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(54) Title: PHARMACEUTICAL COMPOSITIONS AND METHOD OF USING LEVODOPA AND CARBIDOPA

(57) Abstract: The present invention relates to stable compositions of levodopa and carbidopa, methods of treating patients with these compositions, and methods of preparing these compositions.

WO 2005/099678 A1

PHARMACEUTICAL COMPOSITIONS AND METHOD OF USING LEVODOPA AND CARBIDOPA

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/559,864 filed on April 6, 2004, and U.S. Provisional Application No. 60/586,442 filed on July 8, 2004; U.S. Patent Application No. 10/926,702 filed August 26, 2004; and PCT/US04/27607 filed August 26, 2004.

FIELD OF THE INVENTION

This invention relates to stable compositions of levodopa and carbidopa.

BACKGROUND OF THE INVENTION

Parkinson's disease is a neurodegenerative disorder characterized by a progressive degeneration of the dopaminergic pathway in the brain. Parkinson's patients often have symptoms of bradykinesia, rigidity, tremor, poor balance and difficulty walking. Simple movements such as making breakfast or coffee can be very difficult for Parkinson's disease patients. In particular, manipulating small items such as a pill can be very difficult. One of the most common treatments for Parkinson's disease is administration of levodopa. Levodopa functions to cross the blood brain barrier, convert to dopamine, and to replace or supplement low levels of dopamine in the brain. Parkinson's disease patients often take between 200 mg and 2 g of levodopa per day with late stage Parkinsons patients taking toward the later end of this range. Monotherapy with levodopa is often accompanied by unpleasant side effects such as nausea and vomiting. Administration of a combination of levodopa and a dopa decarboxylase inhibitor such as carbidopa decreases the patient side effects while increasing drug efficacy. One of the disadvantages with levodopa/carbidopa tablets is that Parkinson's patients often experience episodes of "wearing off." During these episodes, patients become frozen or have rigid movements. These freezing episodes have significant detrimental consequences to the quality of life for Parkinson's patients. To recover from a freezing episode, patients often administer levodopa/carbidopa tablets under their tongue. Administration of the drug under a patient's tongue will

often not release a patient from a frozen episode for an hour. A controlled release version of levodopa/carbidopa tablets (trademark, "Sinemet CR) is also available to patients. The controlled release version of Sinemet has not provided much better clinical affects. Thus, patients taking Sinemet CR still have "wearing off" and frozen episodes. One of the methods patients have used to avoid or fix these "wearing off" episodes is to create a liquid version of levodopa/carbidopa. Stable liquid levodopa/carbidopa formulations do not exist. Unstable liquid levodopa/carbidopa suspension is a home remedy Parkinson's patients have employed. Patients take a sip of the unstable liquid levodopa/carbidopa suspension when they feel their levodopa levels decreasing. Thus, patients self dose their levodopa concentrations and subsequently their Parkinson's symptoms. Methods of making unstable liquid levodopa/carbidopa are available in the literature. Typically, patients grind up a pill of levodopa/carbidopa and add a liquid such as orange juice or ginger ale. One of the disadvantages of this procedure is the grinding process. A patient entering a "wearing off" episode can have significant difficulty in grinding a pill. The strength and finger manipulation necessary to grind a pill can be missing or inadequate during a wearing off episode. In addition, this unapproved mixing can result in incomplete bioavailability of the levodopa or carbidopa or poor stability. Carbidopa and levodopa are unstable compounds in liquid for long periods of time, and currently there are no stable carbidopa and levodopa liquid formulations. Thus, a need exists for a liquid formulations of carbidopa and levodopa which are safer, more stable, and easier to use than current suspensions.

SUMMARY OF THE INVENTION

Surprisingly, it has now been found that new stable formulations of carbidopa and levodopa can be obtained which can readily be combined with a liquid and used to treat Parkinson's disease patients.

In one aspect, the present invention provides for a dry, solid, tablet, or powder formulation of carbidopa and levodopa which can be mixed with a liquid to form a stable pharmaceutical product.

In another aspect, the present invention provides for a method of treating a Parkinson's disease patient with a liquid formulation of carbidopa and levodopa.

In a further embodiment, a pharmaceutical composition comprises levodopa, carbidopa, acid and a metal chelator. Examples of metal chelators include EDTA and

deferoxamine mesylate. The EDTA may be in the form of a salt or its free base. In one aspect, EDTA concentration is at least 0.01 mg/ml.

In another embodiment the acid can be selected from a carboxylic acid, a mineral acid, citric acid, tartaric acid, ascorbic acid, dehydroascorbic acid, acetic acid, formic acid, methanoic acid, butanoic acid, ethanoic acid, benzoic acid, butyric acid, malic acid, propionic, epoxysuccinic acid, muconic acid, furanacrylic acid, citramalic acid, capric acid, stearic acid, caprioc acid, malonic acid, succinic acid, diethylacetic acid, methylbutryic acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, or sulfuric acid.

In one embodiment, the composition is a stable liquid of levodopa and carbidopa. In one aspect, the stable liquid has less than 10% of carbidopa degradation at 25°C after 7 days. In another aspect, the stable liquid has less than 5% of carbidopa degradation at 25°C after 7 days. In further aspect, the stable liquid has less than 10% of carbidopa degradation at 25°C after 30 days. In an additional aspect, the stable liquid has less than 5% of carbidopa degradation at 25°C after 4 days. In another aspect, the stable liquid has less than 5% of carbidopa degradation at 4°C after 30 days. In one aspect, the stable liquid has less than 5% of carbidopa degradation at 25°C after 250 days. In a further aspect, the stable liquid has less than 5% of carbidopa degradation at 4°C after 360 days. In an additional aspect, the stable liquid has less than 10% of carbidopa degradation at 25°C after 9 days.

In an additional embodiment, a pharmaceutical composition comprises levodopa, carbidopa and acid wherein the pH of said composition is less than or about 3.0. In one aspect, this composition has less than 10% of carbidopa degradation at 25°C after 7 days. In another aspect, this composition has less than 5% of carbidopa degradation at 25°C after 7 days. In further aspect, this composition has less than 10% of carbidopa degradation at 25°C after 30 days. In an additional aspect, this composition has less than 5% of carbidopa degradation at 25°C after 4 days. In another aspect, this composition has less than 5% of carbidopa degradation at 4°C after 30 days. In one aspect, this composition has less than 5% of carbidopa degradation at 25°C after 250 days. In a further aspect, this composition has less than 5% of carbidopa degradation at 4°C after 360 days. In an additional aspect, this composition has less than 10% of carbidopa degradation at 25°C after 9 days. In a further aspect, this composition further comprises further an artificial sweetener or a preservative.

In another embodiment, an aqueous composition comprises levodopa and carbidopa wherein the levodopa is at a concentration of between 2.5 mg/ml and 9mg/ml. In another embodiment, the levodopa is at a concentration of about 4 mg/ml. In one aspect, this composition has less than 10% of carbidopa degradation at 25°C after 7 days. In another aspect, this composition has less than 5% of carbidopa degradation at 25°C after 7 days. In further aspect, this composition has less than 10% of carbidopa degradation at 25°C after 30 days. In an additional aspect, this composition has less than 5% of carbidopa degradation at 25°C after 4 days. In another aspect, this composition has less than 5% of carbidopa degradation at 4°C after 30 days. In one aspect, this composition has less than 5% of carbidopa degradation at 25°C after 250 days. In a further aspect, this composition has less than 5% of carbidopa degradation at 4°C after 360 days. In an additional aspect, this composition has less than 10% of carbidopa degradation at 25°C after 9 days. In a further aspect, this composition further comprises further an artificial sweetener or a preservative.

In a further embodiment, a composition comprises levodopa, carbidopa, acid, and a metal chelator wherein less than 1.2% of the carbidopa has degraded after 24 hours at 25°C. Examples of metal chelators include EDTA and deferoxamine mesylate.

Another embodiment comprises compositions of levodopa, carbidopa, acid, and a metal chelator wherein less than 2.4% of the carbidopa has degraded after 48 hours at 25°C.

Additional compositions of this invention comprise stable formulations with low levels of degradants. In one aspect, a degradant of hydrazine is lower than currently available levodopa/carbidopa suspensions. In one aspect, a liquid pharmaceutical composition comprises levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 0.07ug/ml after 24 hours at 25°C. In another aspect, a liquid pharmaceutical composition comprisises levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 0.32ug/ml after 3 days at 25°C. In a further aspect, a liquid pharmaceutical composition comprises levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 1.6ug/ml after 7 days at 25°C. In a still further aspect, a liquid pharmaceutical composition comprises levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 0.06ug/ml after 7 days at 4°C.

In one embodiment, a liquid formulation of levodopa, carbidopa, acid and a metal chelator is clear or translucent.

In an additional embodiment, a pharmaceutical composition comprises levodopa, carbidopa, acid and a thioether compound. In one aspect, the thioether functions to stabilize the carbidopa. Examples of thioethers include methionine, cysteine, glutathione, thiogylcerol, sodium thiosulfate, and n-acetylmethionine. In another embodiment, a composition comprises levodopa, carbidopa, acid, a thioether and a metal chelator.

One embodiment contains a pharmaceutical composition comprising levodopa at about 2.5 to 6 mg/ml, carbidopa at about 0.625 to 1.5 mg/ml, citric acid at about 5mg/ml to 10 mg/ml, and EDTA at greater than about 0.25 mg/ml. This composition may additionally contain aspartame at about 0.1 mg/ml to about 1 mg/ml or sodium benzoate at about 0.01 mg/ml to about 1 mg/ml.

In a further embodiment, a pharmaceutical composition comprises levodopa at about 2.5 to 6 mg/ml, carbidopa at about 0.25 to 0.6 mg/ml, citric acid at about 5mg/ml to 10 mg/ml, and EDTA at greater than about 0.25 mg/ml. This composition may additionally contain water, aspartame at about 0.1 mg/ml to about 1 mg/ml, or sodium benzoate at about 0.01 mg/ml to about 1 mg/ml.

In one embodiment, a pharmaceutical composition comprises levodopa of about 500 mg to about 1500 mg, carbidopa of about 125 mg to about 375 mg, citric acid of about 1065 mg to about 3195 mg and EDTA of about 13 mg to about 41 mg. This composition may be in the form of a dispersible tablet or in the form of a powder or granules for mixing with a liquid.

In another embodiment, a pharmaceutical composition comprises levodopa of about 1000 mg, carbidopa of about 250 mg, citric acid of about 2130mg, and EDTA of about 27 mg. The composition can further comprise water, aspartame or sodium benzoate.

One embodiment comprises a pharmaceutical composition of levodopa, carbidopa, acid, a metal chelator, and sugar wherein the sugar comprises less than 1% of the composition.

One embodiment comprises a method of dosing levodopa and carbidopa wherein a dry or solid formulation of levodopa and carbidopa is added to a liquid; the formulation is mixed for less than 10 minutes and the formulation is adminstered to a patient. In one aspect of this invention, the administration of the formulation is the first morning dose for a Parkinson's disease patient.

In another embodiment, a liquid composition is capable of dissolving levodopa at about 2.5 to 6 mg/ml and carbidopa at about 0.25 to 0.6 mg/ml. In one aspect, this composition has less than 10% of carbidopa degradation at 25°C after 7 days. In another aspect, this composition has less than 5% of carbidopa degradation at 25°C after 7 days. In further aspect, this composition has less than 10% of carbidopa degradation at 25°C after 30 days. In an additional aspect, this composition has less than 5% of carbidopa degradation at 25°C after 4 days. In another aspect, this composition has less than 5% of carbidopa degradation at 4°C after 30 days. In one aspect, this composition has less than 5% of carbidopa degradation at 25°C after 250 days. . In a further aspect, this composition has less than 5% of carbidopa degradation at 4°C after 360 days. In an additional aspect, this composition has less than 10% of carbidopa degradation at 25°C after 9 days.

A further embodiment of this invention is a method of making a pharmaceutical composition to treat a dopamine disorder comprising the steps of combining levodopa, carbidopa, acid, a metal chelator; and water.

In one embodiment, a liquid composition comprises levodopa and carbidopa wherein the total metal ion concentration is less than 1 ppm. In another aspect, the free metal ion concentration is less than 1 ppm. In one aspect, the composition further comprises an acid. One example of a relevant acid is hydrochloric acid. In other compositions the total metal ion concentration may be below 0.1 ppm, 0.1 ppm, 0.01 ppm, or 1 ppb.

In one method of this invention, a formulation of levodopa and carbidopa comprises one or more excipients or active agents and these excipients or active agents are subjected to chromatography to remove metal ions. Examples of applicable metal ions to remove include iron, lead, zinc or aluminum

Additional aspects of this invention comprise administering a composition of this invention to a patient.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1: Demonstrates the solubility of levodopa in citrate buffer as a function of pH and levodopa concentration.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for stable pharmaceutical compositions comprising carbidopa and levodopa. Prior compositions of levodopa and carbidopa are not sufficiently stable or functional for Parkinson's disease patients. Compositions of this invention can provide advantages over currently marketed levodopa and carbidopa formulations and the current homemade versions of liquid levodopa/carbidopa.

"Liquid levodopa/carbidopa" is defined to be a formulation of levodopa, carbidopa and a liquid wherein one or more tablets of levodopa/carbidopa are combined with a liquid.

"Parkinson's disease patient" is defined to be any person diagnosed by a physician to be suffering from Parkinson's Disease or any person diagnosed to be suffering from a dopamine disorder who could benefit from levodopa treatment.

Improvements in stabilizing compositions of levodopa and carbidopa have been found. One method of improving stability involves reducing the free metal concentration in compositions of levodopa and carbidopa. Another method of improving stability involves reducing the pH of a liquid composition of levodopa and carbidopa. A further method of improving stability involves selecting preferred acids for the stability of levodopa and carbidopa. Additional methods of improving stability of levodopa and carbidopa formulations include avoiding light exposure, addition of sulfides to the composition, and elimination or reduction in aldehydes and ketones in the composition (such as sugars).

This invention provides for formulations of carbidopa and levodopa which have advantages over the prior art in stability and ease of use. It has been found that the currently used homemade versions of liquid levodopa/carbidopa produce multiple degradation products. At least one of these degradation products is hydrazine, a potential carcinogen. Current practice by late stage Parkinson's patients who take 1g of levodopa per day in the form of liquid levodopa/caribdopa could be exposed to toxic levels of hydrazine. Even though current liquid levodopa/carbidopa formulations provide significant benefit to late stage Parkinson's patients, these homemade formulations expose patients to a potential carcinogen. This potential carcinogen has been linked with cancer. ("Toxological Profile for Hydrazines," US Department of Health and Human Services, September 1997). In addition, the degradation of

carbidopa to hydrazine results in lost carbidopa potency, thereby decreasing the shelf life of a product.

A need exists for formulations which are stable and easy for Parkinson's patients to use while still providing the benefit of a liquid formulation of levodopa and carbidopa. A significant effort was made to create liquid formulations comprising levodopa and carbidopa which are stable. After significant testing, it was found that metals destabilize carbidopa. One embodiment of this invention contains levodopa, carbidopa, and a metal chelator. Without being bound to any theory, metal ions are believed to cause carbidopa degradation (Example 12). Examples of chelators include, but are not limited to, EDTA, deferoxamine mesylate, EGTA, fumaric acid, and malic acid. Included within the definition of EDTA are both free acid and salt forms of EDTA. Examples of free acid or salt forms of EDTA include editic acid, disodium edetate, dipotassium edetate, edetate calcium disodium, sodium edetate, and trisodium edetate. Any of editic acid, disodium edetate, dipotassium edetate, edetate calcium disodium, sodium edetate, and trisodium edetate may be excluded from some embodiments of this invention. In one embodiment, EDTA concentration is at least 0.01 mg/ml, at least 0.05 mg/ml, at least 0.1 mg/ml, between 0.01 and 0.5 mg/ml, between 0.05 mg/ml and 0.3 mg/ml, between 0.05 mg/ml and 0.2 mg/ml or about 0.1 mg/ml. In one embodiment, the metal chelator is a salt.

In a further embodiment, compositions of this invention contain low levels of metal, no detectable metal, low levels of free metal ions, or no detectable free metal ions. In one embodiment, low levels of metal are less than 10 ppm of metal ion, 8 ppm of metal ion, 5 ppm of metal ion, 3 ppm of metal ion, 2 ppm of metal ion, 1 ppm of metal ion, less than 0.9 ppm of metal ion, less than 0.8 ppm of metal ion, less than 0.7 ppm of metal ion, less than 0.6 ppm of metal ion, less than 0.5 ppm of metal ion, less than 0.4 ppm of metal ion, less than 0.3 ppm of metal ion, less than 0.2 ppm of metal ion, less than 0.1 ppm of metal ion, less than 0.08 ppm of metal ion, less than 0.05 ppm of metal ion, less than 0.02 ppm of metal ion, less than 0.01 ppm of metal ion, less than 8 ppb of metal ion, less than 5 ppb of metal ion, less than 3 ppb of metal ion or less than 1 ppb of metal ion. In another embodiment, low levels of free metal are less than 10 ppm of free metal ion, 8 ppm of free metal ion, 5 ppm of free metal ion, 3 ppm of free metal ion, 2 ppm of free metal ion, 1 ppm of free metal ion, less than 0.9 ppm of free metal ion, less than 0.8 ppm of free metal ion, less than 0.7 ppm of free metal ion, less than 0.6 ppm of free metal ion, less than 0.5 ppm of free metal ion, less than 0.4

ppm of free metal ion, less than 0.3 ppm of free metal ion, less than 0.2 ppm of free metal ion, less than 0.1 ppm of free metal ion, less than 0.08 ppm of free metal ion, less than 0.05 ppm of free metal ion, less than 0.02 ppm of free metal ion, less than 0.01 ppm of free metal ion, less than 8 ppb of free metal ion, less than 5 ppb of free metal ion, less than 3 ppb of free metal ion or less than 1 ppb of free metal ion. In a further embodiment, compositions with low levels of metal ions contain from 1ppm of metal ions to 1ppb metal ions, from 1ppm of metal ions to 10ppb metal ions, from 1ppm of metal ions to 0.01ppm metal ions, from 0.5ppm of metal ions to 1ppb metal ions, from 0.5ppm of metal ions to 0.01ppm metal ions, from 0.5ppm of metal ions to 10ppb metal ions, from 2ppm of metal ions to 1ppb metal ions, or from 0.8ppm of metal ions to 1ppb metal ions. In a still further embodiment, compositions with low levels of free metal ions contain from 1ppm of free metal ions to 1ppb free metal ions, from 1ppm of free metal ions to 10ppb free metal ions, from 1ppm of free metal ions to 0.01ppm free metal ions, from 0.5ppm of free metal ions to 1ppb free metal ions, from 0.5ppm of free metal ions to 0.01ppm free metal ions, from 0.5ppm of free metal ions to 10ppb free metal ions, from 2ppm of free metal ions to 1ppb free metal ions, or from 0.8ppm of free metal ions to 1ppb free metal ions. Different embodiments of this invention can function to limit free metal ions in both solid and liquid compositions. In other embodiments, compositions may have low levels of specific metal ions. The ranges listed for metal ions are intended to be applicable to specific metal ions also. For example, a composition may have less than 1ppm of iron. As another example, a composition of this invention may have between 1ppm and 1ppb of iron. Examples of metal ions include, but are not limited to, iron, calcium, magnesium, cobalt, copper, iron, manganese, molybdenum, selenium, zinc, aluminum, arsenic, barium, cadmium, chromium, lead, mercury, selenium and silver. In one specific embodiment, a composition of levodopa and carbidopa contains less than 1 ppm of a metal ion. In a further embodiment, a composition of levodopa, carbidopa and acid contains less than 1 ppm of a metal ion. In a still further embodiment, a composition of levodopa and carbidopa contains less than 0.1 ppm of a metal ion. In another embodiment, a composition of levodopa, carbidopa and acid contains less than 0.1 ppm of a metal ion. In some embodiments, the total metal concentration is below a specific level and in other embodiments the total free metal ion concentration is below a specific level. Free metal ions are metal ions which are not bound chemically to other molecules, excluding water.

Metal ions occur in trace amounts in many pharmaceutical preparations including in commercially available preparations of levodopa and carbidopa. In addition, metal ions are present in liquids which could be used in making liquid formulations of levodopa and carbidopa. Methods of this invention remove metal ions from active ingredients, excipients, such as binders, acids, flavors, and from diluents such as water. In one embodiment, compositions of this invention are made by removing metal ions by chromatography. In an additional embodiment, compositions of this invention are made by subjecting all or some excipients and active agents to chromatography. In a further embodiment, compositions of this invention are made by subjecting all or some excipients and active agents to chromatography such that the total metal ion concentration of the resulting composition is less than 1 ppm, less than 0.5 ppm, less than 0.1 ppm, less than 0.01 ppm, or less than 1 ppb. In another embodiment, a composition of levodopa and carbidopa is subjected to chromatography to remove metal ions. Metal ions can be removed from a final composition or from each individual excipient or active from a composition. For example, metal ions could be removed from a formulation of levodopa, caribidopa, and hydrochloric acid or metal ions could be removed from levodopa, carbidopa, and hydrochloric acid individually. In another embodiment, levodopa and carbidopa are mixed with deionized water.

In addition, thioether compounds have been found to stabilize the carbidopa molecule thereby decreasing the degradant formation. Examples of thioethers include, but are not limited to, methionine, cysteine, glutathione, thioglycerol, sodium thiosulfate, and n-acetylmethionine.

Additional embodiments of this invention contain both a thioether and a chelator. The combination of a thioether and a chelator functions to significantly lower the level of carbidopa degradation in compositions of carbidopa and levedopa. Thus, in one embodiment, this invention includes carbidopa, levodopa and one or more agents selected from a metal chelator or a thioether. A further aspect of this invention is a formulation of carbidopa, levodopa and one or more agents selected from a chelator or a thioether wherein less than 10% of carbidopa degrades after 7 days at 25°C.

In one embodiment, compositions of this invention are stable. Stable compositions have less than 10% carbidopa degradation at 25°C after 7 days, less than 5% carbidopa degradation at 25°C after 7 days, less than 10% carbidopa degradation at 25°C after 30 days, less than 5% carbidopa degradation at 25°C after 4 days, less than 5% carbidopa degradation at 4°C after 30 days, less than 5% carbidopa degradation at

25°C after 250 days, less than 5% carbidopa degradation at 4°C after 360 days, or less than 10% carbidopa degradation at 25°C after 9 days. Embodiments of this invention enable formulations with degradant levels below 1 part per million (ppm), below 0.5 ppm, below 0.2 ppm, below 0.1 ppm, below 0.05 ppm, or below 0.01 ppm after storage for 24 hours at room temperature. Embodiments of this invention enable formulations with one specific degradant such as hydrazine with levels below 1 part per million (ppm), below 0.5 ppm, below 0.2 ppm, below 0.1 ppm, below 0.05 ppm, or below 0.01 ppm after storage for 48 hours at room temperature. Embodiments of this invention enable formulations with hydrazine levels below 1 part per million (ppm), below 0.5 ppm, below 0.2 ppm, below 0.1 ppm, below 0.05 ppm, or below 0.01 ppm after storage for one week at 4 degrees Celcius.

In one embodiment, liquid formulations of this invention have less than 15%, 10%, 5%, 3%, 2%, 1%, 0.5%, or 0.25% degradation of carbidopa after one day at 25°C. In another embodiment, liquid formulations of this invention have less than 15%, 10%, 5%, 3%, 2%, 1%, 0.5%, or 0.25% degradation of carbidopa after three days at 25°C. In one embodiment, liquid formulations of this invention have less than 15%, 10%, 5%, 3%, 2%, 1%, 0.5%, or 0.25% degradation of carbidopa after one week at 25°C. In one embodiment, liquid formulations of this invention have less than 15%, 10%, 5%, 3%, 2%, 1%, 0.5%, or 0.25% degradation of carbidopa after one month at 25°C. In a futher embodiment, carbidopa monohydrate is used to aid in carbidopa stability.

In another embodiment, the compositions of the present invention comprising levodopa are suitably stable for pharmaceutical use. In one embodiment, the levodopa, carbidopa or formulations thereof in the form of a liquid of the present invention are stable such that when stored at room temperature for 24 hours, less than 1 % of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. In other embodiments, when stored at 4 degrees C for one week, compositions contain less than 5 % of any one degradant is formed. Alternatively, when stored at room temperature for 24 hours, compositions of this invention contain less than 10 %, less than 5 %, less than 3 %, less than 2 %, less than 1 %, less than 0.5 % of any one degradant. The relative humidity (RH) may be specified as ambient RH, 75 % RH, or as any single integer between 1 to 99 % RH. One specific type of degradant is hydrazine.

In an additional embodidiment, compositions of this invention have improved stability over current practice. In one example, compositions of this invention have 100 times less carbidopa degradation than current practice of mixing ginger ale with Sinemet tablets (at 1mg/ml) after storage at 25°C for 24 hours. In another example, compositions of this invention have 3 times less carbidopa degradation than current practice of mixing orange juice with Sinemet tablets (at 1mg/ml) after storage at 25°C for 24 hours. In another example, compositions of this invention have 15 times less carbidopa degradation than current practice of mixing orange juice with Sinemet tablets (at 1mg/ml) after storage at 25°C for 3 days. In an additional example, compositions of this invention have 60 times less carbidopa degradation than current practice of mixing orange juice with Sinemet tablets (at 1mg/ml) after storage at 25°C for 7 days.

In some embodiments of this invention, the compositions have lower levels of carbidopa degradation compared to current practice. It has been found that the currently used liquid levodopa/carbidopa has carbidopa degradants in the homemade formulation (see Example 3 and 6). For example, patients are often encouraged to mix levodopa/carbidopa tablet with orange juice, which contains ascorbic acid to dissolve the levodopa/carbidopa tablet. The ascorbic acid can cause a reaction which creates a carbidopa degradant. These degradants may cause negative biological affects and decreased drug potency because degraded drug in no longer functional. Experiments with other acids have demonstrated that other carbidopa degradants are possible. Two specific degradents which can form in liquid levodopa/carbidopa formulations are hydrazine and 3,4-dihydroxyphenylacetone (DHPA). Without being bound to any particular theory, it is believed that carbidopa degrades to DHPA and hydrazine in equal proportions. Thus, the presence of DHPA can indicate the presence of hydrazine. Compositions of this invention decrease the levels of these degradents. For example, compositions of this invention may prevent formation of these degradents or keep formation of these degradents below 0.05%, below 0.1%, below 0.2%, below 0.3%, below 0.5%, below 1%, below 2%, below 5%, or below 10% after storage at 25°C for one week.

In another embodiment, the compositions of the present invention comprising levodopa are suitably stable for pharmaceutical use. Preferably, the levodopa, carbidopa or formulations in a solid dosage form thereof of the present invention are stable such that when stored at 30 degrees C for 2 years, less than 0.2 % of any one degradant is formed. The term degradant refers herein to product(s) of a single type of

chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 degrees C for 2 years, less than 0.2 % of any one degradant is formed. Alternatively, when stored at 30 degrees C for 3 months, less than 0.2% or 0.15 %, or 0.1 % of any one degradant is formed, or when stored at 40 degrees C for 3 months, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. Further alternatively, when stored at 60 degrees C for 4 weeks, less than 0.2 % or 0.15 %, or 0.1 % of any one degradant is formed. The relative humidity (RH) may be specified as ambient RH, 75 % RH, or as any single integer between 1 to 99 % RH.

One embodiment of this invention comprises compositions of carbidopa, levodopa and one or more acids. Examples of acids include, but are not limited, to carboxylic acids, mineral acid salts, citric acid, tartaric acid, ascorbic acid, dehydroascorbic acid, acetic acid, formic acid, methanoic acid, butanoic acid, ethanoic acid, benzoic acid, butyric acid, malic acid, propionic, epoxysuccinic acid, muconic acid, furanacrylic acid, citramalic acid, capric acid, stearic acid, caprioc acid, malonic acid, succinic acid, diethylacetic acid, methylbutryic acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, and sulfuric acid. Acid can be added at molar ratios of from about 0.5 moles of levodopa to about 20 moles of acid, from about 0.5 moles of levodopa to about 2 moles of acid, from about 1 mole of levodopa to about 5 moles of acid, from about 1 mole of levodopa to about 7 moles of acid, from about 1 mole of levodopa to about 10 moles of acid, from about 1 mole of levodopa to about 3 moles of acid, or from about 1 mole of levodopa to about 4 moles of acid. One skilled in the art can increase the acid concentration to increase the level of carbidopa or levodopa which can be dissolved in a liquid. Included within this invention is the use of increasing ionic strength to increase the solubility of carbidopa or levodopa. For example, adding HCl into a composition of levodopa, carbidopa and citric acid could further solubilize the levodopa or could allow the solubilization of higher level of levodopa.

In some solid, powder or granule compositions of this invention, water can increase carbidopa degradation. Use of anhydrous acid components can aid in carbidopa stability. In one embodiment, a solid, powder or granule composition comprises levodopa, carbidopa, and an anhydrous acid. In another embodiment, a

solid, powder or granule composition comprises levodopa, carbidopa, and anhydrous citric acid.

In some embodiments, any specific acid can be excluded from compositions of this invention. Examples of acids which can be specifically excluded include, but are not limited to, carboxylic acids, citric acid, tartaric acid, ascorbic acid, dehydroascorbic acid, acetic acid, formic acid, methanoic acid, butanoic acid, ethanoic acid, benzoic acid, butyric acid, malic acid, propionic, epoxysuccinic acid, muconic acid, furanacrylic acid, citramalic acid, capric acid, stearic acid, caprioc acid, diethylacetic acid, methylbutryic acid, hydrochloric acid, malonic acid, succinic acid, phosphoric acid, and sulfuric acid.

Adjustments of ionic strength can be done to affect stability. Example 7 ilustrates that salt can have a slightly negative effect on carbidopa stability. Thus, in some embodiments, ionic strength is adjusted to maintiain optimal stability. For example, in some compositions salt concentration is less than 1 Molar, less than 0.75 Molar, less than 0.5 Molar, less than 0.3 Molar, less than 0.2 Molar, or less than 0.1 Molar.

The pH of a liquid levodopa/carbidopa formulation can affect the stability of the formulation. As demonstrated in Example 8, lowering pH can increase stability of the formulation. Compositions of this invention can have a pH between 1 and 10, between 1 and 8, between 2 and 8, between 2 and 6, between 2 and 4, between 2.5 and 4.5, between 2.5 and 4, between 2.5 and 3.5, between 3 and 8, between 3 and 6, between 3 and 5,

between 3 and 4, between 1 and 4, between 1 .5 and 3.5, between 2 and 3 or less than 5, less than 4, less than 3, less than 2.9, less than 2.8, less than 2.7, less than 2.6, less than 2.5, less than 2.4, less than 2.3, less than 2.2, less than 2.1, or less than 2.

In one embodiment, a composition of this invention comprises levodopa, carbidopa, and acid wherein the pH of said composition is between 1 and 3. In another embodiment, a composition of this invention comprises levodopa, carbidopa, and acid wherein the pH of said composition is between 1 and 2.8. In another embodiment, a composition of this invention comprises levodopa, carbidopa, and acid wherein the pH of said composition is between 1.8 and 2.8.

Pharmaceutical compositions of this invention may comprise levodopa, carbidopa, and one, two, three, four or more additional excipients or additives. Excipients or additives may be inert or may be active and may affect other composition

components. Excipients or additives can include, but are not limited to, acids, bases, salts, surfactants, emulsifiers, detergents, binders, wetting agents, salts, polymers, solvents, antimicrobials, preservatives, fillers, sugars, alcohols, colorants, flavors, and buffers. Excipients can act to stabilize a formulation or to decrease or eliminate degradation of the active agents. Included as embodiments in this invention are compositions which contain any known excipients including those disclosed in the *Handbook of Pharmaceutical Additives* compiled by Michael and Irene Ash, Gower Publishing, 1995.

In some embodiments, any one or more specific agents can be excluded. Examples of agents which can be excluded include, but are not limited to, acids, bases, salts, surfactants, emulsifiers, detergents, binders, wetting agents, salts, polymers, solvents, antimicrobials, preservatives, fillers, sugars, alcohols, or additives disclosed in the *Handbook of Pharmaceutical Additives.*

Additional excipients may include a granulation binder. Specific granulation binders include, but are not limited to hydroxypropylcellulose and hydroxypropylmethylcellulose, and polyvinlypyrolidone. In one embodiment, a water soluble granulation binder is used in formulations of this invention. In another embodiment, between 3 and 10 % by weight, 4 and 6 % by weight, or 4 and 5 % by weight binder is used.

In some embodiments, additional agents are added to the composition to prevent the formation of degradants. Any agent that suffices to limit, reduce, or inhibit the formation of degradants in compositions of this invention is envisioned. Specific examples include, but are not limited to, ammonium bisulfite, ammonium sulfite, ammonium thiosulfate, arsenic sulfide, arsenic trisulfide, calcium dithionite, chromous chloride, ferrous chloride, ferrous oxalate, ß-mercaptoethanol, Dithiothreitol, Vitamin E, Vitamin C, beta-carotene, lycopene, and flavonoids.

One aspect of this invention provides for compositions of carbidopa and levodopa which can be used to treat a Parkinson's patient. In some Parkinson's disease patients, a liquid version of carbidopa and levodopa is more beneficial than other dosing forms. As Parkinson's disease progresses, patients often require continually higher doses of levodopa to maintain movement capabilities. These high level dosing requirements often leave patients more susceptible to freezing episodes. Thus, late stage Parkinson's patients often require high levels of levodopa to avoid freezing episodes. Some embodiments of this invention will be particularly useful to late stage

Parkinson's patients to avoid freezing episodes or to quickly emerge from a freezing episode by providing high concentrations of levodopa to the patient quickly.

The present invention relates to formulations of levodopa and carbidopa can be produced as powders, tablets or granules and mixed with liquid to create a stable liquid formulation. These formulations can be used, for example, for administration to Parkinson's disease patients. The pharmaceutical compositions of this invention may take the form of several different embodiments. In one embodiment, levodopa and carbidopa are formulated as a dry packet which can be mixed with a liquid. In another embodiment, the levodopa and carbidopa are formulated as a pill or tablet which can be mixed with a liquid. In another embodiment, the levodopa and carbidopa can be formulated as any dosage form which can be mixed into a liquid. Examples of applicable dosage forms include, but are not limited to, powders, granules, tablets, capsules, dispersions, solutions, and gels.

Currently marketed levodopa and carbidopa drug products are in solid forms. Often Parkinson's patients may enter freezing episodes and have to wait extended periods for the pharmaceutical product to take its effect. This waiting and freezing period significantly inhibits the freedom and the safety of Parkinson's disease patients. Compositions of this invention may provide a faster onset of action thereby decreasing freezing time. In some embodiments, 80% or more of a composition of this invention may pass through the stomach and begin intestinal absorption within 1, 2, 3, 4, 5, 10, 15, 20, 25 or 30 minutes, or within 1 to 30, 1 to 20, 3 to 20, 3 to 15, 5 to 10, 10 to 30, 10 to 20, or 20 to 30 minutes, thereby speeding absorption into the body. In another embodiment, 90% or more of a composition of this invention may pass through the stomach and begin intestinal absorption within 1, 2, 3, 4, 5, 10, 15, 20, 25 or 30 minutes, or within 1 to 30, 1 to 20, 3 to 20, 3 to 15, 5 to 10, 10 to 30, 10 to 20, or 20 to 30 minutes, thereby speeding absorption into the body.

In addition, compositions of this invention may also include agents which increase stomach motility. One side effect of Parkinson's disease or Parkinson's disease drug therapy is decreased stomach motility. A formulation of levodopa, carbidopa, and a stomach motility modulator could provide Parkinson's disease patients with a fast acting drug. Examples of applicable drugs include, but are not limited to, dopamine antagonists such as cisapride and domperidone. One type of stomach modulator can function to relax the pyloric sphincter and to allow the stomach contents to enter the intestine. Drug formulations which increase stomach motility could allow

dosage of levodopa and carbidopa with food. Many Parkinson's disease patients avoid eating food at a time close to their levodopa dosing schedule. Food is known to decrease levodopa absorption. A formulation of levodopa and carbidopa with a stomach motility agent could allow a patient to eat food while taking their necessary drug dose. Thus, one embodiment entails dosing a formulation of this inventions comprising levodopa, carbidopa and a stomach motility agent 1, 2, 3, 4, 5, 10, 20, 25, or 30 minutes before eating to decrease the effect food can have on levodopa bioavailability.

Embodiments of this invention with and without stomach motility agents may provide faster and more predictable levodopa absorption in the digestive system. Thus one aspect of this invention entails administering an embodiment of this invention with food or in close time proximity to a feeding period. Thus, levodopa absorption may not be affected by food in some embodiments of this invention. A further embodiment includes compositions which are administered with food or within on hour of eating.

In some embodiments, the bioavailability of the compositions of this invention may be higher than currently available marketed products. Higher bioavailability can result in a faster onset of action. For example, the compositions of this invention may increase the concentration of levodopa in the plasma to above 1 nMoles/ml, to above 2 nMoles/ml, to above 3nMoles/ml, to above 4nMoles/ml, to above 5nMoles/ml to above 6 nMoles/ml, or to above 10 nMoles/ml. Compositions above 1 nMoles/ml, above 2 nMoles/ml, above 3nMoles/ml, above 4nMoles/ml, above 5nMoles/ml, above 6 nMoles/ml, or above 10 nMoles/ml of levodopa may prevent, decrease or stop a freezing episode. Thus, in some embodiments of this invention, compositions can decrease or stop a freezing episode. In another embodiment, a composition of this invention can reach a level of 3 nMoles/ml of levodopa in plasma within 10 minutes of ingesting the composition, can reach a level of of 3 nMoles/ml of levodopa in plasma within 15 minutes of ingesting the composition, can reach a level of of 3 nMoles/ml of levodopa in plasma within 20 minutes of ingesting the composition, can reach a level of of 4 nMoles/ml of levodopa in plasma within 10 minutes of ingesting the composition, can reach a level of of 4 nMoles/ml of levodopa in plasma within 15 minutes of ingesting the composition, or can reach a level of 4 nMoles/ml of levodopa in plasma within 20 minutes of ingesting the composition. Patient reliance on levodopa varies. Thus, compositions of this invention can decrease, prevent, or stop a freezing episode by dosing to create an adequate levodopa plasma concentration. A doctor, pharmacist,

or patient can adjust a dose of a formulation of this invention depending upon the particular circumstances of the Parkinson's disease patient.

Parkinson's patients often have difficulty swallowing a pill. Liquid formulations of levodopa and carbidopa can function to decrease or eliminate the difficulty of administering the medication. The current liquid levodopa/carbidopa homemade doses do not dissolve well in the liquid as described in the art. Thus, patients do not know if the carbidopa and levodopa are fully dissolved. In addition, currently described liquid levodopa/carbidopa formulations are typically administered at 1mg/ml of levodopa and can require a Parkinson's patient to drink a liter or more of levodopa/carbidopa liquid per day. Large volumes of liquid can be difficult for a Parkinson's patient to swallow. The compositions of this invention can address these needs. Compositions of this invention can contain higher levels of levodopa or carbidopa than homemade liquid levodopa/carbidopa doses described in the art.

In some embodiments, the liquid formulation may contain a concentration of levodopa up to about 0.5 mg/ml, of up to about 1 mg/ml, of up to about 2 mg/ml, of up to about 3 mg/ml, of up to about 4 mg/ml, of up to about 5 mg/ml, of up to about 10 mg/ml, of up to about 20 mg/ml, of up to about 30 mg/ml or from about 0.5 mg/ml to 30 mg/ml, from about 0.5 mg/ml to 1 mg/ml, from about 1 mg/ml to 5 mg/ml, from about 1 mg/ml to 4 mg/ml, from about 1.5 mg/ml to 2 mg/ml, from about 1.5 mg/ml to 4 mg/ml, from about 2 mg/ml to 5 mg/m, from about 2 mg/ml to 7 mg/m, from about 3 mg/ml to 8 mg/ml, from about 5 mg/ml to 10 mg/ml, from about 4 mg/ml to 10 mg/ml, from about 4.5 mg/ml to 10 mg/ml, from about 4 mg/ml to 8 mg/ml, from about 4 mg/ml to 7 mg/ml, from about 4.5 mg/ml to 6 mg/ml, from about 4.5 mg/ml to 7 mg/ml, from about 4.5 mg/ml to 8 mg/ml, from about 7 mg/ml to 20 mg/ml, from about 10 mg/ml to 30 mg/m, from about 15 mg/ml to 20 mg/m, or from about 20 mg/ml to 30 mg/ml. In some embodiments, the liquid formulations of this invention may contain a concentration of carbidopa of up to 0.5 mg/ml, of up to about 1mg/ml, of up to about 2mg/ml, of up to about 3 mg/ml, of up to about 4g/ml, of up to about 5 mg/ml, of up to about 10 mg/ml, of up to about 20, mg/ml, of up to about 30 mg/ml or from about 0.5 mg/ml to 30 mg/ml, from about 0.5 mg/ml to 1 mg/ml, from about 1 mg/ml to 5 mg/ml, from about 1 mg/ml to 4 mg/ml, from about 1.5 mg/ml to 2 mg/ml, from about 1.5 mg/ml to 4 mg/ml, from about 2 mg/ml to 5 mg/m, from about 2 mg/ml to 7 mg/m, from about 3 mg/ml to 8 mg/ml, from about 5 mg/ml to 10 mg/m, from about 7 mg/ml

to 20 mg/ml, from about 10 mg/ml to 30 mg/m, from about 15 mg/ml to 20 mg/m, or from about 20 mg/ml to 30 mg/ml.

The amount of levodopa or carbidopa to be dissolved can vary depending upon the needs of a patient. A skilled practitioner can determine the necessary dose. In addition, the ratio of carbidopa to levodopa can affect stability. Compositions of this invention can change the ratio of carbidopa to levodopa to decrease or eliminate degradents in the formulation and increase stability (see Example 5). The ratio of carbidopa to levodopa can function to stabilize carbidopa. Prior products contain ratios of 1:4 and 1:10 carbidopa:levodopa. Compositions of this invention can use other ratios which function to provide greater stability to the formulation. In some embodiments, the ratio of carbidopa to levodopa will be from one mole equivalent of carbidopa to three mole equivalents of levodopa, from one mole equivalent of carbidopa to four mole equivalents of levodopa, from one mole equivalent of carbidopa to five mole equivalents of levodopa, from one mole equivalent of carbidopa to six mole equivalents of levodopa, from one mole equivalent of carbidopa to seven mole equivalents of levodopa, from one mole equivalent of carbidopa to eight mole equivalents of levodopa, from one mole equivalent of carbidopa to nine mole equivalents of levodopa, from one mole equivalent of carbidopa to 10 mole equivalents of levodopa, from two mole equivalents of carbidopa to five mole equivalents of levodopa, from one mole equivalent of carbidopa to 15 mole equivalents of levodopa, from one mole equivalent of carbidopa to 20 mole equivalents of levodopa, , from one mole equivalent of carbidopa to 25 mole equivalents of levodopa, or from two mole equivalents of carbidopa to nine mole equivalents of levodopa.

In one embodiment, compositions of this invention also comprise a thickening or gelling agent. Thickening or gelling agents can function to ease swallowing for Parkinson's disease patient. Examples of thickening or gelling agents include, but are not limited to, dextrin, ethyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, hypromellose, methylcellulose, polyethylene glycol, pectin, xantham gum, or zinc stearate.

The compositions of this invention allow easy swallowing of the formulation. Compositions may be mixed with aqueous or water based liquids. Examples of liquids include, but are not limited to, water, juice, tea, milk, carbonated beverages, saline, and dextrose solutions. Liquids which are commonly available in a home provide easy mixing and use. In addition, compositions of this invention may require minimal

dosing volume. In one embodiment, liquids do not contain sugar or contain less than 1% sugar. Examples of sugar include fructose and sucrose. In some embodiments, patients can drink 100 mg of levodopa in a volume from about 5ml to 500 ml, from about 5 ml to 100ml, from about 10 ml to 75 ml, from about 15 ml to 50 ml, from about 20 ml to 30 ml, from about 10 ml to 25 ml, from about 25 to 50 ml, from about 50 ml to 250ml, from about 25 ml to 100 ml, from about 50 ml to 100ml, from about 75 ml to 200 ml, or from about 100 ml to 400 ml. In one embodiment, compositions are mixed with a liquid or water which has had its oxygen content depleted or reduced.

Compositions of this invention provide added stability beyond the stability of liquid levodopa/carbidopa. Examples 3 and 6 illustrate the stability problems associated with prior liquid levodopa/carbidopa formulations. Stable liquid formulations contain no phase separation, drug or excipient separation, and have minimal drug degradation. Compositions of the present invention can remain stable at 4 degrees Celsius for at least 2 hours, at least 4 hours, at least 6 hours, at least 12 hours, at least 24 hours, at least 36 hours, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least one week or at least one month. In addition, some compositions of this invention can be stable at room temperature (22 degrees Celsius) for at least 2 hours, at least 4 hours, at least 6 hours, at least 12 hours, at least 24 hours, at least 36 hours, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least one week, or at least one month.

One embodiment of the invention comprises a composition additionally containing a preservative, antibacterial, antimicrobial or bacteriostatic agent. Preservative, antibacterial, antimicrobial, and bacteriostatic agents can function to preserve the compositions both before mixing in liquid and after mixing in liquid. Examples of preservative, antibacterial, antimicrobial, or bacteriostatic agents include, but are not limited to, benzyl alcohol, metabisulfite, benzoic acid, butylparaben, chlorocresol, dimethylsulfoxide, ethylparaben, glacial acetic acid, imidurea, methylparaben, and propylparaben. One embodiment of this invention contains the preservative sodium benzoate. In one embodiment, compositions of this invention do not have any antibacterial or antimicrobial agent.

In some embodiments, additional agents can be added to improve the taste of the composition. Artificial sweeteners can be used to improve the taste of a composition. As shown in Example 9, sugars can decrease the stability of a liquid formulation of carbidopa and levodopa. Thus, in one embodiment compositions of this

invention use less than 1% sugar. Some artificial sweeteners can be used to improve the taste of a formulation of this invention without causing the stability problems of sugars. Examples of artificial sweeteners includes aspartame, saccharin, sucralose, neotame and acesulfame potassium. One embodiment contains compositions with aspartame.

Included within this invention are compositions of levodopa and carbidopa in different physical forms. Examples of different physical forms of carbidopa and levodopa include, but are not limited to, pharmaceutically acceptable salts, solvates, co-crystals, polymorphs, hydrates, solvates of a salt, co-crystals of a salt, amorphous, and the free form of the drug. Depending upon the physical form of the carbidopa or levodopa, different sets of excipients may be needed in the formulation. Compositions of this invention may include a salt of levodopa or carbdopa to increase stability of the formulation. A salt such as HCl could function to lower the pH of the formulation and thereby increase stability of the formulation as shown in Example 11. Examples of inorganic acid addition salts for levodopa or carbidopa include hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids. Examples of organic acid addition salts for levodopa or carbidopa include maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, and benzenesulfonic acids. In one embodiment, a composition comprises levodopa HCl, carbidopa and an acid. In another embodiment, a composition comprises levodopa, carbidopa HCl, and an acid.

Compositions of this invention may also contain a third, fourth, fifth active ingredient, or more. An additional active ingredient can function to augument or improve the treatment or conditions associated with Parkinson's disease. Examples of additional active ingredients include selegiline, COMT inhibitors such as entacapone or tolcapone, and dopamine agonists such as bromocriptine, ropinirole, pergolide, rotigotine, or pramipexole, dopamine decarboxylase inhibitors such as benserazide, and stomach motility modulators such as cisapride or domperidone.

Carbidopa functions as a peripheral dopamine decarboxylase inhibitor. Thus, carbidopa prevents or limits decarboxylation of levodopa in the peripheral system of the body, thereby allowing most levodopa to cross the blood brain barrier. Included

within this invention are formulations substituting carbidopa with benserazide (another dopamine decarboxylase inhibitor).

In another embodiment of this invention, compositions can contain levodopa and/or carbidopa derivatives. Compositions can contain prodrugs such as levodopa and/or carbidopa ester derivatives. Examples of levodopa derivatives include, but are not limited to, levodopa esters including levodopa methyl ester, levodopa ethyl ester, and the like. Examples of carbidopa derivatives include, but are not limited to, esters including carbidopa methyl ester and carbidopa ethyl ester.

Another aspect of this invention provides for a composition of levodopa without any carbidopa. For some Parkinson's patients, plasma levels of carbidopa may be sufficient or patients may be taking other medications which contain carbidopa. Thus, carbidopa can be removed from any of the compositions of this invention. Patients can take a pill of carbidopa or benserazide and use a liquid formulation of levodopa. An additional embodiment comprises compositions of carbidopa without levodopa.

One embodiment of this invention comprises levodopa, carbidopa and a thioether. Specific examples of this thioether could include, but are not limited to, methionine or cysteine.

Another embodiment comprises levodopa, carbidopa and a metal chelator. Specific examples of metal chelators could include, but are not limited to, EDTA and deferoxamine mesylate.

A further embodiment comprises levodopa, carbidopa, a thioether and a chelator.

In one embodiment, compositions of the invention comprise levodopa, carbidopa and acid. In a further embodiment, the composition comprises levodopa, carbidopa, and an acid wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid. In another aspect of this invention, said acids are anhydrous acids.

Another embodiment comprises compositions of levodopa, carbidopa, acid and a thioether. An additional embodiment comprises compositions of levodopa, carbidopa, acid and a chelator. A further embodiment comprises levodopa, carbidopa, acid, a thioether and a chelator.

In another embodiment, compositions of the invention comprise levodopa, carbidopa and an acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid; and

b. the level of degraded carbidopa is below 0.05%, below 0.1%, below 0.2%, below 0.3%, below 0.5%, below 1%, below 2%, below 5%, or below 10% after 7 days at 25°C.

In another embodiment, compositions of the invention comprise levodopa, carbidopa and an acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid;

b. the level of degraded carbidopa is below 0.05%, below 0.1%, below 0.2%, below 0.3%, below 0.5%, below 1%, below 2%, below 5%, or below 10% after 7 days at 25°C; and

c. the formulation further comprises a preservative such as sodium benzoate

In another embodiment, compositions of the invention comprise levodopa, carbidopa and acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid;

b. . the level of degraded carbidopa is below 0.05%, below 0.1%, below 0.2%, below 0.3%, below 0.5%, below 1%, below 2%, below 5%, or below 10% after 7 days at 25°C; and

c. said carbidopa or levodopa is in the form of a salt.

In another embodiment, compositions of the invention comprise levodopa, carbidopa and acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid; and

b. wherein the pH between 1 and 10, between 1 and 8, between 2 and 8, between 2 and 6, between 2 and 4, between 2.5 and 4.5, between 2.5 and 4, between 2.5 and 3.5, between 3 and 8, between 3 and 6, between 3 and 5,between 3 and 4, between 1 and 4, between 1.5 and 3.5, between 2 and 3 or less than 5, less than 4, less than 3, less than 2.9, less than 2.8, less than 2.7, less than 2.6, less than 2.5, less than 2.4, less than 2.3, less than 2.2, less than 2.1, or less than 2.

In another embodiment, compositions of the invention comprise levodopa, carbidopa and an acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid; and

b. wherein the concentration of levodopa is greater than 2.5 mg/ml, greater than 3 mg/ml, greater than 4 mg/ml, greater than 5 mg/ml, greater than 6 mg/ml, greater than 7 mg/ml, greater than 8 mg/ml or greater than 10g/ml.

In another embodiment, compositions of the invention comprise levodopa, carbidopa and an acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid; and

b. wherein the composition has less than 10% degradation of any active ingredients at room temperature (25 degrees C) for 12 hours, 24 hours, 36 hours, 48 hours, one week, or one month.

In another embodiment, compositions of the invention comprise levodopa, carbidopa and an acid:

a. wherein said acid is hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric acid, maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, or benzenesulfonic acid; and

b. wherein the composition has less than 10% degradation of any active ingredients at 4 degrees C for 1 2 hours, 24 hours, 36 hours, 48 hours, one week, or one month.

In one embodiment, the formulation comprises levodopa at between 1 and 5 mg/ml, carbidopa at between 0.25 and 1.25 mg/ml, an acid, and a metal chelator. In another embodiment, the formulation comprises levodopa at between 1 and 5 mg/ml, carbidopa at between 0.25 and 1.25 mg/ml, an acid, and EDTA. In another embodiment, the formulation comprises levodopa at between 1 and 5 mg/ml, carbidopa at between 0.25 and 1.25 mg/ml, citric acid, and EDTA. In a further embodiment, the formulation comprises levodopa at between 1 and 5 mg/ml, carbidopa at between 0.25 and 1.25 mg/ml, citric acid at between 3 and 10 mg/ml, and EDTA. In a still further embodiment, the formulation comprises levodopa at between 1 and 5 mg/ml, carbidopa at between 0.25 and 1.25 mg/ml, citric acid at between 3 and 10 mg/ml, and EDTA of at least 0.025ug/ml. In one aspect of this invention, the metal chelator is a salt.

In one embodiment, the formulation comprises levodopa at between 2.5 and 5 mg/ml, carbidopa at between 0.625 and 1.25 mg/ml, an acid, and a metal chelator. In one embodiment, the formulation comprises levodopa at between 2.5 and 5 mg/ml, carbidopa at between 0.625 and 1.25 mg/ml, an acid, and EDTA. In another embodiment, the formulation comprises levodopa at between 2.5 and 5 mg/ml, carbidopa at between 0.625 and 1.25 mg/ml, citric acid, and EDTA. In a further embodiment, the formulation comprises levodopa at between 2.5 and 5 mg/ml, carbidopa at between 0.625 and 1.25 mg/ml, citric acid at between 3 and 10 mg/ml, and EDTA. In a still further embodiment, the formulation comprises levodopa at between 2.5 and 5 mg/ml, carbidopa at between 0.625 and 1.25 mg/ml, citric acid at between 3 and 10 mg/ml, and EDTA of at least 0.025ug/ml.

In one embodiment, the formulation comprises levodopa at about 4 mg/ml, carbidopa at between about 1 mg/ml, an acid, and a metal chelator. In one embodiment, the formulation comprises levodopa at about 4 mg/ml, carbidopa at between about 1 mg/ml, an acid, and EDTA. In another embodiment, the formulation comprises

levodopa at about 4 mg/ml mg/ml, carbidopa at about 1 mg/ml mg/ml, citric acid, and EDTA. In a further embodiment, the formulation comprises levodopa at about 4 mg/ml mg/ml, carbidopa at about 1 mg/ml mg/ml, citric acid at between 3 and 10 mg/ml, and EDTA. In a still further embodiment, the formulation comprises levodopa at about 4 mg/ml mg/ml, carbidopa at about 1 mg/ml mg/ml, citric acid at between 3 and 10 mg/ml, and EDTA of at least 0.025ug/ml.

In a still further embodiment, the formulation comprises levodopa at about 4 mg/ml mg/ml, carbidopa at about 1 mg/ml mg/ml, citric acid at between 3 and 10 mg/ml, EDTA of at least 0.025ug/ml and between 0.5 and 7% of a binder. In another embodiment, the formulation comprises levodopa at about 4 mg/ml mg/ml, carbidopa at about 1 mg/ml mg/ml, citric acid at between 3 and 10 mg/ml, EDTA of at least 0.025ug/ml, between 0.5 and 7% of a binder, and a flavor enhancer.

Compositions of this invention can be produced by combining the different agents together and mixing. Agents of this invention are available from commercial sources. Carbidopa can be purchased from Sigma-Aldrich (2002-2003 Biochemicals and Reagents Catalog, page 368). Levodopa can be purchased from Sigma-Aldrich (2002-2003 Biochemicals and Reagents Catalog, page 693). Combinations of levodopa and carbidopa can be found in currently marketed pharmaceuticals. Methods of making levodopa and carbidopa are known in the art. Other stated agents (active and inactive) are available from commercial sources.

Dissolution of a composition of this invention in liquid can occur by any methods known in the art. In some instances, dissolution can occur by mixing, stirring, blending, or homogenizing.

Dissolution of compositions of this invention can provide significant advantages to Parkinson's disease patients. Fast dissolution of components of a composition could aid a patient who suffers from rigidity, tremors and frozen episodes. Faster dissolution can occur by altering particle size of the composition and by granulating the certain compositions. In one embodiment, a composition of levdopa, carbidopa, and a binder has a particle size diameter of between about 5 and 20 um. Examples of applicable binders include polyvinylpyrollidone and hydroxypropylcellulose. Compositions also obtain faster dissolution by granulation in the presence of a binder and in some embodiments an liquid. Wet granulation, as opposed to dry granulation, results in a composition with improved dissolution speed.

In one embodiment, compositions of this invention dissolve at least 3 mg/ml of levodopa in a liquid within 5 minutes. On another embodiment, compositions of this invention dissolve at least 4 mg/ml of levodopa in a liquid within 5 minutes. One suitable liquid is water.

The compositions of this invention can be packaged in a variety of ways. Compositions of this invention can be packaged in individual packets, multiuse vials, multiuse contains or containers of various sizes, configurations or materials. In one embodiment, compositions of this invention are packaged such that exposure to light is minimized.

In some embodiments, compositions of this invention specifically exclude detergents. In other embodiments, compositions of this invention can form stable formulations with only levodopa and not with a derivative of levodopa. In further embodiments, compositions of this invention can form stable formulations with only a derivatative of levodopa and not with levodopa. In some embodiments, compositions of this invention comprise simple formulations of two, three or four different agents without requiring combinations of five or more agents. In other embodiments, compositions of this invention do not require any type of gelling component. Examples of gelling components are, but are not limited to, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol or gelatin.

It should be understood to those skilled in the art that various changes in the form and details described in this application may be made without departing form the scope of the invention. This invention will now be described in further detail, by way of example only, with reference to the accompanying examples.

EXAMPLES

EXAMPLE 1: Solubility of Levodopa in citrate buffer at varying pH and buffer strength

Sample preparation

Solutions were made using Citric acid and tribasic Sodium Citrate dihydrate Initially a 1.0 M citric acid solution was made by weighing out 19.2 g Citric acid (FW 192.1) into a 100 mL volumetric flask and diluting with HPLC grade water. This was repeated with the Sodium Citrate (FW 294.1), by weighting out 29.4 g of sodium citrate

in into a 100 mL volumetric flask and diluting to 1 00 mL with water. A series of 8 of 20 mL scintillation vials were then labeled and prepared as follows:

For 1.0 molar samples of pH 1.5 (pure citric + HCl), 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0 were made. These pH adjustments were made with the sodium citrate (also 1.0 M) to keep a consistent molarity with the citrate. From these mother vials, 2 subsequent sets of solution were made for the molar concentrations 0.45 and 0.15 M. 0.45 M is for a 3:1 buffer and 0.15 M is for a 1:1 buffer. These solutions were also pH adjusted with molar equivalent solution to keep the pH value consistent throughout each dilution and after adding the levodopa. The pH was adjusted with 1N HCl or 1N NaOH as needed.

Results

Sample name	Compound	HPLC conc	Dilution	Conc
Citrate buffer	Levodopa	mg/mL	Factor	mg/mL
1.0M pH 1.5	Levodopa	0.239	75	17.93
1.0M pH 2.5	Levodopa	0.619	12	7.43
1.0M pH 3.0	Levodopa	0.741	8	5.93
1.0M pH 3.5	Levodopa	0.654	8	5.23
1.0M pH 4.0	Levodopa	0.93	5	4.65
1.0M pH 4.5	Levodopa	0.887	5	4.44
1.0M pH 5.0	Levodopa	0.833	5	4.17
1.0M pH 6.0	Levodopa	0.773	5	3.87
0.45M pH 1.5	Levodopa	0.152	75	11.40
0.45M pH 2.5	Levodopa	0.485	12	5.82
0.45M pH 3.0	Levodopa	0.606	8	4.85
0.45M pH 3.5	Levodopa	0.564	8	4.51
0.45M pH 4.0	Levodopa	0.849	5	4.25
0.45M pH 4.5	Levodopa	0.85	5	4.25
0.45M pH 5.0	Levodopa	0.829	5	4.15
0.45M pH 6.0	Levodopa	0.832	5	4.16
0.15M pH 1.5	Levodopa	0.096	75	7.20
0.15M pH 2.5	Levodopa	0.406	12	4.87
0.15M pH 3.0	Levodopa	0.526	8	4.21
0.15M pH 3.5	Levodopa	0.488	8	3.90

0.15M pH 4.0	Levodopa	0.758	5	3.79
0.15M pH 4.5	Levodopa	0.776	5	3.88
0.15M pH 5.0	Levodopa	0.776	5	3.88
0.15M pH 6.0	Levodopa	0.789	5	3.95

EXAMPLE 2: STABILITY OF LEVODOPA AND CARBIDOPA

Sample preparation:

A formulation of: Levodopa / Citric acid / Carbidopa / Sucrose mix at molar ratio of 1:3:0.2:1. This powder mixture was dissolved in water at a concentration of 5.5 mg/ml of levodopa. This solution was filter through a 0.22 micrometer filter (with PVDF membrane) and then stored at temperatures of 4 degrees C, 25 degrees C and 40 degrees C.

A formulation of Levodopa / Ascorbic acid / Carbidopa mix at molar ratio of 1:3:0.25. This powder mixture was dissolved in water at concentration of 1.0 mg/ml of levodopa. This solution was filtered through a 0.22 micrometer filter (with PVDF membrane) and then stored at temperatures of 4 degrees C, 25 degrees C and 40 degrees C.

The sample solutions were submitted for HPLC potency test at each time point. The stability was monitored in percentage change compared to the initial potency.

Sample name	Compound	Initial	1 Day	2 Day	3 Day	7Day
Levodopa/ Citric/ Carbidopa/ Sucrose at 1/3/0.2/1 at 4C	Levodopa	100%	100%	100%	100%	100%
	Carbidopa	100%	100%	100%	101%	100%
Levodopa/ Citric/ Carbidopa/ Sucrose at 1/3/0.2/1 at 25C	Levodopa	100%	100%	100%	100%	100%
	Carbidopa	100%	98%	96%	96%	91%
Levodopa/ Citric/ Carbidopa/ Sucrose at 1/3/0.2/1 at 40C	Levodopa	100%	100%	100%	100%	100%
	Carbidopa	100%	91%	84%	81%	75%
Levodopa/ Ascorbic/ Carbidopa/ at 1/3/0.2 at 4C	Levodopa	100%	100%	100%	N/A	102%
	Carbidopa	100%	101%	101%	N/A	101%
Levodopa/ Ascorbic/ Carbidopa/ at 1/3/0.2 at 25C	Levodopa	100%	100%	100%	N/A	102%
	Carbidopa	100%	99%	97%	N/A	87%
Levodopa/ Ascorbic/ Carbidopa/ at 1/3/0.2 at 40C	Levodopa	100%	100%	101%	N/A	104%
	Carbidopa	100%	94%	88%	N/A	88%

EXAMPLE 3: CARBIDOPA DEGRADENT

Samples of levodopa/carbidopa/citric acid and levodopa/carbidopa/ascorbic acid at a molar ratio of 4:1:1 were made. Samples were kept at 25 degrees Celsius for 24 hours. After 24 hours, samples were assayed on an HPLC. Analysis was carried out on Waters Alliance HPLC system equipped with 2695 separation module and 2996 PDA detector. Reversed phase HPLC method was utilizing Waters Atlantis dC18 column (4.6 x 150 mm, 5um) operated at 30 C and a two component gradient mobile phase. Run time was 30 min at flow rate 1.0 mL/min. Levodopa and carbidopa impurities and degradation products were detected by absorbance at 280 nm and reported as their percent area relative to the parent peak. A new peak was determined to be 3,4-dihydroxyphenylacetone by HPLC/MS. 3,4-dihydroxyphenylacetone (DHPA) is a carbidopa degradent. This degradent is also present in formulations of levodopa/carbidopa/orange juice and in formulations of levodopa/carbidopa/ginger ale.

EXAMPLE 4: STABILITY OF LEVODOPA AND CARBIDOPA FORMULATIONS

Formulations of levodopa, carbidopa and an acid at various pHs were tested for carbidopa stability. Four grams of levodopa and one gram of carbidopa were dissolved with 3 Molar equilavents of various acids relative to levodopa and water as shown in the table below. The pH of each solution was adjusted 1 N HCl or 1 N NaOH. Area levodopa, area carbidopa, % carbdopa remaining and area % of DHPA were calculated.

The "%carbidopa remaining was calculated according to the following equations:

$Carb_{4C}$ theoretical = $carb_{4C}$ * lev_T/lev_{4C}

"% carb remaining" = $carb_T$/ $carb_{4C}$ theoretical * 100

where carbT and LevT refer to carbidopa and levodopa area values for the acid, temperature, and pH being studied, and lev4C and carb4C are the area values of the levodopa and carbidopa samples at 4°C for the pH and acid being studied.

Acid	pH	°C	area levodopa	area carbidopa	% carb remaining	area % DHPA
Acetic acid	2	4	2864780	556275	100.0	0

		25	2920134	562629	99.2	1.14
		40	2927442	555971	97.8	2.29
	2.4	4	1255379	297891	100.0	0
		25	3007344	589068	82.5	0.93
		40	2952343	565106	80.7	3.13
	3	4	2861179	596623	100.0	0
		25	2883225	592870	98.6	1.51
		40	2573780	493081	91.9	3.92
Citric acid	2	4	3142973	603604	100.0	0
		25	3133573	591206	98.2	1.83
		40	2960941	566867	99.7	0.75
	2.4	4	3108393	597902	100.0	0
		25	3122562	599299	99.8	0.71
		40	3181927	600710	98.1	1.73
	3	4	2986595	571393	100.0	0.92
		25	3108402	589580	99.1	1.21
		40	3111696	577629	97.0	2.85
HCl	2	4	2956816	572525	100.0	0
		25	2943735	567786	99.6	0.84
		40	3003245	568938	97.8	2.28
	2.4	4	3014797	581503	100.0	0.80
		25	2837880	545321	99.6	1.15
		40	2947773	549080	96.6	3.30
	3	4	2907279	558606	100.0	0.99
		25	2837293	540713	99.2	1.56
		40	2818351	512352	94.6	4.96
L-(-)-Malic acid	2	4	3139874	604922	100.0	0.62
		25	3091146	592188	99.4	0.90
		40	3121877	587787	97.7	2.22
	2.4	4	3114444	602433	100.0	0.57
		25	3007871	578488	99.4	0.90

		40	3049661	577045	97.8	2.21
	2.6	4	3061962	595963	100.0	0.53
		25	2879955	557074	99.4	0.85
		40	3121864	582676	95.9	2.22
L-(+)-Tartaric acid	2	4	3137768	598319	100.0	0.53
		25	3323491	622853	98.3	1.71
		40	3037389	499461	86.2	10.22
	2.4	4	3164710	598138	100.0	0.64
		25	3191366	589671	97.8	1.94
		40	3165751	512299	85.6	11.36
	3	4	3042627	573035	100.0	0.96
		25	2932384	537924	97.4	2.37
		40	3080403	508334	87.6	9.15
Malonic acid	2	4	3198987	618183	100.0	0.44
		25	2956945	564456	98.8	0.76
		40	3091218	581615	97.4	2.16
	2.4	4	2928983	561988	100.0	0.64
		25	3194883	609472	99.4	1.13
		40	3123140	588045	98.1	2.36
	3	4	3060381	585961	100.0	0.84
		25	3027405	573498	98.9	1.62
		40	3040114	560576	96.3	3.63
H_3PO_4	2	4	3043106	580763	100.0	0.50
		25	3121711	592491	99.5	0.76
		40	2920381	546560	98.1	1.83
	2.4	4	3076836	585580	100.0	0.63
		25	2741837	519759	99.6	0.70
		40	3042791	566757	97.9	2.06
	3	4	3016323	574096	100.0	0.58
		25	2827873	533847	99.2	0.84
		40	2828586	516553	95.9	3.27

Succinic acid	2	4	2967669	586937	100.0	0.77
		25	3062470	602825	99.5	1.20
		40	3107285	594742	96.8	3.19
	2.4	4	2991187	592581	100.0	0.72
		25	2969082	584084	99.3	1.22
		40	2921618	559184	96.6	3.28
	3	4	2905509	621872	100.0	0.91
		25	3003987	603028	93.8	1.54
		40	3059716	579495	88.5	4.10
Sulfuric acid	2	4	2434399	491414	100.0	0.89
		25	2163586	432313	99.0	1.14
		40	2303265	444509	95.6	3.83
	2.4	4	2175680	435950	100.0	1.02
		25	2210814	440745	99.5	1.32
		40	2324408	448587	96.3	4.14
	3	4	2232850	442564	100.0	1.46
		25	2187525	430200	99.2	2.05
		40	2303472	425755	93.3	6.98

This data suggests a selection of a particular acid is important in a liquid formulation of levodopa and carbidopa. It is possible that combinations of these different acids could create a more stable liquid formulation.

EXAMPLE 5: RATIO OF CARBIDOPA TO LEVODOPA

Samples of 1/ 3 /1 Levodopa / citric acid/ sucrose were prepared at 4 mg/ml of levodopa and carbidopa was added at w/w ratios of 0.5, 0.125, and 0.05 relative to levodopa. The samples were diluted for HPLC analysis after 24 hours at 4C, 25C, and 40C.

Area % DHPA relative to carbidopa area as a function of temperature and levodopa/carbidopa ratio.			
	0.50 w/w carb/l-dopa	**0.125 w/w carb/l-dopa**	**0.05 w/w carb/l-dopa**
4 °C	0.60	0.57	0.00
25 °C	0.97	0.73	0.00
40 °C	2.45	1.76	1.51

The data indicates that the ratio of carbidopa to levodopa effects carbidopa stability.

EXAMPLE 6: STABILITY OF LEVODOPA AND CARBIDOPA IN GINGER ALE

The stability of a formulation of levodopa and carbidopa was tested with ginger ale. A formulation of 4 mg/ml of levodopa and 1mg/ml of carbidopa was combined with 100 ml of ginger ale. The formulation was kept at 4 °C, 25 °C and 40 °C for 24 hours. After 24 hours the samples were diluted and assayed by HPLC. The HPLC sample chamber was maintained at 5°C. Analysis was carried out on Waters Alliance HPLC system equipped with 2695 separation module and 2996 PDA detector. Reversed phase HPLC method was utilizing Waters Atlantis dC18 column (4.6 x 150 mm, 5um) operated at 30 C and a two component gradient mobile phase. Run time was 30 min at flow rate 1.0 mL/min. Levodopa and carbidopa impurities and degradation products were detected by absorbance at 280 nm and reported as their percent area relative to the parent peak.

Gingerale has two main peaks at RT = 11.2 min and 19.3 min with lambda max values of 285 and 229.7 nm, respectively. The following table shows the amount of the 3.4-dihydroxyphenylacetone degradate formed after 24 hours. Carbidopa degrades to 3.4-dihydroxyphenylacetone. Thus, measuring this degradate is a measure of carbidopa stability.

Temp	**4 °C**	**25 °C**	**40 °C**
DHPA	6.3	24.4	57.6

A significant level of carbidopa had degraded at 24 hours at 25°C and 40 °C. There are additional smaller degradates at RT 9.77 min (constant amount at 5 °C and 25 °C) and at RT = 14.27 min.

EXAMPLE 7: AFFECT OF IONIC STRENGTH

A formulation of Levodopa / carbidopa / citric acid/ sucrose at a molar ratio of 1/ 0.25/ 3 /1 was prepared at 4 mg/ml of levodopa in NaCl solution with [NaCl] of 0.00, 0.05, 0.125, 0.250, and 0.5 M. After 24 hours the samples were diluted and assayed by HPLC (as described earlier). The HPLC sample chamber was maintained at 5°C. Area % 3, 4-dihydroxyphenylacetone relative to carbidopa area as a function of temperature and ionic strength is shown as a representation of carbidopa stability.

	0 M NaCl	**0.05 M**	**0.125 M**	**0.25 M**	**0.5 M**
4 °C	0.53	0.64	0.54	0.61	0.50
25 °C	0.72	0.81	0.89	0.84	0.88
40 °C	2.08	2.17	2.17	2.44	2.64

Salt appears to have a negative impact on carbidopa stability, which could be due to heavy metal contaminents in the salt.

EXAMPLE 8: AFFECT OF pH ON STABILITY

Samples of carbidopa and citric acid were made. Samples were kept at 4 °C, 25 °C and 40 °C for 24 hours. After 24 hours the samples were diluted and assayed by HPLC. Analysis was carried out on Waters Alliance HPLC system equipped with 2695 separation module and 2996 PDA detector. Reversed phase HPLC method was utilizing Waters Atlantis dC18 column (4.6 x 150 mm, 5um) operated at 30 C and a two component gradient mobile phase. Run time was 30 min at flow rate 1.0 mL/min. Carbidopa impurities and degradation products were detected by absorbance at 280 nm and reported as their percent area relative to the parent peak.

The HPLC sample chamber was maintained at 5°C. Area % 3.4-dihydroxyphenylacetone relative to carbidopa area as a function of temperature and pH is shown as a representation of carbidopa stability.

	4C	25C	40C	
pH 2.0	0.85	2.40	8.78	
pH 2.5	0.99	3.60	11.83	
pH 3.0	1.25	3.92	10.60	
pH 4.0	1.74	22.51	45.33	
pH 5.5	7.92	No data	44.65	

The results indicate that lowering the pH of the formulation increases stability of carbidopa.

Samples of 1/ 0.25/ 3 /1 Levodopa / carbidopa / citric acid/ sucrose were prepared at 4.0 mg/ml of levodopa in water, and the pH of the solution was adjusted to values of 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, and 3.2 with HCl or NaOH as needed. Three aliquots of each solution were transferred into vials, which were stored at 4 °C, 25 °C, and 40°C. After 24 hours the samples were diluted and assayed by HPLC. Area % 3, 4-dihydroxyphenylacetone relative to carbidopa area as a function of temperature and pH is shown as a representation of carbidopa stability.

pH	**4°C**	**25°C**	**40°C**
1.8	---	0.53	1.77
2.0	undetectable	0.53	2.02
2.2	undetectable	0.57	1.99
2.4	undetectable	0.68	2.34
2.6	undetectable	0.82 (0.82)	2.46
2.8	undetectable	--- (1.21)	2.83
3.0	undetectable	--- (2.02)	4.62
3.2	undetectable	--- (2.43)	6.38

EXAMPLE 9: EFFECT OF SUGAR ON STABILITY

Effect of sugars on the formation of DHPA over 24 hours for samples of 4 mg/ml levodopa + 1 mg/ml carbidopa + 3 equiv of citric acid (relative to levodopa) stored at 4, 25, and 40°C. Values reported are "area % DHPA" relative to carbidopa

	4C	25C	40C
no sugar	0	0.39	1.53
0.5 equiv sucrose	0	0.38	1.69
1.0 equiv sucrose	0	0.51	1.94
1.0 equiv fructose	0	0.56	2.27
1.0 equiv glucose	0	0.52	2.39

There is no measurable degradation at 4C. Samples with no sugar are indistinguishable from those with 0.5 % sucrose after 24 hours at RT, but the sugar-free formulation has an advantage at 40C. The amount of degradation increases with increasing sucrose concentration. A corresponding effect could occur with other aldehydes or ketones.

EXAMPLE 10: EFFECT OF PRESERVATIVES ON STABILITY

Samples of 1/ 0.25/ 3 /1 Levodopa / carbidopa / citric acid/ sucrose were prepared at 5.0 mg/ml of levodopa in water and the preservatives sodium benzoate and potassium sorbate were added to the solutions. The preservatives were added at the maximum allowable concentration of 0.1 % each. The solutions were placed on stability for 24 hours and assayed by HPLC. Analysis was carried out on Waters Alliance HPLC system equipped with 2695 separation module and 2996 PDA detector. Reversed phase HPLC method was utilizing Waters Atlantis dC18 column (4.6 x 150 mm, 5um) operated at 30° C and a two component gradient mobile phase. Run time was 30 min at flow rate 1.0 mL/min. Levodopa and carbidopa impurities and degradation products were detected by absorbance at 280 nm and reported as their percent area relative to the parent peak.

In the 25°C potassium sorbate samples, a new peak at RT = 17.54 min was observed. The peak has a λmax value of 321.9. The area % value of the peak is 0.04 %. The peak is also present at the same size when a combination of sodium benzoate and potassium sorbate is used. It is not present in samples that do not contain any potassium sorbate. After 24 hours at 40°C, the peak accounts for 0.19 % of the area.

Placebos were prepared in order to determine whether the new peak is related to the potassium sorbate itself or from an interaction between potassium sorbate and levodopa or carbidopa. The first placebo was potassium sorbate in water stored at 4°C, 25°C, and 40°C for 24 hours. There is a broad hump around RT = 17.5 min in the 4°C

sample, but it almost disappears at 25°C and returns partially at 40°C. The second placebo contains 14.5 mg/ml of citric acid and 1/3 molar equivalents of sucrose (relative to citric acid). The RT = 17.5 min peak is not present in this sample at any of the temperatures studied.

No observable interaction occurs between levodopa or carbidopa and sodium benzoate. At least one new degradent is formed at RT = 17.5 min when potassium sorbate is combined with levodopa and carbidopa.

The impact of each preservative on the area % of the 3,4-dihydroxyphenylacetone degradate was evaluated. No detectable 3,4-dihydroxyphenylacetone was present in the 4°C samples. At 25°C, sodium benzoate had no effect to a slightly negative effect on the area % of 3,4-dihydroxyphenylacetone (0.71 % with vs 0.88 % without), while the size of the degradate doubled in the sample containing potassium sorbate. The trend held at 40°C with no preservative giving 2.69 area%, sodium benzoate giving 2.89 %, and potassium sorbate leading to 10.7 % conversion of carbidopa to 3,4-dihydroxyphenylacetone .

Thus, potassium sorbate increases the rate of 3,4-dihydroxyphenylacetone formation over preservative-free or sodium benzoate-containing solutions.

EXAMPLE 11: EFFECT OF CITRIC ACID CONCENTRATION

The effects of citric acid content and a HCl salt of levodopa on the rate of carbidopa degradation to 3,4-dihydroxyphenylacetone were analyzed. Samples of levodopa HCl salt or free form levodopa at 4 mg/ml, carbidopa at 1mg/ml and sucrose at 4mg/ml were made. As detailed in the chart below, between 0 and 3 equilavents of citric acid (in relation to levodopa) were added. Effects of citric acid concentration on the 24 hour stability of carbidopa were analyzed by looking for formation of 3,4-dihydroxyphenylacetone. The below table list DHPA Area %.

Effect of citric acid concentration with L-dopa HCl			
equiv of citric acid	**4°C**	**25°C**	**40°C**
0	0	1.08	5.95
0.5	0	0.74	3.95
1	0	0.6	3.87
2	0	0.8	3.59

Effect of citric acid concentration with L-dopa			
equiv cit	**4°C**	**25°C**	**40°C**
0	1.32	12.8	24.1
0.5	0.41	1.01	3.89
1	0.24	0.75	2.82
2	0.23	0.84	2.45
3	0.3	0.75	2.26

The procedure was repeated as above with the free form of levodopa with the formulation lacking sucrose.

Effect of citric acid concentration on the 24 hour stability of 1/0.25 weight ratio L-dopa/carbidopa: area % of DHPA formed.			
equiv of citric acid	**4°C**	**25°C**	**40°C**
1	0.32	0.64	2.08
1.3	0.2	0.57	1.9
1.6	0.2	0.53	2.07
2	0.28	0.52	1.79

This data demonstrates that increasing levels of citric acid results in an increased stability of carbidopa. In addition, the HCl salt of levodopa increases stability of the carbidopa.

EXAMPLE 12

An assay was developed to test solutions for hydrazine. A series of solutions with no amount of hydrazine were tested. The following data and plot shows that there is a linear correlation between the UV absorption and the amount of hydrazine in ppm between 0.27ppm and 13.5 ppm

Hydrazine in ppm	UV absorption
13.5	0.32
2.7	0.063
1.35	0.033
0.27	0.007

This hydrazine assay protocol has detection limitation of hydrazine at level of 0.27ppm when 0.10ml of sample was assayed. The sample size was increased to 0.50ml in order to decrease the lower limit of the quantitation to below 0.10ppm. The limit of detection of the larger sample volume is 0.05ppm. The following data indicated a linear correlation between UV absorption and volume of tested sample solution.

Correlation between UV Absorption and Volume of Tested Solution				
Hydrazine standard solution	0.27ppm	0.27ppm	0.05ppm	0.05ppm
Volume of sample solution	0.1ml	0.2ml	0.5ml	1.0ml
UV reading #1	0.006	0.011	0.006	0.011
UV reading #2	0.006	0.011	0.006	0.011
UV reading #3	0.005	0.011	0.006	0.011

It is believed that carbidopa is the source of hydrazine formation in the levedopa/carbidopa formulation solutions. It is believed that DHPA is the main degradant of cabidopa in acidic solution, and a co-product of hydrazine formation. DHPA can be detected by HPLC assay. The following data indicated that there is a good correlation between the % of DHPA and the amount of hydrazine in ppm.

TPI-leading formulation		**Correlation ratio**
% DHPA	Hydrazine (ppm)	%DHPA / ppm of Hydrazine
0.5	0.433	1.154
0.8	0.788	1.016
0.95	0.906	1.049
1.7	1.457	1.167

Several levedopa/carbidopa formulation solutions have been tested with both HPLC assay and hydrazine assay.

Levedopa/Carbidopa Formulation Solutions 2-4 Hours at 25°C	% DHPA	Hydrazine in ppm
Sinemet/Ascorbic solution	0.40	0.33
Levedopa/Carbidopa solution at 4:1 ratio	0.51	0.41
Levedopa/Carbidopa solution at 4:1 ratio + Cystine	0.28	
Levedopa/Carbidopa solution at 4:1 ratio + Methionine	0.31	
Levedopa/Carbidopa solution at 4:1 ratio + Methionine + deferoxamine	0.15	
Levedopa/Carbidopa solution at 4:1 ratio + Cystine + EDTA	0.00	0.00
Levedopa/Carbidopa solution at 4:1 ratio + Cystine + deferoxamine	0.00	0.00
Levedopa/Carbidopa solution at 4:1 ratio + Methionine + EDTA	0.00	0.00

This data demonstrates that thioethers and chelators can be used to decrease hydrazine presence in formulations of levodopa and carbidopa.

EXAMPLE 13

Formulations of TPI-926 were compared to Parkinson's disease patient's current off-label practice of making liquid levodopa and carbidopa drinks. TPI-926 contains:

4 mg/ml of levodopa

1 mg/ml of carbidopa

7.8 mg/ml Citric acid

0.1 mg/ml Na EDTA

0.5 mg/ml of aspartame

The total volume of TPI-926 was 100ml of water. Liquid formulations of levodopa at 1mg/ml and carbidopa at 0.25 mg/ml were made in orange juice and ginger ale by grinding 1 levodopa/carbidopa tablet (100:25) and combining with 100ml of orange juice or ginger ale. A formulation of levodopa, carbidopa and ascorbic acid was made by grinding 1 levodopa/carbidopa tablet (100:25) and combining with 100ml of water and 2 mg/ml of ascorbic acid.

Samples were kept at 4 and 25 degrees C for 24 hours, 3 days, and 7 days. Samples were analyzed for hydrazine and DHPA content by HPLC.

DHPA is a degradent of carbidopa. Thus, DHPA is at a 1:1 ratio compared to degraded carbidopa. A 1% level of DHPA in a sample is expected to correlate with a 1% level of carbidopa degradation.

The concentration per day was calculated by dividing the amount of hydrazine or DHPA of the longest duration sample divided by the number of days.

Hydrazine (mcg/sample) at 4 degrees C

	1 day	3 days	7 days	Per Day
'926	<1.5	<1.5	1.5	0.2
ascorbic in H2O	< 6.0	<6.0	6.2	0.9
OJ	7.3	10.1	n.m.	
Ginger ale	21.2	121.5	n.m.	40.5

Hydrazine (mcg/sample) at 25 degrees C

	1 day	3 days	7 days	Per Day
'926	<1.5	2.6	5.6	0.8
ascorbic in H2O	7.3	32.5	160.3	23
OJ	24.1	37.1	n.m.	
Ginger ale	253	765	n.m.	255

DHPA (mcg/sample) at 25 degrees C

	1 day	3 days	7 days	Per Day
'926	<25.0	<25.0	25.6	3.7
ascorbic in H2O	81	346	1704	238
OJ				
Ginger ale	3210	9038		3013

This data demonstrates that TPI-926 prevents or decreases formation of hydrazine at both 4 and 25 degrees C.

Percent Carbidopa loss was calculated. By converting the total mcg of DHPA to mcg of carbidopa.

TPI-926

100 ml of TPI-926 created 3.7 mcg of DHPA per day. Since DHPA and carbidopa are in molar equilavents, this correspond with 5mcg of carbidopa degradation per day. One tablet of Sinemet contains 25,000mcg of carbidopa. Thus, TPI-926 has a 0.02% degradation rate of carbidopa per day for every 250mg.

Levodopa/carbidopa and Ascorbic Acid in Water

100 ml of the ascorbic acid sample created 238 mcg of DHPA per day. Since DHPA and carbidopa are in molar equilavents, this correspond with 323 mcg of carbidopa degradation per day. One tablet of Sinemet contains 25,000mcg of carbidopa. Thus, ascorbic acid sample has a 1.2% degradation rate of carbidopa per day for every 250mg dose.

Levodopa/Carbidopa in Orange Juice

100 ml of the orange juice sample created 3013 mcg of DHPA per day. Since DHPA and carbidopa are in molar equilavents, this correspond with 4083 mcg of carbidopa degradation per day. One tablet of Sinemet contains 25,000mcg of carbidopa. Thus, this orange juice sample has a 16.3% degradation rate of carbidopa per day for every 250mg.

EXAMPLE 14

Levedopa solubility in ascorbic acid solution an ascorbic acid concentration of 3.5 mg/ml was tested. A sample of 3.5 mg/ml ascorbic acid was made by adding 70.0mg of ascorbic acid into 20ml of water. Then, 80.0mg of levodopa powder was dissolved into the 3.5 mg/ml ascorbic sample by stirring for 24 hour at RT. The projected levodopa concentration was 4 mg/ml. The sample was filtered through a 0.22μ PVDF filter to remove the insoluble levodopa. The filtration was assayed by by HPLC at 10X dilution with water. The HPLC data indicated the concentration of levodopa in the filtration was 2.0mg/ml. Thus, maximum solubility of levodopa in 3.5 mg/ml ascorbic acid solution was 2mg/ml.

EXAMPLE 15

A formulation of levodopa and carbidopa with low levels of metal ions was made. A formulation of:

Levodopa 4mg/ml
Carbidopa 1 mg/ml
Hydrogen chloride 0.02 Normal
EDTA –Na dehydrate 0.11 mg/ml
Saccharin 0.5 mg/ml
Sodium Benzoate 0.10 mg/ml
Deionized water to 1 ml

A deionization procedure with a cation removal cartridge (Hose Nipple Cartridge D8905 from Barnstead International) was utilized for water purification. After all components were dissolved in the purified water, a dialysis step with Chelex-100® was conducted. The pH of the solution was adjusted to within 2.0 ~ 2.3. The level of carbidopa degradation was measured for this formulation. At time 0, 0.125 % of carbidopa had degraded. After two weeks at room temperature (25°C) 0.196% carbidopa had degraded. After one month at room temperature, 0.233 % carbidopa had degraded. After two weeks at 40°C, 0.618% carbidopa had degraded. After one month at 40°C, 1.276 % carbidopa had degraded.

EXAMPLE 16

Rate of formulation dissolution was tested. Levodopa as purchased has a mean particle size of 76 um, where 50% of the particles are less than 67um, 90% of the particles are less than 146 um, and 100% of the particles are less than 364 um. Using the a solid formulation of:
Levodopa 100mg
Carbidopa 27 mg
Citric acid monohydrate 213 mg
EDTA-NA dehydrate 2.75 mg
Aspartame 12.5 mg
Sodium Benzoate 2.5 mg
And levodopa with the above particle ranges, complete levodopa dissolution did not occur within 24 hours in deionized water. Method of mixing the formulation components was shaking.

The same formulation was used except the levodopa was replaced with levodopa with a mean particle size of 5.5um, where 50% of the particles are less than 5.11um,

90% of the particles are less than 10.4 um, and 100% of the particles are less than 19.4 um (the I1 particle size batch). Another formulation was tested with a mean particle size of 17.3 um, where 50% of the particles are less than 13.95 um, 90% of the particles are less than 37 um, and 100% of the particles are less than 78 um (the I6 particle size batch). The I9 batch was granulated by manual grinding with water. This formulation had complete dissolution within 1 hour. Addition of polyvinylpyroliddone and ethanol also improved dissolution as shown below.

Expt. ID	TPI-926 mill cut	Binder	Method of Addition	Liquid	Citric Acid Addition	90% TPI-926 disso*	Complete disso
1	I1	-	-	Water	In granules	<1min	>1 hr* (*significant t <1hr)
4	I1	PVP	5% solid	EtOH	In granules	<1min	~10min
3	I1	PVP	5% solid	EtOH	Blended w/granules	<1min	~5min
A	I1	PVP	5% solid	EtOH	Blended w/granules	<1min	~5min
B	I6	PVP	5% solid	EtOH	Blended w/granules	<4min	>1hr* (*significant t ~ 10min)
C	I1	PVP	10% soln	EtOH	Blended w/granules	<1min	~5min

A particle size of between 7 and 13 um showed fast dissolution. The addition of a binder such aspolyvinlypyrollidone or hydroxypropylcellulose increase dissolution speed.

EXAMPLE 17: CHELATION OF HEAVY METAL IONS BY ADDITION OF EDTA

EDTA (at 0.9mg/ml as the sodium salt) was added to a formulation (levodopa at 4 mg/ml, carbidopa at 1mg/ml, citric acid at 7.79 mg/ml, aspartame at 0.5 mg/ml, sodium benzoate at 0.25 mg/ml) with and without the addition of iron (Fe(III) citrate at 0.3ppm) and copper ($CuSO_4$ at 1ppm). The metal concentrations were chosen to match those of the EPA secondary guideline for drinking water. The measured pH of all

solutions at the initial time was 2.67 ± 0.05. Area % DHPA values are reported relative to carbidopa area. As described earlier, %DHPA correlates with carbidopa degradation and hydrazine formation. The samples were stored at 25°C for 20 hours and assayed using HPLC

Metal	% DHPA with no EDTA	% DHPA with EDTA
Fe	0.893	0.202
Cu	0.640	0.181
No Metal	0.474	0.189

These results demonstrate that metal ions function to accelerate carbidopa degradation and that metal chelators can slow or inhibit this action.

Claims

1. A pharmaceutical composition comprising levodopa, carbidopa, and acid wherein the metal concentration of said composition is less than 1 ppm.

2. A pharmaceutical composition comprising levodopa, carbidopa, acid, and a metal chelator.

3. The composition of claim 2, wherein said metal chelator is selected from the group consisting of:

EDTA.; and

deferoxamine mesylate.

4. The composition of claim 3, wherein said EDTA is in the form of a salt of a free base.

5. The composition of claim 3, wherein said EDTA is at a concentration of at least 0.01 mg/ml.

6. The composition of claim 1, wherein said acid is selected from the group consisting of;

a carboxylic acid, a mineral acid, citric acid, tartaric acid, ascorbic acid, dehydroascorbic acid, acetic acid, formic acid, methanoic acid, butanoic acid, ethanoic acid, benzoic acid, butyric acid, malic acid, propionic, epoxysuccinic acid, muconic acid, furanacrylic acid, citramalic acid, capric acid, stearic acid, caprioc acid, malonic acid, succinic acid, diethylacetic acid, methylbutryic acid, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, and sulfuric acid

7. The composition of claim 1, wherein said acid is not ascorbic acid.

8. The composition of claim 1, wherein said composition does not contain sugar.

9. The composition of claim 1, wherein said composition is a liquid.

10. The composition of claim 9, wherein less than 10% of said carbidopa has degraded at 25°C after 7 days.

11. The composition of claim 9, wherein wherein less than 5% of said carbidopa has degraded at 25°C after 7 days.

12. The composition of claim 9, wherein wherein less than 10% of said carbidopa has degraded at 25°C after 30 days.

13. The composition of claim 9, wherein less than 5% of said carbidopa has degraded at 25°C after 4 days.

14. The composition of claim 9, wherein less than 5% of said carbidopa has degraded at 4°C after 30 days.

15. The composition of claim 9, wherein less than 5% of said carbidopa has degraded at 25°C after 250 days.

16. The composition of claim 9, wherein less than 5% of said carbidopa has degraded at 4°C after 360 days.

17. The composition of claim 9, wherein less than 10% of said carbidopa has degraded at 25°C after 9 days.

18. The composition of claim 1, further comprising an artificial sweetener.

19. The composition of claim 1, wherein said artificial sweetener is aspartame.

20. The composition of claim 1, further comprising a preservative

21. The composition of claim 1, wherein said preservative is sodium benzoate.

22. A pharmaceutical composition comprising levodopa, carbidopa and acid wherein the pH of said composition is less than or about 3.0.

23. The composition of claim 22, wherein less than 10% of said carbidopa has degraded at 25°C after 7 days.

24. The composition of claim 22, wherein wherein less than 5% of said carbidopa has degraded at 25°C after 7 days.

25. The composition of claim 22, wherein wherein less than 10% of said carbidopa has degraded at 25°C after 30 days.

26. The composition of claim 22, wherein less than 5% of said carbidopa has degraded at 25°C after 4 days.

27. The composition of claim 22, wherein less than 5% of said carbidopa has degraded at 4°C after 30 days.

28. The composition of claim 22, wherein less than 5% of said carbidopa has degraded at 25°C after 250 days.

29. The composition of claim 22, wherein less than 5% of said carbidopa has degraded at 4°C after 360 days.

30. The composition of claim 22, wherein less than 10% of said carbidopa has degraded at 25°C after 9 days.

31. The composition of claim 22, further comprising an artificial sweetener.

32. The composition of claim 22, wherein said artificial sweetener is aspartame.

33. The composition of claim 22, further comprising a preservative

34. The composition of claim 22, wherein said preservative is sodium benzoate.

35. An aqueous composition of levodopa and carbidopa wherein said levodopa is at a concentration of between 2.5 mg/ml and 5mg/ml.

36. The composition of claim 35, wherein said levodopa is at a concentration of about 4 mg/ml.

37. The composition of claim 35, wherein less than 10% of said carbidopa has degraded at 25°C after 7 days.

38. The composition of claim 35, wherein wherein less than 5% of said carbidopa has degraded at 25°C after 7 days.

39. The composition of claim 35, wherein wherein less than 10% of said carbidopa has degraded at 25°C after 30 days.

40. The composition of claim 35, wherein less than 5% of said carbidopa has degraded at 25°C after 4 days.

41. The composition of claim 35, wherein less than 5% of said carbidopa has degraded at 4°C after 30 days.

42. The composition of claim 35, wherein less than 5% of said carbidopa has degraded at 25°C after 250 days.

43. The composition of claim 35, wherein less than 5% of said carbidopa has degraded at 4°C after 360 days.

44. The composition of claim 35, wherein less than 10% of said carbidopa has degraded at 25°C after 9 days.

45. The composition of claim 35, further comprising an artificial sweetener.

46. The composition of claim 35, wherein said artificial sweetener is aspartame.

47. The composition of claim 35, further comprising a preservative

48. The composition of claim 35, wherein said preservative is sodium benzoate.

49. A composition of levodopa, carbidopa, acid, and a metal chelator wherein less than 1.2% of said carbidopa has degraded after 24 hours at 25°C.

50. The composition of claim 49, wherein said metal chelator is selected from the group consisting of:

EDTA.; and

deferoxamine mesylate.

51. The composition of claim 50, wherein said metal chelator is EDTA.

52. A composition of levodopa, carbidopa, acid, and a metal chelator wherein less than 2.4% of said carbidopa has degraded after 48 hours at 25°C.

53. The composition of claim 52, wherein said metal chelator is selected from the group consistin of:

EDTA.; and

deferoxamine mesylate.

54. The composition of claim 53, wherein said metal chelator is EDTA.

55. A liquid pharmaceutical composition comprising levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 0.07ug/ml after 24 hours at 25°C.

56. A liquid pharmaceutical composition comprising levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 0.32ug/ml after 3 days at 25°C.

57. A liquid pharmaceutical composition comprising levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 1.6ug/ml after 7 days at 25°C.

58. A liquid pharmaceutical composition comprising levodopa and carbidopa at about 0.4 to 1.5 mg/ml, wherein hydrazine levels are below 0.06ug/ml after 7 days at 4°C.

59. A liquid formulation of levodopa, carbidopa, acid and a metal chelator wherein said solution is clear or translucent.

60. A pharmaceutical composition comprising levodopa, carbidopa, acid and a thioether compound.

61. The composition of claim 60, wherein said thioether functions to stabilize carbidopa.

62. The composition of claim 60, wherein said thioether is selected from the list consisting of:

methionine;
cysteine;
glutathione;
thiogylcerol;
sodium thiosulfate; and
n-acetylmethionine.

63. The composition of claim 60, further comprising a metal chelator.

64. The composition of claim 63, wherein said metal chelator is EDTA.

65. A pharmaceutical composition comprising:

levodopa at about 2.5 to 6 mg/ml;
carbidopa at about 0.625 to 1.5 mg/ml;
citric acid at about 5mg/ml to 10 mg/ml; and
EDTA at greater than about 0.25 mg/ml.

66. The composition of claim 65, further comprising aspartame at about 0.1 mg/ml to about 1 mg/ml.

67. The composition of claim 65, further comprising sodium benzoate at about 0.01 mg/ml to about 1 mg/ml.

68. A pharmaceutical composition comprising:
levodopa at about 2.5 to 6 mg/ml;
carbidopa at about 0.25 to 0.6 mg/ml;
citric acid at about 5mg/ml to 10 mg/ml; and
EDTA at greater than about 0.25 mg/ml.

69. The composition of claim 68, further comprising water.

70. The composition of claim 68, further comprising aspartame at about 0.1 mg/ml to about 1 mg/ml.

71. The composition of claim 68, further comprising sodium benzoate at about 0.01 mg/ml to about 1 mg/ml.

72. A pharmaceutical composition comprising:
levodopa of about 500 mg to about 1500 mg;
carbidopa of about 125 mg to about 375 mg;
citric acid of about 1065 mg to about 3195 mg; and
EDTA of about 13 mg to about 41 mg.

73. The composition of claim 72, wherein said composition is in the form of a dispersible tablet.

74. The composition of claim 72, wherein said composition is in the form of a powder or granules for mixing with a liquid.

75. A pharmaceutical composition comprising:
levodopa of about 1000 mg;
carbidopa of about 250 mg;
citric acid of about 2130mg; and

EDTA of about 27 mg.

76. The composition of claim 75, further comprising water.

77. The composition of claim 75, wherein said composition is in the form of a dispersible tablet.

78. The composition of claim 75, wherein said composition is in the form of a powder or granules for mixing with a liquid.

79. The composition of claim 75, further comprising aspartame of about 125 mg.

80. The composition of claim 75, further comprising sodium benzoate of about 25 mg.

81. A pharmaceutical composition of levodopa, carbidopa, acid, a metal chelator, and sugar wherein said sugar comprises less than 1% of the composition.

82. A method of dosing levodopa and carbidopa comprising the steps of;

a. adding a dry or solid formulation of levodopa and carbidopa to liquid;
b. mixing the formulation for under 10 minutes; and
c. administering about 100mg of levodopa to a patient.

83. The method of claim 82, wherein said administration of levodopa is the first morning dose.

84. A liquid formulation capable of dissolving levodopa at about 2.5 to 6 mg/ml and carbidopa at about 0.25 to 0.6 mg/ml.

85. The composition of claim 84, wherein less than 10% of said carbidopa has degraded at 25°C after 7 days.

86. The composition of claim 84, wherein wherein less than 5% of said carbidopa has degraded at 25°C after 7 days.

87. The composition of claim 84, wherein wherein less than 10% of said carbidopa has degraded at 25°C after 30 days.

88. The composition of claim 84, wherein less than 5% of said carbidopa has degraded at 25°C after 4 days.

89. The composition of claim 84, wherein less than 5% of said carbidopa has degraded at 4°C after 30 days.

90. The composition of claim 84, wherein less than 5% of said carbidopa has degraded at 25°C after 250 days.

91. The composition of claim 84, wherein less than 5% of said carbidopa has degraded at 4°C after 360 days.

92. The composition of claim 84, wherein less than 10% of said carbidopa has degraded at 25°C after 9 days.

93. A method of making a pharmaceutical composition to treat a dopamine disorder comprising the steps of combining levodopa, carbidopa, acid, a metal chelator; and water.

94. The method of claim 93, wherein said levodopa is at a concentration of between 2.5 mg/ml and 6 mg/ml.

95. The method of claim 93, wherein said metal chelator is EDTA.

96. The method of claim 95, wherein said EDTA is at a concentration of greater than 0.25 mg/ml.

97. The method of claim 93, wherein said water is tap water.

98. A method of treating a patient comprising administering a composition of claim 1.

99. A method of treating a patient comprising administering a composition of claim 22.

100. A method of treating a patient comprising administering a composition of claim 35.

101. A method of treating a patient comprising administering a composition of claim 68.

102. Use of a composition of levodopa, carbidopa, acid and a metal chelator for preparing a medicament as a means for treating a dopamine disorder.

103. Use of a composition of levodopa of about 500 mg to about 1500 mg, carbidopa of about 125 mg to about 375 mg, acid and a metal chelator for preparing a medicament as a means for treating a dopamine disorder.

104. Use of a composition of levodopa of about 500 mg to about 1500 mg, carbidopa of about 125 mg to about 375 mg, citric acid and EDTA for preparing a medicament as a means for treating a dopamine disorder.

105. A liquid composition comprising levodopa and carbidopa wherein the metal ion concentration is less than 1 ppm.

106. The composition of claim 105, wherein said composition further comprises an acid.

107. The composition of claim 105, wherein said metal ions are free metal ions.

108. The composition of claim 106, wherein said acid in not citric acid.

109. The composition of claim 105, wherein said metal ion concentration is less than 0.1 ppm.

110. A method of making a formulation of levodopa and carbidopa wherein one or more excipients or active agents of the composition are subjected to chromatography to remove metal ions.

111. The method of claim 109, wherein said metal ion is iron, lead, zinc or aluminum.

112. The method of claim 110, wherein said method further comprises a dialyzing a liquid.

113. A composition of levdopa, carbidopa, and a binder where the particle size of the composition has a diameter of between about 5 and 20 um.

114. The composition of claim 113, wherein said binder is selected from polyvinylpyrollidone and hydroxypropylcellulose.

115. The composition of claim 113, wherein the composition of one or more components of the composition is prepared by granulation.

116. The compositon of claim 115, wherein said granulation is wet granulation.

117. A method of preparing a composition of levodopa, carbidopa, acid and binder comprising the steps of combining the individual components and granulating with an liquid.

118. The method of claim 117, wherein the binder comprises between 3 and 10% by weight of the composition.

119. A composition of levodopa, carbidopa, acid and binder which dissolves at least 3 mg/ml of levodopa within 5 minutes in a liquid.

120. The composition of claim 119, wherein said liquid is water.

121. A composition of levodopa, carbidopa, acid and binder which dissolves at least 4 mg/ml of levodopa within 5 minutes in a liquid.

122. The composition of claim 121, wherein said liquid is water.

123. A composition comprising levodopa, carbidopa monohydrate and acid.

124. A composition comprising levodopa, carbidopa monohydrate, acid and a metal chelator.

125. A composition comprising levodopa, carbidopa, and an anhydrous acid.

126. A composition comprising levodopa, carbidopa, and an anhydrous acid wherein said composition is a solid.

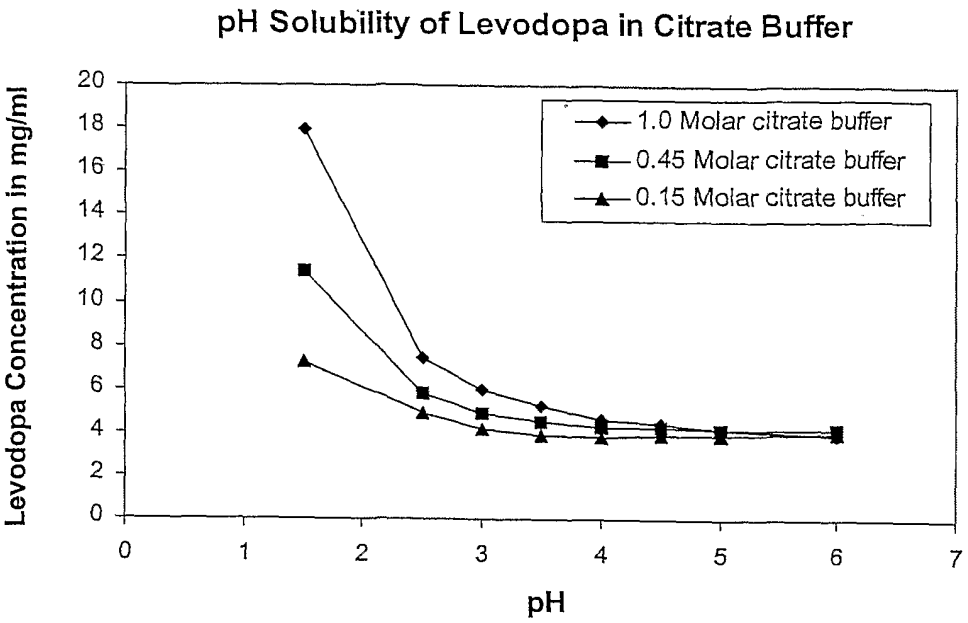
127. A composition comprising levodopa, carbidopa, an anhydrous acid, and a metal chelator;

128. A composition comprising levodopa, carbidopa, and an acid wherein said levodopa is in the form of a salt;

129. A composition comprising levodopa, carbidopa, and an acid wherein said carbidopa is in the form of a salt;

130. A composition comprising levodopa, carbidopa, and a metal chelator wherein said levodopa is in the form of a salt; or

131. A composition comprising levodopa, carbidopa, and a metal chelator wherein said carbidopa is in the form of a salt.


pH Solubility of Levodopa in Citrate Buffer
Levodopa Concentration in mg/ml
20
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
5
6
7
pH
1.0 Molar citrate buffer
0.45 Molar citrate buffer
0.15 Molar citrate buffer

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/09303

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/135, 31/185, 31/13
US CL : 514/649, 673, 185
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)
U.S. : 514/649, 673, 185

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
GOOGLE, WEST search terms include: levodopa, carbidopa, acid, EDTA, (metal near4 chelator), stabl$8

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database PUBMED on Google, Merck Sharp & Dohme Research Laboratories, (West Point, PA), TITUS, DC et al., "Simultaneous high-performance liquid chromatographic analysis of carbidopa, levodopa and 3-O-methyldopa in plasma and carbidopa, levodopa and dopamine in urine using electrochemical detection" ABSTRACT, J Chromatogr. Dec 14, 1990; 534:87-100.	1-81,105-109,113-116,119-131

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"E" earlier application or patent published on or after the international filing date

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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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2005 (23.06.2005)	12 JUL 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Dwayne C. Jones Telephone No. (703) 308-1123

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