What is claimed is:

1. Use of an LD prodrug, or a salt thereof, in the manufacture of a medicament for treating Parkinson's disease in a subject by subcutaneously infusing into the subject an LD prodrug solution of said said LD prodrug, or a salt thereof, at such a rate that:

(a) the circulating plasma concentration of said LD prodrug during said infusion does not exceed 100 ng/mL; and

(b) a circulating plasma LD concentration greater than 400 ng/mL is continuously maintained for a period of at least 8 hours during said infusion.

2. The use according to claim 1, wherein during said infusion the circulating LD plasma concentration varies by less than +/- 20% from its mean for a period of at least 1 hour.

3. A pharmaceutical composition comprising an aqueous LD prodrug solution, wherein said LD prodrug solution comprises a sterile aqueous solution containing about 0.3 M to 4.0 M LDEE hydrochloride salt and having a pH of from 1.0 to 3.5.

4. A container comprising a material that is substantially impermeable to oxygen, said container containing a reconstitutable solid comprising an LD prodrug, or a salt thereof, wherein said container is substantially free of oxygen and wherein said reconstitutable solid, when reconstituted, is suitable for subcutaneous infusion.

5. A pharmaceutical composition comprising an aqueous LD prodrug solution containing greater than 0.3 M LD prodrug, or a salt thereof, wherein said pharmaceutical composition is substantially free of precipitated solid LD when stored at 5 ± 3 °C for a period of 6 months, or at about 37 °C for a period of 24 hours, or when thawed after being stored frozen for at least 3 months.

6. The pharmaceutical composition of claim 5, wherein said pharmaceutical composition comprises a container, said container comprising a material that is substantially impermeable to oxygen and containing said aqueous liquid, wherein said container is substantially free of oxygen and wherein said aqueous liquid is suitable for subcutaneous infusion.

7. The pharmaceutical composition of claim 5 or 6, wherein said LD prodrug solution has a pH of from 4.0 - 6.0 or 4.0 ± 0.5.

8. The pharmaceutical composition of any of claims 5-7, wherein said LD prodrug is LDEE, LDME, or a salt thereof.

9. The pharmaceutical composition of claim 8, wherein said LD prodrug is a hydrochloride salt.

10. The pharmaceutical composition of any of claims 5-9, wherein said LD prodrug solution comprises a buffer comprising citrate, succinate, pyrophosphate, or phosphate.

11. The pharmaceutical composition of any of claims 5-10, wherein said pharmaceutical composition is substantially free of oxygen.

12. The pharmaceutical composition of any of claims 5-11, wherein said pharmaceutical composition is supersaturated in LD.

13. The pharmaceutical composition of any of claims 5-12, wherein the solubility of LD in said LD prodrug solution is at least 5 g per liter at about 25°C.

14. Use of a pharmaceutical composition of any of claims 5-13 in the manufacture of a medicament for treating Parkinson's disease in a subject by subcutaneously infusing into said subject said pharmaceutical composition in an amount sufficient to treat Parkinson's disease.

15. The use according to claims 1, 2 or 14, wherein said LD prodrug is subcutaneously infused at two or more infusion sites per day.

16. The use according to claims 1, 2, 14 or 15, wherein said LD prodrug is subcutaneously infused intermittently at one or more infusion sites.

17. Use of a pharmaceutical composition of any of claims 5-13 in the manufacture of a medicament for treating Parkinson's disease in a subject by administering to said subject said pharmaceutical composition in an amount sufficient to treat Parkinson's disease, wherein said pharmaceutical composition is administered intragastrically, intraduodenally or intrajejunally.

18. An ambulatory infusion pump system for the treatment of Parkinson's disease comprising:

(i) a pharmaceutical composition of any of claims 5-13 in a drug reservoir; and

(ii) at least one cannula or needle in fluid communication with the drug reservoir for infusing said pharmaceutical composition into a subject.

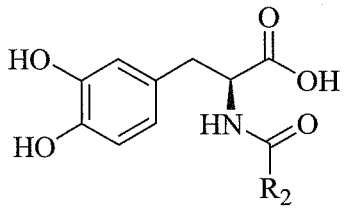
CLAIMS

1. An aqueous, infusible pharmaceutical composition comprising a fluid containing 0.5-4.0 M LD prodrug, or a salt thereof, wherein said fluid is supersaturated in LD.

2. An aqueous, infusible pharmaceutical composition comprising 0.5-4 M LD prodrug, or a salt thereof, and either (a) greater than 0.05 M carbidopa prodrug, or a salt thereof, or (b) carbidopa.

3. A pharmaceutical composition comprising an LD prodrug selected from:

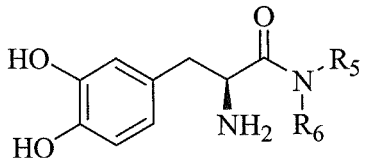
(a) formula (II)



(II),

or a salt thereof, wherein R_2 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, and C_{1-7} heteroalkyl; or wherein R_2 is CH_2CH_3, $CH(OH)CH_3$, CH_2CH_2COOH, $CH_2CH_2CH_3$, benzenepropenyl, phenyl, or $(CHOH)_4CH_2OH$, or a salt thereof;

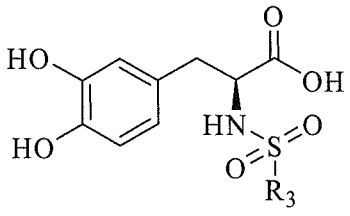
(b) formula (III)



(III),

or a salt thereof, wherein each of R_5 and R_6 is, independently, selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, and C_{1-7} heteroalkyl; or wherein R_5 is H or CH_3, and R_6 is CH_3, CH_2CH_3, $CH_2CH_2CH_3$, benzyl, 2-deoxy-2-glucosyl, or $CH_2CH_2NH_2$, or a salt thereof; or

(c) formula (IV)



(IV),

or a salt thereof, wherein R_3 is selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, and C_{1-7} heteroalkyl; or wherein R_3 is CH_3 or 4-methylbenzyl, or a salt thereof.

4. A pharmaceutical composition comprising a liquid salt of an LD prodrug, said pharmaceutical composition comprising one or more of the following: (a) levodopa methyl ester; (b) an LDA; and (c) an LDE, wherein said liquid salt is not levodopa ethyl ester oleate, levodopa ethyl ester ricinoleate, levodopa ethyl ester palmitate, or levodopa ethyl ester valerate,
optionally, wherein pharmaceutical composition further comprises a non-toxic organic solvent, said non-toxic organic solvent optionally comprising a lipid, a triglyceride, a cholesterol ester, sesame oil, castor oil, cottonseed oil, an edible oil, alcohol, ethanol, glycerol, propylene glycol, N-methyl pyrrolidone, or a mixture thereof.

5. The pharmaceutical composition of any of claims 1-4, wherein said composition is aqueous and comprises greater than 10% water.

6. The pharmaceutical composition of any of claims 1-5, comprising an LD prodrug dissolved in a solution.

7. The pharmaceutical composition of any of claims 1-5, comprising an LD prodrug suspended in a solution.

8. The pharmaceutical composition of any of claims 1-5, comprising a fatty acid salt of an LD prodrug.

9. The pharmaceutical composition of any of claims 1-4, comprising water and an organic solvent, wherein said water and organic solvent form (i) a single phase, or (ii) two or more phases.

10. The pharmaceutical composition of claim 9, wherein said water and said organic solvent form two or more phases, and comprising one or more of the following: (i) an emulsion, (ii) liposomes, and (iii) at least one of said phases is supersaturated in LD.

11. The pharmaceutical composition of any of claims 1-10, wherein said pharmaceutical composition remains substantially free of visibly precipitated LD, and
optionally, wherein said pharmaceutical composition is stored at 5 ± 3 °C for a period of 3, 6, or 12 months, and optionally and is subsequently kept at about 37°C for 24 hours.

12. The pharmaceutical composition of any of claims 1-11, further comprising one or more of the following excipients: (i) a viscosity enhancing agent such that the viscosity of said infusible pharmaceutical composition is >50 cP, or (ii) a crystal growth inhibitor.

13. The pharmaceutical composition of any of claims 1-12, wherein said LD prodrug is selected from LDAs, LDEs, LDCs, LDSs, LDME and LDEE, and salts thereof.

14. A container substantially impermeable to oxygen comprising the pharmaceutical composition of any one of claims 1-13, wherein said pharmaceutical composition is suitable for intragastric infusion.

15. Use of a fluid pharmaceutical composition selected from (i) any one of claims 1-13, and (ii) a fluid infusible pharmaceutical composition comprising levodopa ethyl ester oleate, levodopa ethyl ester ricinoleate, levodopa ethyl ester palmitate, and levodopa ethyl ester valerate, in an amount sufficient to treat Parkinson's disease, in the manufacture of a medicament for treating Parkinson's disease in a subject; wherein said medicament is to be infused into said subject, and
wherein (i) said infusing is continuous or intermittently less than or equal to about every 30 minutes, (ii) said fluid is infused at an average flow rate of less than or equal to about 1.0 mL/hour, and (iii) said fluid passes into the stomach of said subject;
optionally, wherein 2.5 – 10.0 millimoles of LD prodrug are infused in a fluid volume of less than about 7.5 mL, 5 mL, 4 mL or 3 mL within a 24 hour period.

16. A method for preparing an infusible LD prodrug fluid of any of claims 1-13 comprising the steps of:
(a) providing a fluid of pH of 1.0 – 3.5 comprising LD prodrug;

(b) raising the pH of said fluid to 4.0 – 6.0 to form an intragastrically infusible pharmaceutical composition; and

(c) within 48 hours of performing step (b), infusing at least a portion of said pharmaceutical composition into said subject in an amount sufficient to treat Parkinson's disease.

17. Use of an intragastrically infusible pharmaceutical composition comprising LD prodrug in a fluid in the manufacture of a medicament for treating Parkinson's disease in a subject, said medicament comprising:

(a) a first container comprising a fluid; and

(b) a second container comprising a dry, reconstitutable solid LD prodrug, optionally wherein said second container is substantially impermeable to oxygen and water vapor;

wherein the contents of the first container is to be combined with the contents of the second container to form an intragastrically infusible pharmaceutical composition comprising 0.5-4 M LD prodrug, wherein said solid fully dissolves in said fluid in less than 5 minutes at 25 °C; and

wherein said pharmaceutical composition is to be infused such that: (i) said fluid passes into the stomach of said subject, (ii) 2.5 – 10.0 millimoles of said LD prodrug are infused within a 24 hour period, (iii) said infusing is continuous or intermittently less than or equal to about every 30 minutes, (iv) said fluid is infused at an average flow rate of less than or equal to about 1.0 mL/hour (v) said fluid is maintained at about 37 °C while said fluid is being infused; and

optionally, wherein <5% of the prodrug is oxidized and/or hydrolyzed during said infusion.

18. Use of an infusible pharmaceutical composition comprising LD prodrug in the manufacture of a medicament for treating Parkinson's disease in a subject, said medicament comprising:

an ambulatory pump configured for infusion of said infusible pharmaceutical composition, such that said infusible pharmaceutical composition passes into the stomach of said subject; wherein

2.5 – 10.0 millimoles per day of said LD prodrug, in a fluid volume of less than about 10 mL per day is to be infused into the subject, using said pump, such that said LD prodrug passes into the stomach of said subject,

wherein (i) said infusing is continuous or intermittently less than or equal to about every 30 minutes, and (ii) said fluid is infused at an average flow rate of less than or equal to about 1.0 mL/hour, and

wherein said infusible pharmaceutical composition is a non-aqueous fluid containing 0.5-4.0 M LD prodrug,

optionally, wherein <5% of the prodrug is oxidized and/or hydrolyzed during said infusion,

optionally, wherein said non-aqueous fluid comprises a lipid, a triglyceride, a cholesterol ester, sesame oil, castor oil, cottonseed oil, an edible oil, alcohol, ethanol, glycerol, propylene glycol, N-methyl pyrrolidone, or a mixture thereof,

optionally, wherein said ambulatory pump comprises a container for holding said infusible pharmaceutical composition, wherein said container is substantially impermeable to oxygen, and

optionally, wherein said non-aqueous fluid comprises less than 10%, 5%, 3%, 2%, 1.5%, 1%, 0.5%, or less than 0.1% (w/w) water.

19. The use of claim 17 or 18, wherein 2.5 – 10.0 millimoles of said LD prodrug are infused in a fluid volume of less than about 7.5 mL, 5 mL, 4 mL or 3 mL within a 24 hour period; or wherein said pharmaceutical composition remains substantially free of visibly precipitated LD.

20. The use of any of claims 16-19, wherein said treating comprises treating one or more of: a motor complication, a non-motor complication, tremor, akinesia, bradykinesia, dyskinesia, dystonia, cognitive impairment, and disordered sleep.