COMPOSITIONS FOR CONTINUOUS ADMINISTRATION OF DOPA DECARBOXYLASE INHIBITORS

RELATED APPLICATION

This application claims priority to U.S.S.N. 61/179,511, filed May 19, 2009, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to compounds and formulations useful in methods for treating diseases and disorders in which the dopamine level in the brain is reduced, e.g., Parkinson's disease. In particular, the invention relates to arginine salts of carbidopa and levodopa and compositions comprising them.

BACKGROUND OF THE INVENTION

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.

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 CW; 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. Further, such treatments may be associated with dopaminergic adverse events; continuous administration of levodopa or dopa agonists is still associated with off periods that are self-limiting despite continued delivery of the drug. Nutt JG; Mov. Dis. 2008, 23(Suppl. 3):S580-4.

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. Exactly how this dose reduction is accomplished is uncertain. Various formulations comprising levodopa alone or together with inhibitors of enzymes associated with the metabolic degradation of levodopa are well known, for example, decarboxylase inhibitors such as carbidopa and benserazide, catechol-O-methyl transferase (COMT) inhibitors such as entacapone and tolcapone, and monoamone oxidase (MAO)-A or MAO-B inhibitors such as moclobemide, rasagiline or selegiline or safinamide. Currently available oral drugs include SINEMET® and SINEMET®CR sustained-release tablets that include carbidopa or levodopa; STALEVO® tablets containing carbidopa, entacapone and levodopa; and MADOPAR® tablets containing levodopa and benserazide. There is an on-going and urgent need for methods and compositions that can effect continuous stimulation of L-dopa to more effectively treat movement disorders such as Parkinson's disease.

Carbidopa [(-)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate], a white, crystalline compound, only slightly soluble in water, is a dopa decarboxylase inhibitor commonly administered with levodopa. Only 40-70% of an oral dose of carbidopa is absorbed in man, monkey and dog. Although carbidopa has been orally administered with levodopa for over 30 years, no stable liquid formulation having e.g., an effective concentration in a volume suitable for use for subcutaneous or transdermal delivery has ever been achieved. There is an urgent, long standing need for

such carpidopa formulations that can be administered more easily to patients, especially as compared to current invasive modes such as duodenal administration.

SUMMARY

It has now been found in accordance with the present disclosure that an arginine salt of carbidopa can form a stable, liquid formulation, suitable for e.g., continuous subcutaneous, transdermal, intradermal, intravenous and/or intraduodenal administration, at a physiologically acceptable pH. Such disclosed compositions are capable of substantially continuously administering carbidopa to a patient.

It has been further found that substantially continuously administering a dopa decarboxylase inhibitor such as carbidopa, together with discrete (e.g. oral) co-administration of levodopa, may stimulate L-dopa substantially continuously and thus e.g., extend the effectiveness of a levodopa oral dosing regimen and/or reduce the daily dosage of levodopa, while effectively treating a movement and/or neurological disorder such as Parkinson's disease.

The present disclosure relates to an arginine salt of an active agent selected from carbidopa and levodopa that are suitable for e.g., continuous subcutaneous, trandermal, intradermal, intravenous, oral, or intraduodenal administration.

In a first aspect of the present disclosure, there is provided a pharmaceutically acceptable liquid composition comprising arginine and carbidopa, wherein the composition comprises 1% to 6% by weight carbidopa; has a pH of 8 to 9.5 at 25°C; and is stable at 25°C for 48 hours or more.

In a second aspect of the present disclosure, there is provided a kit comprising: a) a first composition suitable for continuous administration comprising the liquid composition of the first aspect; and b) a second composition suitable for oral administration comprising levodopa or a pharmaceutically acceptable salt or ester thereof.

In a third aspect of the present disclosure, there is provided the kit of the second aspect, for use in treating a neurological 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), or amyotrophic lateral sclerosis (ALS).

In a fourth aspect of the present disclosure, there is provided the arginine salt of carbidopa.

In a fifth aspect of the present disclosure, there is provided a pharmaceutically acceptable liquid composition comprising the arginine salt of carbidopa of the fifth aspect, and optionally a pharmaceutically acceptable excipient.

Also contemplated herein are pharmaceutically acceptable liquid (e.g., liquid at room temperature) or gel formulations or compositions that include an arginine salt of carbidopa, e.g., include carbidopa and arginine, that may be suitable for substantially continuous administration to a patient e.g. with or without use of, for example, a transdermal patch or subcutaneous pump (e.g. an insulin-like pump). Such contemplated liquid compositions may include at least 1%, at least 4%, at least 6% or more by weight carbidopa, (e.g. about 2% to about 6% by weight carbidopa) and therefore may facilitate administration of smaller amounts of a pharmacologically acceptable formulation to achieve efficacy as compared to a carbidopa formulation that is only capable of having less than 1% by weight carbidopa. In another embodiment, contemplated herein is a liquid or gel composition that includes a molar ratio of about 1.0:0.5 to about 1: to about 2.5, e.g., 1: 1.0-1.2 molar ratio of carbidopa:basic amino acid, e.g. carbidopa:arginine. A liquid composition that includes carbidopa and arginine, as contemplated herein, may have a

physiologically acceptable pH, e.g. a pH of about 6.5 to 9.5, e.g., about 7 to about 9, or about 8 to about 9, at 25 °C.

In yet another embodiment, contemplated herein is a pharmaceutically acceptable liquid or gel composition that includes a molar ratio of about 1.0:0.5 to about 1:2, e.g., about 1:1.8 molar ratio of levodopa:arginine. For example, provided herein is a liquid composition that may include at least about 4% by weight, or at least 5%, at least about 6% (e.g. about 3% to about 7%) or more by weight levodopa. A liquid composition having levodopa and a basic amino acid, as contemplated herein, may have a pH of about 8 to 10, e.g., about 8.5 to about 9.5, at 25°C.

Exemplary liquid compositions contemplated herein may be liquid solutions, e.g. may be a substantially homogenous mixture that includes carbidopa and arginine, and may include water, or alternatively may be substantially non-aqueous. In other embodiments, contemplated compositions may also include one or more pharmaceutically acceptable excipients such as N-methylpyrrolidone (NMP), polyvinylpyrrolidone (PVP), propylene glycol, antioxidants, or combinations thereof.

In some embodiments, the pharmaceutically acceptable liquid composition of the present disclosure may comprise additional active agents such as entacapone or tolcapone.

Also provided herein is a kit comprising: a) a first composition suitable for continuous administration comprising the liquid or gel formulation of the present disclosure comprising an arginine salt of carbidopa; b) a second composition suitable for oral administration comprising levodopa or a pharmaceutically acceptable salt or ester thereof; and c) optionally instructions administration of the first formulation in conjunction with the second formulation.

The first composition in the kit for continuous administration of the arginine salt of carbidopa may be formulated for transdermal, intradermal, subcutaneous, intravenous, or intraduodenal administration such as by using an infusion pump.

The second composition in the kit, i.e., the levodopa composition may comprise levodopa, a pharmaceutically acceptable salt of levodopa., preferably an arginine salt thereof as disclosed herein, or may be a composition that includes levodopa and further comprises one or more decarboxylase inhibitors such as carbidopa and/or benserazide, or one or more catechol-O-methyl transferase (COMT) inhibitors such as entacapone and/or tolcapone, or one or more MAO-A or MOA-B inhibitors such as selegiline and/or rasagiline, or combination thereof.

Also provided herein is a method for treatment of a disease or disorder characterized by reduced levels of dopamine in a patient's brain (e.g. Parkinson's disease), comprising substantially continuously administering to a patient in need thereof a therapeutically effective amount of a decarboxylase inhibitor, a salt thereof, e.g., an arginine salt of carbidopa, or an ester thereof, and administering a therapeutically effective amount of levodopa or pharmaceutically acceptable salt thereof (e.g., arginine levodopa), or composition comprising levodopa (for example, administering a composition e.g. a tablet, having levodopa as its sole active agent, or a composition that includes levodopa and one or more other active agents such as carbidopa, benserazide, entacapone, tolcapone, selegiline and/or rasagiline

In one embodiment, a method of treating or ameliorating a neurological or movement disorder in a patient in need thereof is provided comprising: administering a therapeutically effective amount of a composition comprising a carbidopa basic amino acid salt (e.g., carbidopa arginine) and administering a therapeutically effective amount of a composition comprising levodopa. For example, a composition comprising carbidopa and arginine may be administered substantially continuously and/or the composition comprising levodopa may be administered at discrete intervals (for example by oral administration one, two, three or more times a day), during the substantially continuous administration of composition comprising a carbidopa arginine salt.

Also provided herein is a method of substantially continuously inhibiting decarboxylase activity and/or a method of increasing the half-life of levodopa in a patient receiving levodopa, comprising administering (e.g. substantially continuously) to the patient a liquid or gel composition comprising a carbidopa salt such as carbidopa arginine. For example, the disclosed methods may result in a half-life of levodopa in the plasma of a patient that is at least 1.5, or at least two times, longer after continuous administration of carbidopa as compared to the half life of levodopa in a patient's serum after administering levodopa with discrete, oral administration of carbidopa.

BRIEF DESCRIPTION OF THE FIGURES

Figs.1A-1C depict the mass spectra of carbidopa (CD) arginine salt.

Figs. 2A-2C depict the mass spectra of levodopa (LD) arginine salt.

Figs. 3A-3C show the mean levels of carbidopa determined in plasma of female Landrace × large white swine (30-35kg) following oral administration of (3A) Stalevo (100/25/200 mg, LD/CD/E), (3B) Dopicar+Lodosyn (125/25 mg LD/CD), (3C) Sinemet CR (100/25 mg, LD/CD) q8 and 12h, with (squares) or without (diamonds) continuous subcutaneous administration of 3% carbidopa solution.

Figs. 4A-4B show brain levels of L-Dopa and dopamine (4A, left and right panels, respectively), and plasma levels of carbidopa and L-Dopa (4B, left and right panels, respectively), determined in CD-1 mice following oral administration of levodopa/carbidopa with or without continuous subcutaneous administration of carbidopa.

Figs. 5A-5B depict mean levels of L-Dopa (5A) and carbidopa (5B) determined in plasma of female Landrace × large white swine (30-35kg) following continuous subcutaneous administration of 0, 2 and 4% carbidopa with oral administration of Sinemet® (100/25 mg) q8h.

Figs. 6A-6B depict mean levels of L-Dopa determined in plasma of two female Landrace × large white swine (30-35kg) (6A,Pig #3; 6B, Pig #4) following continuous subcutaneous administration of 2 and 4% carbidopa with oral administration of Dopicar® (125/12.5 mg LD/CD) + Lodosyn® (12.5 mg CD) q12h..

Fig. 7 shows the mean (±SD) LD (levodopa) concentrations (ng/ml) as determined in plasma of female Landrace × large white swine (30-35kg) following oral administration of Stalevo (LD/CD/E 100/25/200), q8h, with or without continuous subcutaneous benserazide or carbidopa administration (60 mg /day).

Figs. 8A-8B depict plasma levels of (8A) L-dopa and (8B) 3-O-methyldopa (3-OMD) as determined in plasma of female Landrace × large white swine (30-35kg) following continuous subcutaneous administration of 2% carbidopa, with or without 2.5% entacapone, and oral administration of L-dopa/Carbidopa (LD/CD).

Fig. 9 shows the results of transdermal delivery of carbidopa propyl ester (CDPE).

Figs. 10A-10B depict plasma levels of (10A) levodopa and (10B) carbidopa as determined in plasma of female Landrace × large white swine (30-35kg) following oral administration of enteric coated or uncoated LD and CD as arginine salts (designated LDs and CDs, respectively, 100/25 mg LD/CD) as compared to Sinemet (100/25 mg LD/CD).

Fig. 11 depicts the inhibition of L-Dopa decarboxylation by carbidopa and carbidopa propyl ester (CDPE).

Figs. 12A-12B depict the inhibition of L-dopa decarboxylation (12A) and the metabolism of L-dopa to dopamine (12B) by carbidopa and carbidopa propyl ester in liver extract.

DETAILED DESCRIPTION OF THE INVENTION

Disclosed herein is a liquid composition having a physiologically acceptable pH that includes an arginine salt of carbidopa (e.g., arginine and carbidopa) that is stable at room temperature, which can facilitate continuous delivery of an effective amount carbidopa to a patient in a minimally invasive fashion (e.g. a disclosed liquid formulation comprises a significantly high concentration of carbidopa so that administration of large amounts of liquid are not required) Such formulations may facilitate continuous decarboxylase inhibition which prolongs the half life of levodopa. For example, results from *in vivo* studies, as described below, in which L-dopa was administered continuously in parallel with oral administration of carbidopa every 6-8 hours demonstrate a pulsatile pattern of L-dopa plasma levels that coincide with carbidopa oral dosing regimen, but concomitant and/or frequently repeated, e.g., simultaneous dosing of dopa decarboxylase inhibitor (e.g. of carbidopa or a salt thereof, or benserazide) with or without COMT inhibitors with discrete or continuous administration of levodopa is more effective in the treatment of e.g., Parkinson's disease. Further, it has been discovered that the pharmacokinetic profile of, for example, carbidopa (with or without entacapone) supports such new therapies that include substantially continuous administration of dopa decarboxylase inhibitors (e.g. benserazide or carbidopa or a salt thereof) with or without COMT inhibitors together with administration (continuous or at discrete intervals) of e.g. levodopa or a salt thereof.

Provided herein are formulations of carbidopa that unexpectedly allow for stable dissolution of higher concentrations (e.g., greater than 1% by weight) of carbidopa and/or levodopa at e.g. physiologically acceptable pH, for e.g., substantially continuous subcutaneous or transdermal administration. Such formulations may also be suitable for intravenous, intradermal, oral or intraduodenal administration. For example, provided herein are formulations and methods capable of obtaining substantially constant inhibition of dopa decarboxylase activity upon administration, thereby increasing the half life of

administered levodopa and substantially reducing the pulsatility of levodopa plasma levels to avoid low trough levels of plasma levodopa.

A treatment strategy of continuous carbidopa administration in accordance with the present invention may simulate L-dopa substantially continuously. For example, therapies and/or methods of the present invention may extend a levodopa oral dosing regimen to about 2 to about 3 times/day, and/or reduce daily dose of levodopa, and/or reduce or even eliminate the risk of motor complications associated with standard oral levodopa formulations in Parkinson's patients.

Provided herein, in an embodiment, is a pharmaceutically acceptable formulation that includes a carbidopa arginine salt that allows for substantially continuous administration of carbidopa. For example, while carbidopa free base is practically insoluble in alcohol, chloroform or ether and only slightly soluble in water, provided herein, for example, is a stable liquid formulation that includes carbidopa and may be suitable for substantially continuous administration to a patient. Further, such formulations may have a physiologically acceptable pH.

In one aspect, the present invention relates to a carbidopa arginine salt.

The disclosure also provides, in an embodiment, a liquid formulation comprising a carbidopa salt of the invention. For example, a disclosed carbidopa arginine salt may be dissolved in an aqueous solution, e.g., having a pH of about 6 to 9.5, preferably from about 7 to about 9, more preferably from about 8 to 9 at 25°C or at 30°C. Alternatively, carbidopa (free base) and arginine are dissolved together in a liquid (e.g. an aqueous liquid) to form a disclosed liquid formulation. Disclosed liquid formulations may include about 1.0% by weight or more carbidopa or carbidopa arginine salt, for example, may include about 1% to about 20% by weight or more carbidopa, e.g., about 2% to about 10% by weight carbidopa. For example, a liquid formulation may include carbidopa and arginine in molar ratio of about 1: 0.5 to about 1:2.5, or about 1:1 to about a 1:1.2, e.g., about 1:1 or 1:1.1.

Disclosed liquid formulations (e.g. a liquid composition comprising carbidopa and arginine or an arginine salt of carbidopa) may be stable for 24 hours, for 48 hours, for 7 days, or more at 25°C. For example, an exemplary liquid formulation may include a 1:1.1 molar ratio of carbidopa:arginine, with about 2% to about 15%, or about 2% to about 10%, or 2% to about 6% by weight carbidopa. Such a carbidopa:arginine liquid formulation may

be more stable at 7 days as compared to a liquid composition that includes a lysine or histidine salt of carbidopa.

In some embodiments, disclosed liquid formulations or compositions are liquid solutions, i.e. are substantially homogenous liquid mixtures. Such liquid mixtures may comprise water and/or other excipients. In another embodiment, disclosed liquid compositions may be substantially non-aqueous.

For example, as disclosed in Example 6, below, a stable liquid solution can be unexpectedly formed from carbidopa and arginine. Such a solution is stable at room temperature, e.g., is a substantially clear solution, even at high carbidopa concentrations of 2, 3, 4, 6, and/or 8 weight percent carbidopa. Such solutions, e.g. up to about 6 weight percent carbidopa, are stable (e.g., no precipitation) at least for 48 hours. Further, because such disclosed solutions, even at high concentrations of carbidopa, have a physiologically acceptable pH, such solutions can be adjusted to an appropriate pH, but still have a significant amount of carbidopa in a smaller volume so that it facilitates patient administration, without e.g. administering large volumes of solution.

Further, solutions having carbidopa and arginine (e.g., the arginine salt of carbidopa) are unexpectedly more stable even as compared to solutions of carbidopa with other basic amino acids such as histidine or lysine, as shown below in e.g. Example 6.

Contemplated liquid formulations may, in some embodiments, further comprise levodopa or levodopa and arginine, and/or optionally a catechol-O-methyl transferase (COMT) inhibitor, such as entacapone or tolcapone; and/or a monoamine oxidase (MAO)-A or MAO-B inhibitor, such as moclobemide, rasagiline, selegiline or safinamide.

Also provided herein is a liquid formulation comprising an arginine salt of levodopa, or a liquid formulation comprising arginine and levodopa. In an embodiment, provided herein is a liquid formulation that includes levodopa and arginine in a molar ratio of about 1:1.5 to about 1:2.5, or about 1: 1.8 to about 1.20. Such levodopa and arginine formulations or solutions may have a pH of about 8 to about 10, for example, about 8.5 to about 9.5. A disclosed formulation having levodopa and arginine may include about 2%, 3%, 4%, 5%, 6% or more by weight levodopa, e.g., may include about 4% or more by weight levodopa.

In some embodiments, a disclosed liquid formulation will be stable for a period of 1 day, 2 days, 3 days, 1 week, or 1 month or more at room temperature. In preferred embodiments of the invention, a disclosed liquid formulation further comprise a

pharmaceutically acceptable excipient such as e.g., N-methylpyrrolidone (NMP), polyvinylpyrrolidone (PVP), propyleneglycol, or a combination of one or more thereof, and may further comprise one or more antioxidants such as, but not limited to, N-acetyl cysteine, sodium bisulfite, gluthatione, and ascorbic acid. For example, in one embodiment, provided herein is a stable liquid formulation that comprises about 0.5 to about 20% of carbidopa (e.g. about 2% to about 6%), about 0.25 to about 20% arginine, about 0 to about 30% NMP, about 0 to about 5% PVP, and/or about 0 to about 5% of one or more water soluble antioxidants, by weight.

The invention further provides a stable lyophilized powder comprising a carbidopa arginine salt. In one embodiment, such stable lyophilized powder may comprise about 20-99% of the carbidopa salt, about 0-60% NMP, about 0-15% PVP, and about 0-5% of one or more water soluble anti oxidants. The lyophilized powder can be reconstituted into a liquid formulation by addition of water alone or water with NMP, and may include or not include antioxidants.

Liquid formulations of the invention may be designed for continuous administration of a carbidopa or levodopa salt to a patient in need thereof. For example, a patient may be substantially continuously administered (e.g. subcutaneously, transdermally, intraduodenally, intradermally, or intravenously) a formulation that includes the disclosed carbidopa arginine salt, while levodopa, a levodopa salt, or a composition comprising levodopa is orally administered at discrete intervals, e.g., 2, 3, 4, or 5 times a day.

As used herein in the specification, the term "a composition comprising levodopa" contemplates formulations that comprise levodopa, optionally together with one or more decarboxylase inhibitors, one or more catechol-O-methyl transferase (COMT) inhibitors, and/or one or more MAO-A or MAO-B inhibitors. For example, a composition comprising levodopa may include a dosage formulation that comprises levodopa (or a salt thereof) and optionally one or more other drugs, where the dosage formulation may be an immediate release, controlled release, dual release or multiple release formulation suitable for oral administration.

The term "decarboxylase inhibitor" refers to a dopa decarboxylase (DDC) inhibitor, e.g., a drug that inhibits the peripheral metabolism of levodopa to dopamine by aromatic L-amino acid decarboxylase such as carbidopa and benserazide.

The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein 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 agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

The term "physiologically acceptable pH" is understood to mean a pH of e.g., a composition that facilitates administration of the composition to a patient without significant adverse effects, e.g. a pH of about 4 to about 9.

The term "COMT inhibitors" refers to inhibitors that inhibit the degradation of levodopa to 3-methyldopa by catechol-O-methyl transferase and prolong the action of levodopa, such as such as entacapone or tolcapone. For example, compositions comprising levodopa contemplated herein may also include a decarboxylase inhibitor (carbidopa or benserazide) and entacapone, e.g. "triple therapy".

The terms "MAO-A or MAO-B inhibitors" refer to inhibitors that prevent the breakdown of dopamine by monoamine oxidases A or B, e.g., moclobemide, rasagiline, selegiline or safinamide, more preferably, rasagiline.

Also contemplated herein is a kit comprising: a) a first formulation comprising a carbidopa arginine salt and/or carbidopa and arginine, wherein said first formulation is suitable for continuous administration; b) a second formulation comprising levodopa or an arginine salt of levodopa, wherein said second formulation is suitable for oral administration; and c) instructions for administration of formulation a) in conjunction with formulation b). The formulation a) comprising the carbidopa salt may be suitable for continuous administration by any suitable route such as transdermally, intravenously, subcutaneously, intradermally, intramuscularly or intraduodenally.

The first formulation of a contemplated kit comprising the carbidopa salt may be liquid or a lyophilized powder that can be reconstituted into a liquid formulation, or, for example, may form part of a transdermal patch, and may be designed for continuous administration by any suitable route such as, but not limited to, transdermally, intravenously, subcutaneously, intradermally, intramuscularly or intraduodenally. In an embodiment, the first formulation comprises the disclosed carbidopa arginine salt and is suitable for administration subcutaneously. The second formulation of a contemplated kit

may include the levodopa, a levodopa ester, a levodopa salt, or a composition comprising levodopa, and may be presented as any suitable oral dosage such as, but not limited to, pills, tablets, dispersible tablets, capsules, liquid, and the like. In an embodiment, the second formulation may be in the form of an immediate release, controlled release or dual release oral formulation that comprises both levodopa and benserazide, or both levodopa and carbidopa. Such oral formulation in the form of pills, tablets, or the like, may comprise a ratio of carbidopa or benserazide to levodopa of about 1:10 to 1:4, preferably from about 1:4 to 1:1. Other contemplated second formulations include formulations, e.g., tablets that include levodopa, carbidopa, and entacapone, or e.g. a tablet that includes levodopa arginine salt and/or carbidopa arginine salt.

In another embodiment, the kit comprises a first liquid formulation comprising carbidopa and arginine suitable for, but not limited to, transdermal, intravenous, subcutaneous, intradermal, intramuscular, intraduodenal continuous administration, and a second formulation in the form of an immediate release, controlled release or dual release oral formulation comprising levodopa and carbidopa. The oral formulation in the form of pills, tablets, or the like, may comprise a ratio of carbidopa to levodopa from about 1:10 to about 1:4, preferably from about 1:4 to about 1:1.

In another aspect, the present invention relates to a formulation comprising a carbidopa ester such as, but not limited to, the ethyl, propyl, isopropyl or hexyl ester of carbidopa, and salts thereof. Examples of levodopa esters contemplated herein include the alkyl esters, e.g., the methyl, ethyl, propyl, or isopropyl ester, or the benzyl ester.

The compositions of the present invention are useful for treatment of a disease or disorder characterized by reduced and/or fluctuating levels of dopamine in a patient's brain when co-administered substantially continuously to a patient in need together with a therapeutically effective amount of levodopa or salt thereof or a composition comprising levodopa. As shown in the Examples, separate continuous administration of carbidopa, together with administration of levodopa, even with discrete (e.g. oral) administration of levodopa, to a patient results in significantly higher levels of levodopa in the plasma of a patient upon administration as compared to a current standard of discrete carbidopa and levodopa simultaneous dosing. For example, disclosed methods may result in a half-life of levodopa in the plasma of a patient that is at least 1.5, or at least two times, longer after continuous administration of carbidopa as compared to the half life of levodopa in a

patient's serum after administering levodopa without continuous administration of carbidopa (e.g., with discrete, oral administration).

Contemplated administration of e.g., carbidopa and levodopa, following the disclosed methods, typically can be carried out over a defined time period (usually weeks, months or years depending upon the combination selected). Contemplated therapies are intended to embrace administration of multiple therapeutic agents in a manner wherein a dopa decarboxylase inhibitor is administered substantially continuously while levodopa is administered at discrete intervals, as well as administration of contemplated therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Administration can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, intradermal routes, subcutaneously,transdermally, and direct absorption through mucous membrane tissues.

In some embodiments, levodopa can be administered by the same route or by different routes as compared to administration of e.g. a contemplated carbidopa formulation. For example, carbidopa may be administered subcutaneously, e.g., substantially continuously, while levodopa may be administered orally, e.g. at discrete intervals. In an embodiment, a disclosed liquid carbidopa composition (e.g. having carbidopa and arginine) is administered substantially continuously, while an oral composition that includes levodopa (and may also include one or more other active agents such as a dopa decarboxylase inhibitor) is administered at discrete intervals. Alternatively, for example, both levodopa and carbidopa may be administered subcutaneously or transdermally.

The disease or disorder characterized by reduced levels of dopamine in the brain contemplated herein are neurological or movement disorders including 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 and conditions resulting from brain injury including carbon monoxide or manganese intoxication. In one preferred embodiment, the disease to be treated is Parkinson's disease.

In preferred embodiments, the contemplated decarboxylase inhibitor is the arginine salt of carbidopa. A disclosed carbidopa/arginine formulation may be administered substantially continuously using e.g. a liquid formulation, for example, via a pump for subcutaneous infusion (insulin pump) at an average rate of about 10-250 μl/hour,

preferably about1 5-85 μl/hour, in conjunction with oral administration of levodopa, an arginine salt of levodopa, or composition comprising levodopa.

For example, according to the invention, a pharmaceutically effective amount of a composition comprising carbidopa and arginine (the carbidopa arginine salt of the first composition of the kit of the invention) can be administered substantially continuously to a patient for treating a neurological or movement disorder e.g., Parkinson's disease, while the second composition of the kit comprising levodopa or a salt thereof, e.g., the levodopa arginine salt, is administered non-continuously to the patient,

In some embodiments, the composition comprising a carbidopa and arginine may be liquid at room temperature. The composition may be administered substantially continuously over 12 hours, 1 day, 1 week, or more. The composition comprising levodopa may form all or part of an immediate release, controlled release, or dual release oral formulation comprising levodopa and optionally benserazide or carbidopa, and may be administered 1, 2, 3, or 4 or more times a day, for example, by oral administration (e.g. by tablet).

Also provided herein is a method for treatment of a disease or disorder characterized by reduced levels of dopamine in a patient's brain, (e.g., Parkinson's disease) comprising co-administering substantially continuously to a patient in need a therapeutically effective amount of a disclosed levodopa salt.

The invention now being generally described, it 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 Preparation and Characterization of Carbidopa-Arginine Salt

Carbidopa (CD)-Arginine salt was prepared as follows:

Carbidopa [Teva Pharmaceuticals Ltd., Israel] was weighed in a suitable container with L-arginine [Merck] (at molar ratio of 1:1) and a 0.2% sodium bisulfite [Sigma] solution in water was added to obtain a final concentration of 4.0% carbidopa. The mixture was heated to 65±10°C with constant stirring. When the solids were completely dissolved, solution was filtered using 0.45 μM nylon membrane. The filtered solution was

immediately frozen in dry ice and subsequently subjected to lyophilyzation. Off-white crystals were obtained and subsequently subjected to MS analysis. The MS analytical results clearly showed carbidopa and L-arginine ions and fragments (Figure 1a). Peak 249 represents carbidopa + Na (226+ 23) with fragments: 227, 188 & 144 (Fig. 1b); Peak 176 represents arginine +2H (174+2) with fragments: 157,130 & 116 (Fig.1c).

Example 2 Preparation of Carbidopa Solution/Formulation for Subcutaneous Administration

A 4% Carbidopa solution/formulation was prepared as follows:

Carbidopa [Assia Ltd., Israel] was weighed in a suitable container and water was then added to obtain 73% of the total projected batch weight. Mixture was stirred at room temperature for 20 minutes. L-Arginine [Sigma] was added to the mixture to obtain a molar ratio 1:1 with carbidopa. The mixture was heated to 65±10°C with constant stirring. When the solids were completely dissolved, N-methyl 2-pyrrolidone [Pharmasolve, ISP] was added to obtain the final concentration of 10% (*w/w*). Sodium bisulfite [Sigma] solution was prepared and added to obtain a final concentration of 1% (*v/w*). Stirring was continued for additional 30 minutes at 65±3°C. Thereafter, PVP [Polyvinylpyrrolidone, Sigma] solution was prepared and added to obtain a final concentration of 1% (*v/w*). Stirring was continued for 30 minutes at 65±3°C. Heating was stopped and the preparation was allowed to cool down to room temperature. Solution was filtered using a sterile 0.22μM PVDF membrane.

Carbidopa-arginine solutions/formulations, 2 and 3%, were prepared by diluting the 4% carbidopa-arginine solution/formulation with the respective amount of double distilled water (DDW).

Example 3 - Preparation of Carbidopa Solution/Formulation for Subcutaneous Administration

A 6% Carbidopa solution/formulation was prepared as follows:

Carbidopa [Teva Pharmaceuticals Ltd, Israel] and L-arginine [Merck] (molar ratio 1:1.1) were weighed in a suitable container and water was then added to obtain 84% of the total projected batch weight. N-methyl 2-pyrrolidone [Pharmasolve, ISP] was added to obtain the final concentration of 5% (*w/w)* sodium bisulfite [Sigma] solution was prepared and added to obtain a final concentration of 0.1% (*v/w*). The mixture was heated to

65±10°C with constant stirring. When the solids were completely dissolved heating was stopped and the preparation was allowed to cool down to room temperature. Solution was filtered using a sterile 0.22μM PVDF membrane.

Example 4 - Preparation of Carbidopa Solution/Formulation for Subcutaneous Administration

A 4% Carbidopa solution/formulation was prepared as follows:

Carbidopa [Teva] and L-arginine [Merck] (molar ratio 1:1.1) were weighed in a suitable container and water was added to obtain 89% of the total projected batch weight. N-methyl 2-pyrrolidone [Pharmasolve, ISP] was added to obtain the final concentration of 3.5% (*w/w*). Sodium bisulfite [Sigma] solution was prepared and added to obtain a final concentration of 0.05% (*v/w*). The mixture was heated to 65±10°C with constant stirring. When the solids were completely dissolved, heating was stopped and the preparation was allowed to cool down to room temperature. The solution was filtered using a sterile 0.22μM PVDF membrane.

Carbidopa-arginine solutions/formulations, 2 and 3%, were prepared by diluting the 4% Carbidopa-arginine solution/formulation with the respective amount of double distilled water (DDW) containing 3.5% N-MP, with or without 0.05% sodium bisulfite.

Example 5 - Preparation of Carbidopa Formulation for Transdermal Delivery

An 8% Carbidopa formulation was prepared as follows:

Carbidopa [Teva] and L-arginine [Merck] (molar ratio 1:1) were weighed in a suitable container and propylene glycol [Merck] was added to obtain 75% of the total projected batch weight. Sodium bisulfite [Sigma] solution was prepared and added to obtain a final concentration of 0.05%. The mixture was heated to 65±10°C with constant stirring. When the solids were completely dissolved, heating was stopped and the preparation was allowed to cool down to room temperature. PEG-400 [Merck], 10% of the total projected batch weight, was added. The pH was adjusted to 7.5 with 85% lactic acid [Fluka].

Example 6 - Preparation and Stability of Carbidopa-Arginine, Carbidopa-Lysine and Carbidopa-Histidine Solutions/Formulations

Carbidopa solutions/formulations were prepared as follows:

Carbidopa [Teva] was weighed in a suitable container with L-arginine [Merck] or L-lysine [Sigma] or L-histidine [Sigma] (at molar ratio of 1:1, 1:1.1 or 1:2) and water was added. N-methyl 2-pyrrolidone [Pharmasolve, ISP] was added to obtain the final concentration of 5% (*w/w*). Sodium bisulfite [Sigma] solution was prepared and added to obtain a final concentration of 0.05% (*v/w*). The mixture was heated to 68±3 °C with constant stirring. When the solids were completely dissolved, heating was stopped and the preparation was allowed to cool down to room temperature. Stable formulations (2% CD:lysine and 2% CD:arginine 1:1.1 molar ratio) were further subjected to HPLC analysis at t=0 and t=7days at 25 °C.

The results show the significant difference between the three basic amino acids [L-arginine (PI-10.76), L-lysine (PI-9.74) and L-histidine (PI-7.59)] with respect to their effect on the solubility and stability of carbidopa in aqueous solution: Table 1 indicates the solubility and stability of carbidopa in these aqueous solutions with basic amino acids (arginine, lysine or histidine) as determined visually (Table 1A) or by UV HPLC (Table 1B). With arginine, a stable solution of 6% carbidopa was prepared, whereas a solution with only less than 4% could be formulated with lysine (Table 1A). Furthermore, a solution of 2% carbidopa with lysine was less stable than with arginine after 7days at 25 °C (Table 1B). In addition, a stable solution with histidine at concentrations ≥1% could not be made (Table 1A).

Table 1A

Carbidopa and Arginine Solution

CD Concentration (%)	2	4	4	5	6	8
Molar Ratio CD:Arginine	1 to 1	1 to 1	1 to 1.1	1 to 1.1	1 to 1.1	1 to 1.1
pH of the Solution	8.2	8.2	8.4	8.5	8.7	8.9
Solution Appearance	Clear, slightly yellow	Clear, slightly yellow	Clear, slightly yellow	Clear, slightly yellow	Clear, slightly yellow	Clear, slightly yellow
Stability after 48h (visual)	Stable	Stable	Stable	Stable	Stable	Precipitated within 24h

Carbidopa and lysine solutions					
CD Concentration(%)	2	4	2	4	
Molar Ratio CD:Lysine	1 to 1	1 to 1	1 to 1.1	1 to 1.1	

pH of the Solution	8.1	N/A	8.2	8.23	
Solution Appearance	Clear, slightly yellow	Didn't dissolve	Clear, yellow	Precipitated within few minutes	
Stability after 48h (visual)	Precipitated after 2h	N/A	Stable	N/A	
Carbidopa and histidine solutions					
CD Concentration (%)	1	4	2	4	
Molar Ratio CD:Histidine	1 to 1.1	1 to 1.1	1 to 2	1 to2	
PH of the Solution	N/A	N/A	6.7	N/A	
Solution Appearance	Didn't dissolve	Didn't dissolve	Clear, white	Didn't dissolve	
Stability after 48h (visual)	N/A	N/A	Precipitated after 1h	N/A	

Table 1B

Amino Acid (AA)	Molar Ratio CD:AA	CD (%)	Time of Analysis	CD Assay (%)	Impurities Profile (Area %)				
					3-OMD	RT 5.3	RT 12.6	RT 13.6	RT 14.5
Lysine	1:1.1	2	t=0	95.1	0	3.3	0	0.50	1.07
Arginine	1:1.1	2	t=0	94.1	0	4.5	0	0.41	1.05
Lysine	1:1.1	2	t=7d at RT	70.8	0	N/A	0	1.39	26.4
Arginine	1:1.1	2	t=7d at RT	77.6	0	N/A	0	1.34	19.4

N/A = Not Applicable

Example 7 - Preparation of Levodopa-Arginine Salt

Levodopa (LD)-arginine salt was prepared as follows:

Levodopa [Teva] was weighed in a suitable container with L-arginine [Merck] (at molar ratio of 1:1.8) and a 0.2% sodium bislfite [Sigma] solution in water was added to obtain a final concentration of 4.4% L-Dopa. The mixture was heated to 65±10°C with constant stirring. When the solids were completely dissolved, solution was filtered using 0.45 μM nylon membrane. The filtered solution was immediately frozen in dry ice and subsequently subjected to lyophilization. The filtered solution was immediately frozen in dry ice and subsequently subjected to lyophilyzation. Off-white crystals were obtained and

subsequently subjected to MS analysis. The MS analytical results (shown in Fig. 2) clearly showed LD and Arginine ions. LD: 197 with fragments 178.97, 151.96, 136.98 (Figures 2a & 2b); Arginine: 175 with fragments 130, 116 (Figs. 2a & 2c)

Example 8 - Preparation of Carbidopa and Carbidopa/Entacapone Solutions/Formulations for Subcutaneous Administration, and Their Local Safety Evaluation in Pigs

A 10% carbidopa and 4/6% carbidopa/entacapone solutions/formulations were prepared as follows:

Carbidopa [Assia Ltd.] was weighed in a suitable container and water was then added to obtain 73% of the total projected batch weight. Mixture was stirred at room temperature for 20 minutes. L-Arginine [Sigma] was added to the mixture to obtain a molar ratio 1:1 with Carbidopa. The mixture was heated to 65±10°C with constant stirring. When the solids were completely dissolved, N-methyl 2-pyrrolidone [Pharmasolve, ISP] was added to obtain the final concentration of 10% (*w/w*). Sodium bisulfite [Sigma] solution was prepared and added to obtain a final concentration of 1% (*v/w*). Stirring was continued for additional 30 minutes at 65±3°C. Thereafter, PVP [Polyvinylpyrrolidone, Sigma] solution was prepared and added to obtain a final concentration of 1% (*v/w*). Stirring was continued for 30 minutes at 65±3°C. Heating was stopped and the preparation was allowed to cool down to room temperature. Solution was filtered using a sterile 0.22μM PVDF membrane. The filtered solution was immediately frozen in dry ice and subsequently subjected to lyophilization. Lyophilized crystals were re-constituted with double distilled water to obtain 4 and 10% carbidopa solutions. Entacapone [extracted from Comtan®, Novartis] was added to the 4% carbidopa solution to obtain a final concentration of 6% (*w/v*). Both formulations (10% CD and 4/6% CD/E) were continuously administered sc to pigs for a period of 21h to evaluate potential local reactions. Macroscopic and microscopic evaluations indicated that 21h continuous subcutaneous administration of these carbidopa solutions/formulations was safe. (Table 2).

Table 2 indicates the results of a histological evaluation of skin biopsies obtained from female Landrace × large white swine following continuous subcutaneous administration of 10% CD (carbidopa) or 4/6% CD/entacapone for a period of 21h, at a rate of 25 or 82 μl/h.

Table 2

	Pig #1				Pig #2			
	L		R		L		R	
	CD 10%		CD/Ent 4/6%		CD/Ent 4/6%		CD 10%	
Infusion Rate	Pod Activation (h)							
25 µl/hr	21h		-		21h		-	
82 µl/hr	-		21h		-		21h	
Parameter	Histological Observation (Time post patch removal)							
	0	10d	0	10d	0	10d	0	10d
Lesion Localization	Subcutis	No Lesions	No Lesions	No Lesions	No Lesions	No Lesions	Subcutis	No Lesions
Distribution	Peri-vascular						Peri-vascular	
Inflammation Grade	0-1						0-1	
Predominant Cell Type	N						N	
Necrosis	-						-	
Fibrosis	-						-	

Key: Localization: Epidermis, dermis, subcutis; Distribution: Diffuse, multifocal, perivascular; Inflammation Scoring Grade: 0-no inflammation, 1-very mild, 2-moderate, 3-severe; Predominant Cell Type: lymphocytes (L), macrophages (M), neutrophils (N); Necrosis: Yes/No; Fibrosis: Yes/No

Example 9 - The Effect of Continuous Subcutaneous Carbidopa Administration on the Pharmacokinetic Profile of Levodopa and Carbidopa in Pigs

In this experiment, the purpose was to determine the effect of continuous subcutaneous administration of carbidopa, with co-administration of oral L-dopa/carbidopa, on the pharmacokinetics of levodopa in pigs.

Pigs weighing 30-35 kg were administered orally with either Stalevo ® (Novartis, 100/25/200 mg, LD/CD/E), Dopicar® [Teva] + Lodosyn® (Merck & Co) (125/25 mg, LD/CD) or Sinemet CR® (MSD,100/25 mg, LD/CD) thrice or twice daily (q8 or 12h, respectively) with or without carbidopa (60 mg/pig/d) for a total period of 68h. Blood samples were collected at pre-determined time points and plasma levels of L-dopa and carbidopa were analyzed by LC-MS.

Results showed that the co-administration of continuous subcutaneous carbidopa with any oral LD preparation significantly increases (more than ×2) the half live ($t_{1/2}$) and

AUC of levodopa. In contrast, increased carbidopa oral dose or frequency did not considerably improve the PK profile of levodopa, as shown in Table 3. Also, constant, steady-state, levels of CD was maintained at 164±34 ng/ml during the 68 hours of continuous SC administration of carbidopa (60 mg/pig/day). This was in opposition to the fluctuating pattern and very low trough levels of CD obtained after administration of standard treatment (Figs. 3A-3C). No signs of treatment related local or systemic toxicity were observed throughout the entire 68h study period.

The pharmacokinetic parameters of levodopa determined in plasma of female Landrace × large white swine (30-35kg) following oral administration of (A) Stalevo (100/25/200 mg, LD/CD/E), (B) Dopicar+Lodosyn (125/25 mg LD/CD), (C) Sinemet CR (100/25 mg, LD/CD) q8 and 12h (q8h=every 8 hours), with or without continuous subcutaneous (SC) administration of 3% carbidopa (CD) solution, with results depicts in Table 3:

Table 3A.

Oral Treatment	**Stalevo** (100/25/200 mg)				
SC Treatment	**PK Parameters**				
	C_{max}	**T_{max}**	**$T_{1/2}$**	**AUC_{0-8}**	**$AUC_{0-\infty}$**
Without SC CD (*n=8*)	2392 ±1363.9	2.3 ±0.89	1.4 ±0.30	8109 ±4145.2	8309 ±4265.2
With SC CD (*n=12*)	2355 ±1157.1	2.1 ±1.00	2.9 ±0.41	17527 ±8470.8	19330 ±8284.8
Significance* (*p*)	NS	NS	2E-08	0.005	0.001

Table 3B.

Oral Treatment	**LD/CD** (125/25 mg)				
SC Treatment	**PK Parameters**				
	C_{max}	**T_{max}**	**$T_{1/2}$**	**AUC_{0-8}**	**$AUC_{0-\infty}$**
Without SC CD(*n=7*)	2472 ±735.6	0.9 ±0.53	1.1 ±0.22	7200 ±3093.2	7302 ±3071.3
With SC CD (*n=14*)	4050 ±1369.5	0.8 ±0.43	2.5 ±0.43	17922 ±4375.7	19230 ±4625.5
Significance* (*p*)	0.005	NS	1E-07	7.4E-06	3.3E-06

Table 3C.

Oral Treatment	**Sinemet CR** (100/25 mg)				
SC Treatment	**PK Parameters**				
	C_{max}	T_{max}	$T_{1/2}$	AUC_{0-8}	$AUC_{0-\infty}$
Without SC CD (*n=8*)	1691 ±556.2	0.9 ±0.52	1.2 ±0.19	4792 ±1190.8	4929 ±1196.6
With SC CD (*n=15*)	2830 ±929.2	1.2 ±0.92	2.6 ±0.46	12688 ±3516.3	13505 ±3344.4
Significance* (*p*)	0.002	NS	3.2E-08	2.3E-06	3.6E-07

* Using one tailed distribution equal variance T-Test

Example 10 - The Effect of Continuous Subcutaneous Administration of Carbidopa on Brain Distribution of Levodopa and Dopamine in Mice

In this experiment, the purpose was to determine the effect of continuous subcutaneous administration of carbidopa (15 mg/kg/d) on the levels of levodopa and dopamine in the brain following oral administration of levodopa/carbidopa (32/8 mg/kg TID) in mice.

Mice were implanted subcutaneously with Alzet pumps containing Saline (Negative Control), Vehicle or Carbidopa solution. A day following implantation LD/CD was administered orally q8h. The level of levodopa and dopamine in the brain was determined following the 4th oral dose of LD/CD. The results showed dopamine levels seven hours post-administration of oral LD to be significantly higher in the brains of mice continuously administered SC with carbidopa (Fig. 4A), concurrently with higher levels of plasma LD (Fig. 4B).

Example 11 – Dose Effect of Continuous Subcutaneous Carbidopa Administration on Local Toxicity and Pharmacokinetic Profile of Levodopa and Carbidopa in Pigs

In this experiment, the purpose was to determine the dose effect of carbidopa continuously administered subcutaneously to pigs on local tolerance and the pharmacokinetics of L-dopa.

Pigs weighing 30-35 kg were administered orally with Sinemet® (Merck & Co., 100/25 mg, LD/CD,), thrice daily (q8h), or Dopicar® (Teva) + Lodosyn® (Merck & Co., (125/25 mg LD/CD), twice daily (q12h), with continuous subcutaneous vehicle, 2% or 4% carbidopa (0, 40 or 80 mg/pig/d, respectively) for a total period of 24h. Blood samples

were collected at pre-determined time points and plasma levels of L-dopa and carbidopa were analyzed by LC-MS. Skin biopsies were collected from the infusion sites immediately, 1 and 2 weeks post-administration and local tolerance was evaluated by histological analysis of H&E stained slides. No histological treatment-related abnormalities were observed at the sites of infusion.

No significant dose effect on the plasma levels of L-dopa was observed when 2 or 4% carbidopa solutions were co-administered with Sinemet® (Figs. 5A-5B) or Dopicar® + Lodosyn® (Figs. 6A-6B). Thus, under the experimental conditions employed, it was suggested that continuous subcutaneous administration of 2% carbidopa, or less, may be sufficient to maintain optimal inhibition of DDC (dopa decarboxylase) in pigs.

Example 12 - Effect of Continuous Subcutaneous Administration of Carbidopa, with and without Continuous Subcutaneous Administration of Entacapone, on the Pharmacokinetics of Levodopa in Pigs

In this experiment, the purpose was to determine the plasma levels of L-dopa, following continuous subcutaneous administration of carbidopa, with or without entacapone, concomitantly with oral administration of L-dopa/carbidopa in pigs. Plasma levels of L-dopa were measured by HPLC-ECD. The results in Fig. 8 showed that entacapone effectively reduced the levels of 3-OMD (3-ortho-methyldopa) (8B) but it did not further extend the pharmacokinetics of levodopa (8A), suggesting that entacapone and/or COMT inhibition interferes with carbidopa/DDC-dependent, or other, LD metabolic pathways.

Example 13 - The Effect of Continuous Subcutaneous Administration of Benserazide on the Pharmacokinetics of Levodopa in Pigs

In this experiment, the purpose was to determine the plasma levels of L-dopa, following co-administration of oral L-dopa/Carbidopa with continuous subcutaneous administration of another DDC inhibitor, benserazide. Plasma levels of L-dopa were measured by HPLC-ECD.

The results showed that benserazide extended the pharmacokinetic profile of LD, suggesting that continuous dopa-decarboxylase (DDC) inhibition, by any DDC inhibitor, increases the elimination half life of LD, as shown in Fig. 7.

Example 14 - The Transdermal Delivery of Carbidopa Propyl Ester (CDPE) Through Full Thickness Pig Skin Ex-Vivo using the Franz Cell Delivery System.

In this experiment, the purpose was to determine the transdermal delivery of carbidopa propyl ester through a full thickness porcine skin, ex vivo using the Franz cell delivery system. Gel formulations containing CDPE were prepared. Samples were collected from the receiver cell at time 0, 16, 19 and 22 hours after formulation application on to the skin. The amount of CD compounds in the receiver cell fluid was determined by a spectrophotometer at 280 nM. The results shown in Fig. 9 demonstrate that CDPE penetrates the skin in an enhancer-dose dependent manner.

Example 15 - The Effect of Oral Administration of Levodopa Arginine and Carbidopa Arginine Salts on the Pharmacokinetic Profile of Levodopa and Carbidopa

In this experiment, the purpose was to determine the pharmacokinetics of LD and CD administered orally as arginine salts, either enteric-coated or not. Pigs were orally administered with 255/45 mg LD-arginine salt (LDs)/CD-arginine salt (CDs) to 30-35kg pigs in gelatin coated or non-coated capsules (corresponding to 100/25 LD/CD). Plasma levels of LD and CD were measured by HPLC-ECD.

The results in Figs. 10A-10B showed that LDs and CDs were absorbed more rapidly and efficiently as compared to LD/CD (Sinemet®), and that oral administration of enteric coated LDs/CDs extended the PK of plasma LD (10A) and CD (10B).

Example 16 - The Inhibitory Effect of Carbidopa Esters on the Activity of Dopa-Decarboxylases (DDC) In Vitro

In this experiment, the purpose was to determine the inhibitory effect of carbidopa esters (CDEs) on the activity of dopa-decarboxylases. DDC enzymes were obtained from porcine liver homogenate and their activity was measured by comparing LD concentrations with and without carbidopa propyl ester (CDPE). Liver homogenate preparation was based on the method described by Umezawa et al; (J. Antib. 1975, 28(12):947-52).

All samples were separated on high pressure liquid chromatography columns and the identity and concentration of L-Dopa and dopamine were determined by HP UV-HPLC analysis at 280nM.

The results shown in Figs. 11 and 12A-12B demonstrate that CDPE inhibits the decarboxylation of L-dopa to dopamine, in a similar manner to carbidopa and benserazide.

While specific embodiments of the subject 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.

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.

CLAIMS

1. A pharmaceutically acceptable liquid composition comprising arginine and carbidopa, wherein the composition comprises 1% to 6% by weight carbidopa; has a pH of 8 to 9.5 at 25°C; and is stable at 25°C for 48 hours or more.

2. The pharmaceutically acceptable liquid composition of claim 1, wherein the composition comprises at least 1% or 2% or 4% or 6% by weight carbidopa.

3. The pharmaceutically acceptable liquid composition of claims 1 or 2, wherein the carbidopa and the arginine have a molar ratio selected from 1:1 to 1:2.5.

4. The pharmaceutically acceptable liquid composition of claim 1, further comprising a pharmaceutically acceptable excipient preferably selected from N-methylpyrrolidone, polyvinylpyrrolidone, propylene glycol, antioxidants, or combinations thereof.

5. The pharmaceutically acceptable liquid composition of claim 1, further comprising water.

6. The pharmaceutically acceptable liquid composition of claim 1, further comprising entacapone or tolcapone.

7. The pharmaceutically acceptable liquid composition of claim 1, comprising 2% to 6% by weight carbidopa, and arginine, wherein the pH of the liquid composition is 8 to 9 at 25°C.

8. A kit comprising: a) a first composition suitable for continuous administration comprising the liquid composition of any one of claims 1 to 7; and b) a second composition suitable for oral administration comprising levodopa or a pharmaceutically acceptable salt or ester thereof.

9. The kit of claim 8, wherein said first composition for continuous administration is for transdermal, intradermal, subcutaneous, intravenous, or intraduodenal administration.

10. The kit of claim 9, wherein said continuous administration comprises using an infusion pump.

11. The kit of claim 8, wherein the second composition further comprises carbidopa, benserazide, entacapone, tolcapone, or a combination thereof.

12. The kit of claim 8, wherein the second composition comprises a pharmaceutically acceptable salt of levodopa.

13. The kit of claim 12, wherein the second composition comprises the arginine salt of levodopa.

14. The kit of any one of claims 8 to 13, for use in treating a neurological 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), or amyotrophic lateral sclerosis (ALS).

15. The kit according to claim 14, for use in treating or ameliorating Parkinson's disease.

16. The arginine salt of carbidopa.

17. A pharmaceutically acceptable liquid composition comprising the arginine salt of carbidopa of claim 16, and optionally a pharmaceutically acceptable excipient.