transformation of levodopa to dopamine is catalyzed by the aromatic L-amino acid decarboxylase enzyme, a ubiquitous enzyme with particularly high concentrations in the intestinal mucosa, liver, brain and brain capillaries. Due to the possibility of extracerebral metabolism of levodopa, it is necessary to administer large doses of levodopa leading to high extracerebral concentrations of dopamine. The co-administration of LD and a peripheral DOPA decarboxylase (aromatic L-amino acid decarboxylase) inhibitor such as carbidopa or benserazide has been found to reduce the dosage requirements of LD and, respectively, some of the side effects, although not sufficiently.

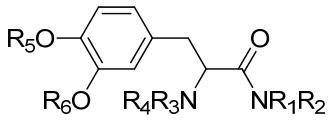
[0006] Finally, certain fluctuations in clinical response to levodopa occur with increasing frequency as treatment continues. In some patients, these fluctuations relate to the timing of levodopa intake, and they are then referred to as wearing-off reactions or end-of-dose akinesia. In other instances, fluctuations in clinical state are unrelated to the timing of doses (on-off phenomenon). In the on-off phenomenon, off-periods of marked akinesia and bradykinesia alternate over the course of a few hours with on-periods of improved mobility which are often associated with troublesome dyskinesia.

[0007] It is well accepted in the art that many of the problems recited above result from the unfavorable pharmacokinetic properties of L-DOPA and, more particularly, from its poor water solubility, bioavailability and fast degradation *in vivo*. Thus, there is still an urgent need for effective therapeutic formulations for treating disorders such as Parkinson's disease.

[0008] US 8,048,926 discloses L-DOPA amide derivatives (referred to as L-DOPA prodrugs), pharmaceutical compositions comprising them, and their use in the treatment of conditions associated with impaired dopaminergic activity/signaling, e.g., Parkinson's disease. The compounds disclosed are said to be characterized by high permeability through the blood brain barrier.

SUMMARY

[0009] The present disclosure provides an aqueous pharmaceutical composition, also referred to herein as "***pharmaceutical composition A***", having a pH of about 3 to about 7 at 25°C, said composition comprising a levodopa amide (LDA) compound of the general formula I:

I 

or an enantiomer, diastereomer, or racemate thereof,

wherein

R_1, R_2, R_3 and R_4 each independently is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, cycloalkyl, aryl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', or -O-C(=O)-R", or R_1 and R_2 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring, or R_3 and R_4, together with the nitrogen atom to which they are attached form a 5- or 6-membered ring; and

R_5 and R_6 each independently is H, (C_1-C_3)alkyl, cycloalkyl, phenyl, or -P(=O)(OR')$_2$,

R' each independently is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, aryl, or heteroaryl bonded through a ring carbon; and

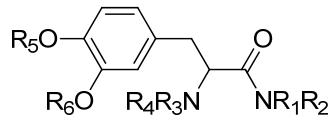
R" is a saturated or unsaturated hydrocarbon chain having at least 10 carbon atoms, and

an organic- or inorganic-acid having n acidic groups, wherein n is an integer of 1 or more,

wherein the molar ratio of said LDA compound to said acid is about 1:1/n to about 1:≥1.1, and said composition is stable for at least 24 hours at room temperature.

[0010] The pharmaceutical composition A defined above may further comprise a decarboxylase inhibitor such as carbidopa, and at least one of a basic amino acid, e.g., arginine, or an amino sugar, e.g., meglumine; and optionally at least one of a buffer, an antioxidant, an additional active agent such as a catechol-O-methyl transferase (COMT) inhibitor or a monoamine oxidase (MAO) inhibitor, and a surfactant.

[0010a] In one aspect of the present disclosure, there is provided an aqueous pharmaceutical composition having a pH of about 3 to about 7 at 25°C, said composition comprising a levodopa amide (LDA) compound of the general formula I:

I 

or an enantiomer, diastereomer, or racemate thereof,

wherein:

R_1, R_2, R_3 and R_4 each independently is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, cycloalkyl, aryl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', or -O-C(=O)-R", or R_1 and R_2 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring, or R_3 and R_4, together with the nitrogen atom to which they are attached form a 5- or 6-membered ring; and

R_5 and R_6 each independently is H, (C_1-C_3)alkyl, cycloalkyl, phenyl, or -P(=O)(OR')$_2$,

R' each independently is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, aryl, or heteroaryl bonded through a ring carbon; and

R" is a saturated or unsaturated hydrocarbon chain having at least 10 carbon atoms,

an acid having n acidic groups wherein n is an integer of 1 or more,

wherein the molar ratio of said LDA compound to said acid is about 1:1/n to about 1:≥1.1, and said composition is stable for at least 24 hours at room temperature.

[0011] The present disclosure also provides an aqueous pharmaceutical composition, also referred to herein as "***pharmaceutical composition B***", having a pH of about 3 to about 9.5, or about 4 to about 8, or about 5 to about 7, or about 5.5 to about 6.5, at 25°C, said composition comprising a salt of a LDA compound of the general formula I as defined above, or an enantiomer, diastereomer, or racemate thereof, a decarboxylase inhibitor, e.g., carbidopa, or a salt thereof, and optionally at least one of a basic amino acid, e.g., arginine, or an amino sugar, e.g., meglumine,

wherein the weight ratio of said decarboxylase inhibitor to said salt of LDA compound is about 1:1 to about 1:100, about 1:2 to about 1:60, about 1:4 to about 1:40, or about 1:10 to about 1:40; and the molar ratio or said decarboxylase inhibitor or salt thereof to said basic amino acid or said amino sugar is about 1:1 to about 1:4, or about 1:1 to about 1:3.5, or about 1:1 to about 1:2.5, and

wherein said composition is stable for at least 24 hours at room temperature.

[0012] The pharmaceutical composition B defined above may further comprise at least one of a buffer, an antioxidant, an additional active agent such as a COMT inhibitor or a MAO inhibitor, and a surfactant.

[0013] The present disclosure further provides an aqueous pharmaceutical composition, also referred to herein as "***pharmaceutical composition C***", having a pH of about 3 to about 6, or about 4 to about 5.5, at 25°C, said composition comprising a salt of a LDA compound of the general formula I as defined above, or an enantiomer, diastereomer, or racemate thereof, and a buffer,

wherein said composition is stable for at least 24 hours at room temperature.

[0014] The pharmaceutical composition C defined above may further comprise at least one of an antioxidant, an additional active agent such as a COMT inhibitor or a MAO inhibitor, and a surfactant.

[0015] In particular embodiments, the LDA compound comprised, either *per se* or as a salt thereof, within each one of the aqueous pharmaceutical compositions of the present disclosure is 2-amino-3-(3,4-dihydroxyphenyl)propanamide, or an enantiomer, diastereomer, or racemate thereof.

[0016] The pharmaceutical compositions disclosed herein are useful for treatment of diseases or disorders characterized by neurodegeneration and/or reduced levels of brain dopamine. Such diseases and disorders include neurological or movement diseases or disorders selected from restless leg syndrome, Parkinson's disease, secondary parkinsonism, Huntington's disease, Parkinson’s like syndrome, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), Shy-Drager syndrome, dystonia, Alzheimer’s disease, Lewy body disease (LBD), akinesia, bradykinesia, and hypokinesia; conditions resulting from brain injury including carbon monoxide or manganese intoxication; and conditions associated with a neurological disease or disorder including alcoholism, opiate addiction, and erectile dysfunction. In a

particular embodiment, the disease treated with the pharmaceutical compositions of the disclosure is Parkinson's disease.

[0017] The present disclosure thus relates to a method for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine, comprising administering to a patient, e.g., an individual, in need thereof a therapeutically effective amount of a pharmaceutical composition A as defined above, provided that said composition comprises a decarboxylase inhibitor and at least one of a basic amino acid or an amino sugar; or a pharmaceutical composition B as defined above.

[0017a] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as defined above, for the preparation of a medicament for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

[0018] The present disclosure also relates to a method for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine, comprising co-administering to a patient, e.g., an individual, in need thereof (i) a first pharmaceutical composition selected from a pharmaceutical composition A as defined above, provided that said composition does not comprise a decarboxylase inhibitor or a salt thereof, or a pharmaceutical composition C as defined above; and (ii) a second pharmaceutical composition comprising a decarboxylase inhibitor and optionally at least one of a basic amino acid or an amino sugar; and/or a COMT inhibitor; and/or a MAO inhibitor.

[0018a] In a further aspect of the present disclosure, there is provided a use of a first pharmaceutical composition as defined above; and a second pharmaceutical composition comprising a decarboxylase inhibitor or a salt thereof, and optionally at least one of a basic amino acid or an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor, as a combination in the preparation of a medicament for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

[0019] The present disclosure further provides a kit comprising (i) a first pharmaceutical composition selected from a pharmaceutical composition A as defined above, provided that said composition comprises neither a decarboxylase inhibitor nor a salt thereof, or a pharmaceutical composition C as defined above; (ii) a second pharmaceutical composition comprising a decarboxylase inhibitor or a salt thereof, and optionally at least one of a basic amino acid or an amino sugar, and/or a COMT inhibitor; and/or a MAO inhibitor; and (iii) optionally instructions for co-administration of said pharmaceutical compositions for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

[0019a] In another aspect of the present disclosure, there is provided a kit comprising (i) a first pharmaceutical composition as defined above; (ii) a second pharmaceutical composition comprising a decarboxylase inhibitor or a salt thereof, and optionally at least one of a basic amino acid or an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor; and (iii) optionally instructions for co-administration of said pharmaceutical compositions for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

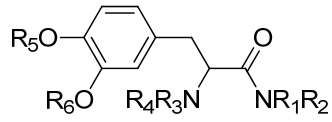
BRIEF DESCRIPTION OF THE FIGURES

[0020] **Fig. 1** depicts the plasma concentrations of LDA and LD in CD-1 mice plasma after Intravenous administration of LDA-HCl (20mg/kg).

[0021] **Fig. 2** depicts the plasma concentrations of LDA and LD in CD-1 mice plasma after Oral administration of LDA-HCl (20mg/kg).

CLAIMS

1. An aqueous pharmaceutical composition having a pH of about 3 to about 7 at 25°C, said composition comprising a levodopa amide (LDA) compound of the general formula I:

I 

or an enantiomer, diastereomer, or racemate thereof,

wherein:

R_1, R_2, R_3 and R_4 each independently is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, cycloalkyl, aryl, -O-C(=O)-R', -C(=O)-OR', -C(=O)-R', -C(=S)-R', -O-C(=O)-NR'R', -O-C(=S)-NR'R', or -O-C(=O)-R", or R_1 and R_2 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring, or R_3 and R_4, together with the nitrogen atom to which they are attached form a 5- or 6-membered ring; and

R_5 and R_6 each independently is H, (C_1-C_3)alkyl, cycloalkyl, phenyl, or -P(=O)(OR')$_2$,

R' each independently is H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, aryl, or heteroaryl bonded through a ring carbon; and

R" is a saturated or unsaturated hydrocarbon chain having at least 10 carbon atoms,

an acid having n acidic groups wherein n is an integer of 1 or more,

wherein the molar ratio of said LDA compound to said acid is about 1:1/n to about 1:≥1.1, and said composition is stable for at least 24 hours at room temperature.

2. The pharmaceutical composition of claim 1, comprising about 1% to about 30%, or about 5% to about 20%, by weight of said LDA compound.

3. The pharmaceutical composition of claim 1, wherein said LDA compound is 2-amino-3-(3,4-dihydroxyphenyl)propanamide, or an enantiomer, diastereomer, or racemate thereof.

4. The pharmaceutical composition of claim 1, wherein said acid is an organic acid such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, maleic acid, malic acid, fumaric acid, tartaric acid, benzoic acid, acetic acid, citric acid, ascorbic acid, lactic acid, gluconic acid, formic acid, oxalic acid, succinic acid, or an acidic amino acid such as glutamic acid and aspartic acid; an inorganic acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and carbonic acid; or any combination of the aforesaid.

5. The pharmaceutical composition of any one of claims 1 to 4, further comprising a decarboxylase inhibitor, and at least one of a basic amino acid or an amino sugar.

6. The pharmaceutical composition of claim 5, wherein said decarboxylase inhibitor is carbidopa, benserazide, or a salt thereof; said basic amino acid is arginine, histidine, or lysine; or said amino sugar is meglumine, D-glucosamine, sialic acid, N-acetylglucosamine, galactosamine, or a combination thereof.

7. The pharmaceutical composition of claim 6, wherein said decarboxylase inhibitor is carbidopa; said basic amino acid is arginine; and said amino sugar is meglumine.

8. The pharmaceutical composition of any one of claims 5 to 7, wherein the weight ratio of said decarboxylase inhibitor to said LDA compound is about 1:1 to about 1:100, about 1:2 to about 1:60, about 1:4 to about 1:40, or about 1:10 to about 1:40; or the molar ratio of said decarboxylase inhibitor to said basic amino acid or said amino sugar is about 1:1 to about 1:4, about 1:1 to about 1:3.5, or about 1:1 to about 1:2.5.

9. The pharmaceutical composition of any one of claims 1 to 8, further comprising a buffer.

10. The pharmaceutical composition of claim 9, wherein said buffer is citrate buffer, citric acid buffer, acetate buffer, sodium acetate buffer, acetic acid buffer, tartrate buffer, tartaric acid buffer, phosphate buffer, succinic acid buffer, Tris buffer, glycine buffer, hydrochloric acid buffer, potassium hydrogen phthalate buffer, sodium

buffer, sodium citrate tartrate buffer, sodium hydroxide buffer, sodium dihydrogen phosphate buffer, disodium hydrogen phosphate buffer, or a mixture thereof.

11. The pharmaceutical composition of any one of claims 1 to 10, further comprising at least one antioxidant.

12. The pharmaceutical composition of claim 11, wherein said antioxidant each independently is ascorbic acid or a salt thereof, a cysteine such as L-cysteine and N-acetyl cysteine, a bisulfite or a salt thereof, or glutathione.

13. The pharmaceutical composition of any one of claims 1 to 12, further comprising a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor.

14. The pharmaceutical composition of claim 13, wherein said COMT inhibitor is entacapone, tolcapone, or opicapone; and said MAO inhibitor is moclobemide, rasagiline, selegiline, or safinamide.

15. The pharmaceutical composition of any one of claims 1 to 14, further comprising a surfactant such as Tween-80.

16. The pharmaceutical composition of any one of claims 1 to 15, formulated for subcutaneous, transdermal, intradermal, transmucosal, intravenous, intraarterial, intramuscular, intraperitoneal, intrathecal, intrapleural, intratracheal, intranasal, sublingual, buccal, intestinal, intraduodenal, rectal, or intraocular administration.

17. Use of a pharmaceutical composition according to any one of claims 5-15, for the preparation of a medicament for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

18. Use of a first pharmaceutical composition according to any one of claims 1-4; and a second pharmaceutical composition comprising a decarboxylase inhibitor or a salt thereof, and optionally at least one of a basic amino acid or an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor, as a combination in the preparation of a medicament for treatment of a

disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

19. The use of claim 18, wherein said decarboxylase inhibitor is carbidopa; said basic amino acid is arginine; said amino sugar is meglumine; said COMT inhibitor is entacapone, tolcapone or opicapone; and said MAO inhibitor is moclobemide, rasagiline, selegiline or safinamide.

20. The use of claim 18 or 19, wherein said first pharmaceutical compositions is administered parenterally, intravenously, subcutaneously, intraduodenally, rectally, intrathecally, sublingually, intradermally, intranasally, or intramuscularly; and said second pharmaceutical compositions is administered parenterally, intravenously, subcutaneously, transdermally, rectally, intrathecally, sublingually, intradermally, intranasally, intramuscularly, or orally.

21. The use of claim 18 or 19, wherein said first pharmaceutical composition and said second pharmaceutical composition are administered by different administration routes.

22. The use of claim 21, wherein said second pharmaceutical composition is administered orally.

23. The use of any one of claims 17 to 22, wherein said disease or disorder is a neurological or movement disorder selected from restless leg syndrome, Parkinson's disease, secondary parkinsonism, Huntington's disease, Parkinson’s like syndrome, progressive supranuclear palsy (PSP), multiple system atrophy (MSA), amyotrophic lateral sclerosis (ALS), Shy-Drager syndrome, dystonia, Alzheimer’s disease, Lewy body disease (LBD), akinesia, bradykinesia, and hypokinesia; conditions resulting from brain injury including carbon monoxide or manganese intoxication; and conditions associated with a neurological disease or disorder including alcoholism, opiate addiction, and erectile dysfunction.

24. The use of claim 23, wherein said disease or disorder is Parkinson's disease.

25. A kit comprising (i) a first pharmaceutical composition according to any one of claims 1-4; (ii) a second pharmaceutical composition comprising a decarboxylase

inhibitor or a salt thereof, and optionally at least one of a basic amino acid or an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor; and (iii) optionally instructions for co-administration of said pharmaceutical compositions for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.