with an inner intestinal/jejunal tube. Each 1 ml of Duodopa® contains 20 mg levodopa and 5 mg carbidopa monohydrate. Despite the current commercial success of DuoDopa®, the product is subject to limitations in product preparation, including (1) risk of sedimentation of drug particles during storage and administration, (2) chemical instability of carbidopa, which leads to hydrazine formation.

[0006] Accordingly, there is a continuing need for improved formulations and methods that can provide continuous and consistent dopamine levels in the brain to effectively treat movement disorders such as Parkinson's disease. The present disclosure provides such improved formulations and methods.

SUMMARY

[0007] Disclosed is a pharmaceutical composition comprising a levodopa active agent and a carbidopa active agent for intraduodenal administration wherein the levodopa active agent is provided in an amount of about 4 weight/weight percent (w/w%) of the composition and carbidopa (*e.g.*, carbidopa monohydrate) is provided in an amount of about 1 weight/weight percent of the composition wherein the levodopa and carbidopa are suspended in an aqueous carrier. The pharmaceutical composition has a desired viscosity suitable for storage under refrigerated conditions and/or delivery (*e.g.*, delivered via a pump) at room temperature (*e.g.*, ~20°C to ~25°C).

[0007a] In one aspect, the present disclosure relates to a pharmaceutical composition for intraduodenal administration comprising:

(a) a levodopa active agent in an amount of 4.0 weight /weight percent of the total composition;

(b) a carbidopa monohydrate active agent in an amount of 1.0 weight/weight percent of the total composition;

(c) one or more polymer-based suspending agents selected from the group consisting of hydroxypropylcellulose, hydroxymethylcellulose, and sodium carboxymethyl cellulose; and

(d) water,

wherein the pharmaceutical composition has:

(i) a high shear viscosity of no more than 4500 cps at 22°C and 24.1 s^{-1};

(ii) a low shear viscosity of no less than 45000 cps at 5°C and 1 s^{-1}; and

(iii) a ratio of low shear viscosity to high shear viscosity of not less than 10.

[0008] Disclosed is a method of treating Parkinson's disease in a patient in need thereof, wherein the method comprises administering to the patient a pharmaceutical composition comprising a levodopa active agent and a carbidopa active agent for intraduodenal administration wherein the levodopa active agent and carbidopa active agent (*e.g.*, carbidopa monohydrate) are provided in an amount of from about 4 weight/weight percent and 1 weight/weight percent of the composition, respectively, suspended in an aqueous carrier. The pharmaceutical composition

has a desired viscosity suitable for storage under refrigerated conditions and/or delivery (*e.g.*, delivered via a pump) at room temperature (*e.g.*, ~20°C to ~25°C).

[0009] Disclosed are methods of manufacturing a pharmaceutical composition of the invention, in particular a high concentration pharmaceutical composition as disclosed, for example, in Example 1 and Figure 1 below.

[0009a] Disclosed is a pharmaceutical composition comprising a levodopa active agent and a carbidopa active agent for intraduodenal administration wherein the levodopa active agent and the carbidopa active agent are suspended in an aqueous carrier, characterized in that the levodopa active agent and the carbidopa active agent in the carrier has a high shear viscosity of no more than about 4500 cps at room temperature and a low shear viscosity of no less than about 45000 cps under refrigerated conditions and a ratio of low shear viscosity to high shear viscosity of not less than 10.

[0009b] In another aspect, the present disclosure relates to a pharmaceutical dosage form comprising the pharmaceutical composition as described herein in a disposable drug reservoir having an oxygen impermeable enclosure disposed therein, wherein the oxygen impermeable enclosure is purged with an inert gas and an oxygen scavenger is added.

[0009c] Disclosed is a method of preparing the pharmaceutical composition as described herein, wherein the method comprises:

adding a levodopa active agent and a carbidopa active agent to water to form a slurry;

adding the slurry to one or more suspending agents to form a suspension; and subjecting the suspension to N_2 sparging.

In another aspect, the present disclosure relates to a method of preparing the pharmaceutical composition as described herein, wherein the method comprises:

adding a levodopa active agent and a carbidopa active agent to water to form a slurry;

adding the slurry to one or more polymer-based suspending agents selected from the group consisting of hydroxypropylcellulose, hydroxymethylcellulose, and sodium carboxymethyl cellulose to form a suspension; and

subjecting the suspension to N_2 sparging.

[0009d] Disclosed is use of a pharmaceutical composition comprising a levodopa active agent and a carbidopa active agent for intraduodenal administration in the manufacture of a medicament for treating Parkinson's disease, wherein the levodopa active agent and carbidopa active agent are suspended in an aqueous carrier, characterized in that the levodopa active agent and the carbidopa active agent in the carrier has a high shear viscosity of no more than about 4500 cps at room temperature and a low shear viscosity of no less than about 45000 cps under refrigerated conditions and a ratio of low shear viscosity to high shear viscosity of not less than 10. In another aspect, the present disclosure relates to use of the pharmaceutical composition as described herein for intraduodenal administration in the manufacture of a medicament for treating Parkinson's disease.

[0009e] In another aspect, the present disclosure relates to a kit comprising the pharmaceutical composition as described herein.

[0009f] In another aspect, the present disclosure relates to a kit comprising the pharmaceutical dosage form as described herein.

[0010] These and additional embodiments of the invention are further described herein.

[0011] Further benefits of the present disclosure will be apparent to one skilled in the art from reading this patent application. The embodiments of the disclosure described in the following paragraphs are intended to illustrate the invention and should not be deemed to narrow the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 is a manufacturing process flowchart for producing an exemplary pharmaceutical formulation of the invention.

[0013] Figure 2 shows the L-Dopa blood level time-concentration profile in mini-pigs of an exemplary pharmaceutical composition of the invention as against two comparators, all given in a six-hour continuous infusion.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for intraduodenal administration comprising:
(a) a levodopa active agent in an amount of 4.0 weight /weight percent of the total composition;
(b) a carbidopa monohydrate active agent in an amount of 1.0 weight/weight percent of the total composition;
(c) one or more polymer-based suspending agents selected from the group consisting of hydroxypropylcellulose, hydroxymethylcellulose, and sodium carboxymethyl cellulose; and
(d) water,
wherein the pharmaceutical composition has:
(i) a high shear viscosity of no more than 4500 cps at 22°C and 24.1 s^{-1};
(ii) a low shear viscosity of no less than 45000 cps at 5°C and 1 s^{-1}; and
(iii) a ratio of low shear viscosity to high shear viscosity of not less than 10.

2. The pharmaceutical composition according to claim 1, wherein the one or more polymer-based suspending agent is sodium carboxymethyl cellulose.

3. The pharmaceutical composition according to claim 1 or 2, wherein the concentration of the liquid vehicle is in an amount of from zero percent to 95 weight/weight percent of the total composition.

4. The pharmaceutical composition according to any one of claims 1-3, wherein the pharmaceutical composition does not experience degradation into DHPA at a rate faster than 0.04 w/w% per week.

5. The pharmaceutical composition according to any one of claims 1-4, wherein the pharmaceutical composition does not experience degradation into DHPPA at a rate faster than 0.04 w/w% per week.

6. The pharmaceutical composition according to any one of claims 1-5, wherein the pharmaceutical composition does not experience degradation producing hydrazine at a rate faster than 0.6 µg/g per week.

7. The pharmaceutical composition according to any one of claims 1-6, wherein the pharmaceutical composition is present in a lower O_2 permeable primary or secondary container.

8. A pharmaceutical dosage form comprising the pharmaceutical composition of any one of claims 1-7 in a disposable drug reservoir having an oxygen impermeable enclosure disposed therein, wherein the oxygen impermeable enclosure is purged with an inert gas and an oxygen scavenger is added.

9. The pharmaceutical dosage form according to claim 8, wherein the pharmaceutical dosage form is suitable for use in a continuous infusion pump capable of delivering the composition in a therapeutically effective manner.

10. A method of preparing the pharmaceutical composition according to any one of claims 1–7, wherein the method comprises:

adding a levodopa active agent and a carbidopa active agent to water to form a slurry;

adding the slurry to one or more polymer-based suspending agents selected from the group consisting of hydroxypropylcellulose, hydroxymethylcellulose, and sodium carboxymethyl cellulose to form a suspension; and

subjecting the suspension to N_2 sparging.

11. The method according to claim 10 further comprising loading the suspension into a lower oxygen permeability container.

12. The method according to claim 10 or 11, wherein, prior to forming the suspension, the levodopa active agent has a particle size distribution of:

(i) D50 less than or equal to 5 μm;

(ii) D90 less than or equal to 11 μm; and

(iii) D100 less than or equal to 22 μm; and

the carbidopa active agent has a particle size distribution of:

(i) D50 less than or equal to 3 μm;

(ii) D90 less than or equal to 7 μm; and

(iii) D100 less than or equal to 21 μm.

13. Use of the pharmaceutical composition of claim 1 for intraduodenal administration in the manufacture of a medicament for treating Parkinson's disease.

14. The use according to claim 13, wherein the medicament is to be substantially continuously administered for a period of at least 16 hours.

15. The use according to claim 14, wherein the medicament is to be substantially continuously administered for a period of at least 24 hours.

16. The use according to any one of claims 13–15, wherein the pharmaceutical composition is to be administered in a pharmaceutical dosage form in a disposable drug reservoir having an oxygen impermeable enclosure disposed therein, wherein the oxygen impermeable enclosure is purged with an inert gas and an oxygen scavenger is added.

17. A kit comprising the pharmaceutical composition of any one of claims 1–7.

18. A kit comprising the pharmaceutical dosage form of claims 8 or 9.