skin is dependent on their ionic form, wherein non-ionized species generally have higher permeability coefficients in comparison to ionized species and further, cations generally have higher permeability coefficients than anions.

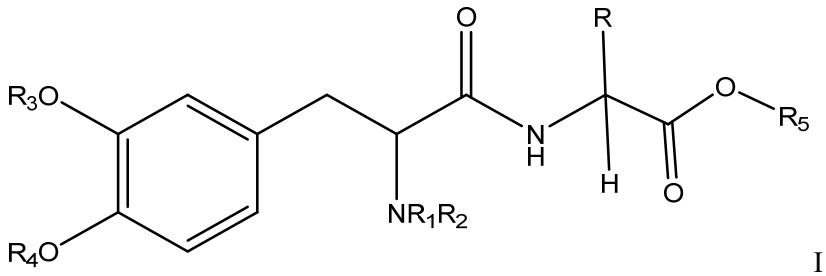
[0009] US 3,803,120, US 4,035,507, US 5,686,423 and US 2002/099013 disclose certain levodopa amino acid and levodopa peptide conjugates; however, details regarding formulations are not provided therein, and when provided, only solid oral formulations are contemplated. The theoretical option of preparing liquid compositions is briefly mentioned in US 3,803,120 (US '120, column 3, lines 49-53); however, no such compositions were prepared and moreover, it is erroneously disclosed that the conjugates are soluble (column 3, lines 65-66).

[0010] As detailed above, there is still a need to effective formulations, and particularly liquid formulations, for treating disorders such as Parkinson's disease.

SUMMARY

[0010a] In an aspect of the present disclosure, there is provided a liquid pharmaceutical composition comprising:

(a) a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein:

R is an amino acid side chain an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains;

R_1 and R_2 are each H;

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

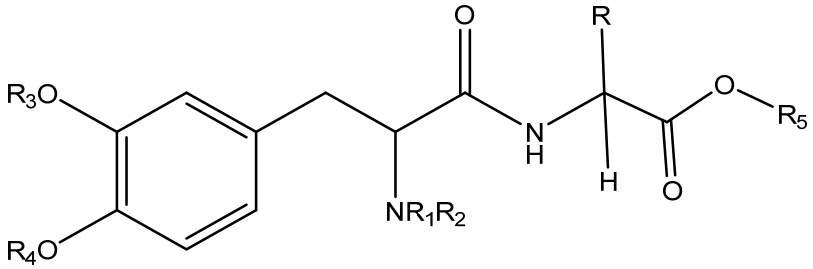
R" is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl; and

(b) carbidopa; and

(c) a pharmaceutically acceptable excipient.

[0010b] In another aspect of the present disclosure, there is provided a use of a liquid pharmaceutical composition in the manufacture of a medicament for treating neurodegenerative conditions and/or conditions characterized by reduced levels of dopamine in the brain, wherein the liquid pharmaceutical composition comprises:

(a) a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R is an amino acid side chain an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains;

R_1 and R_2 are each H;

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl;

(b) carbidopa; and

(c) a pharmaceutically acceptable excipient,

wherein the liquid pharmaceutical composition is to be administered substantially continuously to the patient subcutaneously.

[0011] Provided herein, *inter alia*, are levodopa amino acids (LDAAs), salts thereof (*e.g.*, pharmaceutically acceptable salts thereof), and compositions comprising the same (*e.g.*, pharmaceutically acceptable compositions, for example, liquid pharmaceutical compositions). Also described herein are methods of preparing LDAAs, pharmaceutically acceptable salts thereof, and compositions comprising the same. Also disclosed are methods of using LDAAs, pharmaceutically acceptable salts thereof, and compositions comprising the same in, for example, the treatment of conditions characterized by neurodegeneration and/or reduced levels of dopamine in the brain, e.g., Parkinson's disease.

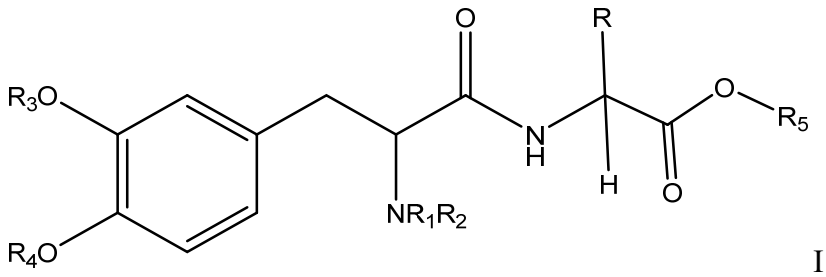
[0012] Disclosed herein is a liquid pharmaceutical composition comprising:

a levodopa amino acid conjugate (LDAA) of the general formula (I):

CLAIMS

1. A liquid pharmaceutical composition comprising:

(a) a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein:

R is an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine, selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains;

R_1 and R_2 are each H;

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1- C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

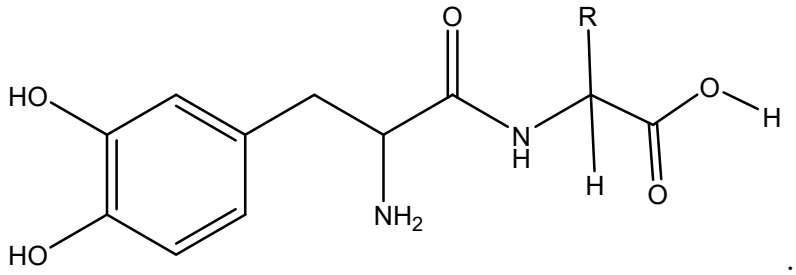
R" is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl;

(b) carbidopa; and

(c) a pharmaceutically acceptable excipient.

2. The liquid pharmaceutical composition according to claim 1, wherein R is an amino acid side chain selected from the group consisting of arginine, lysine, aspartic acid, tyrosine, tryptophan, and lanthionine side chains.

3. The liquid pharmaceutical composition according to claim 1 or 2, wherein the LDAA is represented by:



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4. The liquid pharmaceutical composition according to any one of claims 1-3, further comprising a base, wherein, optionally, the base is selected from the group consisting of arginine, NaOH, tris(hydroxymethyl)aminomethane (TRIS), and any combination thereof.

5. The liquid pharmaceutical composition according to claim 4, wherein said liquid pharmaceutical composition comprises between about 0.1% to about 30% w/v of the base.

6. The liquid pharmaceutical composition according to any one of claims 1-5, wherein said liquid pharmaceutical composition comprises between about 0.25 to about 1.5 % w/v of the carbidopa.

7. The liquid pharmaceutical composition according to any one of claims 1-6, further comprising an antioxidant or a combination of two or more antioxidants.

8. The liquid pharmaceutical composition according to claim 7, wherein the antioxidant is each independently selected from the group consisting of ascorbic acid or a salt thereof, a cysteine, a bisulfite or a salt thereof, glutathione, a tyrosinase inhibitor, a Cu^{2+} chelator, and any combination thereof.

9. The liquid pharmaceutical composition according to claim 7 or 8, wherein said liquid pharmaceutical composition comprises between about 0.05 to about 1.5 % w/v of the antioxidant or the combination of antioxidants.

10. The liquid pharmaceutical composition according to any one of claims 7-9, wherein the antioxidant is each independently a cysteine, optionally wherein the cysteine is L-cysteine and N-acetyl cysteine (NAC), or any combination thereof.

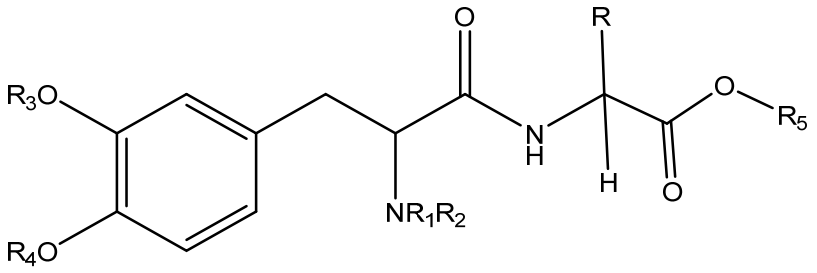
11. The liquid pharmaceutical composition according to any one of claims 1-10, further comprising at least one of: a catechol-O-methyltransferase (COMT) inhibitor, a monoamine oxidase (MAO) inhibitor, a surfactant, a buffer, an acid, a solvent, and any combination thereof.

12. The liquid pharmaceutical composition according to any one of claims 1-11, comprising one LDAA conjugate, or a mixture of two or more different LDAA conjugates, each represented by Formula I, or an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof.

13. The liquid pharmaceutical composition according to any one of claims 1-13, comprising between about 10 to about 45 % w/v of one or more of the LDAA conjugate represented by Formula I.

14. Use of a liquid pharmaceutical composition in the manufacture of a medicament for treating neurodegenerative conditions and/or conditions characterized by reduced levels of dopamine in the brain, wherein the liquid pharmaceutical composition comprises:

(a) a levodopa amino acid conjugate (LDAA) of the general formula (I):



I

an enantiomer, diastereomer, racemate, ion, zwitterion, pharmaceutically acceptable salt thereof, or any combination thereof, wherein

R is an amino acid side chain selected from the group consisting of arginine, histidine, lysine, aspartic acid, glutamic acid, serine, threonine, asparagine, glutamine, cysteine,

selenocysteine, glycine, proline, alanine, valine, isoleucine, leucine, methionine, phenylalanine, tyrosine, tryptophan, and lanthionine side chains;

R_1 and R_2 are each H;

R_3 and R_4 are each independently selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl, phenyl, and-P(=O)(OR')$_2$;

R_5 is selected from the group consisting of H, (C_1-C_3)alkyl, C_3-C_6cycloalkyl and phenyl; R' is independently selected, for each occurrence, from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, C_3-C_6cycloalkyl , phenyl, and heteroaryl bonded to the nitrogen through a ring carbon; and

R" is independently selected, for each occurrence, from the group consisting of a (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl;

(b) carbidopa; and

(c) a pharmaceutically acceptable excipient,

wherein the liquid pharmaceutical composition is to be administered substantially continuously to the patient subcutaneously.

15. The use according to claim 14, wherein the neurodegenerative condition is Parkinson’s disease.