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(71) Applicant: **NEURODERM LTD** [IL/IL]; 3 Golda Meir Street, Weizmann Science Park, 7403648 Ness Ziona (IL).

(72) Inventor: **YACOBY-ZEEVI, Oron**; 204 Hanarkissim Street, 6094600 Bitsaron (IL).

(74) Agents: **AVITAL, Avihu** et al.; BEN-AMI & Associates, P.O. Box 94, 7610002 Rehovot (IL).

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(54) Title: DOPA DECARBOXYLASE INHIBITOR COMPOSITIONS

(57) Abstract: The present invention provides highly stable carbidopa-based pharmaceutical compositions comprising an antioxidant combination consisting of ascorbic acid and at least one additional antioxidant, wherein said combination strongly inhibits carbidopa degradation. These compositions may further comprise levodopa and/or one or both of arginine and meglumine, and are beneficial in treatment of a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease.

DOPA DECARBOXYLASE INHIBITOR COMPOSITIONS

TECHNICAL FIELD

[0001] The present invention provides pharmaceutical compositions of carbidopa and optionally levodopa, containing safe and tolerable concentration of hydrazine, as well as methods of use and kits comprising them.

BACKGROUND

[0002] Parkinson's disease is a degenerative condition characterized by reduced concentration of the neurotransmitter dopamine in the brain. Levodopa (L-dopa or 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.

[0003] However, levodopa has a short half-life in plasma that, even under best common current standard of care, results in pulsatile dopaminergic stimulation. Long-term therapy is therefore complicated by motor fluctuations and dyskinesia that can represent a source of significant disability for some patients. A therapeutic strategy that could ultimately deliver levodopa/dopamine to the brain in a more continuous and physiologic manner would provide the benefits of standard levodopa with reduced motor complications and is much needed by patients suffering from Parkinson's disease and other neurological or movement disorders (Olanow, *Mov. Dis.*, **2008**, 23(Suppl. 3), S613-S622). Sustained-release oral levodopa formulations have been developed, but, at best, such preparations have been found to be no more efficacious than standard tablets. Continuous administration of levodopa by intraduodenal administration or infusion has also been attempted by using ambulatory pumps or patches. Such treatments, especially intraduodenal, are extremely invasive and inconvenient.

[0004] 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. Due to the possibility of extracerebral metabolism of levodopa, it is necessary to administer large doses of levodopa leading to high extracerebral concentrations of dopamine that cause nausea in some patients. Therefore, levodopa is usually administered concurrently with

oral administration of a dopa decarboxylase inhibitor, such as carbidopa or benserazide, which reduces by 60-80% the levodopa dose required for a clinical response, and thus prevents certain of its side effects by inhibiting the conversion of levodopa to dopamine outside the brain.

[0005] Various oral formulations together with inhibitors of enzymes associated with the metabolic degradation of levodopa are well known, e.g., decarboxylase inhibitors such as carbidopa and benserazide, monoamone oxidase (MAO)-A or MAO-B inhibitors such as moclobemide, rasagiline, selegiline, and safinamide, and catechol-O-methyl transferase (COMT) inhibitors such as tolcapone and entacapone. Currently available oral drugs include SINEMET® and SINEMET®CR sustained-release tablets that include carbidopa or levodopa; MADOPAR® tablets containing levodopa and benserazide; and STALEVO® tablets containing carbidopa, entacapone, and levodopa.

[0006] Carbidopa is a non-competitive inhibitor of DOPA decarboxylase. When mixed with levodopa, carbidopa inhibits the peripheral conversion of levodopa to dopamine. This results in increased levodopa available for transport to the CNS. Carbidopa also inhibits the metabolism of levodopa in the GI tract, thus, increasing levodopa bioavailability. It is used in Parkinson's disease to reduce the peripheral effect of dopamine. The loss of the hydrazine functional group represents the major metabolic pathway for carbidopa.

[0007] Hydrazine (N_2H_4) and its salts are used in the pharmaceutical industry as an intermediate to produce drugs with different therapeutic effects including decarboxylase inhibitors, antihypertensives, and antibacterials. It has been the cause of severe adverse effects on the central nervous system, liver, and kidneys. In addition to these effects, experimental animals have also shown the following symptoms: loss of body weight, anaemia, hypoglycaemia, fatty degeneration of the liver, and convulsions. Hydrazine has also been shown to cause DNA damage, gene mutations, and chromosome aberrations (Environmental health criteria No. 68 hydrazine (1987)) and has induced tumor growth in mice, hamsters, and rats after oral, intraperitoneal, and inhalation administration (MacEwan, J.D., Vernot, E.H., Haun C.C., *et al.*, Chronic inhalation toxicity of hydrazine: oncogenic effects (1981). Air Force Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio, NTIS Springfield VA). Since hydrazine is toxic and thought to be a possible human carcinogen, its presence is limited in some of these drug substances in the monographs of the European Pharmacopoeia (Ph. Eur.).

[0008] Accordingly, there is an ongoing and urgent need for liquid formulations and compositions that can achieve continuous dopaminergic stimulation to treat movement disorders such as Parkinson's disease more effectively containing a safe and tolerable amount of hydrazine.

SUMMARY OF INVENTION

[0009] It has now been found, in accordance with the present invention, that carbidopa formulations containing particular combinations of two antioxidants or o-quinone scavengers, wherein one of those antioxidants is ascorbic acid or a salt thereof, are significantly more stable than those formulations containing just a single antioxidant. As particularly found, particular antioxidant combinations consisting of ascorbic acid or a salt thereof, and one or more additional antioxidants, strongly inhibit carbidopa degradation thus significantly reducing, i.e., limiting, formation of undesired degradation products, in particular 3,4-dihydroxyphenyl-2-methylpropionic acid (herein identified "***degradant***") and hydrazine, and substantially stabilizing the formulations. Surprisingly, it has been further found that such carbidopa formulations can be stored at various temperatures and conditions for long periods of time, more particularly up to several years, wherein a safe and tolerable concentration of hydrazine is maintained.

[0010] In one aspect, the present invention thus provides a pharmaceutical composition comprising carbidopa, at least two antioxidants, and a pharmaceutically acceptable carrier, wherein one of said antioxidants is ascorbic acid or a salt thereof, and said composition comprises less than 1 μg/ml hydrazine, as determined by a gas chromatography-mass spectrometry (GCMS), or less than 5% by weight 3,4-dihydroxyphenyl-2-methylpropionic acid relative to the initial amount of carbidopa, as determined by high-performance liquid chromatography (HPLC). Particular such pharmaceutical compositions comprise 0.1% to 10%, preferably 0.5% to 6%, by weight carbidopa, and/or 0.1% to 10%, preferably 0.2% to 2%, by weight, ascorbic acid or a salt thereof.

[0011] In a particular such aspect, the pharmaceutical composition of the present invention further comprises (i) levodopa; (ii) arginine, meglumine, or a combination thereof; or (iii) both (i) and (ii); and may optionally further comprise a surfactant. Particular such pharmaceutical compositions comprise either less than 1% or 1% to 20%, preferably 2% to 16%, by weight, levodopa; and/or 0.1% to 42%, preferably 2% to 40%, by weight, arginine, meglumine, or a combination of both arginine and meglumine.

[0012] Particular pharmaceutical compositions according to the present invention comprise carbidopa; ascorbic acid or a salt thereof; at least one additional antioxidant other than said ascorbic acid or salt thereof, e.g., L-cysteine or a salt thereof, N-acetylcysteine (NAC) or a salt thereof, glutathione or a salt thereof, diacetylcystine or a salt thereof, or sodium bisulfite; levodopa; arginine, meglumine, or a combination thereof; and optionally a surfactant, e.g., polysorbate 80.

[0013] More particular such compositions comprise (i) 0.1% to 10%, preferably 0.5% to 6%, by weight, carbidopa; (ii) 0.1% to 10%, preferably 0.2% to 2%, by weight, ascorbic acid or a salt thereof; (iii) 0.001% to 5%, by weight, L-cysteine or salt thereof; 0.001% to 5%, by weight, NAC; or 0.01% to 2%, by weight, sodium bisulfite; (iv) either less than 1% or 1% to 20%, preferably 2% to 16%, by weight, levodopa; (v) 0.1% to 42%, preferably 2% to 40%, by weight, arginine, meglumine, or a combination thereof; and optionally (vi) 0.01% to 5%, by weight, polysorbate 80, wherein the composition comprises less than 1 µg/ml, preferably less than 0.5 µg/ml, more preferably less than 0.1 µg/ml, hydrazine.

[0014] As shown herein, the pharmaceutical compositions of the present invention are highly stable, wherein the particular combination of antioxidants stabilizes the carbidopa thereby minimizing the degradation of the carbidopa thus inhibiting formation of degradant and hydrazine. Consequently, those composition can be stored at various conditions, e.g., at a temperature ranging from -20°C to 25°C, without being substantially degraded, wherein the hydrazine content of the compositions is maintained at less than 1 µg/ml, preferably less than 0.1 µg/ml, after 1-24 hours, 1-30 days, 1-12 months, or 1-3 years.

[0015] In another aspect, the present invention relates to a method for treating a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease, in a patient, more specifically a mammal in general or a human in particular, said method comprising administering to said patient an effective amount of a pharmaceutical composition as defined above. The method of the invention may include substantially continuous administration of the composition.

[0016] In still another aspect, the present invention relates to a pharmaceutical composition as defined above, for use in treatment of a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease.

[0017] In yet another aspect, the present invention relates to use of a pharmaceutical composition as defined above, for the preparation of a medicament for treatment of a

disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease.

[0018] In a further aspect, the present invention provides a kit comprising at least one, i.e., 1, 2, 3 or more, containers each containing a pharmaceutical composition as defined above, wherein said composition is present in an amount sufficient to treat a patient, i.e., a mammal or a human, for a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease, for at least 1, 2, 3, 4, or 5 days; 1, 2, 3, or 4 week; 1 to 12 (e.g., 1, 2, 3, 6, 9, or 12) months; or 1 to 20 (e.g., 1, 2, 3, 4, 5, 6, 8, 10, or 12) years. In certain embodiments, the composition is present in separate dosages.

[0019] In certain embodiments of any of these aspects, the pharmaceutical composition, method, or kit of the present invention further comprises, or comprises the use of, a second active agent. Such a second agent may be a catechol-O-methyl transferase (COMT) inhibitor, e.g., tolcapone, entacapone, or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0020] **Fig. 1** shows a graph depicting the main impurity ("degradant") at retention time of about 14.5±0.2 min.

[0021] **Figs. 2A-2B** show graphs depicting typical MS spectrum in negative (**2A**) and positive (**2B**) mode of collected main impurity peak from a formulation sample.

[0022] **Figs. 3A-3B** show graphs depicting typical MS/MS daughter scan (ion M/Z=179) spectrum (**3A**) and parent (ion M/Z=105) spectrum (**3B**) in collected main impurity peak from a formulation sample.

DETAILED DESCRIPTION OF THE INVENTION

[0023] The present invention provides pharmaceutical compositions of carbidopa that are highly stable for a long period of time, more particularly for days, weeks, months or years, and contain very low content, i.e., a safe and tolerable amount, of hydrazine. While carbidopa-based compositions containing an antioxidant have already been disclosed in the prior art, the pharmaceutical compositions of the present invention are stabilized by a particular combination of two or more, i.e., 2, 3, 4 or more, antioxidants, wherein one of those antioxidants is ascorbic acid or a salt thereof, and the other antioxidants of the antioxidant combination each independently is selected, e.g., from L-cysteine, NAC, glutathione, diacetylcystine, a salt of the aforesaid, or sodium bisulfite. Such compositions

may comprise active agents other than carbidopa, in particular levodopa, as well as further ingredients for further stabilizing the composition, e.g., arginine (Arg; L-Arg), meglumine or both arginine and meglumine, as well as one or more surfactants.

[0024] In one aspect, the present invention provides a pharmaceutical composition (also referred herein as "a pharmaceutical formulation") comprising carbidopa (and/or an ester thereof), at least two antioxidants (also referred herein as o-quinone scavengers), and a pharmaceutically acceptable carrier, wherein one of said antioxidants is ascorbic acid or a salt thereof, and said composition comprises less than 1 µg/ml hydrazine, as determined by a GCMS, or up to (and not more than) 5% by weight 3,4-dihydroxyphenyl-2-methylpropionic acid relative to the initial amount of carbidopa, as determined by HPLC.

[0025] In certain embodiments, the pharmaceutical composition of the present invention comprises less than 1.0, 0.75, 0.5, 0.25, 0.1, 0.05, or 0.025 µg/ml hydrazine, as determined by a GCMS, particularly less than 0.1 or 0.05 µg/ml hydrazine, or 0.1 to 0.5 µg/ml hydrazine, e.g., as determined by a GCMS; or less than 5%, 4%, 3%, 2%, 1%, 0.5%, 0.3%, 0.2%, 0.1%, or 0.05%, by weight, degradant relative to the initial amount of carbidopa, as determined by HPLC.

[0026] In certain embodiments, the pharmaceutical composition of the present invention comprises 0.1% to 10% by weight carbidopa. In particular such embodiments, the pharmaceutical composition of the present invention comprises 0.5% to 6%, preferably 0.75% to 4%, more preferably 0.75%, 1.4%, 3%, 3.3% or 4%, by weight, carbidopa.

[0027] The pharmaceutical composition of the present invention comprises a combination of two or more antioxidants, wherein one of those antioxidants is ascorbic acid or a salt thereof. Examples of ascorbic acid salts include, without being limited to, sodium ascorbate, potassium ascorbate, calcium ascorbate, ascorbyl stearate, and ascorbyl palmitate, wherein sodium ascorbate being preferred.

[0028] In certain embodiments, the pharmaceutical composition of the present invention comprises 0.1% to 10%, by weight, ascorbic acid or a salt thereof. In particular such embodiments, the composition comprises 0.2% to 2%, preferably 0.4% to 1.3%, more preferably 0.5%, 0.6%, 0.75%, 0.85%, 1.0%, 1.2%, or 1.3%, by weight, ascorbic acid or a salt thereof such as sodium ascorbate, potassium ascorbate, calcium ascorbate, ascorbyl stearate, and ascorbyl palmitate.

[0029] According to the present invention, each one of the antioxidants comprised within the pharmaceutical composition of the present invention, other than ascorbic acid or salt

thereof, may be any antioxidant or o-quinone scavenger, but it is preferably such antioxidant that, together with ascorbic acid or a salt thereof, provides a combination that can strongly inhibit degradation of carbidopa thus minimize hydrazine formation, and consequently substantially stabilize said composition for a sufficient period of time, e.g., for hours, days, weeks, months or years.

[0030] In certain embodiments, each one of the antioxidants other than ascorbic acid or salt thereof independently is selected from L-cysteine (L-Cys) or a cysteine derivative such as NAC, glutathione, diacetylcystine, S-methyl-N-acetylcysteine amide, acetyl derivatives of S-methyl-N-acetylcysteine methylhydrazide, S-methylcysteine morpholineamide, and S-methyl-N-acetylcysteine morpholineamide, a salt of the aforesaid, or a bisulfite such as sodium bisulfite, sodium hydrogen sulfite, or sodium metabisulfite, but preferably from L-cysteine or a salt thereof such as cysteine hydrochloride, NAC, or sodium bisulfite. In particular such embodiments, the pharmaceutical composition of the present invention comprises (i) 0.001% to 5%, preferably 0.01% to 1%, more preferably 0.1% to 0.6%, 0.3%, or 0.4%, by weight, L-cysteine or a salt thereof such as cysteine hydrochloride; and/or (ii) 0.001% to 5%, preferably 0.01% to 1%, more preferably 0.1%, 0.2%, 0.3%, or 0.4%, by weight, NAC; and/or (iii) 0.01% to 2%, preferably 0.075% to 0.75%, more preferably 0.1%, by weight, sodium bisulfite; and/or (iv) 0.001% to 5%, preferably 0.1% to 1%, by weight, glutathione; and/or (v) 0.001% to 5%, preferably 0.01% to 1%, by weight, diacetylcystine or a salt thereof.

[0031] In certain embodiments, the pharmaceutical composition of the present invention comprises 0.1% to 10%, by weight, carbidopa; 0.1% to 10%, by weight, ascorbic acid or a salt thereof such as sodium ascorbate, potassium ascorbate, calcium ascorbate, ascorbyl stearate, or ascorbyl palmitate; and (i) 0.001% to 5%, by weight, L-cysteine or a salt thereof such as cysteine hydrochloride; or (ii) 0.001% to 5%, by weight, NAC; or (iii) 0.001% to 5%, by weight, glutathione; or (iv) 0.001% to 5%, by weight, diacetylcystine or a salt thereof; or (v) 0.01% to 2%, by weight, sodium bisulfite. Particular such embodiments are those wherein the composition comprises 0.5% to 6%, preferably 0.75% to 4%, more preferably 0.75%, 1.4%, 3%, 3.3% or 4%, by weight, carbidopa; 0.2% to 2%, preferably 0.4% to 1.3%, more preferably 0.5%, 0.6%, 0.75%, 0.85%, 1.0%, or 1.2%, by weight, ascorbic acid or a salt thereof; and (i) 0.01% to 1%, preferably 0.1% to 0.6%, by weight, L-cysteine or a salt thereof; (ii) 0.01% to 1%, preferably 0.1% to 0.4%, by weight, NAC; or (iii) 0.075% to 0.75%, by weight, sodium bisulfite.

[0032] In a particular such aspect, the pharmaceutical composition of the present invention according to any one of the embodiments defined above further comprises (i) levodopa (and/or an ester thereof); (ii) arginine, meglumine, a salt of the aforesaid, or a combination thereof; or (iii) both (i) and (ii); and optionally further comprises a surfactant. Particular such compositions do not comprise levodopa.

[0033] In certain embodiments, the pharmaceutical composition of the present invention comprises carbidopa and at least two antioxidants, each as defined in any one of the embodiments above, and further comprises levodopa. Certain particular such compositions comprise less than 1% (e.g., less than 0.5%, 0.25%, 0.1%, 0.05%, or 0.01%), by weight, levodopa, while other compositions comprise 1% to 20%, preferably 2% to 16% (e.g., 2% to 8%, 4% to 8%, 5% to 7%, 8% to 16%, 10% to 15%, 12% to 15%), more preferably 4%, 6%, 12% or 13.2%, by weight, levodopa.

[0034] In certain embodiments, the pharmaceutical composition of the present invention comprises carbidopa and at least two antioxidants, each as defined in any one of the embodiments above, and further comprises arginine, meglumine, or a combination thereof. Particular such compositions comprise 0.1% to 42% (e.g., 0.1% to 40%, 10% to 25% 13% to 18%, 14% to 16%, 12% to 40%, 25% to 40%, 30% to 38%, 10% to 20%, and 20% to 42%), preferably 2% to 40% or 10% to 38%, more preferably 12% to 36% or 15.2% to 32%, by weight, arginine, meglumine, or a combination thereof. It should be understood that while certain particular such compositions comprise arginine only, other particular compositions comprise meglumine only, and further particular compositions comprise both arginine and meglumine.

[0035] In certain embodiments, the pharmaceutical composition of the present invention comprises carbidopa; at least two antioxidants; and (i) levodopa; (ii) arginine, meglumine, or a combination thereof; or (iii) both (i) and (ii), each as defined in any one of the embodiments above, and further comprises a surfactant, e.g., a nonionic surfactant such as polysorbate 20 [polyoxyethylene (20) sorbitan monolaurate], polysorbate 40 [polyoxyethylene (20) sorbitan monopalmitate], polysorbate 60 [polyoxyethylene (20) sorbitan monostearate], polysorbate 80 [polyoxyethylene (20) sorbitan monooleate; Tween® 80], or a combination thereof. Particular such compositions comprise 0.01% to 5%, preferably 0.1% to 0.5% or 0.2% to 0.4%, more preferably 0.3%, by weight, of a nonionic surfactant as listed above, preferably polysorbate 80.

[0036] In certain embodiments, the pharmaceutical composition of the present invention comprises carbidopa and at least two antioxidants, each as defined in any one of the embodiments above, and further comprises 1% to 20%, by weight, levodopa; and 0.1% to 42%, by weight, arginine, meglumine, or a combination thereof. Particular such embodiments are those wherein the composition comprises 2% to 16% (e.g., 2% to 8%, 4% to 8%, 5% to 7%, 8% to 16%, 10% to 15%, 12% to 15%), preferably 4%, 6%, 12% or 13.2%, by weight, levodopa; and 0.1% to 42% (e.g., 0.1% to 40%, 10% to 25% 13% to 18%, 14% to 16%, 12% to 40%, 25% to 40%, 30% to 38%, 10% to 20%, and 20% to 42%), preferably 10% to 38%, more preferably 12% to 36% or 15.2% to 32%, by weight, arginine, meglumine, or a combination thereof. In more particular such embodiments, the composition of the invention further comprises a surfactant, e.g., polysorbate 80, more specifically 0.1% to 0.5% or 0.2% to 0.4%, preferably 0.3%, by weight, polysorbate 80.

[0037] In certain embodiments, the pharmaceutical composition of the present invention comprises (i) 0.1% to 6% by weight carbidopa; (ii) 0.1% to 10% by weight ascorbic acid or a salt thereof; (iii) 0.01% to 1% by weight L-cysteine or a salt thereof, NAC, or glutathione; (iv) 0% to 16% by weight levodopa; and (v) 0.1% to 40% by weight arginine.

[0038] In certain embodiments, the pharmaceutical composition of the present invention thus comprises (i) 0.1% to 10%, by weight, carbidopa; (ii) 0.1% to 10%, by weight, ascorbic acid or a salt thereof such as sodium ascorbate, potassium ascorbate, calcium ascorbate, ascorbyl stearate, and ascorbyl palmitate; (iii) 0.001% to 5%, by weight, L-cysteine or a salt thereof such as cysteine hydrochloride; or 0.001% to 5%, by weight, NAC; or 0.001% to 5%, by weight, glutathione; or 0.001% to 5%, by weight, diacetylcystine or a salt thereof; or 0.01% to 2%, by weight, sodium bisulfite; (iv) 1% to 20%, by weight, levodopa; (v) 0.1% to 42%, by weight, arginine, meglumine, or a combination thereof; and optionally (vi) 0.01% to 5%, by weight, polysorbate 80, wherein the composition comprises less than 1 µg/ml, preferably less than 0.5 µg/ml, more preferably less than 0.1 µg/ml, hydrazine. In particular such embodiments, the composition comprises (i) 0.5% to 6%, preferably 0.75% to 4%, more preferably 0.75%, 1.4%, 3%, 3.3%, or 4%, by weight, carbidopa; (ii) 0.2% to 2%, preferably 0.4% to 1.3%, more preferably 0.5%, 0.6%, 0.75%, 0.85%, 1.0%, 1.2%, or 1.3%, by weight, ascorbic acid or a salt thereof; (iii) 0.01% to 1%, preferably 0.1% to 0.6%, by weight, L-cysteine or a salt thereof; 0.01% to 1%, preferably 0.1% to 0.4%, by weight, NAC; or 0.075% to 0.75%, by weight, sodium bisulfite; (iv) 2% to 16%, preferably 4% to 14%, more preferably 4%, 6%,

12% or 13.2%, by weight, levodopa; (v) 2% to 42%, preferably 10% to 38%, more preferably 12% to 36% or 15.2% to 32%, by weight, arginine, meglumine, or a combination thereof; and optionally (vi) 0.1% to 0.5% or 0.2% to 0.4%, preferably 0.3%, by weight, polysorbate 80. In other particular such embodiments, the composition comprises (i) 0.1% to 3%, preferably 0.5% to 2% or 0.6% to 1.5%, by weight, carbidopa; (ii) 0.1% to 10%, preferably 0.1% to 2% or 0.3% to 0.7%, by weight, ascorbic acid or a salt thereof; (iii) 0.001% to 5%, preferably 0.1% to 2% or 0.3% to 0.5%, by weight, L-cysteine or a salt thereof, NAC, glutathione, or diacetylcystine; (iv) 2% to 8%, preferably 4% to 8% or 5% to 7%, by weight, levodopa; (v) 10% to 25%, preferably 13% to 18% or 14% to 16%, by weight, arginine, meglumine, or a combination thereof; and optionally (vi) 0.01% to 5% or 0.1% to 0.5%, or 0.3%, by weight, polysorbate 80. In further particular such embodiments, the composition comprises (i) 1% to 4%, preferably 1.2% to 4% or 2% to 4%, by weight, carbidopa; (ii) 0.1% to 10%, preferably 0.1% to 2% or 0.3% to 0.7%, by weight, ascorbic acid or a salt thereof; (iii) 0.001% to 1%, preferably 0.1% to 1% or 0.2% to 0.5%, by weight, L-cysteine or a salt thereof, NAC, glutathione, or diacetylcystine; (iv) 8% to 16%, preferably 10% to 15% or 12% to 15%, by weight, levodopa; (v) 12% to 40%, preferably 25% to 40% or 30% to 38%, by weight, arginine, meglumine, or a combination thereof; and optionally (vi) 0.01% to 5% or 0.1% to 0.5%, or 0.3%, by weight, polysorbate 80. In still a further particular such embodiment, the composition comprises (i) 0.1% to 1.5% by weight carbidopa; (ii) 0.1% to 1.5%, preferably 0.4% to 0.6% or 0.4% to 1%, by weight, ascorbic acid or a salt thereof; (iii) 0.1% to 0.7% by weight L-cysteine or a salt thereof, or NAC; (iv) 4% to 8% by weight levodopa; (v) 10% to 20% by weight arginine; and optionally (vi) 0.1% to 0.5% by weight polysorbate 80. In yet a further particular such embodiment, the composition comprises (i) 1% to 4% by weight carbidopa; (ii) 0.1% to 1.5%, preferably 1% to 1.4%, by weight, ascorbic acid or a salt thereof; (iii) 0.1% to 1%, preferably 0.1 to 0.5%, by weight, L-cysteine or a salt thereof, or NAC; (iv) 8% to 16% by weight levodopa; (v) 20% to 40% by weight arginine, meglumine, or a combination thereof.

[0039] In more particular embodiments, the the pharmaceutical composition of the present invention thus comprises (i) 12% to 15% by weight levodopa, 1.2% to 4% by weight carbidopa, 32% to 42%, e.g., 32%, 33%, 34%, 35% or 36%, by weight arginine or meglumine, 1% to 1.3% by weight sodium ascorbate, 0.1-0.5% by weight L-cysteine (or cysteine hydrochloride) or NAC, and optionally polysorbate 80, e.g., 0.3% by weight; or

(ii) 6% by weight levodopa, 0.6% to 1.4% by weight carbidopa, 15% to 16% by weight arginine, 0.5% by weight ascorbic acid, 0.3% by weight polysorbate 80, and 0.5% by weight NAC or 0.4% by weight L-cysteine.

Table 1: Specific pharmaceutical compositions exemplified herein

No.	CD	LD	L-Arg	Meglumine	Ascorbic acid/ Na-ascorbate	L-Cys	NAC	Tween® 80
1	3%	12%	32%		1.2% Na-ascorbate	0.3%[1]		
2	3.3%	13.2%	36%		1.3% Na-ascorbate	0.3%[1]		
3	3.3%	13.2%		36%	1.3% Na-ascorbate	0.3%[1]		
4	3%	12%		32%	1.2% Na-ascorbate		0.3%	
5	3%	12%	32%		1.2% Na-ascorbate		0.3%	
6	1.4%	6%	15.5%		0.5% ascorbic acid	0.4%		0.3%
7	1.4%	6%	15.5%		0.5% ascorbic acid		0.5%	0.3%
8	0.75%	6%	15.2%		0.5% ascorbic acid	0.4%		0.3%
9	0.75%	6%	15.2%		0.5% ascorbic acid		0.5%	0.3%

[1] Or cysteine hydrochloride.

[0040] In certain specific embodiments, the pharmaceutical composition of the present invention is one of those exemplified herein and listed in **Table 1**. These compositions comprise (i) 12% by weight levodopa, 3% by weight carbidopa, 32% by weight arginine, 1.2% by weight sodium ascorbate, and 0.3% by weight L-cysteine or cysteine hydrochloride; (ii) 13.2% by weight levodopa, 3.3% by weight carbidopa, 36% by weight arginine, 1.3% by weight sodium ascorbate, and 0.3% by weight L-cysteine or cysteine hydrochloride; (iii) 13.2% by weight levodopa, 3.3% by weight carbidopa, 36% by weight meglumine, 1.3% by weight sodium ascorbate, and 0.3% by weight L-cysteine or cysteine hydrochloride; (iv) 12% by weight levodopa, 3% by weight carbidopa, 32% by weight meglumine, 1.2% by weight sodium ascorbate, and 0.3% by weight NAC; (v) 12% by weight levodopa, 3% by weight carbidopa, 32% by weight arginine, 1.2% by weight sodium ascorbate, and 0.3% by weight NAC; (vi) 6% by weight levodopa, 1.4% by weigh carbidopa, 15.5% by weight arginine, 0.5% by weight ascorbic acid, 0.4% by weight L-cysteine and 0.3% by weight polysorbate 80; (vii) 6% by weight levodopa, 1.4% by weigh carbidopa, 15.5% by weight arginine, 0.5% by weight ascorbic acid, 0.5% by weight NAC and 0.3% by weight polysorbate 80; (viii) 6% by weight levodopa, 0.75% by weigh carbidopa, 15.2% by weight arginine, 0.5% by weight ascorbic acid, 0.4% by weight L-cysteine and 0.3% by weight polysorbate 80; or (ix) 6% by weight levodopa, 0.75% by

weigh carbidopa, 15.2% by weight arginine, 0.5% by weight ascorbic acid, 0.5% by weight NAC and 0.3% by weight polysorbate 80. The compositions of (i)-(v) above may further comprise polysorbate 80, e.g., 0.3% by weight.

[0041] Pharmaceutical compositions according to the present invention may include further antioxidants such as di-tert-butyl methyl phenols, tert-butyl-methoxyphenols, polyphenols, tocopherols, and ubiquinones, e.g., caffeic acid; and/or a glucose amine which may, e.g., replace some or all of the arginine present in the formulations. Compositions according to the invention may also include a tyrosinase inhibitor such as, without being limited to, captopril, methimazole, quercetin, arbutin, aloesin, N-acetylglucoseamine, retinoic acid, α-tocopheryl ferulate, Mg ascorbyl phosphate (MAP), substrate analogues, e.g., sodium benzoate, and L-phenylalanine, Cu^{++} chelators, e.g., Na_2-EDTA, Na_2-EDTA-Ca, DMSA (succimer), DPA (D-penicillamine), trientine-HCl, dimercaprol, clioquinol, sodium thiosulfate, TETA, TEPA, curcumin, neocuproine, tannin, and cuprizone. The compositions may further include pharmaceutically acceptable fillers, carriers, diluents or adjuvants, as well as other inert ingredients and excipients.

[0042] In certain embodiments, the pharmaceutical composition of the present invention comprises carbidopa; at least two antioxidants; levodopa; arginine, meglumine, or a combination thereof; and optionally a surfactant, each as defined in any one of the embodiments above, wherein the composition has a pH of 9.1 to 10, preferably 9.4-9.8, more preferably 9.6 to 9.8.

[0043] As stated above, the pharmaceutical compositions of the present invention are highly stable due to the particular antioxidant combination which stabilizes the carbidopa in the composition and strongly inhibits its degradation to degradant and hydrazine. Moreover, these compositions can be stored at various conditions and temperatures, e.g., at a temperature of up to 25°C, for long periods of time, more particularly up to several years, while maintaining a safe and tolerable concentration of hydrazine.

[0044] In certain embodiments, the pharmaceutical composition of the present invention according to any one of the embodiments defined above comprises less than 1 μg/ml, preferably less than 0.5 μg/ml, more preferably less than 0.1 μg/ml, hydrazine, as determined by a GCMS, or less than 5%, preferably less than 1%, more preferably less than 0.75%, 0.6%, 0.5%, 0.4%, 0.3%, 0.25%, 0.2%, 0.1%, 0.05%, or 0.01%, by weight degradant relative to the initial amount of carbidopa, as determined by HPLC, after storage

for 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24 hours; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, or 30 days; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months; or 1, 1.5, 2, 2.5, or 3 years, at a temperature in a range of -20°C to 25°C, e.g., at -20°C, 2-8°C, or 25°C.

[0045] The pharmaceutical compositions provided by the present invention may be prepared by conventional techniques, e.g., as described in Remington: The Science and Practice of Pharmacy, 19th Ed., 1995, following one of the procedures described in the Experimental section herein. For example, such compositions may be prepared by mixing all the ingredients, i.e., carbidopa, antioxidants, and optionally levodopa, arginine and/or meglumine, and surfactant, all in the form of powders, in amounts as disclosed above, to form a powder mixture. Water can then be added to the mixture to form a suspension. The water can be pre-heated or the suspension formed can be heated at a temperature and for a time sufficient to dissolve the mixture, e.g., to 40°C to 100°C, 40°C to 80°C, or 60°C to 90°C, e.g., 65±5°C, 72±5°C or 73±3°C, e.g., by adding pre-heated water and/or by placing the mixture in a hot water bath for, e.g., up to 3, 5, 10, 20, 30, 40, 50, 60 minutes, or more, to form a solution, with optional stirring. This is followed by cooling the solution to form the composition. N_2 can be provided the head space of the container. Specific methods of preparation are described in Example 1 below. The pharmaceutical compositions disclosed herein can be sterilized, e.g., using 0.2 μm filters such as nylon-based filters or polyvinylidene difluoride (PVDF) membranes.

[0046] The pharmaceutical composition of the invention may be formulated as a liquid, gel, cream, solid, film, emulsion, suspension, solution, lyophilisate or aerosol, but it is preferably formulated as a liquid. Such compositions may be formulated for any suitable route of administration, but it is preferably formulated for subcutaneous, transdermal, intradermal, intravenous, intramuscular, intratracheal, intrathecal, intraduodenal, or oral, administration. The compositions may also be formulated for inhalation, or for direct absorption through mucous membrane tissues.

[0047] In another aspect, the present invention relates to a method for treatment of a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons in an individual in need thereof, said method comprising administering to said individual an effective amount of a pharmaceutical composition as defined in any one of the embodiments above, i.e., a carbidopa-based composition containing safe and tolerable concentration of hydrazine. The disease, disorder or condition associated with loss of

dopamine or dopaminergic neurons may be a neurological or movement disorders including restless leg syndrome, Parkinson's disease, secondary Parkinsonism, Huntington's disease, Shy-Drager syndrome, and conditions resulting from brain injury including carbon monoxide or manganese intoxication. In one particular embodiment, the neurological disorder is Parkinson's disease.

[0048] According to the method of the present invention, the pharmaceutical composition can be administered over a defined time period, e.g., days, weeks, months, or years; and can be effected by any appropriate route, e.g., subcutaneously, transdermally, intravenously, intramuscularly, intradermally, intratracheally, intrathecally, intraduodenally, or orally, as well as by inhalation, or direct absorption through mucous membrane tissues.

[0049] In certain embodiments, the administration of the pharmaceutical composition according to the method of the present invention is substantially continuous, e.g., subcutaneously or transdermally. The term "substantially continuous", as used herein, means that a single dose of the composition is being administered to said patient or individual over a particular predetermined period of time, e.g., for a period of at least 10, 20 or 30 minutes, 1 hour, 2 hours, 4, hours, 6 hours, 8 hours, 12 hours, 15 hours, 18 hours, 21 hours, or 24 hours, rather than as a bolus, e.g., as a pill taken orally or a bolus injection. Substantially continuous administration of these pharmaceutical compositions can be achieved using, e.g., a transdermal patch or a pump device that continuously administers the composition to the patient over time.

[0050] In certain embodiments, liquid compositions according to the invention, particularly when comprising levodopa, may be administered at a rate of 0.01 ml/hour/site to 0.4 ml/hour/site, e.g., 0.16 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. Such pharmaceutical compositions may thus be administered, e.g., at a rate of 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. In other embodiments, such compositions be administered, e.g., intraduodenally, at a rate of 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 0 to 0.5 ml/hour at rest or at night. In further embodiments, such compositions may be administered 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 0.5 ml/hour (e.g., 0.5±0.25 ml/hour) at rest or night. In still further embodiments, such compositions may be administered at a rate of 0.1 to 1000 µl/hour/site; or at a volume of 2 to 10 ml/24hour/site, preferably 4 to 6 ml/24hour/site; or at a dose of 80 to 800 mg levodopa/day and 20 to 200 mg carbidopa/day; or at a rate of 240 to 360 mg levodopa and 60 to 90 mg carbidopa/day/site.

[0051] In certain embodiments, a pharmaceutical composition according to the invention may be substantially continuously administered, e.g., using a pump for subcutaneous infusion (e.g., insulin pump) 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 0 to 80 µl/hour or 0 to 200 µl/hour for 8 hours (at night); or using a transdermal patch. Substantially continuously administering the composition to a patient can be doubled or tripled by using more than one pump, patch, or infusion site. In certain 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 0 to 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.

[0052] In certain embodiments, the pharmaceutical composition of the invention is used for treatment of said neurological disorder or a movement disorder by acute and immediate administration, e.g., by inhalation or injection.

[0053] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein interchangeably refers to any and all solvents, dispersion media, preservatives, antioxidants, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and ingredients for pharmaceutically active substances is well-known in the art. It should be understood that the compositions of the invention can also contain other active agents providing supplemental, additional, or enhanced therapeutic functions.

[0054] The term "acceptable" with respect to a carrier or an excipient comprised within a pharmaceutical composition refers to any carrier, ingredient or molecular entity that do not produce an adverse, allergic or other untoward reaction when administered to a mammal or

human as appropriate. For human administration, compositions should meet sterility, pyrogenicity, and general safety and purity standards as required by, e.g., the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

[0055] 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 4 to 9.8 (for example, 4±0.3 to 9.5±0.3).

[0056] The term "ambient temperature" as used herein refers to a temperature ranging from 10°C to 30°C. In particular embodiments, ambient temperature can be 25°C.

[0057] Percentages disclosed herein with respect to the pharmaceutical compositions of the invention are by weight unless indicated otherwise.

[0058] In still another aspect, the present invention relates to a pharmaceutical composition as defined above, i.e., a carbidopa-based composition containing safe and tolerable concentration of hydrazine, for use in treatment of a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease.

[0059] In yet another aspect, the present invention relates to use of a pharmaceutical composition as defined above, i.e., a carbidopa-based composition containing safe and tolerable concentration of hydrazine, for the preparation of a medicament for treatment of a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease.

[0060] In a further aspect, the present invention provides a kit comprising at least one, i.e., 1, 2, 3 or more, containers each containing a pharmaceutical composition according to any one of the embodiments above, wherein said composition is present in an amount sufficient to treat an individual in need thereof for a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons, e.g., Parkinson's disease, for at least 1 day, 1 week, 1 month, 2 months, 6 months, or 1 year. The containers comprised within the kit of the invention may be, e.g., pre-filled cartridges or vials suitable for use by a patient or physician.

[0061] In certain embodiments, the kit of the present invention thus comprises a pre-filled cartridge containing a pharmaceutical composition as defined above, e.g., a pre-filled cartridge containing a single dose or a dose suitable for a single administration or multiple administrations to a patient of said composition, and optionally instructions for use. Such containers, vials, pre-filled syringes, or the like, may include, e.g., 1-10 ml of a disclosed

composition. In a particular embodiment, the kit of the invention comprises one or more pre-filled vials, containers or syringes, each containing a disclosed liquid pharmaceutical composition in an amount suitable for filling a syringe pump or patch pump, e.g., 1-10 ml, 1-2 ml, 2-5 ml, 1-2 ml, or 4-10 ml of a disclosed composition.

[0062] Considering the increased stability of the compositions of the present invention, particular kits according to the invention comprise a supply of a composition in an amount sufficient for at least 1, 2, 3, 4, or 5 days; 1, 2, 3, or 4 weeks; 1, 2, 3, 4, 6, or 9 months; or 1 or 1.5 years, of administration to a patient, which can be packaged, e.g., into suitable dosage (e.g., unit dosage) compositions. Such kits can optionally include instructions for their use. For example, a kit for daily use may include one, two or more containers or vials of a disclosed composition, an infusion set, and a disposable patient delivery unit, e.g., syringe.

[0063] The invention now being generally described, will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention in any way.

EXAMPLES

Example 1. Formulation Preparation Procedure

[0064] Levodopa (LD) and carbidopa (CD) formulations can be prepared as follows:

Method #1 (L-Arg solution): L-Arg and Na-bisulfite (Na-Bis) were dissolved in water. The solution was added to the LD and CD powders. The mixture was heated with stirring for 13 min at 75°C until fully dissolved. The LD/CD solution was kept at room temperature (RT) for 10 min to cool down.

Method #2 (all powders together): All powders (LD, CD, and L-Arg) were weighed, and water with Na-Bis was added. The suspension was heated with stirring for 13 min at 75°C until fully dissolved. The LD/CD solution was kept at RT for 10 min to cool down.

Method #3 (same as #2 without Na-Bis pre-heating): All powders (LD, CD, and L-Arg) were weighed together and water was added. The suspension was heated with stirring for 13 min at 75°C until fully dissolved. The LD/CD solution was kept at RT for 10 min to cool down.

Method #4 (preparation in steps): LD and the respective amount of L-Arg were weighed; water and Na-Bis solution were added. The suspension was heated for 7 min at 75°C until fully dissolved, followed by 7 min at RT. CD and the respective amount of L-Arg were weighed and added to the LD/Arg solution at 60°C until fully dissolved. Finally, extra L-Arg was added.

Method #5 (same as #4 without Na-Bis pre-heating): LD and the respective amount of L-Arg were weighed; water was added. The suspension was heated for 7 min at 75°C until fully dissolved followed by 7 min at RT. CD and the respective amount of L-Arg were weighed and added to the LD/Arg solution at 60°C until fully dissolved. Finally, extra L-Arg was added.

[0065] After cooling down, all formulations from all methods were divided in to 3 vials, and water, Na-Bis solution, or Na-Bis-Arg solution was added to each vial.

Example 2. Identification of the main degradant in CD containing formulations

[0066] Liquid formulations with levodopa, carbidopa, and arginine were prepared using the procedure outlined in Example 1, and HPLC analysis was performed according to APH stability-indicating analytical method for carbidopa levodopa formulations with Agilent 1100 system.

[0067] The HPLC system used herein includes the following components manufactured by Agilent: pump system (model G1311A), diode array detector (model G1315B), autosampler (model G1329A), degasser (model G1379A), thermostat (model G1330B), thermostatted column compartment (model G1316A). The column employed was a new Synergi 4µ Fusion-RP 80A, 250×4.6 mm (Phenomenex®).

[0068] HPLC working conditions: wavelength: 280 nm; flow rate: 1.0 ml/min; injection volume: 10 µl; column temperature: 30°C; thermostat temperature: 4°C; stop time: 27 min; pressure: 105 bar.

[0069] Mobile phase preparation: Solvent A: acetonitrile, Solvent B: 20 mM potassium dihydrogen phosphate, pH=2.4. The mobile phase B was prepared by weighing 2.72 g/l of potassium dihydrogen phosphate. pH was adjusted to 2.4 by addition of H_3PO_4. Gradient used was according to **Table 2**.

[0070] Diluent: 0.1M HCl/MeOH 9:1 (8.3 ml HCl 37% to 1L) --> 0.1 M HCl. STD LDOPA=100.00 mg/100ml. STD CDOPA=25.00 mg/100ml.

[0071] Calibration curve is described in **Table 3**.

Table 2

Time	Solvent A	Solvent B	Flow
0	5	95	1.0
5	5	95	1.0
15	60	40	1.0
20	60	40	1.0
20.01	5	95	1.2
27	5	95	1.2

Table 3

STD stock solution 1000/250 ppm	Volumetric bottle, ml	Final concentration LD/CD ppm
NA	10	1000/250
5000 from stock	10	500/125
5000 from 500/125	10	250/62.5
1000 from stock	10	100/25
5000 from 100/25	10	50/12.5
1000 from 100/25	10	10/2.5

[0072] One ml of the sample (levodopa/carbidopa formulation) was transferred to a 25 ml amber volumetric glass flask and filled to volume with diluent (0.1 M HCl/MeOH 9/1). The sample was degraded with hydrogen peroxide.

[0073] The impurity was observed at retention time of about 14.5±0.2 min (**Fig. 1**). To ensure that the peak observed is actually the compound of interest, the main degradant peak was collected from analytical HPLC, evaporated under nitrogen stream and reconstituted with diluent. Obtained samples were tested by HPLC/MS.

[0074] Initially, an MS scan analysis was applied (**Figs. 2A-2B**). The unknown compound shows clear and intensive signal in negative mode and much nosier signal in positive mode. Therefore it was expected to be more a proton donor than acceptor. The base peak in negative mode was M/Z=195 Da that was suspected as (M-H). The mass difference between this ion and peak M/Z=217 is 22 and that should be the sodium adduct. This is the evidence of the presence of carboxyl or/and phenol groups. Due to this fact, the molecular weight was proposed to be 196 Da.

[0075] The peak M/Z=197 $(M+H+)^+$ was not found in positive mode, but the peak M/Z=197 $(M-H_2O)^+$ is observed. This is typical for oxygen containing molecule.

[0076] The daughter and parent MS/MS was performed as well to define molecular structure. Peaks observed in positive mode with M/Z=179, 161, 151, 133, 123, 105 were

found to be relative. They were defined as in-source fragment ions arising from the molecular ion with M/Z=197. The typical MS and MS/MS spectra are shown on figures (**Figs. 3A-3B**).

[0077] The chemical formula of the degradant compound is $C_{10}H_{12}O_4$, with a molecular structure given by 3-(3,4 dihydroxyphenyl)-2-methylpropanoic acid.

Example 3. Effect of ascorbic acid with or without EDTA on LD/CD formulation stability

[0078] Liquid formulations were prepared by weighing all powders (LD, CD, EDTA, ascorbic acid, and L-Arg) and adding water pre-heated to 73±3°C. The suspension was put in a water bath at 73±3°C and stirred for 10 min until fully dissolved. LD/CD solution was kept at RT for 10 min to cool down. Solutions were divided into glass vials and kept at +25°C and at -20°C for the indicated period of time. Prior to analyses, frozen vials were placed at RT until fully thawed. Formulations were then mixed and subjected to stability analyses. The effect of ascorbic acid with or without EDTA on the stability of LD/CD formulations was measured by HPLC. The levels of the degradant presented in **Tables 4** and **5** (as percentage of the initial CD amount) indicate the level of stability of LD/CD formulations, and suggest that EDTA did not have a significant effect on the stability of LD/CD formulations.

Table 4

LD/CD	L-Arg (%)	Ca-EDTA-Na_2 (%)	Ascorbic acid (%)	t=0	
				Degradant	Total* (%)
6/1.4	14.80	0.2	1.0	0.13	0.76
6/1.4	14.80	0	1.0	0.08	0.44

Table 5

LD/CD	L-Arg (%)	Ca-EDTA-Na_2 (%)	Ascorbic acid (%)	t=0		t=1w (25°)	
				Degradant	Total (%)	Degradant	Total* (%)
6.0/1.4	14.80	0.2	1.0	0.054	0.64	0.16	0.79
6.0/1.4	14.80	0	1.0	0.046	0.49	0.15	0.49

* percentage of total amount of ingredients.

Example 4. Effect of L-cysteine on the stability of CD/LD containing solutions

[0079] Liquid formulations were prepared by weighing all powders (LD, CD, L-cysteine, ascorbic acid, and L-Arg) and adding water pre-heated to 73±3°C. The suspension was put

in a water bath at 73±3°C and stirred for 10 min until fully dissolved. LD/CD solution was kept at RT for 10 min to cool down. For CD formulations, CD, L-cysteine, and ascorbic acid were weighed, and pre-heated water (60°C) was added. Solutions were divided into glass vials and kept at +25°C and at -20°C for the indicated period of time. Prior to analyses, frozen vials were placed at RT until fully thawed. Formulations were then mixed and subjected to stability analyses. The effect of L-cysteine on the stability of carbidopa formulations when stored at 25°C, either exposed to air or maintained under anaerobic conditions (N_2), was analyzed using HPLC. The levels of the degradant presented in **Table 6** (as percentage of the initial CD amount) point toward the level of stability of carbidopa formulations.

[0080] As indicated in **Table 6**, ascorbic acid with 0.1% L-cysteine was sufficient to inhibit degradant formation in formulations containing carbidopa (with or without levodopa) when kept under anaerobic conditions at 25°C for at least 5 weeks. As may further be deduced from this Table, L-cysteine reduced degradant formation under aerobic conditions at 25°C in a dose-dependent manner.

[0081] In formulations containing carbidopa and 0.4% L-cysteine, degradant formation was inhibited during the preparation of the formulation. These formulations were stable for at least 5 weeks at 25°C under both aerobic and anaerobic conditions. Formulations containing carbidopa are more stable when they also contain LD upon exposure to air.

Table 6

LD/CD	L-Arg	Ascorbic acid (%)	**L-Cysteine (%)**		Degradant		
					t=0	t=5 days	t=5 weeks
6/1.4	14.8	0.5	**0.1**	N_2	0.08	0.22	0.28
				O_2		**0.59**	**0.77**
		0.5	**0.2**	N_2	0.08	0.20	0.25
				O_2		**0.36**	**0.32**
		0.5	**0.4**	N_2	0.00	0.14	0.14
				O_2		**0.14**	**0.17**
0/4	4.6	0.5	**0.1**	N_2	0.05	0.16	
				O_2		**1.42**	
		0.5	**0.2**	N_2	0.05	0.16	
				O_2		**0.56**	
		0.5	**0.4**	N_2	0.04	0.15	
				O_2		**0.35**	

Example 5. Effect of L-cysteine on 6/1.4% LD/CD formulation stability

[0082] Liquid formulations were prepared as described in Example 3. The effect of L-cysteine on the stability of 6/1.4% levodopa/carbidopa solutions at 25°C was analyzed using HPLC. The levels of the degradant presented in **Tables 7-10** (as percentage of the initial CD amount) point toward the level of stability of the referenced formulations.

[0083] The results show that levodopa/carbidopa formulations were more stable with both ascorbic acid and L-cysteine, as compared to ascorbic acid alone, suggesting that L-cysteine and ascorbic acid have a synergistic effect in preventing degradant formation. Other results showed that L-cysteine alone had no effect at all (data not shown). Furthermore, L-cysteine inhibited degradant formation during formulation preparation and maintained the stability of the formulation for at least up to 5 weeks at 25°C, in a dose dependent manner. Increasing the amount of ascorbic acid reduces degradant formation, but this was significantly less efficient than the combination of ascorbic acid with L-Cys.

Table 7

LD/CD (%)	L-Arg (%)	Ascorbic acid (%)	**L-Cys (%)**	Degradant t = 0
6/1.4	14.8	0.5	0.2	0.02
		0.75	0.0	0.16

Table 8

LD/CD (%)	L-Arg (%)	Ascorbic acid (%)	**L-Cys (%)**	Degradant		
				t=0	t=5 d	t=5 wk
6/1.4	14.8	0.75	**0**	**0.49**	**0.93**	**1.08**
			0.1	0.10	0.35	0.32
		0.50	0.1	0.16	0.28	0.45
			0.4	0.00	0.15	0.13

Table 9

LD/CD (%)	L-Arg (%)	Ascorbic acid (%)	**L-Cys (%)**	Degradant		
				t=0	t=1 d	t=4 d
6/1.4	14.8	0.5	0.4	0.00	0.00	0.27
			0.1	0.25	0.69	1.26
		0.75	0.1	0.23	0.56	0.85
	15.1	1.0	0.2	0.00	0.26	0.51

Table 10

LD/CD (%)	L-Arg (%)	Ascorbic acid (%)	L-Cys (%)	Degradant			
				t=0	t=10 d	t=3 weeks	t=3 months
6/1.4	14.8	0.5	0.1	0.15	0.43	0.46	0.87
		0.75	0.0	1.01	1.40	1.37	2.00

Example 6. Effect of Tween-80 and Na-ascorbate on LD/CD formulation stability

[0084] Liquid formulations were prepared by weighing all powders (LD, CD, L-cysteine, ascorbic acid, Na-ascorbate and L-Arg) and adding water pre-heated to 73±3°C. The suspension was put in a water bath at 73±3°C and stirred for 10 min until fully dissolved. LD/CD solution was kept at RT for 10 min to cool down. Then, Tween-80 was added. Solutions were divided in to glass vials and kept at +25°C and at -20°C for the indicated period of time. Prior to analyses, frozen vials were placed at RT until fully thawed. Formulations were then mixed and subjected to stability analyses. The effect of Tween-80 and Na-ascorbate on the stability of carbidopa/levodopa formulations was analyzed using HPLC. The levels of the degradant presented in **Table 11** (as percentage of the initial CD amount) point toward the level of stability of carbidopa/levodopa formulations.

Table 11

LD:CD (%)	L-Arg (%)	Ascorbic acid: L-Cys (%)	Tw-80 (%)	**Degradant**	
				t=0	**t=1 month**
6.0 : 1.5	14.8	0.5 : 0.4	0	0.07	0.08
6.0 : 1.5	14.8	0.5 : 0.4	0.3	0.10	N/A
6.0 : 1.5	14.8	0.5 : 0.4	0.75	0.15	
6.0 : 1.5	14.8	0.5 : 0.4	2.0	0.00	
6.0 : 1.5	14.8	0.75 : 0.1	0	0.26	
6.0 : 1.5	14.8	0.75 : 0.1	0.75	0.31	
6.0 : 1.5	14.8	0.75 : 0.2	0	0.14	
6.0 : 1.5	14.8	0.75 : 0.2	0.3	0.27	
6.0 : 1.5	14.8	0.75 : 0.2	0.75	0.24	
6.0 : 1.5	14.8	0.75 : 0.2	2.0	0.35	
7.5 : 1.5	18.5	0.75 : 0.2	0	0.19	0.26
7.5 : 1.5	18.5	0.75 : 0.2	0.75	0.35	0.45
7.5 : 1.5	18.5	**0.85**[1] : 0.2	0	0.23	0.20
7.5 : 1.5	18.5	**0.85**[1] : 0.2	0.75	0.25	0.27

[1] Sodium ascorbate; N/A - not available.

[0085] The results demonstrate that Tween-80 did not have an effect on degradant formation. It is also shown that the effect of L-cysteine on the stability of the formulations

was dose dependent. As further shown, the effect of Na-ascorbate and ascorbic acid on the stability of the formulations and degradant formation was similar.

Example 7. Effect of ascorbic acid with or without L-Cys or NAC on long term stability of LD/CD formulations

[0086] Liquid formulations were prepared by weighing all powders (LD, CD, arginine, L-cysteine or NAC, and ascorbic acid or Na-ascorbate) and by adding water pre-heated to 73±3°C. The suspension was put in a water bath at 73±3°C and stirred until fully dissolved. LD/CD solution was kept at RT to cool down. Then Tween-80 was added. Solutions were divided into glass vials and kept at +25°C and at -20°C for the indicated period of time. Prior to analyses, frozen vials were placed at RT until fully thawed. Formulations were then mixed and subjected to stability analyses. The effect of ascorbic acid with or without L-cysteine or NAC on the stability of carbidopa/levodopa formulations was analyzed using HPLC. The levels of the degradant presented in **Table 12** (as percentage of the initial CD amount) indicates the level of stability of carbidopa/levodopa formulations.

[0087] The results shown in **Table 12** suggest that formulations containing both ascorbic acid and NAC are more stable than formulations having only ascorbic acid, at a) T_0, i.e., immediately following formulation preparation, b) for at least 9 months at -20°C, and c) at for least 1 month at ambient temperature.

Table 12

LC/CD (%)	Asc. acid (%)	NAC (%)	Tween-80 (%)	Arg (%)	T_0	Degradant								
						-20°C							25°C	2× F-T (ambient)*
						1m	2m	3m	6m	9m	12m	16.5m	1m	>3m/>7d
5/1.15	0.75	0	0	12.8	0.55	0.6	0.75	0.9	1.0	0.8	-	1.0	**1.2**	-
6/1.4	0.75	0	0	14.8	0.4	0.45	0.45	0.6	0.5	0.8	-	0.6	**0.6**	-
6/1.4	0.5	0.4	0	14.8	0	0	-	-	-	0.25	0.15	-	**0**	-
6/1.4	0.5	0.4	0.3	15.5	0	-	0.1	0.2	0.2	0.2	-	-	**-**	-
6/1.4	0.5	0.5	0.3	15.5	0	0	-	-	-	-	-	-	**0.2**	**0**
6/0.75	0.5	0.5	0.3	15.2	0	0.1	-	-	-	-	-	-	**0**	**0.2**

* 2× F-T - at least 2 freeze-thaw cycles after >3m at -20°C, and >7d at ambient temp.

Example 8. Effect of antioxidants on the stability of CD formulations

[0088] Liquid formulations with carbidopa and arginine were prepared as described above. The effect of antioxidants on the stability of carbidopa formulations was analyzed

using HPLC. The levels of the degradant presented in **Tables 13** and **14** (as percentage of the initial CD amount) point toward the level of stability of carbidopa formulations.

[0089] The results in **Tables 13** and **14** suggest that formulations containing ascorbic acid + L-cysteine were significantly more stable than the formulation containing Na-bisulfite (formulations 3 & 4 *vs.* formulations 1 & 2). The same amount of impurities were measured with 0.075 and 0.1% Na-bisulfite, suggesting that the maximum possible protection with Na-bisulfite was attained.

[0090] In sum, the combination of ascorbic acid/L-cysteine is able to prevent degradant and other impurities formation, such as hydrazine (see other examples), while Na-bisulfite does not protect formulations containing carbidopa to the same extent.

Table 13

7 weeks at (-20°C)	1	2	3	4
	0.1% Na Bisulfite	0.075% Na Bisulfite	0.4% Asc. + 0.2% L-Cys	0.5% Asc. + 0.1% L-Cys
Methyl-Dopa	0.15	0.15	0.15	0.15
Unknown 2	0.18	0.17	**0**	**0**
Degradant	0.54	0.55	**0**	0.16
Sum of all Impurities	**1.14**	**1.15**	**0.44**	**0.65**

Table 14

		Peak 14.3 min (degradant)		
		t=0	**t=3 weeks 2-8°C**	t=3 weeks 25°C
2	4% CD - 3.7% L-Arg 0.075% sodium bisulfite	0.30	**1.12 ± 0.19**	1.08 ± 0.07
3	4% CD - 4.62% L-Arg 0.4% ascorbic + 0.2% L-cysteine	0.06	**0.15 ± 0.01**	0.29 ± 0.07
4	4% CD - 4.62% L-Arg 0.5% ascorbic + 0.1% L-cysteine	0.11	**0.44 ± 0.21**	0.63 ± 0.39

Example 9. Effect of various antioxidants and different concentrations of arginine on the stability of formulations containing 4% CD

[0091] Liquid formulations with carbidopa and arginine (**Table 15**) were prepared as described above. The effect various antioxidants and different concentrations of arginine on the stability of formulations containing 4% CD, and stored under aerobic (air) or anaerobic (N_2) conditions, at ambient (25°C) or cold (2-8°C) temperature was evaluated using HPLC analysis. The levels of the degradant and total impurities as presented in

Tables 16 and **17**, respectively, point toward the level of stability of carbidopa formulations.

[0092] The results as presented in **Tables 16** and **17** indicate that formulations containing more arginine were more stable when exposed to air at 25°C (formulations 2 *vs.* 3). Further, formulations containing Na-bisulfite were less stable than the formulation containing ascorbic acid and L-cysteine (formulations 2 vs. 1, respectively) when stored under nitrogen (anaerobic conditions). N_2 provided significant protection from degradation and degradant formation. Formulations exposed to air were more stable when kept refrigerated, as compared to room (ambient) temperature.

Table 15

	1	**2**	**3**
Carbidopa	4.0	4.0	4.0
L-Arginine	4.6	4.6	3.7
Ascorbic acid	**0.4**	0	0
L-Cysteine	**0.2**	0	0
Na bisulfite 5% (ml)	0	**1.5**	**1.5**
Total solutes	9.2	10.1	9.2
Water	90.8	89.9	90.8
L-Arg (mM)	265	265	212
CD (mM)	177	177	177
Molar ratio L-Arg/CD	1.5	1.5	1.2
pH measured	8.67	8.87	8.62

Table 16

Degradant: Peak area (%)			**t=1 week; 2-8°C**	**t=1 week; 25°C**	
		t=0	Air	**N_2**	Air
1	0.4% ascorbic + 0.2% cysteine (CD:Arg 1.0:1.5)	0.1	1.7	0.2	5.8
2	0.075% Bisulfite (CD:Arg 1.0:1.5)	0.2	1.9	1.2	6.2
3	0.075% Bisulfite (CD:Arg 1.0:1.2)	0.25	2.4	1.2	8.3

Table 17

Total degradation products: Peak area (%)			**t=1 week; 2-8°C**	**t=1 week; 25°C**	
		t=0	Air	N_2	Air
1	0.4% ascorbic + 0.2% cysteine (CD:Arg 1.0:1.5)	0.1	2.5	1.1	7.2
2	0.075% Bisulfite (CD:Arg 1.0:1.5)	0.2	2.6	2.1	7.7
3	0.075% Bisulfite (CD:Arg 1.0:1.2)	0.25	3.1	2.1	9.8

Example 10. Effect of various antioxidants on the stability of formulations containing 4% CD at 40°C

[0093] Liquid formulations with carbidopa and arginine (**Table 18**) were prepared as described above. The effect various antioxidants on the stability of formulations containing 4% CD at 40°C was evaluated using HPLC analysis. The levels of the degradant (as percentage of the initial CD amount) and total impurities, presented in **Tables 19** and **20**, respectively, indicate the level of stability of carbidopa formulations.

Table 18

	1	2	3	4
Carbidopa	4.0	4.0	4.0	4.0
L-Arginine	3.4	3.7	4.6	4.6
N-methylpyrrolidone (NMP)	3.5	0	0	0
Ascorbic acid	0	0	**0.4**	**0.5**
Cysteine	0	0	**0.2**	**0.1**
Na bisulfite	**0.1**	**0.075**	0	0
Total solutes	12.9	9.2	9.2	9.2
Water	87.1	90.8	90.8	90.8
L-Arginine (mM)	195	212	265	265
Carbidopa (mM)	177	177	177	177
Molar ratio L-Arg/CD	**1.1**	**1.2**	**1.5**	**1.5**
pH measured	**8.76**	**8.96**	**9.13**	**9.12**

[0094] The results presented in **Tables 19-20** suggest that formulations containing Na-bisulfite were less stable than the formulations containing ascorbic acid and L-cysteine (formulations 1&2 *vs.* 3&4), both during preparation and when stored at 40°C. Moreover, there was a cysteine dose-response, i.e., the higher the concentration of L-cysteine, the less degradant was formed. No dose response was observed with Na-bisulfite, suggesting that the maximum possible protection may be attained with 0.075% Na-bisulfite.

Table 19 - Degradant

		t=0	t= 2d/40°C	t= 5d/40°C
1	4% CD - 3.4% L-Arg + 3.5% NMP 0.1% sodium bisulfite	0.27 ± 0.01	1.52 ± 0.56	2.60 ± 0.67
2	4% CD - 3.7% L-Arg 0.075% sodium bisulfite	0.30 ± 0.01	1.41 ± 0.54	2.95 ± 0.60
3	4% CD - 4.62% L-Arg 0.4% ascorbic + 0.2% L-Cys	0.06 ± 0.01	0.38 ± 0.14	1.26 ± 0.45
4	4% CD - 4.62% L-Arg 0.5% ascorbic + 0.1% L-Cys	0.11 ± 0.01	0.50 ± 0.23	1.97 ± 0.52

Table 20 - Total impurities

		t=0	t= 2d/40°C	t= 5d/40°C
1	4% CD - 3.4% L-Arg + 3.5% NMP 0.1% sodium bisulfite	0.61	2.00 ± 0.54	3.19 ± 0.65
2	4% CD - 3.7% L-Arg 0.075% sodium bisulfite	0.60	1.86 ± 0.56	3.61 ± 0.60
3	4% CD - 4.62% L-Arg 0.4% ascorbic + 0.2% L-Cys	0.29	0.92 ± 0.16	2.15 ± 0.59
4	4% CD - 4.62% L-Arg 0.5% ascorbic + 0.1% L-Cys	0.34	1.17 ± 0.28	2.82 ± 0.61

Example 11. Effect of ascorbic acid combined with various antioxidants on the stability of formulations containing 4% CD

[0095] Liquid formulations with carbidopa and ascorbic acid with or without additional antioxidants were prepared as described above. The combination effect between ascorbic acid and various antioxidants on the stability of formulations containing 4% CD at 25°C was evaluated using HPLC analysis. The levels of the degradant (as percentage of the initial CD amount) and total impurities presented in **Tables 21** and **22** respectively, point toward the level of stability of carbidopa formulations.

[0096] The results presented in **Tables 21-22** show that ascorbic acid, 0.5%, was insufficient for the prevention of degradant formation in a formulation containing carbidopa. Furthermore, ascorbic acid requires another antioxidant in order to exert its maximum antioxidant activity, e.g., ascorbic acid, 0.5%, and L-cysteine, NAC, or Na-bisulfite inhibited carbidopa degradation in a synergistic manner. Formulations containing ascorbic acid and L-cysteine had the lowest amount of degradant after 3 days at 25°C.

[0097] The effect of Na-bisulfite on carbidopa degradation was similar to that obtained with no antioxidants at all.

Table 21 - Degradant

4% CD	t=0	t=3d at 25°C / N_2	t=2d at 25°C / O_2
Without antioxidants	0.24	1.29	3.27
0.5% Asc	0.54	3.17	5.09
0.5% Asc + 0.2% bisulfite	0.16	0.76	2.98
0.5% Asc + 0.2% cysteine	0.09	0.27	2.67
0.5% Asc + 0.2% NAC	0.14	0.83	3.64
0.75% bisulfite (Control)	0.39	1.23	2.98

Table 22 - Total impurities

4% CD	t=0	t=3d at 25°C / N_2	t=2d at 25°C / O_2
Without antioxidants	1.04	1.88	4.01
0.5% Asc	1.07	3.96	6.40
0.5% Asc + 0.2% bisulfite	0.70	1.29	3.64
0.5% Asc + 0.2% cysteine	0.67	0.74	3.43
0.5% Asc + 0.2% NAC	0.72	1.36	4.49
0.75% bisulfite (Control)	1.13	1.71	3.58

Example 12. Effect of antioxidants on the stability of formulations containing 4% CD at 25°C

[0098] Liquid formulations with carbidopa (4%) and arginine (**Table 23**) were prepared as described above, and the effect of various antioxidants on the stability of those formulations at 25°C was evaluated using HPLC analysis. The levels of the degradant (as percentage of the initial CD amount) and total impurities presented in **Table 24** indicate the level of stability of those formulations.

[0099] The results presented in **Table 24** suggest that ascorbic acid, bisulfite, or cysteine, each used alone, did not inhibit degradant formation. Combinations between bisulfite and cysteine or ascorbic acid did not inhibit degradant formation. There was a synergistic inhibitory effect on degradant formation between ascorbic acid and cysteine, but no such synergism between cysteine and bisulfite was observed. Such synergistic effects can be seen between ascorbic acid and bisulfite (with higher ascorbic acid concentrations). These results further suggest that formulations containing the unique combination of ascorbic acid and cysteine may provide the best means for the inhibition of degradant formation.

[00100] Ascorbic acid, at 0.2%, was not sufficient for the prevention of degradant formation. With 0.2% cysteine, 0.5% ascorbic acid was more effective than 0.2% in reducing the total amount of impurities and degradant formation, suggesting that at least 0.5% ascorbic acid with 0.2% cysteine is desirable.

Table 23

	1	2	3	4	5	6	7
Carbidopa	4.0	4.0	4.0	4.0	4.0	4.0	4.0
L-Arginine	4.6	4.6	4.6	4.6	4.6	4.6	4.6
Ascorbic acid	0.2	**0.5**	0.2	0.0	0.0	0.0	0.2
Cysteine	0.0	0.2	0.2	0.2	0.2	0.0	0.0
Na bisulfite	0.0	0.0	0.0	0.0	0.1	0.1	0.1

Table 24

		Degradant		Total Impurities	
		t=0	t=1wk	t=0	t=1wk
1	0.2% ascorbic acid	0.48	1.43	1.20	2.11
2	0.5% ascorbic acid /0.2% cysteine	0.12	0.17	0.81	0.72
3	0.2% ascorbic acid /0.2% cysteine	0.12	0.21	0.85	0.94
5	0.2% cysteine	0.26	0.53	1.02	1.00
5	0.2% cysteine /0.1% bisulfite	0.71	1.01	1.62	1.66
6	0.1% bisulfite	0.33	0.84	1.16	1.45
7	0.2% ascorbic acid /0.1% bisulfite	0.26	0.70	0.99	1.49

Example 13. Determination of the level of hydrazine in CD and CD/LD formulations

[00101] The determination of hydrazine was carried out by derivatization using Aceton-d6. The hydrazine derivative was analyzed by gas chromatography mass spectrometry (GC/MS). The specific mass of hydrazine derivative was measured in the selected ion monitoring mode (SIM-mode) according to Solvias standard operating procedures (SOP's).

[00102] Liquid formulations with carbidopa, levodopa, and arginine (**Table 25**) were prepared as described above. The levels of hydrazine in the referenced formulations were measured (**Table 26**).

Table 25

Formulation Composition (%)										
Formulation #	1	2	3	4	5	6	7	8	9	10
Carbidopa	4	4	1.4	1.4	1.4	1.4	0.75	1.4	0.75	0.75
Levodopa	-	-	6	6	6	6	6	6	6	6
Arginine	4.6	4.6	14.8	15.5	15.5	15.5	15.2	15.5	15.2	15.2
Ascorbic acid	0.4	0.5	0.75	0.5	0.5	0.5	0.5	0.5	0.5	0.5
L-Cysteine	0.2	0.1	-	0.4	0.4	-	-	0.4	0.4	0.4
NAC	-	-	-	-	-	0.5	0.5	-	-	-
Tween 80	-	-	-	-	-	-	-	-	-	0.3
Sodium Ascorbate	-	-	-	-	-	-	-	-	-	-
Formulation #	11	12	13	14	15	16[1]	17[2]	18	19	20
Carbidopa	1.4	0.75	1.4	1.4	3	1.5	1.5	1.4	3	1.3
Levodopa	6	6	6	6	12	6	6	6	12	12
Arginine	15.5	15.2	15.5	15.5	32.3	15.5	15.5	15.5	32.3	29
Ascorbic acid	0.5	0.5	0.5	0.5	-	0.5	0.5	0.5		
L-Cysteine	0.4	-	-	0.4	0.3	0.4	0.4	0.4		
NAC	-	0.5	0.5	-	-	-	-	-	0.3	0.3
Tween 80	0.3	0.3	0.3	0.3	-	0.3	0.3	0.3		
Sodium Ascorbate	-	-	-	-	1.2	-	-	-	1.2	1.2

[1] Sealed with N_2; [2] Sealed with O_2.

Table 26

			Hydrazine (ppm)									
Storage in vials	**Time and temp prior to analysis (in-use stability)**		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
T=0 (20°C)												
1 month (20°C)	**24 h**	**25°C**	0.82	0.77	0.39							
	48 h		0.73	0.71	0.43							
	24 h	**37°C**	0.76	0.84	0.41							
	48 h		0.87	0.93	0.59							
3 months (-20°C)										<0.1	<0.1	
6 months (-20°C)	3 free-thaw cycles (25°C)						0.1	0.1				
												0.1
9 months (-20°C)												0.1
1 year (-20°C)	24 h	25°C				<0.1						
		37°C				<0.1						
												0.1
24 hr		37°C										
7 days (25°C)							<0.1	<0.1	<0.1			
	24 h	37°C						0.1	<0.1			
1 month (25°C)												

			Hydrazine (ppm)									
Storage in vials	**Time and temp prior to analysis (in-use stability)**		**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
T=0 (-20°C)			<0.1	<0.1	<0.1							
1 month (-20°C)	**24 h**	**25°C**										
	48 h											
	24 h	**37°C**										
	48 h											
3 months (-20°C)								0.1	0.1			
6 months (-20°C)	3 free-thaw cycles (25°C)											
			0.1	<0.1	0.1					0.1		
9 months (-20°C)			0.1			0.1						
1 year (-20°C)	24 h	25°C										
		37°C										
			0.1	<0.1	0.1	0.1						
24 hr		37°C		<0.1	0.1					<0.1		
7 day (25°C)												
	24 h	37°C										
1 month (25°C)							0.1				0.3	0.1

[00103] The results presented in **Table 26** clearly show that the levels of hydrazine were at least 2 fold lower in levodopa formulations *vs.* formulations without levodopa. Furthermore, formulations comprising L-cysteine or NAC showed at least 4-fold lower levels of hydrazine compared to formulations without L-cysteine or NAC.

Example 14. CD/LD formulations

[00104] Based on the discoveries of combinations that have reduced degradant and hydrazine formation, we have developed new CD/LD formulations. These formulations are shown in **Tables 27** and **28**.

Table 27

DS (%)	LD	CD	Arginine	Ascorbic acid	L-Cysteine	NAC	Tween-80	pH
1	6	1.4	15.5	0.5	0.4	-	0.3	9.4-9.6
2	6	1.4	15.5	0.5	-	0.5	0.3	9.4-9.6
3	6	0.75	15.2	0.5	0.4	-	0.3	9.4-9.6
4	6	0.75	15.2	0.5	-	0.5	0.3	9.4-9.6
Margins	6	0.6-1.4	15-16	0.5	0.4	0.5	0.3	9.4-9.6

Table 28

DS (%)	LD	CD	Arg	Meglumine	Na-ascorbate	L-Cys	NAC	Cys-HCl[1]	Tween-80[2]	pH
1	12	3	32	-	1.2	0.3	-	-	-	9.6-9.8
2	13.2	3.3	36	-	1.3	0.3	-	-	-	9.6-9.8
3	13.2	3.3	-	36	1.3	0.3	-	-	-	9.6-9.8
4	12	3	-	32	1.2	-	0.3	-	-	9.6-9.8
5	12	3	32	-	1.2	-	0.3	-	-	9.6-9.8
	12-15	1.2-4	32-42	32-42	1.0-1.3	0.1-0.5			≤2	9.6-9.8

[1] Can replace L-cysteine.
[2] Optionally added to stabilize the formulation.

[00105] Additional formulations that may be used in the context of those disclosed herein are provided in **Table 29**. The formulations may include additional components (e.g., any of those described herein). **Tables 30** and **31** describe further formulations that can be used in the context of those described herein.

Table 29

LD conc. (%)	CD conc. (%)	Amino acid (conc. %)	Other (conc.%)
4.8	1.4	Arg (11.0)	
4.8	1.4	Arg (12.1)	
4.8	1.4	Arg (12.7)	
5.4	1.5	Arg (13.5)	
5.4	1.5	Arg (14.8)	
6	1.5	Arg (14.8)	
6	1.5	Arg (16.0)	
7	2	Arg (17.8)	
7	1.5	Arg (14.1)	Dextrose (5.0)
8	1.5	Arg (15.7)	Dextrose (5.0)
10	1.5	Arg (19.2)	Dextrose (5.0)
6	1.5	Arg (9.3)	NaOH (4.6)
8	1.5	Arg (15.7)	Meglumine (3.2)
8	1.5	Arg (12.2)	Meglumine (7.9)
10	1.5	Arg (19.2)	Meglumine (4.0)
10	1.5	Arg (14.6)	Meglumine (9.9)
7	1.5	Arg (14.1)	Meglumine (2.8)
7	1.5	Arg (10.7)	Meglumine (6.9)
6	1.5	Arg (13.5)	Na-Asc (1.0)
6	1.5	Arg (14.2)	Na-Asc (1.0)
6	1.5	Arg (14.8)	Na-Asc (1.0)
6	1.5	Arg (16.0)	Na-Asc (1.0)
4.8	1.4	Arg (11.0)	Na-Asc (1.0)
4.8	1.4	Arg (11.6)	Na-Asc (1.0)
4.8	1.4	Arg (12.1)	Na-Asc (1.0)
4.8	1.4	Arg (12.7)	Na-Asc (1.0)
6	1.5	Arg (14.8)	Asc (1.0)
6	1.5	Arg (15.8)	Na-Asc (1.0)

6	1.5	Arg (15.8)	Asc (1.0)
6	1.5	Arg (16.8)	Na-Asc (1.0)
6	1.5	Arg (16.8)	Asc (1.0)
5.4	1.5	Arg (12.3)	Na-Asc (1.0)
5.4	1.5	Arg (12.3)	Asc (1.0)
5.4	1.5	Arg (13.5)	Na-Asc (1.0)
5.4	1.5	Arg (13.5)	Asc (1.0)
5.4	1.5	Arg (14.8)	Na-Asc (1.0)
5.4	1.5	Arg (14.8)	Asc (1.0)
6	1.5	Arg (16.0)	Asc(1.0)
7	2	Arg (17.8)	Asc (1.0)
7	2	Arg (17.8)	Na-Asc (1.0)
12	3	Arg (24.4)	
12	3	Arg (29.6)	
12	3	Arg (32.1)	
7	0.5	Arg	
7	1	Arg	
7	1.5	Arg	
7	2	Arg	
6	0.5	Arg (14.2)	
6	1	Arg (14.8)	
6	2	Arg (16.5)	
0	2		

Table 30

Property		**1**	**2**	**3**
API Concentration		2 & 4%	4%	0.6-20%
CD:Arginine ratio		1:1.1-1.2	1:1.5	1: ≥1
Exipients concentration	NMP	3.5%	0	0-15%
	Na-bisulfite	0.1%	0	0-0.2%
	Ascorbic Acid	0	0.75%	0-2% or more
	L-Cysteine or NAC	0	0.1%	0-0.5% or more
	Other anti-oxidants	-	-	0-2%
Osmolality		650-750	300-400	200-1800 for SC No limits for ID
pH		8.2-8.6	8.6-9.1	8-9.8
Stability	25°C	48-72 hrs	≥21 d	2 wks – ≥2 yrs
	4°C	Not stable	≥21 d	2 wks – ≥2 yrs
	-20°C	≥ 1 year	≥21 d	2 wks – ≥2 yrs
SC Infusion/24hrs		2 ml	2 ml	0.1-20 ml

Table 31

Property		4	5	6
API Concentration	CD	0 or 1 or 2%	1-2%	0-4% up to 6%
	LD	3-7%	5-7%	2.5-12% up to 14%
Ratios	LD to CD ratio	6:1-6:3 or LD alone	3.5-4:1	1:1-10:0.5
	CD:Arginine ratio	1:1.2	1:9-14	1: ≥35
	LD:Arginine ratio	1:1.8-2.2	1:2-3.5	1: ≥3.6
	API: Arginine ratio	[1:1.2 CD:Arg + 1:2 LD:Arg] +12.5% Arg	1:2.3-2.5	1: ≥1.8
excipients	NMP	0	0	0
	Na-bisulfite	0.075-0.15%	0	0-0.2%
	Ascorbic acid	0	0.75	0-2% or more
	Other anti-oxidants	-	-	0-2%
Osmolality	9/1 % LD/CD	1300-1500	-	200-1800 for SC No limits for ID
	7/2 % LD/CD	950-1150	1200-1300	
	6/1.5 % LD/CD	800-850	940-980	
	5/1.25% LD/CD	NT	790-830	
pH		8.5-9.5	9.2-9.6	9.1-9.8
Stability	25°C	≥2days	≥2 days	≥2 days
	4°C	<2 days	≥2 days	≥2 days
	-20°C	≥2 days	≥2 days	≥2 days
SC infusion/24 hrs		2 ml	2-6 ml	0.1-10 ml/site
Intraduodenal/24 hrs		--	--	4-24 ml
Intrathecal		--	--	1-1000 µl/day

EQUIVALENTS

[00106] While specific embodiments of the present invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[00107] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims 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 and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

INCORPORATION BY REFERENCE

[00108] 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 pharmaceutical composition comprising carbidopa, at least two antioxidants, and a pharmaceutically acceptable carrier, wherein one of said antioxidants is ascorbic acid or a salt thereof, and said composition comprises less than 1 µg/ml hydrazine, as determined by a GCMS method, or less than 5% by weight 3,4-dihydroxyphenyl-2-methylpropionic acid (herein identified as degradant) relative to the initial amount of carbidopa, as determined by HPLC.

2. The pharmaceutical composition of claim 1, comprising less than 0.5 µg/ml, preferably less than 0.1 µg/ml, of hydrazine, or less than 1%, preferably less than 0.2%, degradant relative to the amount of carbidopa.

3. The pharmaceutical composition of claim 1 comprising 0.1% to 10% by weight carbidopa.

4. The pharmaceutical composition of claim 3, comprising 0.5% to 6%, preferably 0.75% to 4%, more preferably 0.75%, 1.4%, 3%, 3.3% or 4%, by weight, carbidopa.

5. The pharmaceutical composition of claim 1, wherein said salt of ascorbic acid is sodium ascorbate, potassium ascorbate, calcium ascorbate, ascorbyl stearate, or ascorbyl palmitate, preferably sodium ascorbate.

6. The pharmaceutical composition of claim 1, comprising 0.1% to 10%, by weight, ascorbic acid or a salt thereof.

7. The pharmaceutical composition of claim 6, comprising 0.2% to 2%, preferably 0.4% to 1.3%, more preferably 0.5%, 0.6%, 0.75%, 0.85%, 1.0%, or 1.2%, by weight, ascorbic acid or a salt thereof.

8. The pharmaceutical composition of claim 1, wherein the other of said antioxidants each independently is L-cysteine, N-acetylcysteine (NAC), glutathione, diacetylcystine, a salt of the aforesaid, or sodium bisulfite, preferably L-cysteine or a salt thereof such as cysteine hydrochloride, NAC or sodium bisulfite.

9. The pharmaceutical composition of claim 8, comprising:

(i) 0.001% to 5%, preferably 0.01% to 1%, more preferably 0.1% to 0.6%, 0.3%, or 0.4%, by weight, L-cysteine or a salt thereof; and/or

(ii) 0.001% to 5%, preferably 0.01% to 1%, more preferably 0.1%, 0.2%, 0.3%, or 0.4%, by weight, NAC; and/or

(iii) 0.01% to 2%, preferably 0.075% to 0.75%, more preferably 0.1%, by weight, sodium bisulfite; and/or

(iv) 0.001% to 5%, preferably 0.1% to 1%, by weight, glutathione; and/or

(v) 0.001% to 5%, preferably 0.01% to 1%, by weight, diacetylcystine or a salt thereof.

10. The pharmaceutical composition of claim 1, comprising 0.1% to 10%, by weight, carbidopa, 0.1% to 10%, by weight, ascorbic acid or a salt thereof, and:

(i) 0.001% to 5%, by weight, L-cysteine or a salt thereof;

(ii) 0.001% to 5%, by weight, NAC; or

(iii) 0.01% to 2%, by weight, sodium bisulfite.

11. The pharmaceutical composition of claim 10, comprising 0.5% to 6%, preferably 0.75% to 4%, by weight, carbidopa, 0.2% to 2%, preferably 0.4% to 1.3%, by weight, ascorbic acid or a salt thereof, and:

(i) 0.01% to 1%, preferably 0.1% to 0.6%, by weight, L-cysteine or a salt thereof;

(ii) 0.01% to 1%, preferably 0.1% to 0.4%, by weight, NAC; or

(iii) 0.075% to 0.75%, by weight, sodium bisulfite.

12. The pharmaceutical composition of any one of claims 1 to 11, further comprising (i) levodopa; (ii) arginine, meglumine, or a combination thereof; or (iii) both (i) and (ii); and optionally further comprising a surfactant.

13. The pharmaceutical composition of claim 12, comprising either less than 1% or 1% to 20%, by weight, levodopa.

14 The pharmaceutical composition of claim 13, comprising 2% to 16%, preferably 4%, 6%, 12% or 13.2%, by weight, levodopa.

15. The pharmaceutical composition of claim 12, comprising 0.1% to 42%, preferably 2% to 40%, more preferably 12% to 36% or 15.2% to 32%, by weight, arginine, meglumine, or a combination thereof.

16. The pharmaceutical composition of claim 12, comprising arginine.

17. The pharmaceutical composition of claim 12, comprising meglumine.

18. The pharmaceutical composition of claim 12, comprising a surfactant, such as polysorbate 80.

19. The pharmaceutical composition of claim 18, comprising 0.01% to 5%, preferably 0.1% to 0.5%, more preferably 0.3%, by weight, polysorbate 80.

20. The pharmaceutical composition of claim 12, comprising 1% to 20%, by weight, levodopa; and 0.1% to 42%, by weight, arginine, meglumine, or a combination thereof.

21. The pharmaceutical composition of claim 20, comprising 2% to 16%, preferably 4%, 6%, 12% or 13.2%, by weight, levodopa; and 0.1% to 42%, preferably 12% to 36%, more preferably or 15.2% to 32%, by weight, arginine, meglumine, or a combination thereof.

22. The pharmaceutical composition of claim 20 or 21, comprising 0.1% to 0.5%, preferably 0.3%, by weight, polysorbate 80.

23. The pharmaceutical composition of claim 12, comprising:

(i) 0.1% to 10%, by weight, carbidopa;

(ii) 0.1% to 10%, by weight, ascorbic acid or a salt thereof;

(iii) 0.001% to 5%, by weight, L-cysteine or salt thereof; 0.001% to 5%, by weight, NAC; or 0.01% to 2%, by weight, sodium bisulfite;

(iv) 1% to 20%, by weight, levodopa;

(v) 0.1% to 42%, by weight, arginine, meglumine, or a combination thereof; and optionally

(vi) 0.01% to 5%, by weight, polysorbate 80,

wherein the composition comprises less than 1 µg/ml, preferably less than 0.5 µg/ml, more preferably less than 0.1 µg/ml, hydrazine.

24. The pharmaceutical composition of claim 23, comprising:

(i) 0.5% to 6%, preferably 0.75% to 4%, more preferably 0.75%, 1.4%, 3%, or 3.3%, by weight, carbidopa;

(ii) 0.2% to 2%, preferably 0.4% to 1.3%, more preferably 0.5%, 1.2%, or 1.3%, by weight, ascorbic acid or a salt thereof;

(iii) 0.01% to 1%, preferably 0.1% to 0.6%, by weight, L-cysteine or a salt thereof; 0.01% to 1%, preferably 0.1% to 0.4%, by weight, NAC; or 0.075% to 0.75%, by weight, sodium bisulfite;

(iv) 2% to 16%, preferably 4%, 6%, 12% or 13.2%, by weight, levodopa;

(v) 2% to 42%, preferably 12% to 36% or 15.2% to 32%, by weight, arginine, meglumine, or a combination thereof; and optionally

(vi) 0.1% to 0.5%, preferably 0.3%, by weight, polysorbate 80.

25. The pharmaceutical composition of claim 24, comprising:

(i) 12% by weight levodopa, 3% by weight carbidopa, 32% by weight arginine, 1.2% by weight sodium ascorbate, and 0.3% by weight L-cysteine or cysteine hydrochloride;

(ii) 13.2% by weight levodopa, 3.3% by weight carbidopa, 36% by weight arginine, 1.3% by weight sodium ascorbate, and 0.3% by weight L-cysteine or cysteine hydrochloride;

(iii) 13.2% by weight levodopa, 3.3% by weight carbidopa, 36% by weight meglumine, 1.3% by weight sodium ascorbate, and 0.3% by weight L-cysteine or cysteine hydrochloride;

(iv) 12% by weight levodopa, 3% by weight carbidopa, 32% by weight meglumine, 1.2% by weight sodium ascorbate, and 0.3% by weight NAC;

(v) 12% by weight levodopa, 3% by weight carbidopa, 32% by weight arginine, 1.2% by weight sodium ascorbate, and 0.3% by weight NAC;

(vi) 6% by weight levodopa, 1.4% by weigh carbidopa, 15.5% by weight arginine, 0.5% by weight ascorbic acid, 0.4% by weight L-cysteine and 0.3% by weight polysorbate 80;

(vii) 6% by weight levodopa, 1.4% by weigh carbidopa, 15.5% by weight arginine, 0.5% by weight ascorbic acid, 0.5% by weight NAC and 0.3% by weight polysorbate 80;

(viii) 6% by weight levodopa, 0.75% by weigh carbidopa, 15.2% by weight arginine, 0.5% by weight ascorbic acid, 0.4% by weight L-cysteine and 0.3% by weight polysorbate 80; or

(ix) 6% by weight levodopa, 0.75% by weigh carbidopa, 15.2% by weight arginine, 0.5% by weight ascorbic acid, 0.5% by weight NAC and 0.3% by weight polysorbate 80.

26. The pharmaceutical composition of claim 12, comprising levodopa; arginine, meglumine, or a combination thereof; and optionally a surfactant, wherein said composition has a pH of 9.1 to 10, preferably 9.6 to 9.8.

27. The pharmaceutical composition of any one of claims 1 to 26, comprising less than 1 µg/ml, preferably less than 0.1 µg/ml, hydrazine after 1-24 hours, 1-30 days, 1-12 months, or 1-3 years, at a temperature in a range of -20°C to 25°C.

28. The pharmaceutical composition of claim 27, wherein said temperature is -20°C, 2-8°C, or 25°C.

29. The pharmaceutical composition of any one of claims 1 to 26, wherein the composition is formulated as a liquid, gel, cream, solid, film, emulsion, suspension, solution, lyophilisate or aerosol, preferably as a liquid.

30. A method for treating a disease, disorder or condition, associated with loss of dopamine or dopaminergic neurons, in an individual in need thereof, said method comprising administering to said individual an effective amount of a pharmaceutical composition according to any one of claims 1 to 29.

31. The method of claim 30, wherein said disease, disorder or condition is Parkinson's disease.

32. The method of claim 30 or 31, wherein said administration is substantially continuous.

33. A pharmaceutical composition according to any one of claims 1 to 29, for use in treating a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons.

34. Use of a pharmaceutical composition according to any one of claims 1 to 29, in the preparation of a medicament for treatment of a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons.

35. A kit comprising one, two, or more containers each containing a pharmaceutical composition according to any one of claims 1 to 29, wherein said composition is present in an amount sufficient to treat an individual in need thereof for a disease, disorder or condition associated with loss of dopamine or dopaminergic neurons for at least 1 day, 1 week, 1 month, 2 months, 6 months or for one year.

36. The kit of claim 35, wherein said disease, disorder or condition is Parkinson's disease.

Fig. 1

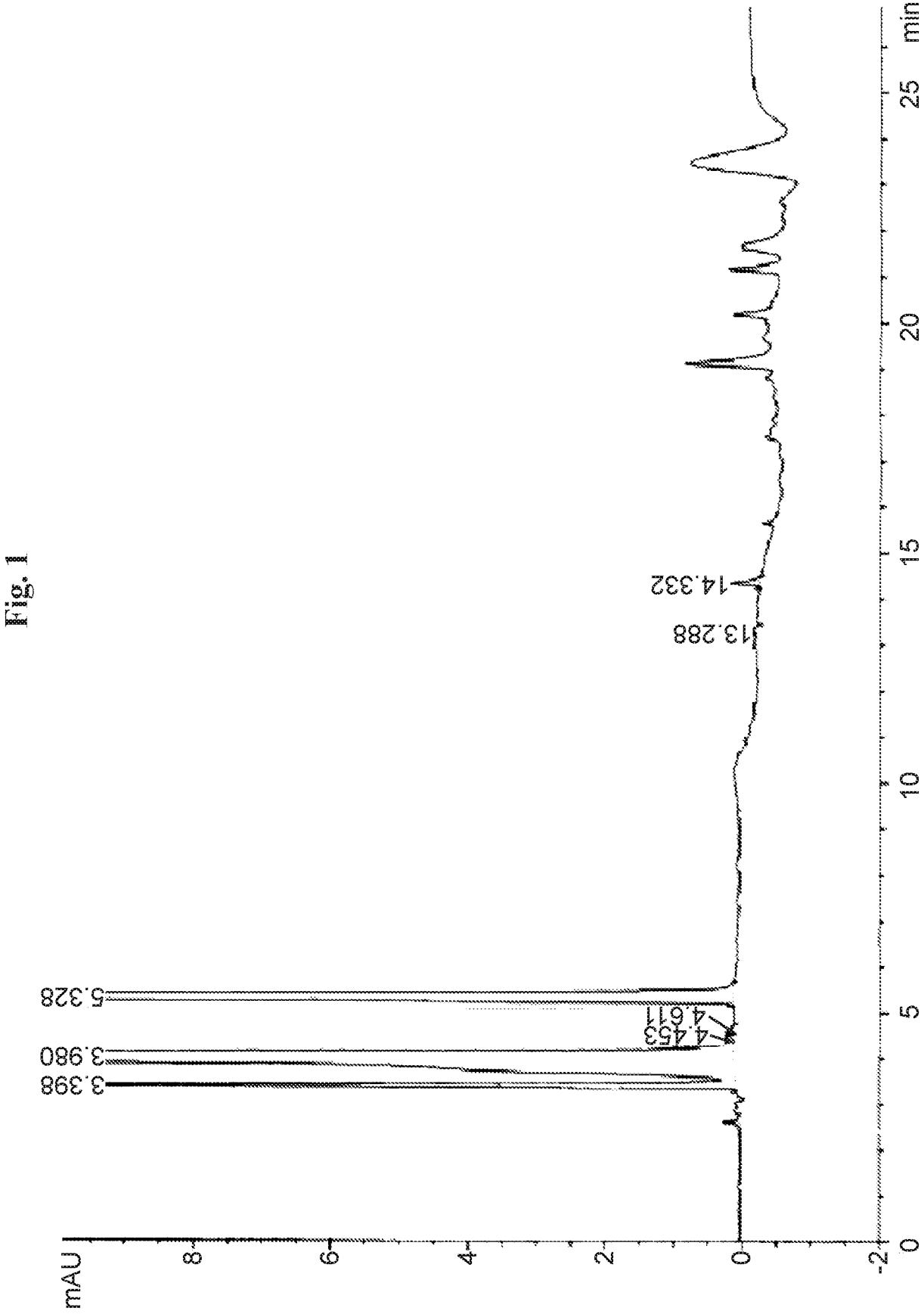
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Fig. 2A

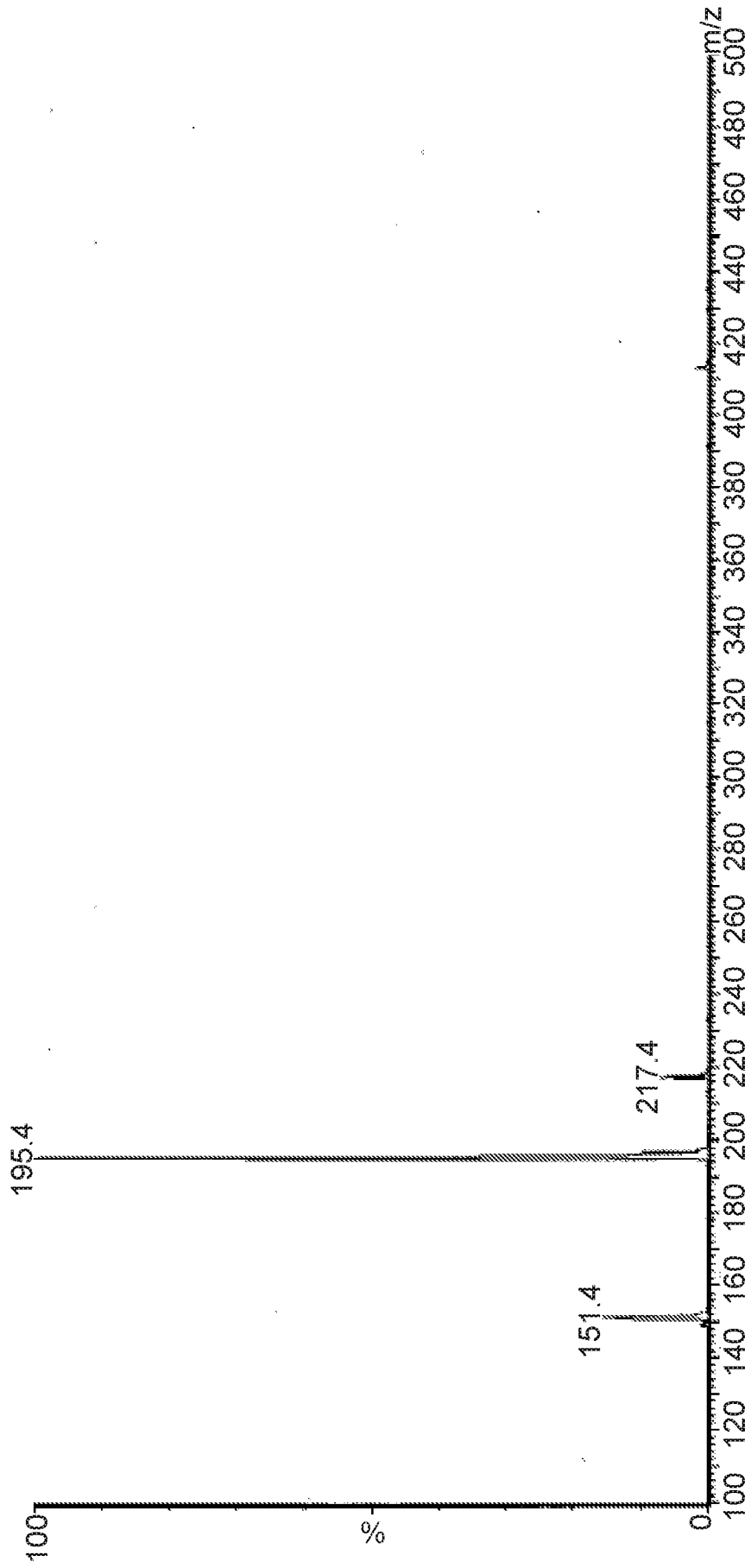
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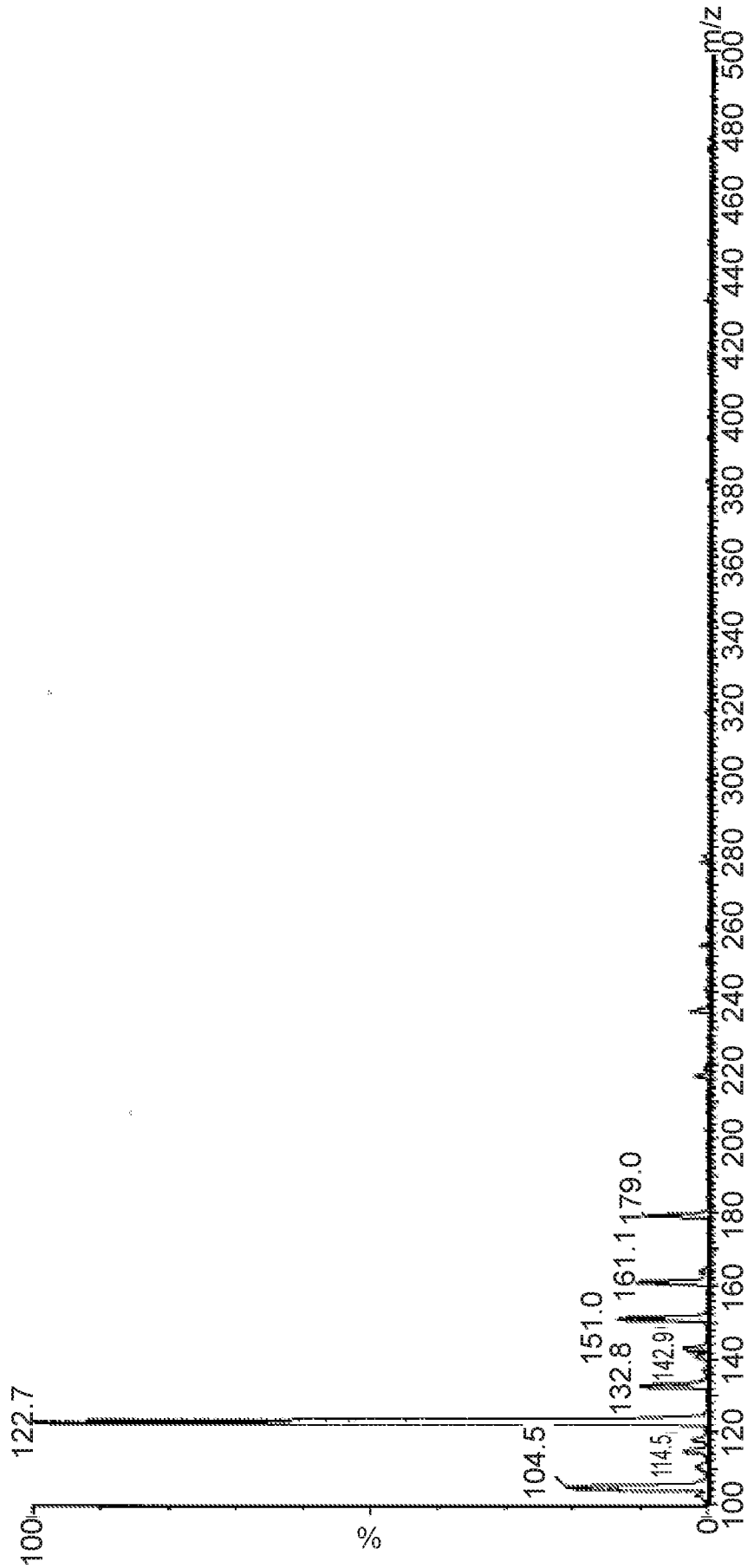
Fig. 2B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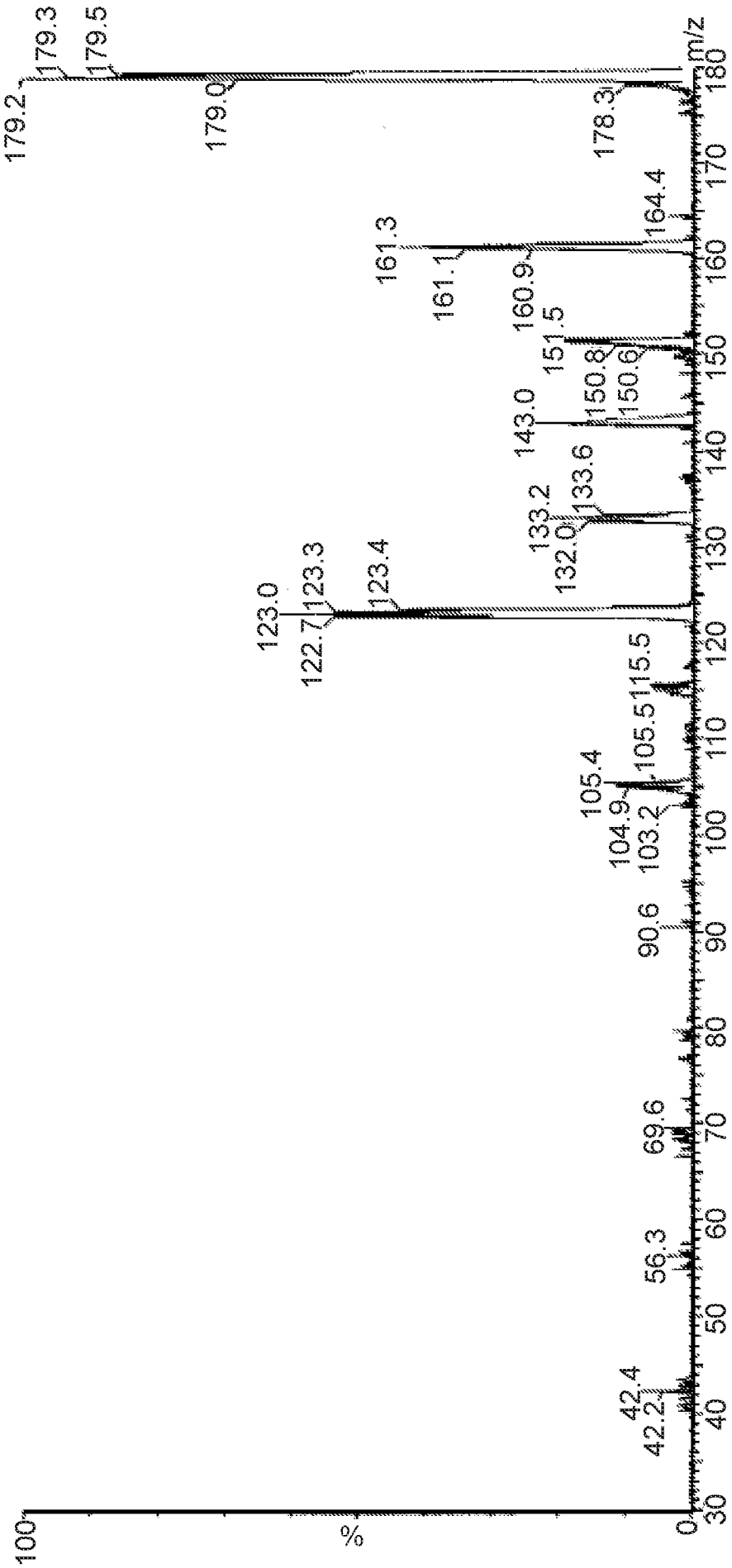
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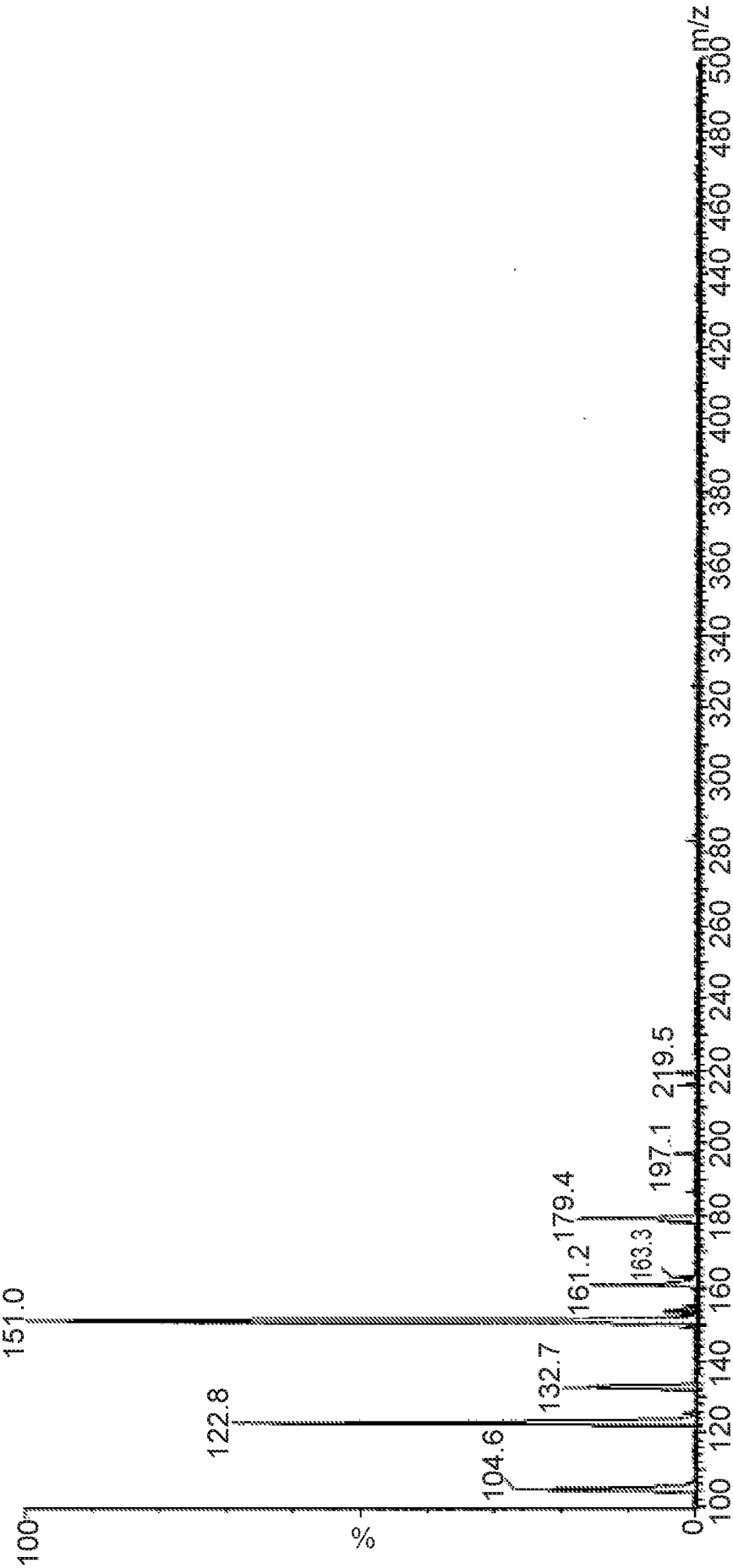
Fig. 3A

Fig. 3B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m/z

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2015/050258

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/18 A61K47/22 A61K31/198
ADD.

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)
A61K

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)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014/051755 A1 (YACOBY-ZEEVI ORON [IL] ET AL) 20 February 2014 (2014-02-20) the whole document claim 48 paragraphs [0005], [0065] - [0070] -----	1-36
X	ERIC J. PAPPERT ET AL: "Clinical/ Scientific Notes - The Stability of Carbidopa in Solution", MOVEMENT DISORDERS, vol. 12, no. 4, 1997, pages 608-623, XP055206267, page 608 - page 609 -----	1,2, 27-29
X,P	WO 2014/141261 A1 (NEURODERM LTD [IL]) 18 September 2014 (2014-09-18) the whole document page 29, paragraphs 41, 42, 57-59; tables K, L -----	1-17,20, 21,23-36

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

☒ See patent family annex.

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"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

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"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
5 August 2015	13/08/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Palma, Vera

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2015/050258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2014249229 A1	04-09-2014
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WO 2014141261 A1	18-09-2014	NONE	