possibility of extracerebral metabolism of levodopa, it is necessary to administer large doses of levodopa leading to high extracerebral concentrations of dopamine that cause nausea in some patients. Therefore, levodopa is usually administered concurrently with oral administration of a dopa decarboxylase inhibitor, such as carbidopa or benserazide, which reduces by 60-80% the levodopa dose required for a clinical response, and thus prevents certain of its side effects by inhibiting the conversion of levodopa to dopamine outside the brain. Various oral formulations together with inhibitors of enzymes associated with the metabolic degradation of levodopa are well known, for example, decarboxylase inhibitors such as carbidopa and benserazide, catechol-O-methyl transferase (COMT) inhibitors such as entacapone and tolcapone, and monoamone oxidase (MAO)-A or MAO-B inhibitors such as moclobemide, rasagiline or selegiline or safinamide. Currently available oral drugs include SINEMET® and SINEMET®CR sustained-release tablets that include carbidopa or levodopa; STALEVO® tablets containing carbidopa, entacapone and levodopa; and MADOPAR® tablets containing levodopa and benserazide. There is an on-going and urgent need for methods and compositions that can effect continuous stimulation of L-dopa to more effectively treat movement disorders such as Parkinson's disease. Nevertheless, no stable liquid formulation having e.g., an effective concentration in a volume suitable for use for subcutaneous or transdermal delivery has ever been achieved.

SUMMARY

[0005] This disclosure generally relates, in part, to a pharmaceutically acceptable composition comprising 1) active components comprising carbidopa and at least about 4% by weight levodopa; and arginine and optionally meglumine. Such compositions may have a pH of about 9.1 to about 9.8 at 25°C.

[0005a] In one aspect of the present disclosure, there is provided a pharmaceutically acceptable liquid composition comprising 2.5% to 7% by weight levodopa; up to 2% by weight carbidopa; 5% to 18% by weight arginine; and 0.25% to 3% by weight ascorbic acid or a pharmaceutically acceptable salt thereof, wherein said composition has a pH of 9.1 to 9.8 at 25°C, and the molar ratio of levodopa plus carbidopa to the arginine is 1:1.8 to 1:3.5.

[0005b] In another aspect of the present disclosure, there is provided a pharmaceutically acceptable liquid composition disclosed herein, for use in treatment of a neurological or movement disorder such as Parkinson's disease.

[0005c] In a further aspect of the present disclosure, there is provided a transdermal patch comprising a pharmaceutically acceptable liquid composition disclosed herein.

[0005d] In another aspect of the present disclosure, there is provided a use of a pharmaceutically acceptable liquid composition disclosed herein in the manufacture of a medicament for treating a neurological or movement disorder such as Parkinson's disease.

[0006] In some embodiments, a disclosed composition having arginine may have a molar ratio of active components to the arginine is about 1:1.8 to about 1:3.5, or about 1:2.3. In an exemplary embodiment, a disclosed composition may include about 4% to about 12% by weight or more of levodopa and/or may include 1% to about 6% by weight carbidopa, e.g. about 1% to about 2% by weight carbidopa.

[0007] When meglumine is present in a disclosed composition, the molar ratio of active components to the arginine may be, for example, about 1:1.1 to about 1:1.9, and the molar ratio of active components to the meglumine may about 1:0.3 to about 1:1.5, e.g., the molar ratio of active components to the meglumine may about 1:0.3 to about 1:1.2, or for

Claims

1. A pharmaceutically acceptable liquid composition comprising 2.5% to 7% by weight levodopa; up to 2% by weight carbidopa; 5% to 18% by weight arginine; and 0.25% to 3% by weight ascorbic acid or a pharmaceutically acceptable salt thereof, wherein said composition has a pH of 9.1 to 9.8 at 25°C, and the molar ratio of levodopa plus carbidopa to the arginine is 1:1.8 to 1:3.5.

2. The pharmaceutically acceptable liquid composition of claim 1, wherein said composition has a pH of 9.2 to 9.8 at 25°C.

3. The pharmaceutically acceptable liquid composition of claim 1 or 2, wherein said pharmaceutically acceptable salt of ascorbic acid is ascorbate, Na-ascorbate, calcium ascorbate, potassium ascorbate, ascorbyl palmitate, or ascorbyl stearate.

4. The pharmaceutically acceptable liquid composition of any one of claims 1 to 3, further comprising an agent that inhibits the formation of oxidation products.

5. The pharmaceutically acceptable liquid composition of claim 4, wherein the agent is L cysteine, N-acetylcysteine (NAC), gluthatione (GSH), Na_2-EDTA, Na_2-EDTA-Ca, sodium bisulfite, or combinations thereof.

6. The pharmaceutically acceptable liquid composition of claim 1 or 2, comprising:

(i) 6% by weight levodopa, 1.5% by weight carbidopa, 1% by weight Na-ascorbate, and 13.5%, 14.2%, 14.8% or 16.0%, by weight arginine;

(ii) 4.8% by weight levodopa, 1.4% by weight carbidopa, 1% by weight Na-ascorbate, and 11%, 11.6%, 12.1% or 12.7%, by weight arginine;

(iii) 6% by weight levodopa, 1.5% by weight carbidopa, 1% by weight ascorbic acid or Na-ascorbate, and 14.8%, 15.8%, 16% or 16.8%, by weight arginine;

(iv) 5.4% by weight levodopa, 1.5% by weight carbidopa, 1% by weight ascorbic acid or Na ascorbate, and 12.3%, 13.5 or 14.8%, by weight arginine; or

(v) 7% by weight levodopa, 2% by weight carbidopa, 1 % by weight ascorbic acid or Na ascorbate, and 17.8% by weight arginine.

7. The pharmaceutically acceptable liquid composition of any one of claims 1 to 6, formulated for continuous subcutaneous, transdermal, intraduodenal or intravenous administration.

8. The pharmaceutically acceptable liquid composition of any one of claims 1 to 7, for use in treatment of a neurological or movement disorder such as Parkinson’s disease.

9. A transdermal patch comprising a pharmaceutically acceptable liquid composition according to any one of claims 1 to 6.

10. Use of a pharmaceutically acceptable liquid composition of any one of claims 1 to 7 in the manufacture of a medicament for treating a neurological or movement disorder such as Parkinson’s disease.