CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an active agent selected from R-(+)-N-propargyl-1-aminoindan (rasagiline), S-(-)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof, formulated for extended release of said active agent.

2. The pharmaceutical composition of claim 1, wherein said pharmaceutically acceptable salt is selected from the mesylate salt, the esylate salt, the tosylate salt, the sulfate salt, the sulfonate salt, the phosphate salt, the carboxylate salt, the maleate salt, the fumarate salt, the tartrate salt, the benzoate salt, the acetate salt, the hydrochloride salt, or the hydrobromide salt of either R-(+)-N-propargyl-1-aminoindan or S(-)-N-propargyl-1-aminoindan, preferably the mesylate salt of R-(+)-N-propargyl-1-aminoindan.

3. The pharmaceutical composition of claim 1, formulated to provide continuous sustained release, pulsatile release, or multi-phase release of said active agent.

4. The pharmaceutical composition of claim 3, for oral administration.

5. The pharmaceutical composition of claim 4, in the form of a monolithic matrix; a tablet, preferably a bi- or multi-layered tablet, matrix tablet, disintegrating tablet, dissolving tablet, or chewable tablet; a capsule or sachet, preferably filled with granules, grains, beads, or pellets; or a depot system based on a biodegradable polymer such as poly(D,L-lactide) (PLA), polyglycolide (PGA), and poly(D,L-lactide-co-glycolide) (PLGA).

6. The pharmaceutical composition of any one of claims 1 to 5, having the following dissolution profile in USP Apparatus 1 (basket) at 50-150 rpm in pH value of up to 7.4 at 37°C:

Time (hours)	Average % active agent released	Preferred average % active agent released
2	<30	<30
6	30-70	30-60
12	50-85	50-70
24	>70	>70

7. The pharmaceutical composition of claim 6, wherein said active agent is R-(+)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof.

8. An extended-release pellet comprising:

(i) an inert pellet core;

(ii) a drug layer coating said pellet core, said drug layer comprising an active agent selected from R-(+)-N-propargyl-1-aminoindan, S-(-)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof, optionally suitably admixed with a binder and/or a film-former polymer, and further optionally admixed with a glidant;

(iii) optionally an isolating/protecting sub-coating layer coating said drug layer; and

(iv) an extended-release coating layer coating said sub-coating layer, if present, or said drug layer, wherein said extended-release coating layer comprises:

(a) at least one pH-independent polymer and optionally a pore-forming agent, wherein the extended-release pellet has a pH-independent *in vitro* release characteristic;

(b) a pH-independent polymer, a hydrophilic release modulator polymer, and optionally a hydrophobic or hydrophilic plasticizer, and/or a glidant; or

(c) a mixture of a pH-dependent enteric-coating polymer and a pH-independent polymer, wherein the extended-release pellet has a close to zero order *in vitro* release characteristic at pH value of up to pH 7.4.

9. The extended-release pellet of claim 8, wherein said sub-coating layer comprises a film-former polymer and optionally a glidant.

10. The extended-release pellet of claim 8 or 9, wherein:

(i) said binder is a polyvinyl pyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), microcrystalline cellulose, or a combination thereof;

(ii) said film-former polymer is PVP, HPMC, HPC, microcrystalline cellulose, or a combination thereof;

(iii) said glidant is talc, colloidal silicon dioxide, glyceryl monostearate, or a combination thereof;

(iv) said pH-independent polymer is ethyl cellulose, Surelease®, Eudragit® RL, Eudragit® RS, Eudragit® NE, or a combination thereof;

(v) said pH-dependent enteric-coating polymer is Eudragit® S, Eudragit® L 55, Kollicoat®, hydroxypropylmethyl cellulose phthalate (HPMCP), alginates, carboxymethylcellulose, or a combination thereof;

(vi) said pore-forming agent is PVP, PEG, HPMC, HPC, methylcellulose, 1,2-propylene glycol, lactose, sucrose, talc, or a combination thereof;

(vii) said hydrophilic release modulator polymer is HPMC, HPC, PVP, PEG, or a combination thereof; and

(viii) said plasticizer is dibutyl sebacate; dibutyl phthalate; citrate esters such as triethylcitrate and triacetin; propylene glycol; low molecular weight poly(alkylene oxides) such as PEG, poly(propylene glycols), and poly(ethylene/propylene glycols); or a combination thereof.

11. The extended-release pellet of any one of claims 8 to 10, comprising:

(i) an inert pellet core; a drug layer comprising said active agent admixed with PVP as a film-former polymer/binder and with talc extra fine as a glidant; and an extended-release (ER) coating layer comprising ethylcellulose as a pH-independent polymer, and PEG as a pore-forming agent, wherein the amount of said film-former polymer/binder is up to 90% by weight of the entire drug layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said glidant is up to 30% by weight of the entire drug layer, or from 0.1% to 10% by weight of the entire pellet; the amount of said pH-independent polymer is from 50% to 90% by weight of the entire ER coating layer, or from 10% to 30% by weight of the entire pellet; and the amount of said pore-forming agent is from 1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10% by weight of the entire pellet; or

(ii) an inert pellet core; a drug layer comprising said active agent admixed with PVP as a film-former polymer/binder and with talc extra fine as a glidant; an isolating/protecting sub-coating layer comprising PVP as a film-former polymer; and an ER coating layer comprising ethylcellulose as a pH-independent polymer, PEG as a pore-forming agent, and talc extra fine as a glidant, wherein the amount of said film-former

polymer/binder in said drug layer is up to 90% by weight of the entire drug layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said glidant in said drug layer is up to 30% by weight of the entire drug layer, or from 0.1% to 10% by weight of the entire pellet; the amount of said film-former polymer in said sub-coating layer is up to 100% by weight of the entire sub-coating layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said pH-independent polymer is from 50% to 90% by weight of the entire ER coating layer, or from 10% to 30% by weight of the entire pellet; the amount of said pore-forming agent is from 1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10% by weight of the entire pellet; and the amount of said glidant in said ER coating layer is from 0.1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10%, by weight of the entire pellet.

12. The extended-release pellet of any one of claims 8 to 11, wherein said active agent is R-(+)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof.

13. An oral pharmaceutical composition comprising extended-release pellets according to any one of claims 8 to 12.

14. The oral pharmaceutical composition of claim 13, wherein said extended-release pellets are blended with one or more suitable excipients and either filled into a capsule or compressed into a tablet.

15. The pharmaceutical composition of any one of claims 1 to 7, 13 or 14, for use in treatment of a neurodegenerative disease or an injury to the nervous system.

16. The pharmaceutical composition of claim 15, wherein said neurodegenerative disease is Parkinson's disease or Alzheimer's disease, and said injury to the nervous system is acute brain damage, such as stroke, or traumatic brain injury.

17. A method for preparing an extended release formulation comprising extended release pellets each according to claim 8 , said method comprising the steps of:

(i) dissolving said active agent, optionally suitably admixed with said binder and/or said glidant, in a suitable solvent system to prepare a uniform suspension;

(ii) applying a coat of the suspension obtained in (i) to inert pellets such as inert nonpareil seeds;

(iii) optionally coating the active agent-loaded pellets obtained in (ii) with said insulating/protecting sub-coating layer;

(iv) coating the pellets obtained in (ii) or (iii) with said extended-release coating layer which enables an extended release of said active agent thereby obtaining said extended release formulation; and

(v) optionally blending the coated pellets obtained in (iv) with a suitable excipient.

18. The method of claim 17, wherein said extended release formulation is either filled into capsules or compressed into tablets.

CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an active agent selected from R-(+)-N-propargyl-1-aminoindan (rasagiline), S-(-)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof, formulated for extended release of said active agent.

2. The pharmaceutical composition of claim 1, wherein said pharmaceutically acceptable salt is selected from the mesylate salt, the esylate salt, the tosylate salt, the sulfate salt, the sulfonate salt, the phosphate salt, the carboxylate salt, the maleate salt, the fumarate salt, the tartrate salt, the benzoate salt, the acetate salt, the hydrochloride salt, or the hydrobromide salt of either R-(+)-N-propargyl-1-aminoindan or S(-)-N-propargyl-1-aminoindan, preferably the mesylate salt of R-(+)-N-propargyl-1-aminoindan.

3. The pharmaceutical composition of claim 1, formulated to provide continuous sustained release, pulsatile release, or multi-phase release of said active agent.

4. The pharmaceutical composition of claim 1, for oral administration.

5. The pharmaceutical composition of claim 4, in the form of a monolithic matrix; a tablet, preferably a bi- or multi-layered tablet, matrix tablet, disintegrating tablet, dissolving tablet, or chewable tablet; a capsule or sachet, preferably filled with granules, grains, beads, or pellets; or a depot system based on a biodegradable polymer such as poly(D,L-lactide) (PLA), polyglycolide (PGA), and poly(D,L-lactide-co-glycolide) (PLGA).

6. The pharmaceutical composition of claim 4, comprising extended-release pellets each comprising:

(i) an inert pellet core;

(ii) a drug layer coating said pellet core, said drug layer comprising said active agent optionally suitably admixed with a binder and/or a film-former polymer, and further optionally admixed with a glidant;

(iii) optionally an isolating/protecting sub-coating layer coating said drug layer; and

(iv) an extended-release coating layer coating said sub-coating layer, if present, or said drug layer, wherein said extended-release coating layer comprises:

(a) at least one pH-independent polymer and optionally a pore-forming agent, wherein the extended-release pellet has a pH-independent *in vitro* release characteristic;

(b) a pH-independent polymer, a hydrophilic release modulator polymer, and optionally a hydrophobic or hydrophilic plasticizer, and/or a glidant; or

(c) a mixture of a pH-dependent enteric-coating polymer and a pH-independent polymer, wherein the extended-release pellet has a close to zero order *in vitro* release characteristic at pH value of up to pH 7.4.

7. The pharmaceutical composition of claim 6, wherein said sub-coating layer comprises a film-former polymer and optionally a glidant.

8. The pharmaceutical composition of claim 6 or 7, wherein:

(i) said binder is a polyvinyl pyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), microcrystalline cellulose, or a combination thereof;

(ii) said film-former polymer is PVP, HPMC, HPC, microcrystalline cellulose, or a combination thereof;

(iii) said glidant is talc, colloidal silicon dioxide, glyceryl monostearate, or a combination thereof;

(iv) said pH-independent polymer is ethyl cellulose, Surelease®, Eudragit® RL, Eudragit® RS, Eudragit® NE, or a combination thereof;

(v) said pH-dependent enteric-coating polymer is Eudragit® S, Eudragit® L 55, Kollicoat®, hydroxypropylmethyl cellulose phthalate (HPMCP), alginates, carboxymethylcellulose, or a combination thereof;

(vi) said pore-forming agent is PVP, PEG, HPMC, HPC, methylcellulose, 1,2-propylene glycol, lactose, sucrose, talc, or a combination thereof;

(vii) said hydrophilic release modulator polymer is HPMC, HPC, PVP, PEG, or a combination thereof; and

(viii) said plasticizer is dibutyl sebacate; dibutyl phthalate; citrate esters such as triethylcitrate and triacetin; propylene glycol; low molecular weight poly(alkylene oxides) such as PEG, poly(propylene glycols), and poly(ethylene/propylene glycols); or a combination thereof.

9. The pharmaceutical composition of any one of claims 6 to 8, comprising:

(i) an inert pellet core; a drug layer comprising said active agent admixed with PVP as a film-former polymer/binder and with talc extra fine as a glidant; and an extended-release (ER) coating layer comprising ethylcellulose as a pH-independent polymer, and PEG as a pore-forming agent, wherein the amount of said film-former polymer/binder is up to 90% by weight of the entire drug layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said glidant is up to 30% by weight of the entire drug layer, or from 0.1% to 10% by weight of the entire pellet; the amount of said pH-independent polymer is from 50% to 90% by weight of the entire ER coating layer, or from 10% to 30% by weight of the entire pellet; and the amount of said pore-forming agent is from 1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10% by weight of the entire pellet; or

(ii) an inert pellet core; a drug layer comprising said active agent admixed with PVP as a film-former polymer/binder and with talc extra fine as a glidant; an isolating/protecting sub-coating layer comprising PVP as a film-former polymer; and an ER coating layer comprising ethylcellulose as a pH-independent polymer, PEG as a pore-forming agent, and talc extra fine as a glidant, wherein the amount of said film-former polymer/binder in said drug layer is up to 90% by weight of the entire drug layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said glidant in said drug layer is up to 30% by weight of the entire drug layer, or from 0.1% to 10% by weight of the entire pellet; the amount of said film-former polymer in said sub-coating layer is up to 100% by weight of the entire sub-coating layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said pH-independent polymer is from 50% to 90% by weight of the entire ER coating layer, or from 10% to 30% by weight of the entire pellet; the amount of said pore-

forming agent is from 1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10% by weight of the entire pellet; and the amount of said glidant in said ER coating layer is from 0.1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10%, by weight of the entire pellet.

10. The pharmaceutical composition of claim 6, wherein said extended-release pellets are blended with one or more suitable excipients and either filled into a capsule or compressed into a tablet.

11. The pharmaceutical composition of any one of claims 1 to 10, having the following dissolution profile in USP Apparatus 1 (basket) at 50-150 rpm in pH value of up to 7.4 at 37°C:

Time (hours)	Average % active agent released	Preferred average % active agent released
2	<30	<30
6	30-70	30-60
12	50-85	50-70
24	>70	>70

12. The pharmaceutical composition of claim 11, wherein said active agent is R-(+)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof.

13. An extended-release pellet comprising:

(i) an inert pellet core;

(ii) a drug layer coating said pellet core, said drug layer comprising an active agent selected from R-(+)-N-propargyl-1-aminoindan, S-(-)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof, optionally suitably admixed with a binder and/or a film-former polymer, and further optionally admixed with a glidant;

(iii) optionally an isolating/protecting sub-coating layer coating said drug layer; and

(iv) an extended-release coating layer coating said sub-coating layer, if present, or said drug layer, wherein said extended-release coating layer comprises:

(a) at least one pH-independent polymer and optionally a pore-forming agent, wherein the extended-release pellet has a pH-independent *in vitro* release characteristic;

(b) a pH-independent polymer, a hydrophilic release modulator polymer, and optionally a hydrophobic or hydrophilic plasticizer, and/or a glidant; or

(c) a mixture of a pH-dependent enteric-coating polymer and a pH-independent polymer, wherein the extended-release pellet has a close to zero order *in vitro* release characteristic at pH value of up to pH 7.4.

14. The extended-release pellet of claim 13, wherein said sub-coating layer comprises a film-former polymer and optionally a glidant.

15. The extended-release pellet of claim 13 or 14, wherein:

(i) said binder is a polyvinyl pyrrolidone (PVP), hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), microcrystalline cellulose, or a combination thereof;

(ii) said film-former polymer is PVP, HPMC, HPC, microcrystalline cellulose, or a combination thereof;

(iii) said glidant is talc, colloidal silicon dioxide, glyceryl monostearate, or a combination thereof;

(iv) said pH-independent polymer is ethyl cellulose, Surelease®, Eudragit® RL, Eudragit® RS, Eudragit® NE, or a combination thereof;

(v) said pH-dependent enteric-coating polymer is Eudragit® S, Eudragit® L 55, Kollicoat®, hydroxypropylmethyl cellulose phthalate (HPMCP), alginates, carboxymethylcellulose, or a combination thereof;

(vi) said pore-forming agent is PVP, PEG, HPMC, HPC, methylcellulose, 1,2-propylene glycol, lactose, sucrose, talc, or a combination thereof;

(vii) said hydrophilic release modulator polymer is HPMC, HPC, PVP, PEG, or a combination thereof; and

(viii) said plasticizer is dibutyl sebacate; dibutyl phthalate; citrate esters such as triethylcitrate and triacetin; propylene glycol; low molecular weight poly(alkylene oxides) such as PEG, poly(propylene glycols), and poly(ethylene/propylene glycols); or a combination thereof.

16. The extended-release pellet of any one of claims 13 to 16, comprising:

(ix) an inert pellet core; a drug layer comprising said active agent admixed with PVP as a film-former polymer/binder and with talc extra fine as a glidant; and an extended-release (ER) coating layer comprising ethylcellulose as a pH-independent polymer, and PEG as a pore-forming agent, wherein the amount of said film-former polymer/binder is up to 90% by weight of the entire drug layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said glidant is up to 30% by weight of the entire drug layer, or from 0.1% to 10% by weight of the entire pellet; the amount of said pH-independent polymer is from 50% to 90% by weight of the entire ER coating layer, or from 10% to 30% by weight of the entire pellet; and the amount of said pore-forming agent is from 1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10% by weight of the entire pellet; or

(x) an inert pellet core; a drug layer comprising said active agent admixed with PVP as a film-former polymer/binder and with talc extra fine as a glidant; an isolating/protecting sub-coating layer comprising PVP as a film-former polymer; and an ER coating layer comprising ethylcellulose as a pH-independent polymer, PEG as a pore-forming agent, and talc extra fine as a glidant, wherein the amount of said film-former polymer/binder in said drug layer is up to 90% by weight of the entire drug layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said glidant in said drug layer is up to 30% by weight of the entire drug layer, or from 0.1% to 10% by weight of the entire pellet; the amount of said film-former polymer in said sub-coating layer is up to 100% by weight of the entire sub-coating layer, or from 0.5% to 20% by weight of the entire pellet; the amount of said pH-independent polymer is from 50% to 90% by weight of the entire ER coating layer, or from 10% to 30% by weight of the entire pellet; the amount of said pore-forming agent is from 1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10% by weight of the entire pellet; and the amount of said glidant in said ER coating layer is from 0.1% to 20% by weight of the entire ER coating layer, or from 0.1% to 10%, by weight of the entire pellet.

17. The extended-release pellet of any one of claims 13 to 16, wherein said active agent is R-(+)-N-propargyl-1-aminoindan, or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition of any one of claims 1 to 12, for use in treatment of a neurodegenerative disease or an injury to the nervous system.

19. The pharmaceutical composition of claim 18, wherein said neurodegenerative disease is Parkinson's disease or Alzheimer's disease, and said injury to the nervous system is acute brain damage, such as stroke, or traumatic brain injury.

20. A method for preparing an extended release formulation comprising extended release pellets each according to claim 13 , said method comprising the steps of:

(i) dissolving said active agent, optionally suitably admixed with said binder and/or said glidant, in a suitable solvent system to prepare a uniform suspension;

(ii) applying a coat of the suspension obtained in (i) to inert pellets such as inert nonpareil seeds;

(iii) optionally coating the active agent-loaded pellets obtained in (ii) with said insulating/protecting sub-coating layer;

(iv) coating the pellets obtained in (ii) or (iii) with said extended-release coating layer which enables an extended release of said active agent thereby obtaining said extended release formulation; and

(v) optionally blending the coated pellets obtained in (iv) with a suitable excipient.

21. The method of claim 20, wherein said extended release formulation is either filled into capsules or compressed into tablets.