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°C ± 0.5°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°C ± 0.5°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°C ± 0.5°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 pyrollidone, 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 trimaletate, 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 (Cmax) which occurs at least 12 hours after the administration.

36. The method of claim 35 wherein Cmax occurs at least 14 hours after the administration.

37. The method of claim 35 wherein Cmax 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 (Cmax) 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_{0-6}) after administration is less than about 2% of total $AUC_{0-\infty}$.

45. The solid, oral pharmaceutical composition of claim 39, wherein the serum area under the curve at 10 hours (AUC_{0-10}) after administration is less than about 7% of total $AUC_{0-\infty}$.

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°C ± 0.5°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.

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, 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°C ± 0.5°C.

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 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°C ± 0.5°C.

4. The solid, oral pharmaceutical composition of any of claims 1-3, 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°C ± 0.5°C, and wherein, when the composition is administered to a human, a plot of plasma concentration versus time after administration exhibits a maximum between 12 and 20 hours after administration.

5. The solid, oral pharmaceutical composition of any of claims 1-4, wherein the core comprises amphetamine, dextroamphetamine, methylphenidate, or an isomer, racemic mixture, prodrug or pharmaceutical salt of any thereof.

6. The solid, oral pharmaceutical composition of any of claims 1-5, wherein the core comprises one or more excipients selected from polyvinyl pyrollidone, hydroxypropylmethyl cellulose, lactose, sucrose, microcrystalline cellulose and combinations of any thereof.

7. The solid, oral pharmaceutical composition of claim 1-6, wherein the delayed release layer comprises cellulose acetate phthalate, cellulose acetate trimaletate, 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 a combination of any thereof.

8. The solid, oral pharmaceutical composition of any of claims 1-7, wherein the plasticizer is dibutyl sebacate (DBS), tributyl citrate, acetyl tributyl citrate, acetyl triethyl citrate, mineral oil, castor oil or a fixed oil.

9. The solid, oral pharmaceutical composition of any of claims 1-8, wherein the delayed release layer comprises methacrylic acid copolymer Type B, mono- and diglycerides, dibutyl sebacate and polysorbate 80.

10. The solid, oral pharmaceutical composition of any of claims 1-9, wherein the sustained release layer comprises a water-insoluble and water-permeable polymer and a water soluble polymer.

11. The solid, oral pharmaceutical composition of any of claims 1-10, 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.

12. The solid, oral pharmaceutical composition of any of claims 1-11, wherein the sustained release layer comprises ethyl cellulose, hydroxypropyl cellulose and magnesium stearate.

13. The solid, oral pharmaceutical composition of any of claims 1-12 contained in a water soluble capsule providing a single dose of the solid, oral pharmaceutical composition.

14. 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 (Cmax) from 10 to 16 hours after administration.

15. The solid, oral pharmaceutical composition of claim 14, wherein the serum area under the curve at 6 hours (AUC_{0-6}) after administration is less than about 2% of total $AUC_{0-\infty}$

16. The solid, oral pharmaceutical composition of claim 14 or 15, wherein the serum area under the curve at 10 hours (AUC_{0-10}) after administration is less than about 7% of total $AUC_{0-\infty}$

17. Use of a composition of any preceding claim for manufacture of a medicament for treatment of a condition in a subject with a disorder or condition responsive to the administration of a central nervous system stimulant.

18. Use of claim 17, 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.