(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 September 2020 (10.09.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/178810 A1

(51) International Patent Classification:
A61K 9/00 (2006.01) *A61K 47/12* (2006.01)
A61K 31/165 (2006.01) *A61K 47/18* (2017.01)
A61K 31/198 (2006.01) *A61K 47/20* (2006.01)
A61K 45/06 (2006.01) *A61P 25/16* (2006.01)
A61K 47/02 (2006.01)

(21) International Application Number:
PCT/IL2020/050202

(22) International Filing Date:
24 February 2020 (24.02.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/813,290 04 March 2019 (04.03.2019) US

(71) Applicant: **NEURODERM, LTD.** [IL/IL]; 3 Pekeris St., Rabin Science Parl, 7670212 Rehovot (IL).

(72) Inventors: **ZAWOZNIK, Eduardo**; 6 Netiv Hashayarot St., 7683506 Mazkeret Batya (IL). **MAINFELD, Alex**; 9 Aharon Katznelson St., 4972114 Petach Tikva (IL). **SELA, Einat**; 4A Harav Neria Moshe Zvi St., 7653718 Rehovot (IL). **GAZAL, Elena**; 6 Sharabi Yaacov Saadia St., 7653718 Rehovot (IL). **SHALTIEL-KARYO, Ronit**; 18 Haganim Street, Apt. 33, 4704319 Ramat HaSharon (IL).

(74) Agent: **GORDON, Irit** et al.; FISHER IP GROUP, P.O.Box 12352, 4673300 Herzliya Pituach (IL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*

WO 2020/178810 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING LEVODOPA AMIDE DERIVATIVES AND USES THEREOF

(57) Abstract: Formulations comprising a levodopa amide derivative and a monovalent, divalent and/or trivalent acid, which are stable for at least 24 hours at room temperature are provided.

PHARMACEUTICAL COMPOSITIONS COMPRISING LEVODOPA AMIDE DERIVATIVES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/813,290, filed March 4, 2019, the entire contents of which are herein incorporated by reference for all purposes.

TECHNICAL FIELD

[0002] The present invention relates, at least in part, to formulations comprising a levodopa amide derivative, particularly, but not exclusively, pharmaceutical formulations, and use thereof.

BACKGROUND

[0003] Parkinson's disease is a degenerative condition characterized by reduced concentration of the neurotransmitter dopamine in the brain. Levodopa (hereon designated L-dopa or LD), L-3,4-dihydroxyphenylalanine) is an immediate metabolic precursor of dopamine that, unlike dopamine, is able to cross the blood brain barrier, and is most commonly used for restoring the dopamine concentration in the brain. For the past 40 years, levodopa has remained the most effective therapy for the treatment of Parkinson's disease.

[0004] However, conventional treatments for Parkinson's disease with L-dopa have proven to be inadequate for many reasons of record in the medical literature. For example, some patients become less responsive to levodopa such that previously effective doses eventually fail to produce any therapeutic benefit; and the systemic administration of levodopa, although producing clinically beneficial effects at first, is complicated by the need to increase the dosages that may result in adverse side effects. For such reasons, the benefits of levodopa treatment often diminish after about 3 or 4 years of therapy, irrespective of the initial therapeutic response.

[0005] The peripheral administration of levodopa is further complicated by the fact that only about 1-3% of the levodopa administered actually enters the brain unaltered, the remainder being metabolized extracerebrally, predominantly by decarboxylation, to dopamine, which does not penetrate the blood brain barrier. The metabolic 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. Susceptibility of LD to possible extracerebral metabolism often necessitates administration of large doses of levodopa, leading to high extracerebral concentrations of dopamine. The co-

administration of LD and a peripheral LD 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.

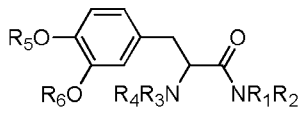
[0006] Finally, certain fluctuations in clinical response to levodopa occur with increasing frequency as treatment continues. In some patients, these fluctuations relate to the timing of levodopa intake, and they are then referred to as wearing-off reactions or end-of-dose akinesia. In other instances, 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] In addition, formulation of L-dopa is challenged, inter alia, due to its poor water solubility.

[0008] Derivatization of L-dopa as a means to improve water solubility and/or stability has been described in the art. For example, US 8,048,926 and WO 2017/090039 disclose L-dopa amide derivatives and/or pharmaceutical compositions comprising them, for use in the treatment of, e.g., Parkinson's disease.

SUMMARY

[0009] In an aspect of the present disclosure, a formulation is provided, comprising an acid and at least one levodopa amide (LDA) derivative of the general formula I:



(I)

or an enantiomer, diastereomer, or racemate thereof,

wherein:

(i) R1, R2, R3 and R4, 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 R1 and R2 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring, or R3 and R4, together with the nitrogen atom to which they are attached form a 5- or 6-membered ring;

R5 and R6, 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.

[0010] In some embodiments, the formulation disclosed comprises a monovalent acid and the molar ratio of the at least one LDA derivative to the acid is from about 1:0.10 to about 1:0.89, for example, from about 1.00:0.60 to about 1.00:0.89.

[0011] In some embodiments, the formulation disclosed comprises a divalent or trivalent acid, and the molar ratio of the at least one LDA derivative to the acid is from about 1.00:0.20 to about 1.00:1.15, excluding molar ratios of 1.00:0.50 and 1.00:0.33, when the pH is from about 6.0 to about 7.0.

[0012] The amount of at least one LDA derivative in a disclosed formulation may be from about 5% to about 25%, or from about 5% to about 20% by weight, for example, from about 10% to about 25%, or from about 10% to about 20%, or about 15% by weight of at least one LDA derivative;

[0013] The pH of a disclosed formulation may be from about 2.0 to about 11.0 at 25°C, for example, from about 5.0 to about 7.5, from about 6.0 to about 9.5, from about 7.1 to about 9.5 or from about 6.0 to about 7.0. Any of the formulations disclosed herein is stable for at least 24 hours at room temperature.

[0014] An LDA derivative in a disclosed formulation may be, for example, the compound 2-amino-3-(3,4-dihydroxyphenyl) propanamide, an enantiomer, and/or a racemate thereof.

[0015] The acid in a disclosed formulation may be one or more of an organic acid such as, but not limited to, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hippuric acid, maleic acid, malic acid, fumaric acid, tartaric acid, benzoic acid, acetic acid, citric acid, ascorbic acid, lactic acid, lactobionic acid, gluconic acid, galactaric acid, gluceptic (glucoheptanoic) acid, D-glucuronic acid, glutaric (pentanedioic) acid, glycolic (hydroxyacetic) acid, isethionic (2-hydroxy-ethanesulfonic) acid, formic acid, propionic (propanoic) acid, succinic (butanedioic) acid, oxalic acid, xinafoic (1-hydroxy-2-naphthoic) acid, carbidopa, an acidic amino acid such as glutamic acid, levodopa and aspartic acid, or a lipophilic acid such as a fatty acid; an inorganic acid such as, but not limited to, hydrochloric acid, hydrobromic acid, phosphoric acid (H_3PO_4), sulfuric acid (H_2SO_4), and carbonic acid; or any combination thereof.

[0016] In some embodiments, a disclosed formulation comprises one or more organic solvents, for example, N-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA), tetrahydrofuran (THF), ethanol, isopropanol, propylene glycol (PG), tetraglycol, transcutol and polyethylene glycol (PEG) (e.g., PEG 400).

[0017] In some embodiments, the formulation is a pharmaceutical composition intended for medicinal application. A disclosed formulation and/or pharmaceutical composition may further comprise one or more of:

(i) a decarboxylase inhibitor, for example, carbidopa, benserazide, a salt thereof, or a combination thereof;

(ii) a basic amino acid or an amino sugar. The basic amino acid may be, for example, arginine, histidine, lysine, or a combination thereof, and the amino sugar may be, for example, meglumine, D-glucosamine, sialic acid, N-acetylglucosamine, galactosamine, or a combination thereof;

(iii) a buffer, such as citrate buffer, acetate buffer, sodium acetate buffer, tartrate 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, borate buffer, carbonate buffer or a mixture thereof;

(iv) at least one antioxidant, for example, ascorbic acid or a salt thereof, L-cysteine, a cysteine derivative such as N-acetyl cysteine (NAC), bisulfite or a salt thereof, glutathione, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tocopherol, gentisic acid, or any combination thereof;

(v) a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor. For example, the COMT inhibitor may be entacapone, tolcapone, or opicapone, and the MAO inhibitor may be moclobemide, rasagiline, selegiline, or safinamide; and

(vi) a surfactant such as Tween®-80.

[0018] In some exemplary embodiments, a disclosed pharmaceutical composition may comprise carbidopa as the decarboxylase inhibitor, optionally along with the basic amino acid arginine and/or the amino sugar meglumine. In accordance with these embodiments, the molar ratio of a LDA derivative to the decarboxylase inhibitor may be from about 1:1 to about 100:1, from about 2:1 to about 60:1, from about 4:1 to about 40:1, or from about 10:1 to about 40:1. For example, 4:1, 8:1 or 23:1.

[0019] The pharmaceutical compositions disclosed herein are useful for treatment of diseases or disorders characterized by neurodegeneration and/or reduced levels of brain dopamine, for example, Parkinson's disease.

[0020] In a further aspect of the present disclosure, a method of treatment is provided, for treatment of disorders characterized by neurodegeneration and/or reduced levels of brain dopamine, the method comprising administering to a patient in need thereof a therapeutically effective amount of a disclosed pharmaceutical composition, thereby treating the patient.

[0021] The present disclosure further provides 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 in need thereof a first pharmaceutical composition comprising a LDA derivative and an acid; and a second pharmaceutical composition comprising a decarboxylase inhibitor or a salt thereof, and optionally at least one of a basic amino acid such as arginine, an amino sugar, catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor, thereby treating the patient.

[0022] The diseases and disorders treatable by a disclosed method include, for example, 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 an exemplary embodiment, the disease is Parkinson's disease.

[0023] The disclosure further relates, in an aspect thereof, to a kit comprising (i) a first pharmaceutical comprising at least one LDA derivative and an acid as defined herein; (ii) a second pharmaceutical composition comprising one or more of a decarboxylase inhibitor or a salt thereof, a basic amino acid, an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, and/or a monoamine oxidase (MAO) inhibitor; and (iii) optionally, instructions for co-administration of the pharmaceutical compositions. A contemplated kit may be used in treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine, for example, Parkinson's disease.

DETAILED DESCRIPTION

[0024] The disclosure relates, at least in part, to formulations comprising a levodopa amide (LDA) derivative and particularly, but not exclusively, to pharmaceutical compositions comprising a LDA derivative and use thereof for treating diseases and disorders characterized by neurodegeneration and/or reduced levels of brain dopamine, more particularly a neurological or movement disorder such as Parkinson's disease.

[0025] Levodopa amide derivatives, particularly when used in a pharmaceutical composition, may be referred to as prodrugs or precursors of levodopa.

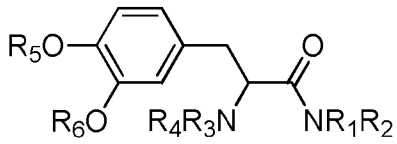
[0026] The term "prodrug" herein refers to an inactive substance that is converted to a drug within the body. Hence, a prodrug may itself be biologically inactive and circulate harmlessly until activated by some metabolic process or a clinically relevant event in the body, by the action of, for example, enzymes or other chemicals, so as to produce an active therapeutic drug. Prodrug approaches include chemical modifications of drugs to improve, e.g., stability, permeability and/or bioavailability, in the circulation system and/or in the target cell and tissues, while minimally affecting the pharmacokinetic profile of the drug. For example, a prodrug may feature modification of the charge and lipophilicity of a drug in favor of blood brain barrier (BBB) permeability. Chemical modifications to produce prodrugs include, for example, esterification (i.e. reacting a carboxylic group -COOH in the drug with an alcohol ROH to form an ester -COOR and water), amidation (i.e. formation of an amide group -CO-NH_2 by replacing in a carboxylic group a carboxylic OH with NH_2), and/or salt form formation of the active drug. Additional prodrugs may be, for example, phosphoesters, carbamates or imines forms of the active drug, and the like.

[0027] Levodopa amides prodrugs, when administered to a subject, for example a human subject, are hydrolyzed *in vivo* by amido peptidase so as to afford release of levodopa (LD) in the periphery (and may be even in the brain). Conversion of LD to dopamine is therefore moderated, and a sustained level of dopamine at dopaminergic neurons is generated (Atlas et al., CNS Neuroscience & Therapeutics, 22: 461-467, 2016). The release profile of LD may enable the administration of lower doses of levodopa amide derivatives to thereby produce clinically meaningful effects with reduced adverse side effects and prolonged treatment period.

[0028] Levodopa is relatively rapidly metabolized to dopamine, thus, for example, in medicinal applications, LD is optionally co-administrated/co-formulated with a decarboxylase inhibitor and/or a COMT inhibitor so as to improve the pharmacokinetics of LD.

[0029] Levodopa amide derivatives contemplated in a disclosed formulation are described, for example, in U.S. Patent Application No. 8,048,926, International Application Publication No. WO 2017/09003 and Zhou et al. (Eur. J. Med. Chem. 45:4035-4042, 2010), the content of which is incorporated herein by reference.

[0030] For example, a contemplated formulation may comprise one or more levodopa amide derivatives presented by the general formula I:



(I)

or an enantiomer, diastereomer, or racemate thereof,

wherein:

R1, R2, R3 and R4, 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 R1 and R2 together with the nitrogen atom to which they are attached and/or or R3 and R4, together with the nitrogen atom to which they are attached, independently, form a 5- or 6-membered ring;

R5 and R6 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.

[0031] The term "alkyl" as used herein means a straight or branched saturated hydrocarbon group having 1-6 carbon atoms and includes, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isoamyl, 2,2-dimethylpropyl, n-hexyl, and the like. Exemplary alkyl groups are (C_1-C_3)alkyl groups such as methyl and ethyl. The alkyl group may be unsubstituted or substituted. In an exemplary embodiment, the alkyl is substituted with amino group. For example, the substituted alkyl is (C_1-C_3)alkyl-NH_2

[0032] The terms "alkenyl" and "alkynyl" as used herein mean straight and branched hydrocarbon radicals having 2-6 carbon atoms and one or more double or triple bonds, respectively, and include ethenyl, propenyl, 3-buten-1-yl, 2-ethenylbutyl, and the like, and

propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, 3-hexynyl, and the like. Some exemplary embodiments feature C_2-C_3 alkenyl and alkynyl radicals, particularly C_2 alkenyl and alkynyl.

[0033] The term "cycloalkyl" as used herein means a cyclic or bicyclic hydrocarbyl group having 3-10 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, bicyclo[3.2.1]octyl, bicyclo[2.2.1]heptyl, and the like. Some exemplary embodiments feature (C_5-C_{10})cycloalkyls, particulalry (C_5-C_7)cycloalkyls. The cycloalkyl group may be unsubstituted or substituted.

[0034] The term "aryl" as used herein denotes an aromatic carbocyclic group having 6-14 carbon atoms consisting of a single ring or multiple rings either condensed or linked by a covalent bond such as, but not limited to, phenyl, naphthyl, phenanthryl, and biphenyl. The aryl group may be unsubstituted or substituted.

[0035] The term "heteroaryl", as used herein, refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having one or more heteroatoms selected from nitrogen, oxygen and sulfur, and a completely conjugated pi-electron system. Non-limiting examples of heteroaryl groups include pyrrole, furane, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline and purine.

[0036] Non-limiting examples of LDA derivatives encompassed by general formula I include compounds in which R1-R6 are as are listed in Table 1 below:

Table 1. Exemplary compounds encompassed by general formula I

R1	R2	R3	R4	R5	R6
H	H	H	H	-C(O)C(CH_3)$_3$	-C(O)C(CH_3)$_3$
H	H	H	H	-C(O)CH_2CH(CH3)$_2$	-C(O)CH_2CH(CH3)$_3$
H	H	H	H	-C(O)C(CH_3)$_2$$CH_2$$CH_3$	-C(O)C(CH3)$_2$$CH_2$$CH_3$
H	H	H	H	-C(O)CH_2C(CH_3)$_3$	-C(O)CH_2C(CH3)$_3$
H	H	H	H	-C(O)$CH_2$$CH_3$	-C(O)$CH_2$$CH_3$
H	H	H	H	H	H
-CH_3	H	H	H	H	H
-$CH_2$$CH_3$	H	H	H	H	H
-CH(CH_3)$_2$	H	H	H	H	H
-CH_3	-CH_3	H	H	H	H
-$CH_2$$CH_2$-phenyl	H	H	H	H	H
H	H	H	H	-CH_3	-CH_3
H	-CH_3	H	H	-CH_3	-CH_3
-$CH_2$$CH_3$	H	H	H	-CH_3	-CH_3
-CH(CH_3)$_2$	H	H	H	-CH_3	-CH_3
-CH_3	-CH_3	H	H	-CH_3	-CH_3
-CH(CH_3)$_2$	-CH_3	H	H	H	H
-$CH_2$$CH_3$	-CH_3	H	H	H	H
-$CH_2$$CH_2$$CH_3$	-CH_3	H	H	H	H
-CH_2-phenyl	-CH_3	H	H	H	H
-$CH_2$$CH_2$$NH_2$	-CH_3	H	H	H	H

[0037] In some embodiments, the levodopa amide derivative is the compound 2-amino-3-(3,4-dihydroxyphenyl)propanamide, also termed herein "levodopa amide free base" (LDA FB).

[0038] In some embodiments, the LDA derivative is an acid addition salt of 2-amino-3-(3,4-dihydroxyphenyl) propanamide, for example, HCl salt, fumaric acid salt, lactate salt, maleic acid salt, gluceptic acid salt, phosphoric acid salt, sulfuric acid, and the like.

Formulations

[0039] In an aspect of the present disclosure, a formulation is provided, comprising a levodopa amide compound and an acid selected from a monovalent, divalent, and/or trivalent acid, and, optionally, a pharmaceutically acceptable carrier.

[0040] The term "formulation", as used herein, refers to any mixture of different components or ingredients prepared in a certain way, i.e., according to a particular formula, and used for a specific purpose such as, but not limited to, medicinal, agricultural, veterinarian, horticulture, environmental or applied in a chemical process. For example, a formulation may include one or more active ingredients combined or formulated together with, for example, one or more carriers, excipients, stabilizers and the like. The formulation may comprise solid and/or non-solid, e.g., liquid, gel, semi-solid (e.g. gel, wax) or gas components.

[0041] The term "pharmaceutical composition", as used herein, refers to a formulation designed for medicinal utilization such as, but not limited to, therapeutic or diagnostic utilization, comprising one or more biologically and/or chemically active agents, combined or formulated together with one or more pharmaceutically and physiologically acceptable carriers, which can be administered to a subject (e.g., human or non-human subject) in a specific form, such as, but not limited to, a tablet, linctus, ointment, infusion or injection. A pharmaceutical composition is sometimes also referred to herein as "medicinal formulation".

[0042] Some embodiments described herein pertain to liquid pharmaceutical compositions, for example aqueous pharmaceutical compositions.

[0043] In some embodiments, a contemplated LDA derivative formulation, e.g., a pharmaceutical formulation is a suspension.

[0044] The terms "active agent" and "active ingredients", as used herein are interchangeable and refer to a compound, which is accountable for a desired biological or chemical effect. In the context of embodiments described in the present disclosure, the active agent may be at least one of the levodopa amide compounds as defined herein. In embodiments pertaining to medicinal formulations, the active agent may be a levodopa amide derivative, for example, as represented by formula I herein or a pharmaceutically acceptable salt thereof, carbidopa, a carbidopa prodrug or a pharmaceutically acceptable slat thereof, and the biological desired effect is treatment, amelioration, prevention, mitigation and/or curing of a central nervous system (CNS) disease or disorder such as Parkinson's disease. A levodopa amide derivative or a pharmaceutically acceptable salt thereof, carbidopa, a carbidopa prodrug or a pharmaceutically acceptable slat thereof, each is also referred to herein as a "main active agent" or "prime active agent", interchangeably.

[0045] As used herein, the terms "pharmaceutically acceptable", "pharmacologically acceptable" and "physiologically acceptable" are interchangeable and mean approved by a

regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. These terms include formulations, molecular entities, and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by, e.g., the U.S. Food and Drug Administration (FDA) agency, and the European Medicines Agency (EMA).

[0046] Herein, the phrase "physiologically suitable carrier" refers to an approved carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of a possible active agent. Physiologically suitable carriers in liquid medicinal formulations may be, for example, solvents or dispersion media.

[0047] In an aspect of the present disclosure, provided herein is, formulation comprising a LDA derivative and one or more acids selected from a monovalent, divalent or a trivalent acid. The formulation may be, for example, an aqueous formulation, and the acid may serve, for example, as a counter ion of the basic LDA derivative, thereby facilitating solubilization thereof.

[0048] The amount of LDA derivative in a contemplated formulation may be in the range of from about 1% to about 25%, for example, from about 5% to about 20%, from about 1% to about 5%, from about 3% to about 8%, from about 5% to about 10%, from about 5% to about 15%, from about 8% to about 15%, from about 5% to about 20%, from about 10% to about 15%, from about 10% to about 20%, from about 12% to about 18%, from about 15% to about 20%, from about 5% to about 25%, from about 17% to about 23%, or from about 20% to about 25%, and any ranges, sub ranges and individual values therebetween.

[0049] In some embodiments, a contemplated formulation comprises from about 5% to about 20%, from about 10% to about 25%, about 5%, about 10%, about 15% or about 25% by weight of a levodopa amide derivative.

[0050] In some embodiments, a formulation described herein may comprise an organic solvent. One or more organic solvents may be used in a contemplated formulation, for example, for solubilizing the LDA derivative. Formulation comprising organic solvent(s) may comprise lower amount of acids than would be otherwise required to solubilize the LDA derivative.

[0051] Non-limiting examples of organic solvents suitable for the purpose of embodiments described herein include: methanol, N-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide

(DMSO), dimethyl acetamide (DMA), tetrahydrofuran (THF), ethanol, isopropanol, propylene glycol (PG), glycerin, tetraglycol, transcutol, and polyethylene glycol (PEG), dioxane and dimethyl formamide (DMF).

[0052] The amount of the organic solvent in a contemplated formulation may range from 0 to about 99.9%, for example, from about 0% to about 5%, from about 0% to about 10%, from about 5% to about 15%, from about 10% to about 15%, from about 13% to about 20%, from about 15% to about 25%, from about 20% to about 25%, from about 25% to about 35%, from about 30% to about 50%, from about 35% to about 65%, from about 40% to about 50%, from about 40% to about 60%, from about 50% to about 65%, from about 60% to about 65%, from about 63% to about 70%, from about 65% to about 75%, from about 70% to about 80%, from about 75% to about 85%, from about 80% to about 95%, or from about 90% to about 99%, and any ranges and subranges therebetween.

[0053] In exemplary embodiments, a contemplated formulation may contain about 1%, about 2%, about 5%, about 10%, about 15%, about 20%, about 40%, about 60%, about 80% organic solvent, for example, NMP or DMSO.

[0054] In some embodiments, a described formulation is a LDA derivative-containing liquid formulation, for example an aqueous formulation containing one or more LDA derivatives, having a pH of from about 2 to about 11 at 25°C, for example, a pH of from about 2.0 to about 9.0, from about 6.0 to about 11.0, from about 2.0 to about 3.5, from about 2.5 to about 4.3, from about 3.0 to about 4.5, from about 3.3 to about 5.5, from about 4.0 to about 5.5, from about 5.0 to about 7.5, from about 5.2 to about 7.5, from about 5.5 to about 5.8, from about 6.0 to about 6.5, from about 6.0 to about 7.0, from about 6.5 to about 7.3, from about 6.5 to about 8.0, from about 6.5 to about 6.9, from about 6.5 to about 7.0, from about 6.0 to about 9.5, from about 6.6 to about 7.1, from about 6.7 to about 7.0, from about 6.8 to about 7.0, from about 6.9 to about 7.2, from about 7.0 to about 7.2, from about 7.0 to about 7.5, from about 7.1 to about 8.5, from about 7.1 to about 7.3, from about 7.2 to about 7.4, from about 7.2 to about 7.8, from about 7.5 to about 7.8, from about 7.3 to about 7.5, from about 7.4 to about 7.6, from about 7.5 to about 8.5, from about 7.7 to about 8.3, from about 7.1 to about 9.5, from about 8.0 to about 8.8, from about 7.5 to about 8.5, from about 8.5 to about 9.0, from about 8.5 to about 9.5, from about 9.0 to about 9.5, from about 9.5 to about 10.0, from about 9.5 to about 10.5, or from about 9.5 to about 11.0, and any ranges, sub ranges and individual values therebetween.

[0055] In exemplary embodiments, provided herein is a pharmaceutical composition, for example, aqueous, having a pH of from about 2.0 to about 9.0, from about 6.0 to about 11.0,

from about 6.5 to about 7.5, from about 6.6 to about 7.1, from about 6.7 to about 7.0, from about 7.1 to about 9.5, from about 7.1 to about 8.5, or from about 6.5 to about 8.0 at 25°C, the composition comprising one or more acids and from about 1% to about 30%, or from about 5% to about 20%, by weight of a levodopa amide derivative.

[0056] The molar ratio of the LDA derivative and a one or more acids in a contemplated formulation (herein generally referred to as "LDA derivative:acid" or simply "LDA:acid") may be from about 1.0:0.1 to about 1.0:2.0 or more. For example, the molar ratio LDA:acid may be from about 1.0:0.1 to about 1.0:0.89, from about 1.0:0.1 to about 1.0:0.5, from about 1.0:0.2 to about 1.0:0.5, from about 1.0:0.3 to about 1.0:0.6, from about 1.0:0.4 to about 1.0:0.6, from about 1.0:0.2 to about 1.0:0.7, from about 1.0:0.5 to about 1:0.8, from about 1.0:0.5 to about 1.0:1.0, from about 1.0:0.05 to about 1.00:1.15, from about 1.0:0.6 to about 1.0:0.8, from about 1.0:0.7 to about 1.0:0.87, from about 1.0:0.6 to about 1.0:0.89, from about 1.0:0.8 to about 1.0:0.9, from about 1.0:0.8 to about 1.0:1.0, from about 1.0:0.9 to about 1.0:1.1, from about 1.0:0.95 to about 1.0:1.2, from about 1.0:1.0 to about 1.0:1.2, from about 1.0:1.5 to about 1.0:2.0, about 1.0:0.5, about 1.0:0.33, about 1.0:0.25, or about 1.0:0.2, and any ranges and individual values therebetween.

[0057] To be noted, the ratio term "LDA:acid", as used herein, encompasses the molar ratio of a LDA derivative and one particular acid present in the formulation, for example, a monovalent, divalent or trivalent acid, as well as the molar ratio of one or more LDA derivatives and one, two, three, four or more acids (e.g., all acids) present in the formulation.

[0058] The acid in a formulation may be an organic acid, an inorganic acid, or any combination thereof. The acid may serve as a counter ion for solubilizing one or more LDA derivatives present in the formulation. Examples of suitable organic acids include, without being limited to, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, hippuric acid, maleic acid, malic acid, fumaric acid, tartaric acid, benzoic acid, acetic acid, citric acid, ascorbic acid, lactic acid, lactobionic acid, gluconic acid, galactaric acid, gluceptic (glucoheptanoic) acid, D-glucuronic acid, glutaric (pentanedioic) acid, glycolic (hydroxyacetic) acid, isethionic (2-hydroxy-ethanesulfonic) acid, formic acid, propionic (propanoic) acid, succinic (butanedioic) acid, oxalic acid, xinafoic (1-hydroxy-2-naphthoic) acid, carbidopa, an acidic amino acid selected from glutamic acid, levodopa and aspartic acid, or a lipophilic acid such as a fatty acid. Examples of suitable inorganic acids include, but are not limited to, hydrochloric acid (HCl), hydrobromic acid (HBr), phosphoric acid (H_3PO_4), sulfuric acid (H_2SO_4), and carbonic acid.

[0059] In exemplary embodiments, a disclosed pharmaceutical composition comprises hydrochloric acid, succinic acid, glutamic acid, citric acid, tartaric acid and/or acetic acid as a counter ion.

[0060] In some embodiments, the acid is a monovalent acid, for example, acetic acid, ascorbic acid, lactic acid (unspecified form), gluconic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, benzoic acid, boric acid, butyric acid, caprylic acid, deoxycholic acid, diatrizoic acid, erythorbic acid, formic acid, gentisic acid ethanolamine, lactobionic acid, levulinic acid, hydrochloric acid, hydrobromic acid, hippuric acid, gluceptic acid, glucuronic acid, glycolic acid, isethionic acid, isostearic acid, methylboronic acid, myristic acid, nitric acid, oleic acid, palmitic acid, propionic acid, sorbic acid, stearic acid, undecylenic acid, xinafoic acid and carbonic acid. In the context of such embodiments, the molar ratio of a LDA derivative and monovalent acid may be, for example, from about 1.0:0.10 to about 1.0:1.00, from about 1.00:0.10 to about 1.00:0.89, from about 1.0:0.30 to about 1.0:0.90, from about 1.0:0.40 to about 1.0:0.80, from about 1.0:0.50 to about 1.0:0.70, about 1.0:0.50, about 1.0:0.75, about 1.0:0.80, about 1.0:0.85, about 1.0:0.89, about 1.0:1.10, about 1.0:1.70, about 1.0:1.80, about 1.0:1.90, about 1.0:2.00, or about 1.0:≥2.0.

[0061] In some embodiments, the acid is a divalent acid, for example, adipic acid, maleic acid, malic acid, fumaric acid, tartaric acid, galactaric acid, glutaric acid, oxalic acid, succinic acid, glutamic acid, glutamic acid hydrochloride, aspartic acid, phosphoric acid sebacic acid and sulfuric acid. In the context of such embodiments, the molar ratio of a LDA derivative and divalent acid may be, for example, about 1.0:0.4, about 1.0:0.75, about 1.0:0.8, about 1.0:0.85, about 1.0:1.1, about 1.0:1.7, about 1.0:1.8, about 1.0:1.9, about 1.0:2.0, or about 1.0:≥2.0.

[0062] In some embodiments, the acid is a trivalent acid, for example, citric acid, fatty acid glycerides, and hydrogenated tallow acid, and the molar ratio of a LDA derivative and trivalent acid may be, for example, about 1.0:0.4, about 1.0:0.5, about 1.0:0.75, about 1.0:0.8, about 1.0:0.85, about 1.0:1.1, about 1.0:1.7, about 1.0:1.8, about 1.0:1.9, about 1.0:2.0, or about 1.0:≥2.0.

[0063] In an exemplary embodiment, a contemplated formulation may have a pH of from about 2.0 to about 9.0, from about 7.1 to about 8.5, from about 6.7 to about 7.1, from about 6.0 to about 9.5, or from about 6.5 to about 8.0 at 25°C, the formulation may comprise a monovalent acid, and from about 1% to about 30%, or from about 5% to about 20%, by weight of a LDA compound, wherein the composition is stable for at least 24 hours at room temperature.

[0064] In an exemplary embodiment, a contemplated formulation may have a pH of from about 4.0 to about 11.0, from about 6.5 to about 7.5, from about 6.6 to about 7.1, from about 6.7 to about 7.0, or from about 7.1 to about 9.5 at 25°C, the composition may comprise a divalent or trivalent acid, and from about 1% to about 30%, or from about 5% to about 20%, by weight of a LDA derivative, wherein the molar ratio of the LDA compound to the acid is from about 1:0.1 to about 1:1.2, but excluding molar ratios of 1:0.50 and 1:0.33 when the pH is from about 6.0 to about 7.0, wherein the composition is stable for at least 24 hours at room temperature.

[0065] A formulation, for example a contemplated pharmaceutical composition, may comprise a pharmaceutically acceptable salt, e.g., an acid addition salt of a levodopa amide compound.

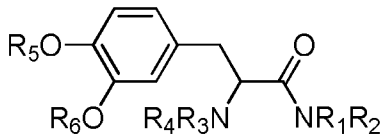
[0066] As used herein, the term "pharmaceutically acceptable salt", refers to a salt of a compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, or allergic response, and are commensurate with a reasonable benefit/risk ratio. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, hippuric acid, methanesulfonic acid, ascorbic acid, malonic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, fumaric, benzoic acid, cinnamic acid, a sulfonic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; and (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion such as lithium, sodium or potassium, an alkaline earth ion such as calcium or magnesium, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, dicyclohexylamine, and the like.

[0067] Other pharmaceutically acceptable salts, include adipate, alginate, ascorbate, aspartate, benzenesulfonate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, digluconate, dodecylsulfate, ethanesulfonate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, laurate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oleate, palmitate, pamoate, pectinate,

persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, and valerate salts.

[0068] A contemplated formulation may be stable for at least 24 hours. Exemplary formulations may be stable for at least 24, for at least 48, for at least 72, for at least 96 hours, for at least 1, 2 or 3 weeks, or for at least 1, 2 or 3 months, and even for at least 1 year, at room temperature or at -20 to -80°C.

[0069] In any of the embodiments described herein, a disclosed formulation may have an acid, for example a monovalent, divalent or trivalent acid, and at least one LDA derivative represented by the general formula I:



(I)

or an enantiomer, diastereomer, or racemate thereof, wherein:

R1, R2, R3 and R4, 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 R1 and R2 together with the nitrogen atom to which they are attached and/or or R3 and R4, together with the nitrogen atom to which they are attached, independently, form a 5- or 6-membered ring;

R5 and R6 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.

[0070] In exemplary embodiments, a contemplated formulation, for example a medicinal formulation, may comprise an acid and a LDA compound of formula I herein, a salt thereof (e.g., a pharmaceutically acceptable slat), an enantiomer, diastereomer, and/or racemate thereof, wherein:

(i) R1, R2, R3 and R4 each is H;

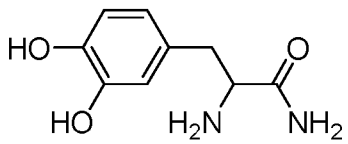
(ii) one of R1 and R2, and/or one of R3 and R4, each is -C(=O)-R' wherein R' is (C_1-C_6)alkyl, for example (C_1-C_3)alkyl such as methyl, ethyl or propyl, and the others of R1, R2, R3 and R4 each is H;

(iii) one of R1 and R2, and/or one of R3 and R4 is -C(=O)-(C_1-C_6)alkyl, for example -C(=O)-(C_1-C_3)alkyl such as -C(=O)-methyl or -C(=O)-ethyl, and the others of R1, R2, R3 and R4 each is H.

[0071] In an exemplary embodiment, a contemplated pharmaceutical composition may comprise a LDA derivative of formula I herein, a pharmaceutically acceptable salt thereof, an enantiomer, diastereomer, and/or racemate thereof, wherein R5 and R6 each independently is (C_1-C_3)alkyl, for example, methyl or ethyl, or H. In alternative exemplary embodiments, R5 and R6 each is H.

[0072] In an exemplary embodiment, a contemplated pharmaceutical composition may comprise a LDA derivative of formula I herein, a pharmaceutically acceptable salt thereof, an enantiomer, diastereomer, and/or racemate thereof, wherein (i) R1, R2, R3 and R4 each is H; or one of R1 and R2, and/or one of R3 and R4, each is -C(=O)-(C_1-C_6)alkyl, for example, -C(=O)-(C_1-C_3)alkyl, and the others of R1, R2, R3 and R4 each is H; and (ii) R5 and R6 each independently is (C_1-C_3)alkyl, preferably methyl or ethyl, or H. In particular such embodiments, (i) R1, R2, R3, R4, R5 and R6 each is H; or one of R3 and R4 is -C(=O)-(C_1-C_6)alkyl, for example -C(=O)-(C_1-C_3)alkyl, and the others of R1, R2, R3 and R4, as well as R5 and R6, each is H.

[0073] In some exemplary embodiments, a contemplated formulation comprises the compound 2-amino-3-(3,4-dihydroxyphenyl) propanamide (levodopa amide free base) represented by the structural formula:



or a pharmaceutically acceptable salt thereof, an enantiomer or racemate thereof.

[0074] In an aspect of any of the embodiments described herein, a described pharmaceutical composition may further comprise a decarboxylase inhibitor or a prodrug thereof, added to the formulation in order to inhibit an undesired enzymatic decarboxylation of levodopa to dopamine outside the central nervous system (CNS). The decarboxylase inhibitor may be, for example, carbidopa, benserazide, a prodrug thereof (e.g., an ester of a carbidopa), or a salt thereof, e.g., the arginine-, histidine-, or lysine-salt of carbidopa or of a prodrug thereof.

[0075] The molar ratio of a LDA derivative to a decarboxylase inhibitor may be from about 1:1 to about 100:1, from about 2:1 to about 60:1, from about 5:1 to about 40:1, or from about 10:1 to about 40:1.

[0076] In exemplary embodiments, molar ratio of a LDA derivative to a decarboxylase inhibitor is, for example, 4:1, 8:1 or 23:1.

[0077] Any one of the formulations contemplated herein may include, besides one or more LDA derivatives and optionally a decarboxylase inhibitor which may be regarded as the prime active agents, at least one ingredient selected from a secondary active agent, a stabilizer to e.g., provide stabilization to the active agent(s) and optionally protect it against breakdown (e.g., hydrolysis) before it reaches its end target, a buffering agent to maintain a desired pH of the formulation, physiologically suitable carriers, and/or excipients such as diluents, lubricants, glidants, disintegrants, preservatives, flavors, bulking agents (e.g. mannitol), antioxidants (e.g., ascorbic acid or sodium bisulfite), local anesthetics and combinations thereof.

[0078] In some embodiments, a disclosed pharmaceutical composition may comprise one or more LDA derivatives, one or more acids, a decarboxylase inhibitor (or a prodrug thereof) and, optionally, either one of, or at least one of, a basic amino acid or an amino sugar. The basic amino acid and/or the amino sugar may be added to a disclosed formulation so as to help is solubilizing the decarboxylase inhibitor. The basic amino acid may be, for example, arginine, histidine, or lysine. The amino sugar may be, for example, meglumine, D-glucosamine, sialic acid, N-acetylglucosamine, galactosamine or a combination thereof.

[0079] In some of any of the embodiments described herein, a contemplated pharmaceutical composition may further comprise a buffer. Examples of buffers that may be used in accordance with described embodiments include, without being limited to, citrate buffer, acetate buffer, sodium acetate buffer, tartrate buffer, phosphate buffer, borate buffer, carbonate 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.

[0080] Any of the active agents as defined herein may undergo oxidation and/or degradation resulting in release of various degradants. For example, hydrazine may result from oxidative degradation of carbidopa or a prodrug thereof. Hydrazine is a carcinogen, thus, it is important to reduce the release of hydrazine into the pharmaceutical compositions.

[0081] Disclosed formulations may include active agents such as one or more LDA derivatives, carbidopa, a carbidopa prodrug, and/or pharmaceutically acceptable salts thereof and any combination thereof, and further include one or more agents that inhibit the formation of oxidation products as well as the formation of other degradants after the prodrugs are administered into the body. Such agents may be e.g., antioxidants, tyrosinase inhibitors and/or Cu^{2+} chelators.

[0082] As used herein, the term "antioxidant" refers to a substance which slows down the damage that can be caused to other substances by the effects of oxygen. In other words, an antioxidant inhibits the oxidation of other molecules. Antioxidants include two different groups of substances: industrial chemicals which are added to products to prevent oxidation, and natural chemicals found in foods and body tissue. Non-limiting examples of antioxidants include ascorbic acid (vitamin C) or a salt thereof (e.g., sodium ascorbate, calcium ascorbate, potassium ascorbate, ascorbyl palmitate, and ascorbyl stearate); cysteine or a cysteine derivative such as L-cysteine, N-acetyl cysteine (NAC), glutathione, thiol precursor such as L-2-oxo-4-thiazolidine carboxylic acid (OTC), or a salt thereof; lipoic acid; uric acid; carotenes; α-tocopherol (vitamin E); and ubiquinol (coenzyme Q).

[0083] Further antioxidants contemplated herein are phenolic antioxidants such as di-*tert*-butyl methyl phenols, *tert*-butyl-methoxyphenols, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), polyphenols, tocopherols, ubiquinones (e.g., caffeic acid, *tert*-butylhydroquinone (TBHQ)), propyl gallate, flavonoid compounds, cinnamic acid derivatives, coumarins, and others.

[0084] Other contemplated antioxidants that may form part of a disclosed formulation include sulfite salts such as sodium hydrogen sulfite or sodium bisulfite (e.g. sodium metabisulfite).

[0085] Ascorbic acid is a monosaccharide oxidation-reduction (redox) catalyst found in both animals and plants. Ascorbic acid acts as an oxygen scavenger to reduce molecular oxygen.

[0086] Thiol containing compounds such as cysteine, NAC, glutathione and thiol precursors such as OTC have several potential antioxidant effects. These agents can directly scavenge radicals via hydrogen donation from their SH group, resulting in formation of a thiyl (S) radical.

[0087] Disclosed formulations can include one, two, or more antioxidants. For example, a disclosed formulation can include one, two, or more of an agent selected from the group

consisting of ascorbic acid or a salt thereof, for example, sodium ascorbate, calcium ascorbate, potassium ascorbate, ascorbyl palmitate, and ascorbyl stearate, particularly sodium ascorbate, and cysteine or a cysteine derivative, for example, L-cysteine, NAC, glutathione, or a salt thereof.

[0088] In an exemplary embodiment, a disclosed formulation may include ascorbic acid, or a salt thereof.

[0089] Contemplated formulation that comprise ascorbic acid or a salt thereof (e.g., sodium ascorbate), may include from about 0.01% to about 1.0% by weight, or more, ascorbic acid (or salt thereof). For example, from about 0.01% to about 0.05%, from about 0.03% to about 0.1%, from about 0.1% to about 0.2%, from about 0.1% to about 0.3%, from about 0.2% to about 0.35%, from about 0.2% to about 0.5%, from about 0.3% to about 0.45%, from about 0.4% to about 0.6%, from about 0.5% to about 0.65%, from about 0.5% to about 0.8%, from about 0.6% to about 0.9%, or from about 0.7% to about 0.95%, or from about 0.8% to about 1.0%, by weight ascorbic acid or salt thereof such as sodium ascorbate.

[0090] In exemplary embodiments, a disclosed formulation may include, for example, about 0.01%, about 0.10%, about 0.25%, about 0.40%, about 0.50%, about 0.60%, about 0.70%, about 0.75%, about 0.80%, about 0.85%, about 0.90%, about 0.95%, or about 1.00%, by weight sodium ascorbate or ascorbic acid as antioxidant.

[0091] In some embodiments, a disclosed formulation may comprise L-cysteine or a pharmaceutically acceptable salt thereof, NAC or a pharmaceutically acceptable salt thereof, glutathione or a pharmaceutically acceptable salt thereof, and/or sodium bisulfite or a pharmaceutically acceptable salt thereof.

[0092] In some embodiments, disclosed formulations may include a bisulfite, e.g., sodium bisulfite or other sulfite salts, e.g., sodium hydrogen sulfite or sodium metabisulfite.

[0093] Contemplated pharmaceutical compositions may comprise from about 0.001% to about 1.0% by weight, or more, L-cysteine. For example, in some embodiments a disclosed pharmaceutical composition includes from about 0.01% to about 1.00%, from about 0.1% to about 0.6% or from about 0.3% to about 0.5% by weight L-cysteine or a pharmaceutically acceptable salt thereof.

[0094] In exemplary embodiments, a disclosed pharmaceutical composition includes about 0.3%, about 0.4% or about 0.5% by weight L-cysteine or a pharmaceutically acceptable salt thereof.

[0095] Contemplated pharmaceutical compositions may include NAC at varying concentrations in a range of, for example, from about 0.001% to about 1.0%, or more. In exemplary embodiments, a disclosed pharmaceutical composition comprises from about 0.01% to about 0.5% by weight NAC.

[0096] In exemplary embodiments, a disclosed pharmaceutical composition includes about 0.1%, about 0.2%, about 0.3%, about 0.4% or about 0.5% by weight NAC or a pharmaceutically acceptable salt thereof.

[0097] Contemplated pharmaceutical compositions may include sodium bisulfite at varying concentrations ranging, for example, from about 0.01% to about 1.0%, or more. In exemplary embodiments a disclosed pharmaceutical composition includes from about 0.075% to about 0.75% by weight sodium bisulfite or a pharmaceutically acceptable salt thereof.

[0098] In exemplary embodiments, a disclosed pharmaceutical composition includes about 0.1% by weight sodium bisulfite.

[0099] Contemplated pharmaceutical compositions may include glutathione at varying concentrations ranging, for example, from about 0.001% to about 1.0% by weight, or more. For example, in some embodiments a disclosed pharmaceutical composition includes from about 0.1% to about 0.7% by weight glutathione or a pharmaceutically acceptable salt thereof.

[0100] Contemplated formulation may comprise, for example, NAC, L-cysteine, glutathione, and/or a pharmaceutically acceptable salt thereof.

[0101] For example, a disclosed pharmaceutical composition may include: from about 0.001% to about 0.5%, from about 0.010% to about 1.0%, from about 0.1% to about 0.6%, about 0.3% or about 0.4% by weight L-cysteine or a pharmaceutically acceptable salt thereof such as L-cysteine hydrochloride; from about 0.001% to about 0.5%, from about 0.01% to about 1.0%, about 0.1%, about 0.2%, about 0.3%, or about 0.4% by weight NAC; from about 0.01% to about 1.0%, from about 0.075% to about 0.75%, or about 0.1% by weight sodium bisulfite; and/or from about 0.001% to about 0.5%, or from about 0.1% to about 1.0% by weight glutathione.

[0102] In exemplary embodiments, a formulation includes from about 0.001% to about 1.0%, from about 0.01% to about 1.0%, from about 0.1% to about 0.5%, or from about 0.1% to about 1% by weight of a compound selected from the group consisting of NAC, L-cysteine, glutathione, and/or a pharmaceutically acceptable salt thereof.

[0103] For example, a disclosed formulation can include from about 0.01% to about 1.0%, e.g., from about 0.05% to about 0.3%, from 0.2% to about 0.6%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, or about 0.5% by weight of NAC and/or L-cysteine.

[0104] Formulations including at least two antioxidants (e.g., one of them being L-cysteine or NAC) can result in substantially lower levels of oxidation products, for example, hydrazine, as compared to formulations with fewer antioxidants. For example, when two antioxidants are included in the formulation, they may be ascorbic acid and L-cysteine, or ascorbic acid and NAC, or sodium ascorbate and L-cysteine, or sodium ascorbate and NAC.

[0105] In some embodiments, a contemplated formulation may comprise a first antioxidant which is ascorbic acid or a salt thereof, and a second antioxidant which is L-cysteine and/or a cysteine derivative, or a pharmaceutically acceptable salt thereof such as cysteine hydrochloride, NAC, sodium bisulfite, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tocopherol or gentisic acid. Exemplary embodiments contemplate a pharmaceutical composition comprising ascorbic acid and L-cysteine, sodium ascorbate and NAC, ascorbic acid and NAC, sodium ascorbate and L-cysteine, ascorbic acid and glutathione, or sodium ascorbate and glutathione.

[0106] In an exemplary embodiment, a disclosed formulation may include ascorbic acid, or salt thereof, and a cysteine derivative.

[0107] Oxidation of carbidopa or a prodrug thereof may further occur in the body, for example, by tyrosinase, a copper-containing enzyme, which is involved in the conversion of an o-diphenol (or a di-hydroxy phenyl) moiety to the corresponding o-quinone.

[0108] Tyrosinase inhibitors contemplated herein include, but not limited to, captopril, methimazole, quercetin, arbutin, aloesin, N-acetylglucoseamine, retinoic acid, α-tocopheryl, ferulate, Mg ascorbyl phosphate (MAP), substrate analogues (e.g., sodium benzoate, L-phenylalanine) and/or Cu^{2+} chelators.

[0109] Non-limiting examples of Cu^{2+} chelators include, Na_2-EDTA, Na_2-EDTA-Ca, DMSA (succimer), D-penicillamine (DPA), trientine-HCl, dimercaprol, clioquinol, sodium thiosulfate,

triethylenetetramine (TETA), tetraethylenepentamine (TEPA), curcumin, neocuproine, tannin, and/or cuprizone.

[0110] Contemplated pharmaceutical compositions may include a surfactant. Non-limiting examples of surfactants include polysorbate 20, 40, 60 and/or 80, (Tween®-20, Tween®-40, Tween®-60 and Tween®-80, respectively), Span 20, Span 40, Span 60, Span 80, Span 85, polyoxyl 35 castor oil (Cremophor EL), polyoxyethylene-660-hydroxystearate (macrogol 660), triton or Poloxamer 188 (Pluronic® F-68).

[0111] For example, polysorbate 80 (Tween® 80) may be present in varying amounts, ranging, for example, from about 0.01% to about 5.0%, from about 0.1% to about 0.5%, or about 0.3% by weight of polysorbate 80 or another surfactant.

[0112] A contemplated pharmaceutical composition may, optionally, further comprise one or more excipients.

[0113] Herein the term "excipient" refers to an inert substance added to a pharmaceutical composition (formulation) to further facilitate process and administration of the active ingredients. “Pharmaceutically acceptable excipients”, as used herein, encompass preservatives, antioxidants, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents in combination with pharmaceutically active agents is well known in the art. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, terpens and polyethylene glycols.

[0114] Excipients suitable for formulations described herein may comprise, for example, an enhancer and/or a gelation agent and/or a thickening agent. Contemplated enhancers include pyrrolidones such as N-methyl-2-pyrrolidone (NMP) or polyvinyl alcohol (PVP), polyols, terpenes (nonaromatic compounds found in essential oils, which may be extracted from flowers, fruits, and other natural products), glycerol, lauroglycol, propylene glycol, diethylene glycol monoethyl ether, and/or propylene glycol monocaprylate. Contemplated thickening agents include cellulose polymers such as hydroxypropyl cellulose, and/or carbomer polymers and derivatives, e.g., polysaccharides (agarose) polyacrylic polymers, poloxamers, and mixtures thereof.

[0115] Further excipients are exemplified by terpenes such as, but not limited to, d-limonene, dipentene (d/l-limonene), α-pinene, γ-terpinene, β-mircene, p-cimene, α-pinene, α-

phellandrene, citronellol, geraniale (citrale), nerol, beta-carotene, menthol, geraniol, farnesol, phytol, their homologs, derivatives, enantiomers, isomers including constitutional isomers, stereoisomerisms, regioisomers, and geometric isomers, and any combinations thereof.

[0116] Further excipients are exemplified by ethanolamines, e.g., monoethanolamine, diethanolamine, triethanolamine, phenyl ethanolamine, acetyl ethanolamine, or benzoyl ethanolamine.

[0117] In some embodiments, a disclosed pharmaceutical composition may further comprise one or more active agents, herein termed "secondary active agents" which may be added to the formulation so as to support, enhance, intensify, promote or strengthen the biological activity of the main or prime active agent(s). Additionally or alternatively, the secondary active compounds may provide supplemental or additional therapeutic functions. Non-limiting examples of a secondary active agent include a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) (either MAO-A or MAO-B) inhibitor. Particular COMT inhibitors include, without limiting, entacapone, tolcapone and opicapone; and particular MAO inhibitors can be selected from, e.g., moclobemide, rasagiline, selegiline, or safinamide.

[0118] Further secondary active agents may be exemplified by adamantans (e.g., amantadine), nicotinic receptor agonists (e.g., nicotine, galantamine), dopamine receptor agonists (e.g., apomorphine, rotigotine).

[0119] When a contemplated medicinal formulation comprises a LDA derivative and a decarboxylase inhibitor, these main active agents can be combined and formulated in the same pharmaceutical composition, namely, as a single unit dosage from or, alternatively, can be present in separate pharmaceutical compositions, namely a plurality of dosage unit forms, for example, two or more dosage unit forms, each comprising one or more of a first active agent (e.g., a LDA derivative, for example a compound corresponding in structure to a compound of formula I), and/or a second active agent (e.g., a decarboxylase inhibitors, for example carbidopa or a prodrug thereof).

[0120] For example, a medicinal formulation disclosed herein can comprise a first unit dosage form comprising one or more LDA derivatives (e.g., a derivative of formula I and/or a pharmaceutically acceptable salt thereof) and an acid (e.g., a monovalent, divalent or trivalent acid), and a second unit dosage form comprising one or more decarboxylase inhibitors (e.g., carbidopa, a prodrug thereof and/or a pharmaceutically acceptable salt thereof).

[0121] Alternatively, a formulation can comprise a L-dopa prodrug such as one or more LDA derivatives and a decarboxylase inhibitor such as carbidopa, a prodrug thereof and/or a pharmaceutically acceptable salt thereof in the same pharmaceutical composition.

[0122] A disclosed pharmaceutical composition may be formulated as a liquid, gel, cream, solid, film, emulsion, suspension, solution, lyophylisate or aerosol. For example, a contemplated pharmaceutical composition may be formulated as a liquid. When the pharmaceutical compositions comprise a plurality of dosage unit forms, for example two dosage unit forms, they can be formulated in different forms. For example, a first unit dosage form comprising, e.g. one or more LDA derivatives and acid, may be formulated as a liquid formulation, and the second unit dosage form comprising, e.g., carbidopa, can be formulated as a solid formulation.

[0123] Disclosed pharmaceutical compositions may be formulated for any suitable route of administration, e.g., for subcutaneous, transdermal, intradermal, transmucosal, intravenous, intraarterial, intramuscular, intraperitoneal, intratracheal, intrathecal, intraduodenal, intrapleural, intranasal, sublingual, buccal, intestinal, intraduodenally, rectal, intraocular, or oral administration. The compositions may also be formulated for inhalation, or for direct absorption through mucous membrane tissues.

[0124] When the pharmaceutical composition comprises a plurality of dosage unit forms, for example two dosage unit forms, they can be administered in different routes. For example, a first unit dosage form, comprising e.g., a LDA derivative and acid may administered subcutaneously as a liquid formulation, and a second unit dosage form comprising e.g., carbidopa, can be administered orally as a pill.

[0125] In embodiments described herein, the pharmaceutical compositions disclosed are aqueous, liquid formulations particularly useful for subcutaneous administration e.g., via in infusion pump.

[0126] In some embodiments, a contemplated formulation is designed for oral administration. Oral compositions, in accordance with such embodiments, may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and may be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like. Such compositions may further comprise one or more ingredients selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients, which are

suitable for the manufacture of tablets. These excipients may be, e.g., inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, or sodium phosphate; granulating and disintegrating agents, e.g., corn starch or alginic acid; binding agents, e.g., starch, gelatin or acacia; and lubricating agents, e.g., magnesium stearate, stearic acid, or talc. The tablets may be either uncoated or coated utilizing known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated using the techniques described in the U.S. Patent Nos. 4,256,108, 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for control release. The oral compositions may also be in the form of oil-in-water emulsions.

[0127] A composition in the form of a capsule for oral administration may be prepared by filling the suitable gelatin capsule with dry LDA derivative, for example, one or more LDA derivatives of the general formula I herein, and a filler such as methylcellulose or sodium carboxymethyl cellulose, and, optionally, coating the capsule with enteric coating. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, PVP, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0128] Pharmaceutical compositions for oral administration include push-fit capsules made of gelatin as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules may contain the active ingredients in admixture with filler such as lactose, binders such as starches, lubricants such as talc or magnesium stearate and optionally stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for the chosen route of administration.

[0129] For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

[0130] For administration by inhalation, the compositions are conveniently delivered in the form of an aerosol spray presentation from a pressurized pack or a nebulizer with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit

may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the active agent and a suitable powder base such as lactose or starch.

[0131] The compositions described herein may be formulated for parenteral administration, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multidose containers with optionally, an added preservative. The compositions may be suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0132] Pharmaceutical compositions for parenteral administration include aqueous solutions of the active ingredients in water-soluble form. Additionally, suspensions of the active ingredients may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acids esters such as ethyl oleate, triglycerides or liposomes. Aqueous injection suspensions may contain substances, which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient(s) may be in powder form for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use.

[0133] Pharmaceutical compositions for rectal administration may be prepared as suppositories or retention enemas, using for example conventional suppository bases such as cocoa butter or other glycerides.

[0134] Contemplated pharmaceutical compositions may also be formulated for local administration, such as a depot preparation. Such long acting formulations may be administered by implantation, e.g., subcutaneously or intramuscularly, or by intramuscular injection. Thus, the composition may be formulated, e.g., with suitable polymeric or hydrophobic materials, e.g., as an emulsion in an acceptable oil, or ion exchange resins, or as sparingly soluble derivatives such as sparingly soluble salts.

[0135] Formulations for topical administration may include, without limiting, lotions, suspensions, ointments gels, creams, drops, liquids, sprays emulsions and powders. For example, a disclosed composition in the form of gel for topical administration may be prepared by adding sodium metabisulfite, enhancers, e.g., lauroglycol, Capryol 90, and a gelation agent

such as hydroxypropyl cellulose, e.g., Klucel HFC or MF grades, or poly(acrylic) acid, polymethyacrylate (e.g., Carbopol 934P pH 5-6 with or without about 1-5% Eudragit RL-100), to an aqueous solution of a LDA derivative, e.g., one or more LDA derivatives of the general formula I. For example, a composition in the form of gel may be prepared by combining a LDA derivative, tolcapone, arginine in water, and propylene glycol containing enhancers gelled with hydroxypropyl cellulose, e.g., Klucel HFX.

[0136] Contemplated herein, in part, is a dermal patch suitable for transdermal or subcutaneous administration of an active agent that comprises a composition as disclosed herein.

[0137] In some embodiments, a pharmaceutical composition as disclosed herein is designed for a slow release of the LDA derivative, and therefore includes particles including said compound and a slow release carrier (typically, a polymeric carrier). Slow release biodegradable carriers are well known in the art. These are materials that may form particles that may capture therein an active compound(s) and slowly degrade/dissolve under a suitable environment (e.g., aqueous, acidic, basic, etc.), and thereby degrade/dissolve in body fluids and release the active compound(s) therein. The particles can be, e.g., nanoparticles, i.e., in the range of, e.g., from about 1 to about 500 nm, from about 50 to about 200 nm, or from about 100 nm, in diameter.

[0138] Also contemplated herein is a stable lyophilized powder comprising a LDA derivative, e.g., one or more LDA derivatives of the general formula I, a pharmaceutically acceptable salt thereof, an enantiomer, diastereomer, or racemate thereof. Such a lyophilized powder can be reconstituted into a liquid formulation by addition of water with or without antioxidants, surfactants and other excipients.

[0139] The pharmaceutical compositions disclosed herein are useful for treatment of diseases or disorders characterized by neurodegeneration and/or reduced levels of brain dopamine.

[0140] The term "physiologically acceptable pH" is understood to mean a pH of, e.g., a formulation or composition that facilitates administration of the formulation or composition to a patient without significant adverse effects, e.g., a pH of about 4 to about 9.8 (for example, about 4 ± 0.3 to about 9.5 ± 0.3).

[0141] "Ambient temperature" as understood by a person of skill in the art refers to a temperature of from about 10°C to about 30°C. In exemplary embodiments, ambient temperature can be 25°C.

[0142] Percentages disclosed herein are by weight unless indicated otherwise.

Methods of Treatment

[0143] In an aspect of the disclosure, provided herein is a method of treatment of a subject inflicted with a neurological disease or disorder, the method comprising administrating to the subject an effective amount of a formulation described herein, thereby threating the subject.

[0144] In some embodiments, the method comprises administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a levodopa amide derivative, for example one or more LDA derivatives represented by formula I as defined herein, and a monovalent, divalent and/or trivalent acid, wherein the molar ratios of the LDA derivative and the monovalent, divalent or trivalent acid are as defined herein.

[0145] For example, the composition administered to a subject in need thereof may comprise form about 5% to about 25% of a LDA derivative of formula I, and a monovalent acid such as, but not limited to, HCl, and the molar ratio of the LDA compound to the acid may be from about 1.00:0.80 to about 1.00:0.89.

[0146] For example, the composition administered to a subject in need thereof may comprise form about 5% to about 25% of a LDA derivative of formula I, and a divalent or trivalent acid such as, but not limited to, tartaric acid, citric acid, or glutamic acid, and the molar ratio of the LDA compound to the acid is, e.g., from about 1.00:0.30 to about 1.00:0.55.

[0147] In some embodiments, the formulation administered according to a contemplated method may comprise one or more LDA derivatives as defined herein as a first active agent, and at least one decarboxylase inhibitor as a second active agent, for example carbidopa, a carbidopa prodrug and/or a pharmaceutically acceptable salt thereof, and a monovalent, divalent and/or trivalent acid, wherein the molar ratios of the LDA derivative(s) and the monovalent, divalent and/or trivalent acid are as defined herein. Such a formulation may further comprise one or more of a basic amino acid, an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor, as defined herein. The molar ratio of the LDA derivative to the decarboxylase inhibitor may be from about 1:1 to about 100:1, for example, from about 2:1 to about 60:1, from about 4:1 to about 40:1, or from about 10:1 to about 40:1. In exemplary embodiments, the molar ratio LDA derivative: decarboxylase inhibitor is 4:1, 8:1 or 23:1.

[0148] In some embodiments, the formulation administered according to a contemplated method may comprise a LDA derivative, for example, one or more LDA derivatives of formula I, and at least one COMT inhibitor such as entacapone, tolcapone, or opicapone, and, optionally, and/or MAO inhibitor such as moclobemide, rasagiline, selegiline, or safinamide, and a monovalent, divalent and/or trivalent acid, wherein the molar ratios of the LDA derivative(s) and the monovalent, divalent or trivalent acid are as defined herein.

[0149] In some embodiments, the method comprises co-administering to a patient in need thereof at least two separate pharmaceutical compositions, the first pharmaceutical composition comprising one or more LDA derivatives as defined herein, and a monovalent, divalent and/or trivalent acid, wherein the molar ratios of the LDA derivative(s) and the monovalent, divalent and/or trivalent acid are as defined herein; and a second pharmaceutical composition comprising a decarboxylase inhibitor or a salt thereof, and, optionally, one or more of a basic amino acid, an amino sugar, a COMT inhibitor, or a MAO inhibitor.

[0150] For example, a contemplated method may comprise administration of a second pharmaceutical composition comprising carbidopa, a carbidopa prodrug and/or a pharmaceutically acceptable salt thereof as the decarboxylase inhibitor, optionally together with a basic amino acid such as arginine, an amino sugar such as meglumine, a COMT inhibitor such as entacapone, tolcapone or opicapone, and/or a MAO inhibitor such as moclobemide, rasagiline, selegiline or safinamide.

[0151] In some embodiments, the first pharmaceutical composition is essentially devoid of a decarboxylase inhibitor, and may, optionally, be devoid of a COMT inhibitor and/or a MAO inhibitor.

[0152] In some of any of the embodiments described herein, a pharmaceutical composition administered in a contemplated method may optionally be in a liquid form.

[0153] The neurological disease or disorder being treated by a contemplated method may be a neurological disorder such as a disorder associated with reduced dopamine or loss of dopaminergic neurons, or a movement disorder. Such diseases and disorders include, for example: neurological or movement disorders including restless leg syndrome, Parkinson's disease, secondary parkinsonism, Huntington's disease, Parkinson's like syndrome, PSP, MSA, ALS, Shy-Drager syndrome, dystonia, Alzheimer's 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.

[0154] In an exemplary embodiment, the disease is Parkinson's disease.

[0155] Treating a disease, as referred to herein, means ameliorating, inhibiting the progression of, delaying worsening of, and even completely preventing the development of a disease, for example inhibiting the development of neurological manifestations in a person who has neurological disease or disorder. Treatment refers to a therapeutic intervention that ameliorates a sign or symptom of a disease or a pathological condition after it has begun to develop. In particular examples, however, treatment is similar to prevention, except that instead of complete inhibition, the development, progression or relapse of the disease is inhibited or slowed.

[0156] "Administration" as referred to herein is introduction of the pharmaceutical composition described herein into a subject by a chosen route. Administration of the active compound or pharmaceutical composition can be by any route known to one of skill in the art, and as appropriate for the particular condition and location under treatment. Administration can be local or systemic. Examples of local administration include, but are not limited to, topical administration, subcutaneous administration, intramuscular administration, intrathecal administration, intrapericardial administration, intra-ocular administration, topical ophthalmic administration, or administration to the nasal mucosa or lungs by inhalational administration. In addition, local administration includes routes of administration typically used for systemic administration, for example by directing intravascular administration to the arterial supply for a particular organ. Thus, in particular embodiments, local administration includes intra-arterial administration, subcutaneous administration, intraduodenally administration, and intravenous administration when such administration is targeted to the vasculature supplying a particular organ. Local administration also includes the incorporation of active compounds and agents into implantable devices or constructs, such as vascular stents or other reservoirs, which release the active agents and compounds over extended time intervals for sustained treatment effects.

[0157] Systemic administration includes any route of administration designed to distribute an active compound or composition widely throughout the body via the circulatory system. Thus, systemic administration includes, but is not limited to, intra-arterial and intravenous administration. Systemic administration also includes, but is not limited to, topical administration, subcutaneous administration, intraduodenally administration, intramuscular

administration, or administration by inhalation, when such administration is directed at absorption and distribution throughout the body by the circulatory system.

[0158] An effective amount of a compound, for example, of a compound of formula I herein or a pharmaceutically acceptable salt thereof, or of a decarboxylase inhibitor, e.g., carbidopa or a prodrug thereof, is a quantity of compound sufficient to achieve a desired effect in a subject being treated. An effective amount of a compound can be administered in a single dose, or in several doses, for example daily, during a course of treatment. However, the effective amount of the compound will be dependent on the compound applied, the subject being treated, the severity and type of the affliction, and the manner of administration of the compound.

[0159] In accordance with a contemplated method, a disclosed pharmaceutical composition may be administered to a patient in need thereof via one or more routes such as, but not limited to, parenteral routes selected from subcutaneous, transdermal, intradermal, intratracheal, intraocular, intramuscular, intraarterial, intraduodenally or intravenous.

[0160] In some embodiments, the pharmaceutical compositions are administered continuously, for example by a designated pump. Alternatively, or additionally, formulations may be administered non-continuously, e.g., as bolus, injection, a pill taken orally or eye drops.

[0161] In some embodiments, a disclosed method features subcutaneous and substantially continuous administration of a disclosed pharmaceutical.

[0162] By "substantially continuous" administration is meant that a dose of the formulation being administered is not administered as a bolus, e.g., a pill taken orally or a bolus injection, but rather that a single dose of the composition is being administered to a patient or individual over a particular predetermined period of time. For example, substantially continuous administration can involve administration of a dosage at over a period of at least 10 minutes, 20 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 15 hours, 18 hours, 21 hours, 24 hours, 12 to 16 hours, 16 to 18 hours, 18 to 20 hours, or 20 to 24 hours, to administer a single dose. Substantially continuous administration can be achieved using a transdermal patch or a pump device that continuously administers the formulation to a patient over time.

[0163] In some embodiments, administration includes acute and immediate administration such as inhalation or injection.

[0164] In some embodiments, in accordance with a contemplated method, a disclosed aqueous pharmaceutical composition may be administered, e.g., subcutaneously, at a rate of

from 0.01 ml/hour/site to 0.4 ml/hour/site, e.g., from 0.08 ml/hour/site to 0.24 ml/hour/site. Such rates may be constant throughout the day and night or varied according to patient's need, e.g., may reflect a patient resting or sleeping schedule and waking or higher activity level schedule.

[0165] For example, a contemplated method may comprise administration of a disclosed pharmaceutical composition at a rate of, for example, 0.32 ml/hour/site in the morning (e.g., for 2-4 hours before waking), 0.24 ml/hour/site during the daytime or activity time (e.g., for 10 to 12 hours), and/or 0.08 ml/hour/site at rest or at night.

[0166] For example, subcutaneous administration may be effected at a rate of 1.25 ml/hour during the daytime or activity time (e.g., for 2-3 hours before or after waking and for 10 to 14 hours thereafter), and 0 to 0.05 ml/hour (e.g., 0.05±0.005 ml/hour) at rest or night.

[0167] In some embodiments, a contemplated method may comprise intraduodenal administration of a disclosed composition, at a rate of, for example, 1.0 ml/hour during the daytime or activity time (e.g., for 2-3 hours before waking and for 10 to 12 hours thereafter), and from 0.0 to 0.5 ml/hour at rest or at night.

[0168] In some embodiments, a subject in need thereof is being treated with at least two separate formulations, i.e., at least two dosage unit forms, for example, a first formulation comprising, e.g., a levodopa amide compound and/or a pharmaceutically acceptable salt thereof, and an acid, and a second formulation comprising, for example, a decarboxylase inhibitor, e.g., carbidopa, a prodrug thereof and/or a pharmaceutically acceptable salt thereof. In accordance with these embodiments, the at least two dosage unit forms may be administered simultaneously, or sequentially at a predetermined time interval.

[0169] Two or more dosage unit forms may be administered to a subject by the same route of administration or, alternatively, by different routes of administration. For example, a first dosage form (e.g., a LDA derivative formulation) may be administered subcutaneously, and a second unit dosage form (e.g., a carbidopa formulation) may be administered orally or intravenously, either simultaneously or at different times.

[0170] In some embodiments, a particular dosage form may be administered by two or more different routes, for example, both subcutaneously and orally either simultaneously of subsequently.

[0171] For example, a first composition may be administered parenterally, intravenously, subcutaneously, intraduodenally, rectally, intrathecally, sublingually, intradermally, intranasally,

or intramuscularly; and a second composition may be administered parenterally, intravenously, subcutaneously, transdermally, rectally, intrathecally, sublingually, intradermally, intranasally, intramuscularly, or orally.

[0172] Two or more dosage unit forms may be administered to a subject at the same rate, or at different rates. For example, administration, e.g., subcutaneous administration, of a first formulation containing one or more LDA derivatives and an acid, in accordance with a contemplated method, may be effected at a rate of 0.1 to 1000 µl/hour/site; or at a volume of from about 2 to about 10 ml/24 hour/site, for example, from about 4 to about 6 ml/24 hour/site; or at a dose of from about 80 to about 800 mg LDA/day, and a second formulation containing e.g., carbidopa (a prodrug thereof or a pharmaceutically acceptable salt thereof), may be administered at a dose of from about 20 to 200 mg carbidopa/day; or the first formulation may be administered at a rate of from about 240 to about 360 mg LDA derivative, and the second formulation may be administered at a rate of from about 60 to about 90 mg carbidopa/day/site.

[0173] In exemplary embodiments, the LDA derivative being administered in accordance with a contemplated method is the levodopa amide free base compound.

[0174] In accordance with a method of treatment described herein, a disclosed pharmaceutical composition may be substantially continuously administered, e.g., using a pump for subcutaneous infusion at an average rate of 10-1000 µl/hour (e.g., 10-250 µl/hour), 300 ± 100 µl/hour, or 200 ± 40 µl/hour continuously for 24 hours; 440 ± 200 µl/hour or 200 ± 50 µl/hour continuously for 16 hours (during waking hours) and from 0 to about 80 µl/hour or 0 to 200 µl/hour for 8 hours (at night); or using a transdermal patch.

[0175] Substantially continuously administering a disclosed composition to a patient can be doubled or tripled by using more than one pump, patch, or infusion site. In exemplary embodiments, substantially continuously administering using, e.g., a liquid composition, can be at an average rate of 0.2-2 µl/hour, or 1 ± 0.5 µl/hour continuously for 24 hours; 1 ± 0.5 µl/hour continuously for 16 hours (during waking hours) and from 0 to about 0.5 µl/hour for 8 hours (at night), via a pump, transdermal patch, or a combination of delivery devices that are suitable for, e.g., subcutaneous, intravenous, intrathecal, and/or intraduodenal administration.

[0176] Contemplated administration, following the disclosed methods, typically can be carried out over a defined time period, usually weeks, months, or years, by any of the administration routes and means defined herein.

[0177] In an aspect of the present disclosure, there is provided a kit comprising a pharmaceutical composition as defined in any of the embodiments described herein and, optionally, instructions and means for administration of the pharmaceutical composition to subject in need thereof.

[0178] In some embodiments, the kit comprises a formulation comprising one or more LDA derivatives as defined herein, and an acid selected from a monovalent, divalent and/or trivalent acid, wherein the molar ratios of the one or more LDA derivatives and the acid are as defined herein.

[0179] In some embodiments, the kit comprises a first pharmaceutical composition comprising one or more LDA derivatives or salts thereof, and an acid selected from a monovalent, divalent and/or trivalent acid, wherein the molar ratios of the LDA derivative(s) and the acid are as defined herein; (ii) a second pharmaceutical composition comprising one or more decarboxylase inhibitors or salts thereof; (iii) optionally, one or more of a basic amino acid, an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor; and (iv) optionally, instructions for co-administration of the pharmaceutical compositions.

[0180] A contemplated kit is useful for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine, for example Parkinson's disease.

[0181] The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

Example 1. Compositions comprising levodopa amide and a monovalent acid

[0182] Levodopa amide free base (herein designated "LDA FB"), 2-amino-3-(3,4-dihydroxyphenyl)propanamide, demonstrates low solubility in water. In order to increase its solubility, a common practice is to dissolve it by introduction of counter ion. Since LDA comprises a basic amino group, the counter ion can be an acid which may be organic or inorganic acid.

[0183] Compositions comprising LDA FB at various concentrations and an organic or inorganic monovalent acid were prepared using the minimal amount of acid required to obtain complete dissolution of LDA FB.

(i) Compositions comprising HCl as the monovalent acid.

[0184] Levodopa amide free base was weighted in scintillation vials, WFI was added, and the suspension was stirred. The concentrations (weight percent of total composition (w/w)) of LDA FB were 5% (254.8 mM), 10% (509.68 mM), and 20%. The solution was turbid/suspension. Then, 2N HCl solution was added to the vials to obtain molar ratios LDA FB:HCl of 1.00:0.20, 1.00:0.50, 1.00:0.75, 1.00:0.80, 1.00:0.85 and 1.00:0.89. No heating was applied, and pH was measured only in the clear solutions. The appearances of the resulting LDA FB solutions are depicted in Table 2.

Table 2. Compositions comprising LDA FB and the monovalent acid HCl

LDA FB conc. (w/w)	5%	5%	10%	20%	10%	20%	5%	10%	20%	20%	20%
HCl conc. (%)	0.186	0.83	0.93	1.86	1.66	3.31	0.79	1.58	3.16	2.98	2.79
Molar ratio HCl/LDA FB	0.2	0.89	0.5	0.5	0.89	0.89	0.85	0.85	0.85	0.80	0.75
Appearance (dissolution)	no dissol	clear	no dissol	no dissol	clear	clear	clear	clear	clear	no dissol	no dissol
pH	*NA	6.3	NA	NA	6.26	6.11	6.46	6.27	6.22	NA	NA
Stability overnight	NA	stable	NA	NA	stable	stable	stable	stable	stable	NA	NA

*NA= not applicable

[0185] Molar ratios of HCl to LDA FB of 0.85 and higher resulted in full dissolution of LDA FB, implying that levodopa amide free base was converted into its hydrochloric salt, whereas in molar ratios lower than 0.85, no clear solution was obtained, even following overnight stirring. Compositions with molar ratio $\geq$ 0.85 were stable for at least 24 hours.

(ii) Compositions comprising ascorbic acid as the monovalent acid.

[0186] Vials with suspensions of 5%, 10% and 20% (w/w) LDA FB in water were prepared as described in (i) above. Then, ascorbic acid (in its solid form) were added so as to obtain molar ratios LDA FB:ascorbic acid of 1.00:0.20, 1.00:0.50, 1.00:0.75, 1.00:0.80, 1.00:0.85 and 1.00:0.89. No heating was applied, and pH was measured only in the clear solutions. The appearances of the resulting LDA FB solutions are depicted in Table 3.

Table 3. Compositions with LDA FB and ascorbic acid

LDA FB conc. (w/w)	5%	10%	20%	5%	10%	20%	5%	10%	20%	20%	20%
Ascor. acid conc. (w/w)	0.9%	4.5%	8.9%	4.0%	8.0%	16.0%	3.8%	7.6%	15.3 %	13.5 %	14.4 %
Molar ratio Asc/LDA FB	0.2	0.5	0.5	0.89	0.89	0.89	0.85	0.85	0.85	0.75	0.8
Apperance (dissolution)	no dissol	no dissol	no dissol	clear	clear	clear	clear	clear	clear	no dissol	no dissol
pH	NA	NA	NA	6.19	6.26	6.28	6.47	6.5	6.45	NA	NA
Stability overnight	NA	NA	NA	stable	stable	stable	stable	stable	stable	NA	NA

[0187] Molar ratio of ascorbic acid to LDA FB of 0.85 and higher resulted in dissolution of LDA FB, implying that levodopa amide free base was converted into its ascorbate salt, whereas in molar ratios lower than 0.85, no dissolution was observed, even following overnight stirring. Compositions with molar ratio ≥ 0.85 were stable for at least 24 hours.

(iii) Compositions comprising methanesulfonic acid as the monovalent acid.

[0188] Vials with suspensions of 5%, 10% and 20% (w/w) LDA FB in water were prepared as described in (i) above. Then, methanesulfonic acid was added to the vials so as to obtain molar ratios LDA FB:methanesulfonic acid of 1.00:0.20, 1.00:0.50, 1.00:0.75, 1.00:0.80, 1.00:0.85 and 1.00:0.89. No heating was applied, and pH was measured only in the clear solutions. The resulting appearances of the LDA FB solutions are depicted in Table 4.

Table 4. Compositions with LDA FB and methanesulfonic acid

LDA FB conc. (w/w)	5%	10%	20%	5%	10%	20%	5%	10%	20%	20%	20%
Methansul. acid conc. (w/w)	0.5%	2.5%	4.9%	2.2%	4.4%	8.7%	2.1%	4.2%	8.3%	7.4%	7.8%
Molar ratio Meth/LDA FB	0.20	0.50	0.50	0.89	0.89	0.89	0.85	0.85	0.85	0.75	0.80
Appearance (dissolution)	no dissol	no dissol	no dissol	clear	clear	clear	clear	clear	clear	no dissol	no dissol
pH	NA	NA	NA	5.67	6.42	6.02	6.16	6.23	6.26	NA	NA
Stability overnight	NA	NA	NA	stable	stable	stable	stable	stable	stable	NA	NA

[0189] As seen in Table 4, molar ratio of methanesulfonic acid to LDA FB of 0.85 and higher resulted in dissolution of LDA FB, implying that levodopa amide free base was converted into its mesylate salt, whereas in molar ratios lower than 0.85, no dissolution was observed, even with overnight stirring. Compositions with molar ratio ≥ 0.85 were stable for at least 24 hours. These results are comparable to the results obtained for the other monovalent acids HCl (an inorganic acid) and ascorbic acid (an organic acid).

Example 2. Compositions comprising LDA FB and a divalent acid

[0190] A divalent acid is expected to be as twice effective in dissolving levodopa amide free base as a monovalent acid, namely, the expected molar ratio of LDA FB:divalent acid is 1.0:0.5. Compositions comprising LDA FB at various concentrations and an organic or inorganic divalent acid were prepared using the minimal amount of acid required to obtain complete dissolution of LDA FB.

(i) Compositions comprising tartaric acid as the divalent acid.

[0191] Vials with suspensions of 5%, 10% and 20% (w/w) LDA FB in water were prepared as described in Example 1(i) above. Then, tartaric acid (in its solid form) was added to the vials until clear solutions were obtained. No heating was applied, and pH was measured only in the clear solutions. The resulting appearances of the LDA FB solutions are depicted in Table 5.

Table 5. Compositions with LDA FB and tartaric acid

LDA FB conc. (w/w)	5%	10%	20%	5%	10%	20%
Tartaric acid conc. (w/w)	1.15%	2.29%	4.59%	1.53%	3.06%	6.12%
Molar ratio Tartaric/LDA FB	0.3	0.3	0.3	0.4	0.45	0.45
Appearance (dissolution)	no dissol	not dissol	no dissol	clear	clear	clear
pH	NA	NA	NA	6.75	6.48	6.39
Stability overnight	NA	NA	NA	stable	stable	stable

[0192] As seen in Table 5, higher concentration of LDA FB (10% and 20%) required higher concentrations of tartaric acid and, moreover, higher LDA FB:tartaric acid molar ratios in order to completely dissolve LDA FB and, assumingly, converting levodopa amide free base into its tartaric salt. For example, at low LDA FB concentration of 5%, molar ratio of 0.4 was sufficient to dissolve LDA FB, whereas for dissolution 10% and 20% LDA FB, the molar ratio increased

to 0.45. However, unexpectedly, the final molar ratio LDA FB:divalent acid was less than 1.0:0.5. Compositions with molar ratio acid:LDA FB ≥ 0.40 were stable for at least 24 hours. These results apply to all isomers of tartaric acid.

(ii) Compositions comprising glutamic acid as the divalent acid.

[0193] Glutamic acid is an amino acid which has two carboxyl groups and is expected to act as a divalent acid that would dissolve LDA derivatives, particularly LDA FB, in a molar ratio LDA:glutamic acid of 1.0:0.5.

[0194] Vials with suspensions of 20% (w/w) LDA FB in water were prepared as described in Example 1(i) above. Then, glutamic acid (in its solid form) was added to the vials until clear solutions were obtained. No heating was applied, and pH was measured only in the clear solutions. The appearances of the resulting LDA FB solutions are depicted in Table 6.

Table 6. Compositions with LDA FB and glutamic acid

LDA FB conc. (w/w)	20%	20%	20%
Molar ratio glutamic acid/LDA FB	0.50	0.75	1.00
Appearance (dissolution)	no dissolution	somehow turbid	clear
pH	NA	6.63	6.32
Stability overnight	NA	NA	stable

[0195] Complete dissolution of LDA FB and conversion thereof to the glutamate salt was assumingly obtained at a molar ratio 0.75 < glutamic acid/LDA FB < 1.00. These unexpected results imply that at the pH of the aqueous LDA FB solution (~6.5) glutamic acid acts as monovalent acid and not as a divalent or even a sesquivalent acid.

[0196] Compositions with molar ratio acid/LDA ~ 1.0 were stable for at least 24 hours.

(iii) Compositions comprising sulfuric acid as the divalent acid.

[0197] Vials with suspensions of 5%, 10% and 20% (w/w) LDA FB in water were prepared as described in Example 1(i) above. Then, liquid sulfuric acid was added to the vials. No heating was applied, and pH was measured only in the clear solutions. The resulting LDA FB solutions are depicted in Table 7.

Table 7. Compositions with LDA FB and sulfuric acid

LDA FB conc. (w/w)	5%	10%	20%	5%	10%	20%
Molar ratio Tartaric/LDA FB	0.3:1	0.3:1	0.3:1	0.4:1	0.45:1	0.45:1
Sulfuric acid conc. (w/w)	0.75%	1.50%	3.00%	1.00%	2.00%	4.00%
Appearance (dissolution)	no dissol	no dissol	no dissol	clear	clear	clear
pH	NA	NA	NA	1.6	2.94	2.12
Stability overnight	NA	NA	NA	stable	stable	stable

[0198] As seen in Table 7, higher concentration of LDA FB (10% and 20%) required higher concentrations of sulfuric acid and, moreover, higher LDA FB/sulfuric acid molar ratios in order to completely dissolve LDA FB and converting it into its sulfuric salt. For example, at low LDA FB concentration of 5%, molar ratio of 0.4 was sufficient to dissolve LDA FB, whereas for dissolution of 10% and 20% LDA FB, the molar ratio increased to 0.45, however, the final molar ratio LDA FB:divalent acid was less than the expected 1.0:0.5 ratio. The pH in the clear solutions was lower, implying that in the presence of very strong, concentrated acids such as sulfuric acid that has a relatively low pKa (-3, 1.99), the buffering capacity of levodopa amide free base is challenged.

[0199] Compositions with molar ratio acid/LDA FB $\geq$ 0.40 were stable for at least 24 hours.

Example 3. Compositions comprising LDA FB and a trivalent acid

[0200] A trivalent acid is expected to be three times as effective in dissolving levodopa amide free base in comparison to a monovalent acid, namely, the expected molar ratio of LDA FB:trivalent acid is 1.00:0.33. Compositions comprising LDA FB at various concentrations and the organic trivalent citric acid were prepared using the minimal amount of acid required to obtain complete dissolution of LDA FB.

(i) Compositions comprising citric acid as the trivalent acid.

[0201] Vials with suspensions of 5%, 10%, 20%, 30% and 35% (w/w) LDA FB in water were prepared as described in Example 1(i) above. Then, citric acid (in its solid form) was added to the vials until clear solutions were obtained. No heating was applied, and pH was measured in clear solutions only. The resulting appearances of the LDA FB solutions are depicted in Table 8.

Table 8. Compositions with LDA LDA FB and citric acid

LDA FB conc. (w/w)	5%	10%	20%	5%	10%	20%	30%	35%
Citric acid conc. (w/w)	0.98%	1.96%	3.92%	1.47%	2.94%	5.88%	8.81%	12.34%
Molar ratio Citric/LDA FB	0.2	0.2	0.2	0.3	0.3	0.3	0.36	0.36
Appearance (dissolution)	no dissol	no dissol	no dissol	clear	clear	clear	clear	clear
pH	NA	NA	NA	6.59	6.57	6.52	5.57	5.73
Stability overnight	NA	NA	NA	stable	stable	stable	stable	stable

[0202] As seen in Table 8, molar ratio LDA FB:citric acid was 1.0:0.3 for low LDA FB concentration of 5% (w/w) as well as for higher concentration of 10% and 20% LDA FB. This molar ratio was lower than the expected molar ration of 0.33. However, increasing LDA FB concentration to 30% and 35% (w/w) necessitated higher concentrations of citric acid and, moreover, higher LDA FB:citric acid molar ratios in order to completely dissolve LDA FB and converting the free base into its citrate salt. Compositions with up to 20% LDA FB and molar ratio citric acid/LDA FB of 0.30 were stable for at least 24 hours.

(ii) Compositions comprising phosphoric acid as the trivalent acid.

[0203] Vials with suspensions of 5%, 10%, 20% and 30% (w/w) LDA FB in water were prepared as described in Example 1(i) above. Then, predetermined amounts of liquid *ortho* phosphoric acid (85%) were added to the vials until clear solutions were obtained. No heating was applied, and pH was measured in clear solutions only. The resulting LDA FB solutions are depicted in Table 9.

Table 9. Compositions with LDA LDA FB and ortho phosphoric acid

LDA FB conc. (w/w)	5%	10%	20%	5%	10%	20%
Phosphoric acid conc. (w/w)	0.88%	1.76%	3.53%	1.18%	2.35%	4.70%
Molar ratio Phosphoric/LDA FB	0.3	0.3	0.3	0.45	0.45	0.45
Appearance (dissolution)	no dissol	no dissol	no dissol	clear	clear	clear
pH	NA	NA	NA	6.59	6.57	6.52
Stability overnight	NA	NA	NA	stable	stable	stable

[0204] As seen in Table 9, a molar ratio LDA FB:phosphoric acid of 1.0:0.3, as obtained for the other trivalent such as citric acid, was not sufficient for dissolving LDA FB even at very low LDA FB concentrations (e.g., 5% w/w). Instead, unexpectedly, phosphoric acid presented, under the reaction conditions pH value lower than 12, which characterizes a weak divalent acid. The pKas for *ortho* phosphoric acid (H_3PO_4) are 2.2, 7.2 and 12.32, thus under pH 12 only two hydrogen atoms are actually acidic. Dissolution was obtained only in vials with molar ratio phosphoric acid:LDA FB of 0.45:1.0. Even at molar ratio of 0.4:1.0 and low concentration of LDA FB, additional acid was needed to completely solubilize LDA FB, implying that *ortho* phosphoric acid acts like a weak divalent acid, weaker than tartaric acid and significantly weaker than citric acid, under the experimental conditions tested.

[0205] Compositions with molar ratio phosphoric acid/LDA FB $\geq$ 0.45 were stable for at least 24 hours.

Example 4. Formulations comprising levodopa amide free base, HCl, ascorbic acid and N-acetyl cysteine (NAC)

[0206] Formulations with increasing concentrations of LDA FB and HCl as the counter ion were prepared, further comprising ascorbic acid and N-acetyl cysteine (NAC) as antioxidants.

[0207] The following components were weighted, transferred to pre-weighted bottles and mixed: HCl (3N), ascorbic acid, NAC and water. The bottles were placed in a heating bath with water at 58 ± 3°C. Then, LDA FB was weighted and added to each of the bottles. Nitrogen was purged to the preparation bottles head space, the bottles were tightly closed and constantly stirred while in the heating bath. Any un-dissolved material remaining in the inner surface of the bottle caps was removed (dissolved) by mixing (2-3 inversions of the bottle). The preparation was stirred moderately for additional ~10 minutes, verifying that all material was completely dissolved, and then the preparation bottles were removed from the heated bath and stirring continued slowly at room temperature. Optionally, Tween® 80 solution was added to the compositions while purging with N_2. The preparations were stirred continuously for ~15 minutes, and then transferred into volumetric flasks and completed to volume (100 ml) with water. The pH was set to be in the range of 6.4-7.0.

[0208] The formulations (F1-F7) and the molar ratios HCl:LDA FB are presented in Table 10.

Table 10: Formulations with LDA FB, NAC and ascorbic acid, and HCl as counter-ion

Ingredient (% w/w)	F1	F2	F3	F4	F5	F6	F7
LDA FB	6.0	10.0	12.5	15.0	17.5	20.0	25.0
HCl (3 N)	1.91	3.92	5.17	6.43	7.69	8.94	11.46
Ascorbic acid	0.50	0.50	0.50	0.50	0.50	0.50	0.50
NAC	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Molar ratio HCl/LDA FB	0.63	0.78	0.82	0.85	0.87	0.89	0.91

[0209] The results presented in Table 10 clearly demonstrate that inclusion of acidic antioxidants in the formulation can reduce the amount of acidic counter ion required for LDA FB dissolution at lower LDA FB concentrations (6-15% w/w). However, when the concertation of LDA FB is elevated, the required amount of acidic counter-ion increases accordingly as well as the molar ratio LDA FB:HCl.

Example 5. Compositions with levodopa amide free base, a monovalent acid and an organic co-solvent

[0210] The effect of adding the organic solvent N-methyl-2-pyrrolidone (NMP) as co-solvent on molar ratios LDA:monovalent acid required to completely dissolve a LDA derivative was tested using the exemplary LDA derivative levodopa amide free base. It has been previously established that molar ratios LDA FB:HCl of 1.0:0.2 and 1.0:0.5 were not sufficient for dissolving 5%, 10% and 20% (w/w) LDA FB in aqueous suspensions. It has been further previously established by the inventors that an aqueous solution of 5% NMP is not sufficient for dissolving 10% and 20% LDA FB in absence of acid.

[0211] An amount of ~750.6 mg LDA FB was weighted in scintillation vials. This amount accounted for a final LDA FB concentration of 15% by weight of total final composition. Mixtures of NMP and water having NMP:water ratios 20:80, 40:60, 60:40, and 80:20, were prepared, and 4000 mg of each solution was transferred to scintillation vial. A vial containing 4000 mg of water only served as control.

[0212] To each of these vials LDA FB was added portion-wise while stirring continuously, allowing for maximum dissolution before the next portion was added. The maximum amount of LDA FB fully dissolved in a NMP-water solution was noted and the remaining LDA FB was

then added forming a slurry. To these slurries, 3 N HCl was added portion-wise, allowing it to properly react (i.e., dissolve LDA FB) before the next portion was added. HCl was added until solutions became clear implying that all LDA FB has been dissolved. The results are summarized in Table 11(i).

Table 11(i). Composition with HCl and NMP as co-solvent

LDA FB conc. (w/w)	15%	15%	15%	15%
Molar ratio HCl/LDA FB	-	0.21	0.38	0.72
NMP (w/w)	80	60	40	20
Volume ratio water:NMP	20:80	40:60	60:40	80:20
pH	9.46	7.22	7.02	6.64
Stability overnight	stable	stable	stable	stable

[0213] As seen in Table 11(i), the use of an organic co-solvent such as NMP in aqueous LDA FB compositions substantially decreased the amount of acid needed to obtain complete dissolution of LDA FB. For example, use of 20%, 40% or 60% (w/w) of NMP lowered the LDA FB:HCl molar ratio to 1.00:0.72, 1.00:0.38 and 1.00:0.21, respectively. In further experiments, addition of 10% NMP to water increased by 30% dissolution of LDA FB at low LDA FB:HCl molar ratios (results not shown).

[0214] The ability of additional organic solvents to dissolve LDA FB without the addition of water and/or acid was tested. The results are presented in Table 11(ii).

Table 11(ii). Intrinsic LDA FB solubilities in various organic solvents

Solvent	% LDA FB solubilized
DMSO	33
dimethyl acetamide (DMA)	25
Ethanol	5
Propylene glycol (PG)	11
Polyethylene glycol (PEG)	11
TetraGlycol	11
Transcutol	11

Example 6. Compositions comprising levodopa amide free base, various acids and carbidopa

[0215] Formulations with carbidopa (CD; MW 226.2), FB and HCl as the counter-ion were prepared. Ascorbic acid and N-acetyl cysteine (NAC) were added as antioxidants. Optionally, arginine was added in order to solubilize the acidic CD.

[0216] The following components were weighted, transferred to pre-weighted bottles and mixed: HCl, ascorbic acid, NAC and water. The bottles were placed in a heating bath with water at 58 ± 3°C. Then, LDA FB, CD and arginine were weighted and added to the bottles. Nitrogen was purged to the preparation bottles head space, the bottles were tightly closed and constantly stirred in the heating bath. Any un-dissolved material remaining in the inner surface of the bottle caps was removed (dissolved) by 2-3 inversions of the bottle. The preparations were stirred moderately for additional ~10 minutes while verifying that all material was completely dissolved, and then the preparation bottles were removed from the heated bath and stirring continued slowly at room temperature. Pre-prepared Tween® 80 solution was added to the formulations while purging with N_2. The preparations were stirred continuously for ~15 minutes, and then transferred into volumetric flasks and completed to volume (100 ml) with water. The pH was set to be in the range of 6.4-7.0.

[0217] Exemplary formulations F8 and F9 are presented in Table 12:

Table 12. Formulations with LDA FB, CD and HCl

Ingredient (% w/w)	F8	F9
HCl fuming (37%)	1.80	1.80
Ascorbic acid	0.50	0.50
NAC	0.50	0.50
LDA FB	15.0	15.0
Carbidopa	0.75	0.75
L-Arginine	0.00	0.60
Tween®-80	0.30	0.30
HCl:LDA FB molar ratio	0.65	0.65

[0218] As clearly demonstrated in Table 12, substantially lower contraction of acidic counter-ion was needed for solubilizing LDA FB when ascorbic acid, NAC and CD, all of which are acids, were added to the formulation. For example, a molar ratio of HCl:LDA FB was as low as 0.7:1.0 for a 15% LDA FB formulation.

[0219] The amount of counter-ion required to completely dissolve LDA FB in aqueous formulations comprising CD, ascorbic acid, NAC and nomo-, di-, or trivalent acid selected from acetic acid, tartaric acid, glutamic acid, phosphoric acid and methanesulfonic serving as counter-ion source, was assessed.

[0220] Exemplary formulations F10 and F17 are presented in Table 13:

Table 13. Formulations with LDA FB, CD and various acids

Ingredient (% w/w)	F10	F11	F12	F13	F14	F15	F16	F17
Citric acid	3.15	0	0	0	0	0	0	0
Tartaric acid	0	3.70	0	0	0	0	0	0
Phosphoric acid	0	0	4.85	0	0	2.55	0	0
Acetic acid	0	0	0	3.00	0	0	0	0
Glutamic acid	0	0	0	0	0	0	7.20	0
Methanesulfonic acid	0	0	0	0	0	0	0	4.70
Ascorbic acid	0.50	0.50	0.50	0.50	0.5	0.50	0.50	0.50
N-Acetylcysteine (NAC)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
LDA FB	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Carbidopa	0.81	0.81	0.81	0.81	0.81	0.81	0.80	0.80
L-Arginine	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
Tween 80	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Molar ratio acid/LDA FB	0.644	0.645	0.647	0.649	0.646	0.681	0.640	0.640

[0221] The results presented in Table 13 confirm that when ascorbic acid, NAC and CD are provided to aqueous LDA FB formulations, lower amount of acidic counter-ion are required to obtain complete dissolution of LDA FB. For example, in a 15% LDA FB formulation a molar ratio acid:LDA FB of 0.640-0.681 was obtained for all acids tested irrespective of the acid being mono, di, or trivalent acid.

EQUIVALENTS

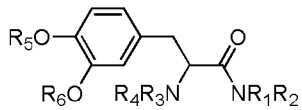
[0222] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification are approximations that may vary by up to plus or minus 10% depending upon the desired properties to be obtained by the present disclosure.

INCORPORATION BY REFERENCE

[0223] The entire contents of all patents, published patent applications, websites, and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

CLAIMS

1. A formulation having a pH of from about 2.0 to about 11.0, from about 5.0 to about 7.5, from about 6.7 to about 7.1, or from about 6.0 to about 9.5 at 25°C, the formulation comprising a monovalent acid and from about 1% to about 25%, or from about 5% to about 20%, by weight of at least one levodopa amide (LDA) derivative of the general formula I:



(I)

or an enantiomer, diastereomer, or racemate thereof,

wherein:

R1, R2, R3 and R4, each independently, is selected from the group consisting of 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', and -O-C(=O)-R", or R1 and R2 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring, or R3 and R4, together with the nitrogen atom to which they are attached form a 5- or 6-membered ring;

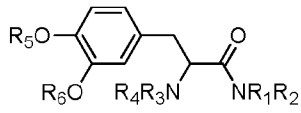
R5 and R6 each independently is selected from the group consisting of H, (C_1-C_3)alkyl, cycloalkyl, phenyl, -P(=O)(OR')$_2$ and -C(O)-(C_1-C_6)alkyl;

R', each independently, is selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, aryl, and heteroaryl bonded through a ring carbon; and

R" is a saturated or unsaturated hydrocarbon chain having at least 10 carbon atoms, wherein the molar ratio of the at least one LDA derivative to the acid is from about 1.00:0.10 to about 1.00:0.89, and the formulation is stable for at least 24 hours at room temperature.

2. A formulation having a pH of from about 2.0 to about 11.0, from about 5.0 to about 7.5, from about 6.7 to about 7.1, or from about 6.0 to about 9.5 at 25°C, the formulation comprising a divalent or trivalent acid and from about 1% to about 25%,

or from about 5% to about 20%, by weight of at least one levodopa amide (LDA) derivative of the general formula I:



(I)

or an enantiomer, diastereomer, or racemate thereof,

wherein:

R1, R2, R3 and R4, each independently, is selected from the group consisting of 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', and -O-C(=O)-R", or R1 and R2 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring, or R3 and R4, together with the nitrogen atom to which they are attached form a 5- or 6-membered ring;

R5 and R6 each independently is selected from the group consisting of H, (C_1-C_3)alkyl, cycloalkyl, phenyl, -P(=O)(OR')$_2$ and -C(O)-(C_1-C_6)alkyl;

R', each independently, is selected from the group consisting of H, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, cycloalkyl, aryl, and heteroaryl bonded through a ring carbon; and

R" is a saturated or unsaturated hydrocarbon chain having at least 10 carbon atoms, wherein the molar ratio of the at least one LDA derivative to the acid is from about 1.00:0.20 to about 1.00:1.15, excluding molar ratios of 1.00:0.50 and 1.00:0.33, when the pH is from about 6.0 to about 7.0, and wherein the formulation is stable for at least 24 hours at room temperature.

3. The formulation of claim 1 or 2, comprising from about 10% to about 20% or from about 5% to about 15% by weight of at least one LDA derivative.

4. The formulation of any one of claims 1 to 3, wherein the LDA derivative is 2-amino-3-(3,4-dihydroxyphenyl) propanamide, an enantiomer, a racemate and/or a pharmaceutically acceptable salt thereof.

5. The formulation of any one of claims 1 to 4, wherein the acid is selected from the groups consisting of inorganic acids, sulfonic acids, carboxylic acids, fatty acids

and derivatives thereof, halogenated acids, nucleic acids, amino acids, alpha hydroxy acids, and glycosidic acids.

6. The formulation of claim 5, wherein the acid is an organic acid selected from the group consisting of alginic acid, boric acid, caprylic acid, butyric acid, dehydroacetic acid, deoxycholic acid, diatrizoic acid, edetic acid, erythorbic acid, benzenesulfonic acid, p-toluenesulfonic acid, hippuric acid, maleic acid, hydrogenated tallow acid, hydroxyethylpiperazine ethane, isostearic acid, malic acid, fumaric acid, tartaric acid, benzoic acid, acetic acid, adipic acid, citric acid, ascorbic acid, L-lactic acid, D-lactic acid, lactobionic acid, levulinic acid, gentisic acid ethanolamine, gluconic acid, galactaric acid, gluceptic (glucoheptanoic) acid, D-glucuronic acid, glutamic acid hydrochloride, glutaric (pentanedioic) acid, glycolic (hydroxyacetic) acid, isethionic (2-hydroxy-ethanesulfonic) acid, formic acid, l-metaphosphoric acid, methylboronic acid, myristic acid, nitric acid, oleic acid, octadecene-1 maleic acid copolymer, palmitic acid, pentetic acid, poly(bis(p-carboxyphenoxy)propane anhydride):sebacic acid, poly(dl-lactic-co-glycolic acid) (50:50; 12000 mw), poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid 7:3:1; 280000 mw), polyacrylic acid (250000 mw), polygalacturonic acid, a polyoxyethylene fatty acid ester, propionic (propanoic) acid, succinic (butanedioic) acid, oxalic acid, xinafoic (1-hydroxy-2-naphthoic) acid, carbidopa, an acidic amino acid selected from glutamic acid, levodopa and aspartic acid, sorbic acid, stearic acid a fatty acid glyceride, a fatty acid pentaerythriol ester, undecylenic acid; an inorganic acid selected from hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, sulfonic acid, polystyrene sulfonic acid, carbonic acid, methanesulfonic acid and ethanesulfonic acid, or any combination thereof.

7. The formulation of any one of claims 1 to 6, further comprising at least one antioxidant.

8. The formulation of claim 7, wherein the antioxidant is selected from the group consisting of ascorbic acid or a salt thereof, L-cysteine, a cysteine derivative, bisulfite or a salt thereof, glutathione, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tocopherol and gentisic acid and any combination thereof.

9. The formulation of claim 8, wherein the cysteine derivative is N-acetyl cysteine (NAC).

10. The formulation of any one of claims 1 and 3 to 9, comprising from about 10% to about 25% by weight of the at least one LDA derivative and a monovalent acid, wherein the molar ratio of the LDA compound to the acid is from about 1.00:0.60 to about 1.00:0.89.

11. The formulation of any one of claims 2 to 9, comprising from about 10% to about 25% by weight of the at least one LDA derivative and a divalent or trivalent acid, wherein the molar ratio of the LDA derivative to the acid is from about 1.00:0.20 to about 1.00:1.15, excluding molar ratios of 1.00:0.50 and 1.00:0.33, when the pH is from about 6.0 to about 7.0.

12. The formulation of any one of claims 1 to 11, further comprising an organic solvent.

13. The formulation of claim 12, wherein the organic solvent is selected from the group consisting of N-methyl-2-pyrrolidone (NMP), dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA), tetrahydrofuran (THF), ethanol, isopropanol, propylene glycol (PG), tetraglycol, transcutol, polyethylene glycol (PEG), dioxane and dimethyl formamide (DMF).

14. The formulation of any one of claims 1 to 13, further comprising a decarboxylase inhibitor.

15. The formulation of claim 14, wherein the decarboxylase inhibitor is selected from the group consisting of carbidopa, benserazide, a salt thereof, and a combination thereof.

16. The formulation of claim 1 to 15, further comprising at least one of a basic amino acid or an amino sugar.

17. The formulation of claim 16, wherein the basic amino acid is selected from the group consisting of arginine, histidine, lysine, and a combination thereof; and the

amino sugar is selected from the group consisting of meglumine, D-glucosamine, sialic acid, N-acetylglucosamine, galactosamine and a combination thereof.

18. The formulation of any one of claims 14 to 17, wherein the decarboxylase inhibitor is carbidopa; the basic amino acid is arginine; and the amino sugar is meglumine.

19. The formulation of any one of claims 14 to 18, wherein the molar ratio of the LDA derivative to the decarboxylase inhibitor is from about 1:1 to about 100:1, from about 2:1 to about 60:1, from about 4:1 to about 40:1, or from about 10:1 to about 40:1 and any ranges, subranges or individual values therebetween.

20. The formulation of claim 19, wherein the molar ratio LDA derivative:decarboxylase inhibitor is 4:1, 8:1 or 23:1.

21. The formulation of any one of claims 1 to 20, further comprising a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor.

22. The formulation of claim 21, wherein the COMT inhibitor is selected from the group consisting of entacapone, tolcapone, and opicapone; and the MAO inhibitor is selected from the group consisting of moclobemide, rasagiline, selegiline, and safinamide.

23. The formulation of any one of claims 1 to 22, further comprising a surfactant selected from the group consisting of polysorbate 20, 40, 60 and/or 80, (Tween®-20, Tween®-40, Tween®-60 and Tween®-80, respectively), Span 20, Span 40, Span 60, Span 80, Span 85, polyoxyl 35 castor oil (Cremophor EL), polyoxyethylene-660-hydroxystearate (macrogol 660), triton and Poloxamer 188 (Pluronic® F-68).

24. The formulation of any one of claims 1 to 23, further comprising a buffer.

25. The formulation of claim 24, wherein the buffer is selected from the group consisting of citrate buffer, acetate buffer, sodium acetate buffer, tartrate buffer, phosphate buffer, borate buffer, carbonate 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, and a mixture thereof.

26. The formulation of any one of claims 1 to 25, wherein the pH is from about 4.0 to about 8.5, or from about 5.0 to about 7.5 or from about 6.0 to about 7.0.

27. The formulation of any one of claims 1 to 26, for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

28. The formulation of claim 27, comprising from about 10% to about 25% by weight of a LDA derivative and a monovalent acid selected from the group consisting of acetic acid, ascorbic acid, lactic acid (unspecified form), gluconic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, benzoic acid, boric acid, butyric acid, caprylic acid, deoxycholic acid, diatrizoic acid, erythorbic acid, formic acid, gentisic acid ethanolamine, lactobionic acid, levulinic acid, hydrochloric acid, hydrobromic acid, hippuric acid, gluceptic acid, glucuronic acid, glycolic acid, isethionic acid, isostearic acid, methylboronic acid, myristic acid, nitric acid, oleic acid, palmitic acid, propionic acid, sorbic acid, stearic acid, undecylenic acid, xinafoic acid and carbonic acid, wherein the molar ratio of the LDA derivative to the acid is from about 1.00:0.85 to about 1.00:0.89.

29. The formulation of claim 27, comprising from about 10% to about 25% by weight of a LDA derivative and a divalent acid selected from the group consisting of adipic acid, maleic acid, malic acid, fumaric acid, tartaric acid, galactaric acid, glutaric acid, oxalic acid, succinic acid, glutamic acid, glutamic acid hydrochloride, aspartic acid, phosphoric acid sebacic acid and sulfuric acid, or a trivalent acid selected from the group consisting of citric acid, fatty acid glycerides, and hydrogenated tallow acid, wherein the molar ratio of the LDA derivative to the acid is from about 1.00:0.30 to about 1.00:0.45.

30. The formulation of to any one of claims 27 to 29, wherein the disease or disorder is Parkinson's disease.

31. A method for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine, comprising administering

to a patient in need thereof a therapeutically effective amount of a formulation according to any one of claims 1-30, thereby treating the patient.

32. A method for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine, comprising administering to a patient in need thereof a therapeutically effective amount of a formulation comprising one or more levodopa amide (LDA) derivatives and a monovalent, divalent and/or trivalent acid as defined in any one of claims 1 to 13.

33. The method of claim 31 or 32, wherein the formulation is administered parenterally, intravenously, subcutaneously, intraduodenally, rectally, intrathecally, sublingually, intradermally, intranasally, or intramuscularly.

34. 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 in need thereof a therapeutically effective amount of a first formulation according to any one of claims 1 to 13; and a therapeutically effective amount of a second formulation comprising a decarboxylase inhibitor or a salt thereof and, optionally, one or more of a basic amino acid, an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, or a monoamine oxidase (MAO) inhibitor, thereby treating the patient.

35. The method of claim 34, wherein the decarboxylase inhibitor is carbidopa; the basic amino acid is arginine; the amino sugar is meglumine; the COMT inhibitor is entacapone, tolcapone or opicapone; and the MAO inhibitor is moclobemide, rasagiline, selegiline or safinamide.

36. The method of claim 34 or 35, wherein the first formulation is administered parenterally, intravenously, subcutaneously, intraduodenally, rectally, intrathecally, sublingually, intradermally, intranasally, or intramuscularly; and the second formulation is administered parenterally, intravenously, subcutaneously, transdermally, rectally, intrathecally, sublingually, intradermally, intranasally, intramuscularly, or orally.

37. The method of any one of claims 34 to 36, wherein the first formulation and the second formulation are administered by different administration routes.

38. The method of claim 37, wherein the second formulation is administered orally.

39. The method of any one of claims 31 to 38, wherein the 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.

40. The method of claim 39, wherein the disease is Parkinson's disease.

41. A kit comprising a first formulation according to any one of claims 1 to 13; (ii) optionally, a second formulation comprising one or more of a decarboxylase inhibitor or a salt thereof, a basic amino acid, an amino sugar, a catechol-O-methyl transferase (COMT) inhibitor, and/or a monoamine oxidase (MAO) inhibitor; and (iii) optionally, instructions for co-administration of the formulations.

42. The kit of claim 41, for treatment of a disease or disorder characterized by neurodegeneration and/or reduced levels of brain dopamine.

43. The kit of claim 42, wherein the disease is Parkinson's disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2020/050202

A. CLASSIFICATION OF SUBJECT MATTER
See extra sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See extra sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Databases consulted: Google Patents, CAPLUS, REGISTRY, Google Scholar, PatBase
Search terms used: levodopa amide(LDA),monovalent acid,neurodegeneration,reduced levels of brain dopamine,Parkinson's disease.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017090039 A2 NEURODERM LTD[IL] 01 Jun 2017 (2017/06/01) [0009],[0010],[0017],[0019],[0041-0043],claims 1-2.	1-43
A	WO 2015136538 A1 NEURODERM LTD[IL] 17 Sep 2015 (2015/09/17) whole document	1-43
A	US 2016106765 A1 ABBVIE INC[US] 21 Apr 2016 (2016/04/21) whole document	1-43

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2020	20 May 2020

Name and mailing address of the ISA:	Authorized officer
Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il	VOLKOV Karina Telephone No. 972-73-3927136

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050202

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
WO 2017090039 A2	01 Jun 2017	WO 2017090039 A2	01 Jun 2017
		WO 2017090039 A3	31 Aug 2017
		AU 2016358511 A1	21 Jun 2018
		BR 112018010564 A2	21 Nov 2018
		CA 3006028 A1	01 Jun 2017
		CL 2018001395 A1	12 Oct 2018
		CN 108495617 A	04 Sep 2018
		EP 3380076 A2	03 Oct 2018
		IL 259484 D0	31 Jul 2018
		JP 2018535230 A	29 Nov 2018
		RU 2018119194 A	25 Dec 2019
		RU 2018119194 A3	20 Apr 2020
		SG 11201804395P A	28 Jun 2018
		US 2017296491 A1	19 Oct 2017
		ZA 201803485 B	28 Aug 2019
WO 2015136538 A1	17 Sep 2015	WO 2015136538 A1	17 Sep 2015
		AU 2015228369 A1	27 Oct 2016
		CA 2942244 A1	17 Sep 2015
		CN 106413754 A	15 Feb 2017
		CN 106413754 B	29 Nov 2019
		EP 3116475 A1	18 Jan 2017
		IL 247668 D0	30 Nov 2016
		JP 2017507973 A	23 Mar 2017
		JP 6591995 B2	16 Oct 2019
		JP 2020011977 A	23 Jan 2020
		MX 2016011837 A	27 Apr 2017
		RU 2016135952 A	13 Apr 2018
		RU 2016135952 A3	12 Sep 2018
		RU 2684105 C2	04 Apr 2019

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050202

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		US 2015352212 A1	10 Dec 2015
		US 10022320 B2	17 Jul 2018
		US 2017157079 A1	08 Jun 2017
		US 10258585 B2	16 Apr 2019
		US 2019151233 A1	23 May 2019
		US 10624839 B2	21 Apr 2020
		US 2020046665 A1	13 Feb 2020
US 2016106765 A1	21 Apr 2016	US 2016106765 A1	21 Apr 2016
		US 9446059 B2	20 Sep 2016
		AR 102389 A1	22 Feb 2017
		AU 2015335941 A1	04 May 2017
		BR 112017008198 A2	26 Dec 2017
		CA 2965379 A1	28 Apr 2016
		CN 107206013 A	26 Sep 2017
		DK 3209302 T3	13 May 2019
		EP 3209302 A1	30 Aug 2017
		EP 3209302 B1	24 Apr 2019
		EP 3569587 A1	20 Nov 2019
		ES 2739536 T3	31 Jan 2020
		HR P20191285 T1	18 Oct 2019
		HU E044115 T2	28 Oct 2019
		IL 251829 D0	29 Jun 2017
		IL 251829 A	26 Sep 2019
		IL 268885 D0	31 Oct 2019
		JP 2017537066 A	14 Dec 2017
		JP 6567049 B2	28 Aug 2019
		JP 2019218356 A	26 Dec 2019
		KR 20170071599 A	23 Jun 2017
		LT 3209302 T	10 Jun 2019
		MX 2017005236 A	26 Jul 2017

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IL2020/050202

Patent document cited search report	Publication date	Patent family member(s)	Publication Date
		PH 12017500746 A1	30 Oct 2017
		PL 3209302 T3	31 Oct 2019
		PT 3209302 T	19 Jul 2019
		RS 58972 B1	30 Aug 2019
		RU 2017117413 A	26 Nov 2018
		RU 2017117413 A3	30 May 2019
		SG 11201703170R A	30 May 2017
		SI 3209302 T1	28 Jun 2019
		TR 201908296 T4	21 Jun 2019
		TW 201630924 A	01 Sep 2016
		US 2018079762 A1	22 Mar 2018
		US 10174061 B2	08 Jan 2019
		US 2016362431 A1	15 Dec 2016
		US 2019375770 A1	12 Dec 2019
		WO 2016065019 A1	28 Apr 2016

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2020/050202

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (20200101) A61K 9/00, A61K 31/165, A61K 31/198, A61K 45/06, A61K 47/02, A61K 47/12, A61K 47/18, A61K 47/20, A61P 25/16

CPC (20160501) A61K 9/00, A61K 31/165, A61K 31/198, A61K 45/06, A61K 47/02, A61K 47/12, A61K 47/183, A61K 47/20, A61P 25/16

B. FIELDS SEARCHED:

* Minimum documentation searched (classification system followed by classification symbols)

IPC (20200101) A61K 9/00, A61K 31/165, A61K 31/198, A61K 45/06, A61K 47/02, A61K 47/12, A61K 47/18, A61K 47/20, A61P 25/00, A61P 25/16

CPC (20160501) A61K 9/00, A61K 31/165, A61K 31/198, A61K 45/06, A61K 47/02, A61K 47/12, A61K 47/183, A61K 47/20, A61P 25/00, A61P 25/16