount of coated pellets (g)		1430		

## Example 8

**[000168]** A formulation was made with a pellet core as in Example 1, a sustained release coating as in Example 7 and a pH dependent coating with a 30% weight gain as in Example 3.

Component	mg/1g pellet	%w/w
Dextroamphetamine Sulfate USP	22.00	13.75
Avicel PH-101	65.00	40.63
Starch 1500	10.00	6.25
Methocel E5 P LV <sup>I</sup>	3.00	1.88
Ethocel Std 10	12.48	7.80
Klucel EF	3.12	1.95
Dibutyl Sebacate	0.90	0.56
Mag Stearate 2257	13.50	8.44
Eudragit S100	24.18	15.11
Imwitor 900K	2.43	1.52
Dibutyl Sebacate	2.43	1.52
Tween 80	0.96	0.60
	160.00	100.00

## Example 9

**[000169]** A formulation was made with a pellet core as in Example 1, a sustained release coating as in Example 7 and a pH dependent coating with a 50% weight gain as in Example 4.

Component	mg/1g pellet	%w/w
Dextroamphetamine Sulfate USP	22.00	12.22
Avicel PH-101	65.00	36.11
Starch 1500	10.00	5.56
Methocel E5 P LV <sup>1</sup>	3.00	1.67
Ethocel Std 10	12.48	6.93
Klucel EF	3.12	1.73
Dibutyl Sebacate	0.90	0.50
Mag Stearate 2257	13.50	7.50
Eudragit S100	40.30	22.39
Imwitor 900K	4.05	2.25
Dibutyl Sebacate	4.05	2.25
Tween 80	1.60	0.89
	180.00	100.00

## Example 10

**[000170]** Another example of a sustained release coating according to the disclosure is prepared with the following components.

**[000171]** Core batch size - 1100.0 g

**[000172]** Coating wt. gain – 30%

**[000173]** Solids – 12.0 %

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
Ethocel Std 10	13.22		44.08	145.5
Klucel EF	3.1		11.02	36.4
Dibutyl Sebacate	1.47		4.90	16.2
Mag Stearate 2257	12.00		40.00	132.0
Ethanol		95		2299.0
DI Water		5		121.0
			100.00	2750.0

Component	mg/1g pellet	solvent ratio	%w/w	g/batch
Theoretical amount of coated pellets (g)		1430		

## Example 11

**[000174]** A formulation was made with a pellet core as in Example 1, a sustained release coating as in Example 10 and a pH dependent coating with a 30% weight gain as in Example 3.

Component	mg/1g pellet	%w/w
Dextroamphetamine Sulfate USP	22.00	13.75
Avicel PH-101	65.00	40.63
Starch 1500	10.00	6.25
Methocel E5 P LV <sup>1</sup>	3.00	1.88
Ethocel Std 10	13.22	8.27
Klucel EF	3.31	2.07
Dibutyl Sebacate	1.47	0.92
Mag Stearate 2257	12.00	7.50
Eudragit S100	24.18	15.11
Imwitor 900K	2.43	1.52
Dibutyl Sebacate	2.43	1.52
Tween 80	0.96	0.60
	160.00	100.00

## Example 12

**[000175]** An example of a core pellet free of starch or osmagent as described herein contains the following components as produced in a 2 kg batch. These core pellets are used in Examples 17-21.

Component	mg/1g pellet	% w/w	g/batch
Dextroamphetamine Sulfate, USP	220	22.0	440
Microcrystalline	780	78.0	1560

Cellulose, NF			
Total	1000	100.0	2000
DI Water	removed during processing		1440

## Example 13

**[000176]** An example of a slow sustained release coating as described herein for use in Slow Release Formulation (1 and 2) 25%SR + 20% or 30% pH Coating.

## SR Coat Slow Release (1 and 2)

Coating Wt gain: 25.0  
Solids %: 12.0

Component	mg/g	solvent ratio	%w/w	g/batch
Ethyl Cellulose, NF	81.5		8.15	123
Hydroxypropyl Cellulose, NF	20.4		2.04	31
Dibutyl Sebacate, NF	5.9		0.59	9
Magnesium Stearate, NF	58.0		5.80	88
Ethanol ( <i>denatured</i> )		95		1742
DI Water		5		92
Theoretical amount of coated pellets (g)		1250		

## Example 14

**[000177]** An example of a slow enteric coatings as described herein for use in Slow Release Formulation (1 and 2) 25%SR + 20% or 30% pH Coating.

## S100 pH Dependent Coat Slow Release (1)

Coating Wt gain: 20%  
Solids %: 10%  
Batch size (g) 1500  
Core pellet amount (g) 1250

Component	mg/g	solvent ratio	%w/w	g/batch
Methacrylic Acid Copolymer Type-B	133.7		13.37	202
Mono-and Di-glycerides, NF	13.4		1.34	20
Dibutyl Sebacate, NF	13.4		1.34	20
Polysorbate 80, NF	5.3		0.53	8
Ethanol ( <i>denatured</i> )		94.4		2138
DI Water		5.6		113

Theoretical amount of coated pellets (g)	1500			

## S100 pH Dependent Coat Slow Release (2)

Coating Wt gain:	30%
Solids %:	10%
Batch size (g)	1625
Core pellet amount (g)	1250

Component	mg/g	solvent ratio	%w/w	g/batch
Methacrylic Acid Copolymer Type-B	185.1		18.51	302
Mono-and Di-Glycerides, NF	18.6		1.86	30
Dibutyl Sebacate, NF	18.6		1.86	30
Polysorbate 80, NF	7.4		0.74	12
Ethanol ( <i>denatured</i> )		94.4		3206
DI Water		5.6		169
Theoretical amount of coated pellets (g)		1625		

## Example 15

**[000178]** An example of a medium sustained release coating as described herein for use in Medium Release Formulation (1 and 2) 20%SR + 20% or 30% pH Coating.

## SR Coat Medium Release (1 and 2)

Coating Wt gain:	20%
Solids %:	12%

Component	mg/g	solvent ratio	%w/w	g/batch
Ethyl Cellulose, NF	134.0		13.40	98
Hydroxypropyl Cellulose, NF	33.5		3.35	25
Dibutyl Sebacate, NF	9.7		0.97	7
Magnesium Stearate, NF	95.5		9.55	70
Ethanol ( <i>denatured</i> )		95		1393
DI Water		5		73
Amount of coated pellets (g)		1200		

## S100 pH Dependent Coat Medium Release (1)

Coating Wt gain:	20.0
Solids %:	10.0

Batch size (g) 1440  
Core pellet amount (g) 1000

Component	mg/g	solvent ratio	%w/w	g/batch
Methacrylic Acid Copolymer Type-B	120.3		12.03	193
Mono-and Di-Glycerides, NF	13.6		1.36	19
Dibutyl Sebacate, NF	13.6		1.36	19
Polysorbate 80, NF	5.4		0.54	8
Ethanol ( <i>denatured</i> )		94.4		2077
DI Water		5.6		123
Amount of coated pellets (g)		1440		

#### S100 pH Dependent Coat Medium Release (2)

Coating Wt gain: 30%  
Solids %: 10%  
Batch size (g) 1560  
Core pellet amount (g) 1200

Component	mg/g	solvent ratio	%w/w	g/batch
Methacrylic Acid Copolymer Type-B	185.1		18.51	290
Mono-and Di-Glycerides, NF	18.6		1.86	29
Dibutyl Sebacate, NF	18.6		1.86	29
Polysorbate 80, NF	7.3		0.73	12
Ethanol ( <i>denatured</i> )		94.4		3210
DI Water		5.6		190
Amount of coated pellets (g)		1560		

#### Example 16

[000179] An example of fast release coatings for Fast Release Formulation 20% SR + 20% pH Coating.

SR Coat Fast Release



Coating Wt gain: 20.0  
Solids %: 12

Component	mg/g	solvent ratio	%w/w	g/batch
Ethyl Cellulose, NF	57.5		5.75	83
Hydroxypropyl Cellulose, NF	14.4		1.44	21
Dibutyl Sebacate, NF	4.2		0.42	6
Magnesium Stearate, NF	6.22		6.22	90
Ethanol ( <i>denatured</i> )		95		1393
DI Water		5		73
Amount of coated pellets (g)				
		1200		

#### S100 pH Dependent Coat Fast Release

Coating Wt gain: 20%  
Solids %: 10%  
Batch size (g) 1440  
Core pellet amount (g) 1200

Component	mg/g	solvent ratio	%w/w	g/batch
Methacrylic Acid Copolymer Type-B	133.7		13.37	193
Mono-and Di-Glycerides, NF	13.4		1.34	19
Dibutyl Sebacate, NF	13.4		1.34	19
Polysorbate 80, NF	5.3		0.53	8
Ethanol ( <i>denatured</i> )		94.4		2077
DI Water		5.6		123
Amount of coated pellets (g)				
		1440		

#### Example 17

**[000180]** An example of a composition of Dextroamphetamine Sulfate, 30 mg capsules (Slow Release Formulation 1, ) with a core as described in Example 12, 25% sustained release coating weight gain, +20% delayed release (enteric) coating weight gain.

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)
		30 mg

		Quantity per unit (mg)	%
Dextroamphetamine Sulfate, USP	Active ingredient	30.00	14.59
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	106.36	51.74
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	16.76	8.15
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	4.19	2.04
Dibutyl Sebacate, NF	Film Plasticizer	1.21	0.59
Magnesium Stearate, NF	Hydrophobic Film Component	11.93	5.80
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	27.48	13.37
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	2.76	1.34
Dibutyl Sebacate, NF	Film Plasticizer	2.76	1.34
Polysorbate 80, NF	Solubilizer	1.09	0.53
Talc USP, EP		1.02	0.50
Total		205.56	100.0

## Example 18

**[000181]** An example of a composition of Dextroamphetamine Sulfate, 30 mg capsules (Slow Release Formulation 2, ) with a core as in Example 12, 25% sustained release coating weight gain, +30% delayed release (enteric) coating weight gain.

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		30 mg	
		Quantity per unit (mg)	%
Dextroamphetamine Sulfate, USP	Active ingredient	30.00	13.47
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	106.36	47.76
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	16.76	7.53
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	4.19	1.88
Dibutyl Sebacate, NF	Film Plasticizer	1.21	0.54
Magnesium Stearate, NF	Hydrophobic Film Component	11.93	5.36

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		30 mg	
		Quantity per unit (mg)	%
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	41.22	18.51
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	4.14	1.86
Dibutyl Sebacate, NF	Film Plasticizer	4.14	1.86
Polysorbate 80, NF	Solubilizer	1.64	0.74
Talc USP, EP		1.11	0.50
Total		222.7	100.0

## Example 19

**[000182]** An example of a composition of Dextroamphetamine Sulfate, 30 mg capsules (Medium Release Formulation 1) with a core as in Example 12, 20% sustained release coating weight gain, +20% delayed release (enteric) coating weight gain.

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		30 mg	
		Quantity per unit (mg)	%
Dextroamphetamine Sulfate, USP	Active ingredient	30.00	15.44
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	106.36	54.73
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	13.40	6.90
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	3.35	1.72
Dibutyl Sebacate, NF	Film Plasticizer	0.97	0.50
Magnesium Stearate, NF	Hydrophobic Film Component	9.55	4.91
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	26.38	12.03
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	2.65	1.36
Dibutyl Sebacate, NF	Film Plasticizer	2.65	1.36
Polysorbate 80, NF	Solubilizer	1.05	0.54
Talc USP, EP		0.98	0.50
Total		194.34	100.0

## Example 20

**[000183]** An example of a composition of Dextroamphetamine Sulfate, 30 mg capsules (Medium Release Formulation 2) with a core as in Example 12, 20% sustained release coating weight gain, +30% delayed release (enteric) coating weight gain.

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		30 mg	
		Quantity per unit (mg)	%
Dextroamphetamine Sulfate, USP	Active ingredient	30.00	14.03
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	106.36	49.75
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	13.40	6.27
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	3.35	1.57
Dibutyl Sebacate, NF	Film Plasticizer	0.97	0.45
Magnesium Stearate, NF	Hydrophobic Film Component	9.55	4.47
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	39.57	18.51
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	3.98	1.86
Dibutyl Sebacate, NF	Film Plasticizer	3.98	1.86
Polysorbate 80, NF	Solubilizer	1.57	0.73
Talc USP, EP		1.06	0.50
Total		213.79	100.0

## Example 21

**[000184]** An example of a composition of Dextroamphetamine Sulfate, 30 mg capsules (Fast Release Formulation) with a core as in Example 12, 20% sustained release coating weight gain, +20% delayed release (enteric) coating weight gain.

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		30 mg	
		Quantity per unit (mg)	%
Dextroamphetamine Sulfate, USP	Active ingredient	30.00	15.20

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		30 mg	
		Quantity per unit (mg)	%
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	106.36	53.90
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	11.34	5.75
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	2.84	1.44
Dibutyl Sebacate, NF	Film Plasticizer	0.82	0.42
Magnesium Stearate, NF	Hydrophobic Film Component	12.27	6.22
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	26.38	13.37
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	2.65	1.34
Dibutyl Sebacate, NF	Film Plasticizer	2.65	1.34
Polysorbate 80, NF	Solubilizer	1.05	0.53
Talc USP, EP		0.98	0.50
Total		197.34	100.0

## Example 22

**[000185]** The five formulations described in Examples 17-21 were subjected to dissolution testing as described. The dissolution data are shown in the following table.

TIME (HOURS)	FAST (446604) 20%SR, 20%EC	MEDIUM (446603) 20%SR; 30%EC	MEDIUM (446605) 20%SR; 20%EC	SLOW (446602) 25% SR; 20%EC	SLOW (446606) 25%SR; 30% EC
0.	0.0	0.0	0.0	0.0	0.0
2.	1.6	2.9	0.2	0.0	0.5
4.	2.4	5.7	0.6	0.0	1.3
6.	4.0	9.9	1.4	0.0	2.1
7.	6.6	13.1	2.5	1.1	2.7
8.	9.7	16.3	5.0	3.0	3.1
9.	15.0	19.6	11.9	7.9	3.3
10.	25.8	23.0	25.7	18.0	4.4
12.	57.7	39.1	60.6	47.6	14.4
14.	81.5	64.0	81.4	71.9	41.7
16.	91.7	79.7	90.5	85.1	66.4
20.	97.7	89.8	96.2	94.8	85.7

**[000186]** A graph of the dissolution data is shown in Fig. 16. As can be seen in the graph, the formulations provided a delayed release of from 6-10 hours followed by a sustained increasing release over the next 10 hours.

#### Example 23

**[000187]** A parallel, five-arm, open-label, single-dose, fasting study of Dextroamphetamine 30 mg capsules in healthy, non-smoking male subjects was conducted, administering the five formulations described in Examples 13-17 to 56 healthy male volunteers aged 18 to 45 years during each trial.

**[000188]** Five formulations were administered orally during the trial:

**[000189]** Treatment A: 1 Dextroamphetamine Sulfate Capsule, 30 mg, CII (20% SR, 30% ER coat, Medium Release);

**[000190]** Treatment B: 1 Dextroamphetamine Sulfate Capsule, 30 mg, CII (25% SR, 20% ER coat, Slow Release);

**[000191]** Treatment C: 1 Dextroamphetamine Sulfate Capsule, 30 mg, CII (20% SR, 20% ER coat, Fast Release),

**[000192]** Treatment D: 1 Dextroamphetamine Sulfate Capsule, 30 mg, CII (25% SR, 30% ER coat, Slow Release);

**[000193]** Treatment E: 1 Dextroamphetamine Sulfate Capsule, 30 mg, CII (20% SR, 20% ER coat, Medium Release).

**[000194]** The pharmaceuticals were administered daily at 8 AM and serum amphetamine concentrations were determined hourly for 20 hours. Using the validated method (D24 Version 00), dextroamphetamine and the internal standard, amphetamine-d5, were extracted from human plasma (200.0  $\mu$ L), with potassium ethylenediaminetetraacetic acid ( $K_2$ EDTA) as an anticoagulant, by liquid-liquid extraction, evaporation under nitrogen, and reconstitution in 200.0  $\mu$ L of mobile phase (0.05% Trifluoroacetic Acid : Acetonitrile, 80 : 20, v/v). An aliquot of this extract was injected into a High Performance Liquid Chromatography (HPLC) system, detected using an API 3000 with HSID tandem mass spectrometer, and quantitated using peak area ratio method.

**[000195]** Method sensitivity and selectivity were achieved by detecting distinct precursor to product ion mass transitions for dextroamphetamine (136.2→119.1) and the internal standard, amphetamine-d5 (141.2→124.1), at defined retention times under reverse chromatographic conditions.

**[000196]** Evaluation of the assay, using defined acceptance criteria, was carried out by the construction of an eight (8) point calibration curve (excluding zero concentration) covering the range of 0.200 ng/mL to 51.200 ng/mL for Dextroamphetamine in human plasma. The slope and intercept of the calibration curves were determined through weighted linear regression analysis ( $1/\text{conc.}^2$ ). Two calibration curves and duplicate QC samples (at three concentration levels) were analyzed along with each batch of the study samples. Peak area ratios were used to determine the concentration of the standards, quality control samples, and the unknown study samples from the calibration curves.

**[000197]** The serum concentrations are shown in Fig. 17, in which the beginning time of day is set to 9 PM. An overlay of the pharmacokinetic data of three commercial formulations, Dexedrine, Adderall XR and Vyvanse are overlaid with the data of Fig. 17 in Fig. 18.

**[000198]** As shown in the table below early exposure 0-6 hr and 0-10 hr was highest for Treatment A and this correlated with the early dissolution observed for this formulation. Exposure from 0 to  $T_{\text{max}}$  was marginally higher for Treatment A than the other treatments, but was more variable than Treatments B and C. Treatment C was higher than B but was more variable. For Treatment D the exposure 0 to  $T_{\text{max}}$  was relatively high (considering total  $\text{AUC}_{0-\text{inf}}$ ), but the Treatment D  $T_{\text{max}}$  values occurred later than the other treatments.

Treatment	AUC <sub>0-6</sub> (ng·hr/mL)		AUC <sub>0-10</sub> (ng·hr/mL)		AUC <sub>0-T<sub>max</sub></sub> (ng·hr/mL)		AUC <sub>0-inf</sub> (ng/mL)	
	Mean (N)	CV (%)	Mean (N)	CV (%)	Mean	CV (%)	Mean	CV(%)
A	16.7 (10)	29.9	63.8	23.9	286.0	60.2	991.5	42.6
B	2.1 (12)	78.8	32.9	41.2	234.6	20.6	1142.4	16.7
C	6.5 (10)	38.1	30.7	40.5	278.5	37.4	1250.3	20.7
D	1.6 (12)	44.7	7.3	41.3	266.0	50.7	869.9	27.7
E	2.1 (12)	33.3	27.3	34.0	264.2	60.2	1069.5	35.8

The mean  $T_{\text{max}}$  values for treatments A, B, C, D and E were 17.9, 16.4, 17.7, 22.6 and

17.8 hours, respectively.

**[000199]** The early exposure (0-6 and 0-10) provided by these formulations was very low relative to  $AUC_{0-inf}$  and is shown in the Table below together with  $AUC_{0-Tmax}$  in terms of percentages of the mean values of these partial exposure metrics relative to mean values of  $AUC_{0-inf}$  for each of the five treatments

Treatment	$AUC_{0-6}$	$AUC_{0-10}$	$AUC_{0-Tmax}$
A	1.7	6.4	28.8
B	0.1	2.9	20.5
C	0.5	2.5	22.3
D	0.2	0.8	30.6
E	0.2	2.6	24.7

The exposure was less than 2% for all treatments (0-6 hours) and less than 5% for the  $AUC$  (0-10 hours) except for Treatment A (6.4%).

**[000200]** Seventeen subjects experienced a total of 25 adverse events (“AEs”) during the study. The most frequent AEs are expressed as fractions, relative to the total number of AEs experienced after each treatment.

**[000201]** No AE was reported more than once after administration of Treatment A [Dextroamphetamine Sulfate Capsule, 30 mg, CII (20% SR, 30% pH coat, Medium Release)], Treatment C [Dextroamphetamine Sulfate Capsule, 30 mg, CII (20% SR, 20% pH coat, Fast Release)] and Treatment D [Dextroamphetamine Sulfate Capsule, 30 mg, CII (25% SR, 30% pH coat, Slow Release)].

**[000202]** After administration of Treatment B (Dextroamphetamine Sulfate Capsule, 30 mg, CII (25% SR, 20% pH coat, Slow Release), the most frequently AEs were headache (2/7) and somnolence (2/7).

**[000203]** After administration of Treatment E [(Dextroamphetamine Sulfate Capsule, 30 mg, CII (20% SR, 20% pH coat, Medium Release)], the most frequently AE was dry mouth (2/8).

**[000204]** No AE was reported after the end-of-study exam.

**[000205]** Five AEs were “probably” related to the study drug, and 12 AEs were “possibly” related to the study drug. All subjects who experienced AEs during this study recovered completely.



[000206] No serious adverse events (SAEs) were reported.

Example 24

**Composition of Methylphenidate, 54 mg Capsules (Slow Release Formulation, 25%SR  
Weight Gain + 30% pH Dependent Weight Gain)**

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		54 mg	
		Quantity per unit (mg)	%
Methylphenidate Hydrochloride, USP, CII	Active ingredient	54.00	13.54
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	191.45	48.00
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	30.16	7.56
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	7.54	1.89
Dibutyl Sebacate, NF	Film Plasticizer	2.18	0.55
Magnesium Stearate, NF	Hydrophobic Film Component	21.48	5.39
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	74.19	18.60
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	7.46	1.87
Dibutyl Sebacate, NF	Film Plasticizer	7.46	1.87
Polysorbate 80, NF	Solubilizer	2.95	0.74
<b>Total</b>		<b>398.87</b>	<b>100.0</b>

Example 25

**Composition of Methylphenidate, 54 mg Capsules (Slow Release Formulation, 20%SR  
Weight Gain + 20% pH Dependent Weight Gain)**

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		54 mg	
		Quantity per unit (mg)	%
Methylphenidate Hydrochloride, USP, CII	Active ingredient	54.00	15.28
Microcrystalline Cellulose, NF (Avicel PH-101)	Binder	191.45	54.16
Ethyl Cellulose, NF (Ethocel Standard 10 Premium)	Film Former	20.42	5.78
Hydroxypropyl Cellulose, NF (Klucel EF Pharm)	Film Former	5.11	1.45
Dibutyl Sebacate, NF	Film Plasticizer	1.48	0.42
Magnesium Stearate, NF	Hydrophobic Film Component	22.09	6.25

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		54 mg	
		Quantity per unit (mg)	%
Methacrylic Acid Copolymer Type-B (Eudragit S 100)	Film Former	47.48	13.43
Mono-and Di-Glycerides, NF (Imwitor 900K)	Film Plasticizer	4.77	1.35
Dibutyl Sebacate, NF	Film Plasticizer	4.77	1.35
Polysorbate 80, NF	Solubilizer	1.89	0.53
<b>Total</b>		<b>353.46</b>	<b>100.0</b>

**[000207]** All of the compositions and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the methods described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents that are chemically or physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

## CLAIMS

1. A solid, oral pharmaceutical composition comprising a plurality of particles, each comprising:
  - a core comprising a therapeutic amount of a central nervous system stimulant and at least one pharmaceutically acceptable excipient;
  - a sustained release layer enclosing the core; and
  - a delayed release layer enclosing the sustained release layer,wherein the composition provides a 4 to 12 hour period during which no more than about 10% of the central nervous system stimulant is released when the composition is placed in a simulated gastric environment.
2. The solid, oral pharmaceutical composition of claim 1, in which the core further comprises a disintegrant, osmagent, or a pore forming agent.
3. The solid, oral pharmaceutical composition of claim 1, wherein the in vitro dissolution rate of the dosage form is between 0 and 10% drug released after 8 hours, between 2 and 30% released after 10 hours, between 15 and 60% released after 12 hours and between 45% and 95% released after 15 hours, and wherein the amount of drug released each hour increases from the period between 20% released and 65% released when measured by the USP Paddle Method at 75 rpm in 750 ml aqueous solution of 0.1N HCl for two hours followed by phosphate buffered solution at pH 6.8 and  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ .
4. The solid, oral pharmaceutical composition of claim 3, wherein the in vitro dissolution rate of the dosage form is between 0 and 10% drug released after 6 hours, between 15 and 28% released after 10 hours, between 40 and 60% released after 12 hours and between 80% and 95% released after 15 hours, and wherein the amount of active ingredient released per each hour increases from the period between 20% released and 65% released, when measured by the USP Apparatus I in which the composition is placed in 700 ml aqueous solution of 0.1N HCl pH 1.1, for up to 2 hours followed by 2-6hr in sodium phosphate buffer at pH 6.0; followed by 6-20 hr in sodium phosphate buffer, pH 7.2 at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ .
5. The solid, oral pharmaceutical composition of claim 3, wherein no more than 10% of the agent is released within 6 hours and no more than 50% of the agent is released

within 12 hours when placed in aqueous solution of 0.1N HCl for two hours followed by phosphate buffered solution at pH 6.8 and  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ , and wherein, when the composition is administered to a human, a plot of plasma concentration versus time after administration exhibits a single maximum between 12 and 20 hours after administration.

6. The solid, oral pharmaceutical composition of claim 1, wherein the core comprises a substantially spherical bead.
7. The solid, oral pharmaceutical composition of claim 6, wherein the core comprises a non-pareil bead coated with a layer comprising the central nervous system stimulant and at least one pharmaceutically acceptable excipient.
8. The solid, oral pharmaceutical composition of claim 1, wherein the core comprises amphetamine, dextroamphetamine, methylphenidate, or an isomer, racemic mixture, prodrug or pharmaceutical salt of any thereof.
9. The solid, oral pharmaceutical composition of claim 8, wherein the core comprises amphetamine or a pharmaceutical salt thereof.
10. The solid, oral pharmaceutical composition of claim 8, wherein the core comprises dextroamphetamine or a pharmaceutical salt thereof.
11. The solid, oral pharmaceutical composition of claim 8, wherein the core comprises methylphenidate or a pharmaceutical salt thereof.
12. The solid, oral pharmaceutical composition of claim 8, wherein the core comprises lisdexamfetamine dimesylate or a pharmaceutical salt thereof.
13. The solid, oral pharmaceutical composition of claim 1, wherein the core comprises one or more excipients selected from polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, lactose, sucrose, microcrystalline cellulose and combinations of any thereof.
14. The solid, oral pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable excipient is microcrystalline cellulose.
15. The solid, oral pharmaceutical composition of claim 1, wherein the delayed release layer comprises a pH dependent polymer or copolymer that is insoluble in aqueous medium at pH lower than 5.0.
16. The solid, oral pharmaceutical composition of claim 1, wherein the delayed release layer comprises cellulose acetate phthalate, cellulose acetate trimaleate, hydroxyl

propyl methylcellulose phthalate, polyvinyl acetate phthalate, acrylic polymers, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, shellac, methacrylic acid copolymers, Eudragit L30D, Eudragit L100, Eudragit FS30D, Eudragit S100 or combinations of any thereof.

17. The solid, oral pharmaceutical composition of claim 1, wherein the delayed release layer comprises a plasticizer.

18. The solid, oral pharmaceutical composition of claim 17, wherein the plasticizer is dibutyl sebacate (DBS), tributyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, mineral oil, castor oil or a fixed oil.

19. The solid, oral pharmaceutical composition of claim 10, wherein the delayed release layer comprises methacrylic acid copolymer Type B.

20. The solid, oral pharmaceutical composition of claim 10, wherein the delayed release layer comprises methacrylic acid copolymer Type B, mono- and diglycerides, dibutyl sebacate and polysorbate 80.

21. The solid, oral pharmaceutical composition of claim 1, wherein the sustained release layer comprises a water-insoluble and water-permeable polymer.

22. The pharmaceutical composition of claim 21, wherein the sustained release layer further comprises a water soluble polymer.

23. The solid, oral pharmaceutical composition of claim 1, wherein the sustained release layer comprises a cellulose ether derivative, an acrylic resin, a copolymer of acrylic acid and methacrylic acid esters with quaternary ammonium groups, a copolymer of acrylic acid and methacrylic acid esters or a combination of any thereof.

24. The solid, oral pharmaceutical composition of claim 1, wherein the sustained release layer comprises ethyl cellulose, hydroxypropyl cellulose and magnesium stearate.

25. The solid, oral pharmaceutical composition of claim 2, wherein the disintegrant, osmagen or pore former is corn starch, potato starch, a pre-gelatinized starch, a modified starch, a sweetener, a clay, bentonite, microcrystalline cellulose, carboxymethylcellulose calcium, croscarmellose sodium, alginic acid, sodium alginate, cellulose polyacrilin potassium, an alginate, sodium starch glycolate, a gum, agar, guar, locust bean, karaya, pectin, tragacanth, crospovidone or low substituted hydroxypropyl cellulose.

26. The solid, oral pharmaceutical composition of claim 2, wherein the disintegrant, osmagent, or a pore forming agent is a salt, an acid, a base, a chelating agent, sodium chloride, lithium chloride, magnesium chloride, magnesium sulfate, lithium sulfate, polyol, mannitol, sulfatol, xylitol, a carbohydrate, an electrolyte, potassium chloride, sodium sulfite, calcium bicarbonate, sodium sulfate, calcium sulfate, calcium lactate, d-mannitol, urea, tartaric acid, raffinose, sucrose, alpha-d-lactose monohydrate, glucose, alpha-hydroxy acids, citric acid, ascorbic acid, or a combination of any thereof.
27. The solid, oral pharmaceutical composition of claim 1, further comprising an abuse deterrent agent.
28. The solid, oral pharmaceutical composition of claim 1, further comprising a nasal irritant.
29. The solid, oral pharmaceutical composition of claim 28, wherein the nasal irritant is a capsaicinoid or sodium lauryl sulfate.
30. A water soluble capsule containing a single dose of the solid, oral pharmaceutical composition of claim 1.
31. The water soluble capsule of claim 30, wherein the single dose is from 1 to 50 mg central nervous system stimulant.
32. The solid, oral pharmaceutical composition of claim 1, further comprising a seal between the drug containing core and the sustained release layer.
33. A method of treating a condition in a subject with a disorder or condition responsive to the administration of a central nervous system stimulant, comprising orally administering an effective amount of the solid, oral pharmaceutical composition of claim 1 to the subject.
34. The method of claim 33, wherein the effective amount is administered once a day.
35. The method of claim 33 wherein the administration of the effective dose on a once-a-day basis provides a delayed release of the central nervous system stimulant from 4 to 12 hours, followed by an increasing plasma concentration, which for a 24 hour period commencing with administration of the effective dose results in a single maximum serum concentration (C<sub>max</sub>) which occurs at least 12 hours after the administration.
36. The method of claim 35 wherein C<sub>max</sub> occurs at least 14 hours after the administration.

37. The method of claim 35 wherein C<sub>max</sub> occurs at greater than 15 hours after the administration.
38. The method of claim 33, wherein the disorder or condition is attention deficit disorder, attention deficit hyperactivity disorder, excessive daytime sleepiness, major depressive disorder, bipolar depression, negative symptoms in schizophrenia, chronic fatigue, fatigue associated with chemotherapy or binge eating disorder.
39. A solid, oral pharmaceutical composition comprising a therapeutic amount of a central nervous system stimulant wherein the composition, when orally administered to a human, provides a delayed release of the central nervous system stimulant from 4 to 12 hours and a maximum serum concentration (C<sub>max</sub>) from 10 to 16 hours after administration, and wherein a plot of the serum concentration versus time after release exhibits a single maximum.
40. The solid, oral pharmaceutical composition of claim 39, wherein no more than about 10% of the central nervous system stimulant is released within 6 hours when placed in a simulated gastric environment.
41. The solid, oral pharmaceutical composition of claim 39, wherein no more than about 10% of the central nervous system stimulant is released within 8 hours when placed in a simulated gastric environment.
42. The solid, oral pharmaceutical composition of claim 39, wherein no more than about 10% of the central nervous system stimulant is released within 10 hours when placed in a simulated gastric environment.
43. The solid, oral pharmaceutical composition of claim 39, wherein no more than about 10% of the central nervous system stimulant is released within 12 hours when placed in a simulated gastric environment.
44. The solid, oral pharmaceutical composition of claim 39, wherein the serum area under the curve at 6 hours (AUC<sub>0-6</sub>) after administration is less than about 2% of total AUC<sub>0-∞</sub>.
45. The solid, oral pharmaceutical composition of claim 39, wherein the serum area under the curve at 10 hours (AUC<sub>0-10</sub>) after administration is less than about 7% of total AUC<sub>0-∞</sub>.
46. A solid, oral pharmaceutical composition comprising:

a core comprising a therapeutic amount of a central nervous system stimulant and at least one pharmaceutically acceptable excipient;

a sustained release layer coating the core; and

a delayed release layer coating the sustained release layer,

wherein the core is substantially free of a disintegrant, osmagent, or a pore forming agent;

and further wherein when the composition is administered to a human, no more than about 10% of the central nervous system stimulant is detectable in the serum from three to twelve hours after administration and serum concentration of central nervous system agent increases from the onset of absorbance to a period of from 12 to 16 hours after administration.

47. A solid, oral pharmaceutical composition comprising a central nervous system stimulant wherein the in vitro dissolution rate of the dosage form is between 0 and 10% drug released after 8 hours, between 2 and 30% released after 10 hours, between 15 and 60% released after 12 hours and between 45% and 95% released after 15 hours, and wherein the amount of active ingredient released each hour increases from the period between 20% released and 65% released, when measured by the USP Apparatus I in which the composition is placed in 700 ml aqueous solution of 0.1N HCl pH 1.1, for up to 2 hours followed by 2-6hr in sodium phosphate buffer at pH 6.0; followed by 6-20 hr in sodium phosphate buffer, pH 7.2 at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ .

48. A method of treating a condition in a subject with a disorder or condition responsive to the administration of a central nervous system stimulant, comprising orally administering an effective amount of a solid, oral pharmaceutical composition comprising:

a core comprising a therapeutic amount of a central nervous system stimulant and at least one pharmaceutically acceptable excipient;

a sustained release layer coating the core; and

a delayed release layer coating the sustained release layer,

and further wherein when the composition is administered to a human, no more than about 10% of the central nervous system stimulant is detectable in the serum from four to twelve hours after administration.



49. The method of claim 48, wherein the disorder or condition is attention deficit disorder, attention deficit hyperactivity disorder, excessive daytime sleepiness, major depressive disorder, bipolar depression, negative symptoms in schizophrenia, chronic fatigue, fatigue associated with chemotherapy or binge eating disorder.