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(56) Related Art  
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vs. IR or CR

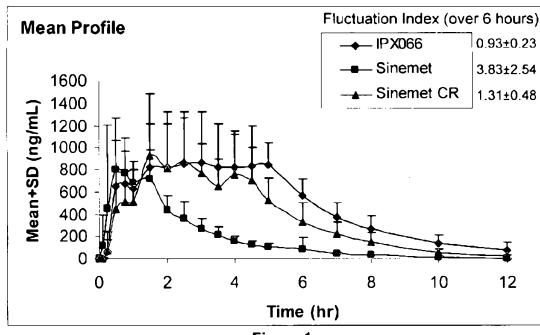


Figure 1

(57) **Abstract:** The current invention provides a controlled release oral solid formulation of levodopa comprising levodopa, a decarboxylase inhibitor, and a carboxylic acid. Also provided by this invention is multiparticulate, controlled release oral solid formulations of levodopa comprising: i) a controlled release component comprising a mixture of levodopa, a decarboxylase inhibitor and a rate controlling excipient; ii) a carboxylic acid component; and iii) an immediate release component comprising a mixture of levodopa and a decarboxylase inhibitor.

**CONTROLLED RELEASE FORMULATIONS OF LEVODOPA AND USES THEREOF**

5

Throughout this application various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

10 **FIELD OF THE INVENTION**

The present invention relates to controlled release pharmaceutical compositions of levodopa (LD), formulated with an acid and a decarboxylase inhibitor, to yield enhanced pharmaceutical pharmacokinetic attributes. These formulations are useful for the 15 treatment of conditions such as neurological diseases associated with reduced or impaired dopamine levels.

**BACKGROUND OF THE INVENTION**

20 Combinations of levodopa (LD) and a decarboxylase inhibitor (typically carbidopa (CD)) to treat Parkinson's disease (PD) are known in the pharmaceutical arts and are considered by many to be the 'gold standard' treatment for symptoms of PD. Currently, several formulations containing a combination of LD and CD are commercially available, e.g., SINEMET®, STALEVO®, PARCOPA®, and ATAMET®. Nonetheless, a need remains 25 for an oral LD formulation that provides steadier plasma concentrations of LD with minimal 'peak-to-trough' fluctuations during daily dosing and that yields a longer duration-of-effect than the currently available oral dosage forms of CD/LD.

30 Patients suffering from PD frequently have periods in which their mobility becomes difficult, often resulting in an inability to move. Abnormally low levels of dopamine, a neurotransmitter that affects mobility and control of the skeletal-muscular system, is commonly believed to be the cause of these motor symptoms in PD patients. However, administration of dopamine is not effective to treat Parkinson's disease because dopamine

does not cross the blood-brain barrier. To resolve this problem, PD patients are administered levodopa, the metabolic precursor of dopamine, but levodopa is not without its issues either.

5 While levodopa crosses the blood-brain barrier and is rapidly converted to dopamine, LD is problematic because of its rapid decarboxylation by tissues other than the brain. Thus, when LD is administered alone, large doses are required because only a small portion is transported to the brain unchanged. Furthermore, when levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion  
10 of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits the decarboxylation of peripheral levodopa and does not cross the blood-brain barrier. Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa has been popular to make levodopa more available for transport to the brain.

15

In addition to these difficulties associated with absorption of LD, over time patients treated with LD also exhibit symptoms of "wearing off". PD patients treated with LD may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations (also commonly  
20 referred to as the 'on-off' phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of these motor fluctuations are not completely understood, some patients may be attenuated by treatment regimens that produce steady plasma levels of LD. Thus, a void remains in the LD treatment of PD patients, as plasma concentration levels remain difficult to control.

25

Currently available controlled release formulations of CD/LD are meant to allow for a continuous release of drug over a prolonged period of time in an attempt to maintain tight LD plasma ranges. However, the use of these controlled release dosage forms are problematic in that many PD patients wake up in the morning having little or no mobility  
30 due to the wearing off of the dose taken the day/evening before. Once the previous dose has worn off, such patients are usually unwilling, or even unable, to wait for the extended

period of time required for a controlled release dosage form to deliver the necessary plasma levels of LD. While the use of an immediate release formulation of LD can reduce this 'wait time', the use of an immediate release formulation of LD require more frequent dosing and are associated with more fluctuating plasma LD concentrations. DUODOPA®, 5 an intraduodenal infusion therapy approved outside of the United States, demonstrates significantly reduced motor complications and reduced 'off' time. The cumulative experiences from DUODOPA® and experimental infusion studies show that the maintenance of stable plasma LD concentrations and the avoidance of low trough levels appear to be effective in reducing 'off' time, increasing 'on' time without disabling 10 dyskinesia, and reduce the severity of dyskinesia in comparison to the standard oral formulations. However, such infusion therapies are extremely inconvenient to the patient.

15 The results of infusion therapies, such as DUODOPA®, strongly suggest a rationale for the development of a LD treatment that provide constant, or relatively steady, LD plasma concentrations to optimize relief of PD symptoms and to minimize 'off' times and dyskinesias. Indeed, a need remains for a more convenient, i.e., oral, dosage form that will improve the administration of LD to PD patients by narrowing blood plasma ranges 20 of LD, which in turn will result in reduced 'off times', prolonged 'on time', and decreased time to 'on'. The present invention fills this void by providing a novel controlled release oral solid dosage form of LD that is formulated with a decarboxylase inhibitor and an acid, to yield the desired pharmacokinetic attributes, i.e., steadier plasma concentrations of LD over a prolonged period of time.

### **Summary of the Invention**

According to a first aspect of the present invention, there is provided a multiparticulate, controlled release oral solid formulation of levodopa comprising:

25 a. a controlled release component comprising a mixture of levodopa, a carbidopa and a rate controlling excipient;

b. a carboxylic acid component; and

c. an immediate release component comprising a mixture of levodopa and a carbidopa,

30 wherein the carboxylic acid component (b) is a distinct component.

According to a second aspect of the present invention, there is provided a controlled release oral solid formulation of levodopa in accordance with the first aspect of the present invention having a levodopa plasma or serum concentration profile comprising:

5        a. a time of administration,  
          b. a first concentration, and  
          c. a second concentration,

wherein, said first concentration is equal to the maximum concentration of said profile; said second concentration is the minimum concentration occurring at a time later  
10        than said first concentration and earlier than or equal to about six hours following said time of administration; and wherein said second concentration is greater than or equal to about fifty percent of said first concentration.

According to a third aspect of the present invention, there is provided a controlled release oral solid formulation of levodopa in accordance with the first aspect of the  
15        present invention having a median levodopa plasma or serum concentration profile comprising:

20        a. a time of administration;  
          b. a first concentration at a first time, that occurs within one hour of said time of administration;  
          c. a second concentration at a second time, that occurs after said first time;  
          d. a third concentration at a third time, that occurs at least four hours after said second time;

25        wherein, said second concentration is equal to the maximum concentration of said profile; said first concentration is equal to about fifty percent of said second concentration; said third concentration is equal to about fifty percent of said second concentration.

The current invention provides a controlled release oral solid formulation of levodopa comprising levodopa, a decarboxylase inhibitor, and a carboxylic acid that is not levodopa nor the decarboxylase inhibitor. Also provided by this invention is  
30        multiparticulate, controlled release oral solid formulations of levodopa comprising:

i) a controlled release component comprising a mixture of levodopa, a decarboxylase

inhibitor and a rate controlling excipient; ii) a carboxylic acid component; and iii) an immediate release component comprising a mixture of levodopa and a decarboxylase inhibitor.

5 The current invention additionally claims a controlled release oral solid formulation of levodopa providing a relative steady levodopa plasma or serum concentration profile over a prolonged period of time; this controlled release oral solid formulation of levodopa having a levodopa plasma or serum concentration profile comprising: a) a time of administration; b) a first concentration; and c) a second concentration, wherein, the first  
10 concentration is equal to the maximum concentration of said profile; the second concentration is the minimum concentration occurring at a time later than said first concentration and earlier than or equal to about six hours following the time of administration; and wherein the second concentration is greater than or equal to about fifty percent of the first concentration.

15 Further, the invention provides methods for making and using the pharmaceutical formulations of the invention. Methods for reducing motor fluctuations in a patient suffering from Parkinson's disease, reducing off time in a patient suffering from Parkinson's disease, increasing on time in a patient suffering from Parkinson's disease,  
20 reducing time to 'on' in a patient suffering from Parkinson's disease and otherwise enhancing dopamine levels in a subject suffering from a disease associated with reduced or impaired dopamine levels are provided by the presently claimed invention.

#### **BRIEF DESCRIPTION OF DRAWINGS**

25 **Figure 1** is a graph showing that IPX066 formulations provide infusion-like plasma profile for longer than about six hours.

30 **Figure 2** shows a graph illustrating the *in vivo* plasma concentration profiles for IPX066-B-05-07 Formulations A, B and C compared to a reference (Sinemet<sup>®</sup>), as described in Example 1, *infra*.

**Figure 3** shows a graph illustrating the *in vivo* plasma concentration profiles for IPX066-B-06-02 Formulations A, B, D and E compared to a reference (Sinemet<sup>®</sup>), as described in Example 2, *infra*.

5

**Figure 4** shows a graph illustrating the *in vivo* plasma concentration profiles for IPX066-B-07-01 Formulations A, B and C compared to a reference (Sinemet<sup>®</sup>), as described in Example 3, *infra*.

10 **Figure 5** shows a graph illustrating the *in vivo* plasma concentration profiles for IPX066 formulations.

**Figure 6** is a table showing the robust lower intrasubject variability of the IPX066 formulations compared to Sinemet<sup>®</sup> CR.

15

### **DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to controlled release pharmaceutical formulations comprising LD, a decarboxylase inhibitor and a carboxylic acid for treating neurological diseases or conditions associated with reduced or impaired dopamine levels. The pharmaceutical formulations of the invention provide steadier, or more constant, LD plasma concentrations in patients, resulting in decreased motor-fluctuations, reduced “off” time and increased “on” time in PD patients.

25

### **DEFINITIONS**

All scientific and technical terms used in this application have meanings commonly used in the art unless otherwise specified. As used in this application, the following words or phrases have the meanings specified.

30

The term "acid" refers to a chemical compound that, when dissolved in water, gives a solution with a pH less than 7. The "acid" can be organic. It can have a pKa in the range of e.g., 2-5. Examples of acids suitable for the invention include, but are not limited to, 5 tartaric acid, adipic acid, succinic acid, citric acid, benzoic acid, acetic acid, ascorbic acid, edetic acid, fumaric acid, lactic acid, malic acid, oleic acid, sorbic acid, stearic acid, palmitic and boric acid or mixtures thereof.

The term "effective amount" means an amount of a compound/composition according to the present invention effective in producing the desired therapeutic effect.

10

A "tablet" or "pill" comprises a pharmaceutical formulation pressed into a form. The form can be in any shape, for example, round, oblong, triangular or other shapes.

15

A "capsule" comprises a pharmaceutical formulation in which the pharmaceutical formulation is encased in a hard or soft soluble container. The container can be in the form of gelatin or other material.

20

The term "modified release" (also known as MR) includes delayed release (also known as DR) and controlled release (also known as CR, sustained release (SR), prolonged release (PR) or extended release (ER)).

The term "delayed release" (also known as DR) relates to a pharmaceutical formulation or component that releases the active ingredients after a period of delay.

25

The term "controlled release" (also known as CR) refers to a pharmaceutical formulation or component thereof that releases, or delivers, one or more pharmaceutical agents over a prolonged period of time, in this case over a period of more than one hour.

30

The term "immediate release" (also known as instant release or IR) refers to a pharmaceutical formulation or component thereof which releases, or delivers, one or

more pharmaceutical agents substantially immediately upon administration and will result in substantially complete dissolution within about one hour (or less).

The terms "release excipient" or "rate controlling excipient" may be used

5 interchangeably. Release excipients or rate controlling excipients include all excipients and/or polymers that control the release of a pharmaceutical agent(s), e.g., LD, CD and in this case acid, after administration in a subject. Examples of release excipients or rate controlling excipients include, but are not limited to, hypromellose, hydroxypropyl cellulose, ethyl cellulose and prop-2-enoic acid. Delay release polymers, as a subset of 10 release excipients or rate controlling excipients, are used to delay the release of a pharmaceutical agent(s) after administration to a subject. Examples of delay release polymers include, but are not limited to, enteric polymers and/or neutral methacrylic polymers such as Eudragit® L100-55, Eudragit® S100 or Eudragit® FS30D (Rohm).

15 The "USP paddle method" refers to the Paddle and Basket Method as described in United States Pharmacopoeia, Edition XXII (1990).

The term "peak-to-trough ratio" refers to a comparison of the values for a peak (e.g., a

high point in a line graph) plasma level of active agent and a trough (e.g., a low point in a

20 line graph) level over a set amount of time. For example, in a line graph with plasma LD values ranging from 400 ng/ml (peak) compared to 200 ng/ml (trough) over a four hour period, gives a peak-to-trough ratio of 2 for that time. More than one peak-to-trough ratio can be illustrated in a graph.

25 The term "about" when used in connection with percentages means +/-1%.

The "Mean Plasma Concentration" of a substance (e.g., LD or CD) as used herein, refers

to the mean concentration of the substance found in multiple plasma samples. The mean

30 plasma concentration is obtained by adding the concentrations of the substance found in

the plasma samples then dividing the sum by the number of plasma samples.

The “upper small intestine” refers to the portion closest to the stomach and includes the duodenum and jejunum.

5 The term “outer coat” refers to a covering or barrier applied to a pharmaceutical formulation or component thereof and may be an enteric coat.

Diseases associated with reduced or impaired dopamine levels includes neurological or movement disorders such as restless leg syndrome, Alzheimer’s disease, dystonia, schizophrenia, Parkinson’s disease and secondary parkinsonism, Huntington’s disease,

10 Attention-Deficit / Hyperactivity Disorder (ADHD), Shy-Drager syndrome and conditions resulting from brain injury, including carbon monoxide or manganese intoxication.

The term “treating” a disease associated with reduced or impaired dopamine levels, means to manage a disease with the pharmaceutical formulation of the invention.

15 Treatment can decrease the symptoms of a disease, reduce the severity of a disease, alter the course of disease progression, ameliorate and/or cure a disease associated with the neurological or movement disorders associated with reduced or impaired dopamine levels.

20 COMPOSITIONS OF THE INVENTION

A significant aspect of the invention relates to the unexpected discovery of the effect of carboxylic acid, in controlling the absorption of LD such that the resulting formulations yield ‘tighter,’ i.e. steadier, LD plasma concentrations.

25 The invention provides controlled release oral solid formulations of levodopa comprising levodopa, a decarboxylase inhibitor, and a carboxylic acid. In one embodiment of the invention, the carboxylic acid is neither levodopa nor a decarboxylase inhibitor. In accordance with the practice of the invention, the carboxylic acid may be physically separated from the levodopa and the decarboxylase inhibitor. The pharmaceutical formulations can include a single acid or a mixture of acids.

In one embodiment, the carboxylic acid may be a polycarboxylic acid. In another embodiment, the carboxylic acid may be a dicarboxylic acid. Suitable examples of carboxylic acids include, but are not limited to, tartaric acid, adipic acid, succinic acid, 5 citric acid, benzoic acid, acetic acid, ascorbic acid, edetic acid, fumaric acid, lactic acid, malic acid, oleic acid, sorbic acid, stearic acid, palmitic acid and boric acid or mixtures thereof. In a particular embodiment, the dicarboxylic acid is a tartaric acid.

A suitable example of a decarboxylase inhibitor includes but is not limited to carbidopa.

10

In accordance with the practice of the invention, the formulation may be a tablet or a caplet. The tablet or caplet may be single-layered or multi-layered. The tablet or caplet may be a matrix tablet or caplet.

15

Also in accordance with the practice of the invention, the formulation may be a multiparticulate formulation. In an embodiment of the invention, the multiparticulates are encapsulated. In another embodiment, the multiparticulates are not encapsulated. The multiparticulates may be pressed into a tablet. Alternatively, the multiparticulates may be in a sprinkle form that can be sprinkled directly onto food or liquids for easy 20 ingestion.

25

In an embodiment of the invention, the formulation reduces intrasubject variability in levodopa absorption. The intrasubject variability may be calculated as the standard deviation of the levodopa concentration divided by the mean levodopa concentration determined over the range of about 0.5 hours after administration to about six hours after administration for a single dose of the formulation to an individual subject which when averaged over at least 12 subjects; is less than or equal to about 0.40.

30

The controlled release oral solid formulation of the invention may comprise carbidopa and levodopa in a ratio of about 1:1 to about 1:10. In one embodiment, the ratio of carbidopa to levodopa is about 1:4.

The controlled release oral solid formulation of the invention may have a ratio of moles of dicarboxylic acid to levodopa of less than 4:1. In one embodiment, the ratio of moles of dicarboxylic acid to levodopa is greater than 1:4 and less than 3:2. In another 5 embodiment, the ratio of moles of dicarboxylic acid to levodopa is greater than 1:2 and less than 4:3. In yet another embodiment, the ratio of moles of dicarboxylic acid to levodopa is greater than 2:3 and less than 5:4. In a further embodiment, the ratio of moles of dicarboxylic acid to levodopa is greater than 1:1 and less than 4:3.

10 The controlled release oral solid formulation of the invention may comprise from about 25 mg to about 2000 mg levodopa. In one embodiment, the formulation comprises about 50 to 600 mg of levodopa.

15 The controlled release oral solid formulation of the invention may comprise from about 10 mg to about 300 mg carbidopa. In an embodiment of the invention, the controlled release oral solid formulation comprises about 10 to 80 mg of carbidopa.

The invention also provides multiparticulate, controlled release oral solid formulations of 20 levodopa. A multiparticulate, controlled release oral solid formulation of the invention comprises 1) a controlled release component comprising a mixture of levodopa, a decarboxylase inhibitor and a rate controlling excipient; 2) a carboxylic acid component; and 3) an immediate release component comprising a mixture of levodopa and a decarboxylase inhibitor. In an embodiment of the invention, the decarboxylase inhibitor is carbidopa. The multiparticulate, controlled release oral solid formulation of the 25 invention may reduce intrasubject variability in levodopa absorption.

In accordance with the practice of the invention, the controlled release component may be 30 a distinct component (e.g., separate from the carboxylic acid and immediate release components). In an embodiment of the invention, the carboxylic acid component is a distinct component (e.g., separate from the controlled release and immediate release components). In yet another embodiment, the immediate release component is a distinct

component (e.g., separate from the controlled release and carboxylic acid components). In still another embodiment of the invention, the controlled release component, the immediate release component and the carboxylic acid component are each manufactured as distinct, separable beads.

5

In an embodiment of the invention, all of the components (namely, the controlled release, carboxylic acid, and immediate release components) of the multiparticulate, controlled release oral solid formulation are coformulated into a single component.

10 The multiparticulate, controlled release oral solid formulation of the invention may further comprise one or more controlled release carboxylic acid components comprising a carboxylic acid and a rate controlling excipient. Suitable examples of carboxylic acids include but are not limited to tartaric acid, adipic acid, succinic acid, citric acid, benzoic acid, acetic acid, ascorbic acid, edetic acid, fumaric acid, lactic acid, malic acid, oleic acid, sorbic acid, stearic acid, palmitic acid and boric acid or mixtures thereof. In a particular embodiment, the carboxylic acid is tartaric acid. Further, the controlled release carboxylic acid components may comprise a carboxylic acid core coated with one or more enteric polymers. In a particular embodiment, the multiparticulate, controlled release oral solid formulation has at least two controlled release carboxylic acid components that 15 release the carboxylic acid at different rates.

20

25 In accordance with the practice of the invention, the rate controlling excipient of the multiparticulate, controlled release oral solid formulation may be an enteric polymer or a mixture of more than one type of enteric polymer. In one embodiment, the rate controlling excipient is a neutral methacrylic polymer.

In an embodiment of the multiparticulate, controlled release oral solid formulation of the invention, the controlled release component further comprises a carboxylic acid. The carboxylic acid may be a dicarboxylic acid.

30

In an embodiment of the multiparticulate, controlled release oral solid formulation of the invention, the controlled release component comprises a core of levodopa and decarboxylase inhibitor coated with one or more enteric polymers.

- 5 The multiparticulate, controlled release oral solid formulation provides an embodiment wherein carbidopa and levodopa is present in a ratio of about 1:1 to about 1:10. In one embodiment, the ratio of carbidopa to levodopa is 1:4.
- 10 The multiparticulate, controlled release oral solid formulation of the invention provides an embodiment wherein the ratio of moles of carboxylic acid to levodopa is less than 4:1. In one embodiment, the multiparticulate, controlled release oral solid formulation, has a ratio of moles of carboxylic acid to levodopa of greater than 1:4 and less than 3:2. In another embodiment, the multiparticulate, controlled release oral solid formulation has a ratio of moles of carboxylic acid to levodopa of greater than 1:2 and less than 4:3. In yet 15 another embodiment, the multiparticulate, controlled release oral solid formulation has a ratio of moles of carboxylic acid to levodopa of greater than 2:3 and less than 4:3. In an additional embodiment, the multiparticulate, controlled release oral solid formulation has a ratio of moles of dicarboxylic acid to levodopa of greater than 1:1 and less than 4:3.
- 20 The multiparticulate, controlled release oral solid formulation of the invention provides an embodiment comprising from about 25 mg to about 1200 mg levodopa. In one embodiment, the multiparticulate, controlled release oral solid formulation comprises about 50 to about 600 mg of levodopa.
- 25 The multiparticulate, controlled release oral solid formulation of the invention provides an embodiment comprising from about 10 mg to about 300 mg carbidopa. In an embodiment, the multiparticulate, controlled release oral solid formulation comprises 20 mg to about 80 mg of carbidopa.

The pharmaceutical formulations of the invention can further comprise excipients including, but not limited to, surfactants (ionic and non-ionic), lipophilic vehicles, and hydrophilic vehicles.

5 In accordance with the practice of the invention, examples of a rate controlling excipient include, but are not limited to, hydroxypropyl cellulose, hypromellose, ethyl cellulose, and prop-2-enoic acid. One suitable example of a prop-2-enoic acid is Carbopol® (Noveon or Dow Chemical Co.). Examples of delay release polymers include a neutral methacrylic polymer such Eudragit® FS30D, Eudragit® S100, Eudragit® L100-55 and/or 10 any mixture or combination thereof (Rohm). Eudragit® L100-55 is an enteric polymer which can be used in coated dosage forms to target the drug release in the upper small intestine where the pH is above 5.5. Eudragit® S100 can be used to achieve targeted drug release in the lower small intestine to the colon, where the pH is above 7. The modified release components of the formulations of this invention can be formulated with any, 15 and/or a mixture, of the above polymers, to achieve the desired LD plasma concentration profiles. The choice of the polymers that can be used in the invention includes, but is not limited to, Eudragit®, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate LF, hydroxypropyl methylcellulose acetate succinate HF, and others.

20

The pharmaceutical formulations of the invention can further comprise other excipients commonly known and used by those of skill in the art, including a plasticizer agent (e.g., triethyl citrate), lubricant (such as talc and magnesium stearate), and disintegrant (such as croscarmellose sodium and crospovidone), or any combination thereof.

25

The invention provides a controlled release oral solid formulation of levodopa having or exhibiting a levodopa plasma or serum concentration profile, which profile comprises a time of administration, a first concentration and a second concentration. The controlled release oral solid formulation of levodopa may further comprise at least one carboxylic acid, for example, tartaric acid.

In accordance with the practice of the invention the first concentration may be equal to the maximum levodopa plasma or serum concentration of the profile, the second concentration may be the minimum concentration occurring at a time later than said first concentration and earlier than or equal to about six hours following the time of 5 administration. The second concentration may be greater than or equal to about fifty percent of said first concentration.

10 In one embodiment of the formulation, the levodopa plasma or serum concentration profile is a median levodopa plasma or serum concentration profile. In another embodiment, the levodopa concentration profile is the mean levodopa plasma or serum concentration profile.

15 In a further embodiment, the levodopa plasma or serum concentration profile further comprises a third concentration. The levodopa profile in this third concentration may be greater than or equal to fifty percent of the first concentration. Further, the third concentration may occur a time earlier than said first concentration and within about ninety minutes of the time of administration. In a specific embodiment, levodopa in the third concentration may be greater than or equal to sixty percent of the first concentration and the second concentration may be greater than or equal to sixty percent of the first 20 concentration.

25 In accordance with the practice of the invention, the second concentration may be the minimum concentration occurring between one hour after said time of administration and the second time. In one embodiment, the first concentration is between 825 and 1505 ng/mL for a 380 mg dose of levodopa.

30 The levodopa plasma or serum concentration profile may have a ratio of mean AUC which is measured in units of ng h/mL, to the mass of levodopa in the formulation, where said mass is measured in mg, is between 11:1 and 25:1. In one embodiment, the ratio is between 14:1 and 19:1. Additionally, the levodopa plasma or serum concentration profile may have a ratio of mean AUC which is measured in units of ng h/mL, to said first

concentration, where said concentration is measured in units of ng/mL, of between 9:2 and 6:1.

5 The levodopa plasma or serum concentration profile may have a mean AUC of between 4330 and 8000 ng h/mL for a 380 mg dose of levodopa. In one embodiment, the mean AUC is between 5000 and 7000 ng h/mL for a 380 mg dose of levodopa.

10 The levodopa plasma or serum concentration profile may have a ratio of the first concentration which is measured in units of ng/mL, to the mass of levodopa in the formulation, where said mass is measured in mg, of between 3:1 and 5:1. In one embodiment, the ratio is between 5:2 and 7:2. In another embodiment, the ratio is greater than or equal to about 3:1.

15 In one embodiment, the levodopa plasma or serum concentration profile comprises a time of administration, a first concentration at a first time that occurs within one hour of the time of administration; a second concentration at a second time, that occurs after said first time; and a third concentration at a third time, that occurs at least four hours after said second time. The second concentration may be equal to the maximum concentration of levodopa in the profile; the first concentration may be equal to about fifty percent of the 20 second concentration; said third concentration may be equal to about fifty percent of the second concentration.

25 In another embodiment, the controlled release oral solid formulation has a levodopa plasma or serum concentration profile substantially the same as levodopa formulation IPX066 in Figure 1 for a 380 mg dose of levodopa, or having a levodopa plasma or serum concentration profile substantially proportional to said formulation in Figure 1 for a dose other than 380 mg.

30 In yet another embodiment, the controlled release oral solid formulation has a levodopa plasma or serum concentration profile such that the ratio of the maximum concentration

of the profile to the concentration at any time between one hour and seven hours after administration of the formulation is less than or equal to 4:1.

In a further embodiment, the controlled release oral solid formulation of levodopa has a  
5 median levodopa plasma or serum concentration profile comprising: a first concentration  
at a first time; a second concentration at a second time, that occurs within about one hour  
after said first time; a third concentration at a third time, that occurs at least four hours  
after said second time; and a maximum concentration. The second concentration may be  
10 equal to the maximum concentration of said profile; the first concentration is equal to  
fifty percent of said second concentration; the third concentration is equal to fifty percent  
of the second concentration.

*Coating of the Pharmaceutical Formulation*

15 Another aspect of the invention relates to the method of preparation of the enteric coating  
of the formulations containing an acid, e.g., tartaric acid. The acid causes a slow and  
variable drug release rate. The prolonged and slow drug release rate may be due to the  
interference of the dissolution of the enteric coat, affected by the presence of the acid in  
the core. The interference can be significantly reduced by partially neutralizing the  
20 enteric polymers of the coating, for example, by adding a base (e.g., NH<sub>3</sub> or NH<sub>4</sub>OH) to  
the coating formulation so as to increase the pH of the coating. The neutralizing  
technique can be equally effective for different enteric polymers including, but not limited  
to, Eudragit<sup>®</sup> L100, S100, and FS100.

25 **METHODS OF THE INVENTION**

The invention provides a method of enhancing dopamine levels in a subject suffering  
from a condition associated with reduced or impaired dopamine levels comprising  
30 administering to a subject an effective amount of a pharmaceutical formulation of the  
invention thereby enhancing dopamine levels in the subject suffering from a condition  
associated with reduced or impaired dopamine levels.

The invention also provides methods for enhancing or maintaining dopamine levels in a subject suffering from a condition associated with reduced or impaired dopamine levels comprising administering to the subject an effective amount of a pharmaceutical formulation of the invention thereby maintaining dopamine levels in the subject suffering from a condition associated with reduced or impaired dopamine levels.

Enhancing or maintaining dopamine levels in a subject can treat the subject suffering from a condition associated with reduced or impaired dopamine levels. Examples of a condition associated with reduced or impaired dopamine levels include, but is not limited to, Alzheimer's disease, dystonia, schizophrenia, and Parkinson's disease.

The invention further provides methods of reducing motor fluctuations in a patient suffering from Parkinson's disease comprising administering to the patient an effective amount of any of the formulations of the invention thereby providing a plasma concentration of levodopa effective to reduce motor fluctuations in the patient. In one embodiment of the invention, the formulation is administered in six-hour intervals.

Additionally provided are methods of reducing off time in a patient suffering from Parkinson's disease comprising administering to the patient an effective amount of any of the formulations of the invention thereby providing a plasma or serum concentration of levodopa effective to reduce off time in the patient.

Further, the invention provides methods of increasing "on" time in a patient suffering from Parkinson's disease comprising administering to the patient an effective amount of any of the formulations of the invention thereby providing a plasma or serum concentration of levodopa effective to increase on time in the patient.

Also provided are methods of reducing time to 'on' (e.g., accelerating the efficacy of levodopa) in a patient suffering from Parkinson's disease comprising administering to the patient an effective amount of any of the formulations of the invention thereby providing

a plasma or serum concentration of levodopa effective to reduce the time to on in the patient.

Determining “on” and “off” time can be based on measuring conventional parameters

5 such as the Uniform Parkinson’s Disease Rating Scale (UPDRS) motor exam, walking time, and/or tapping number. For each of these parameters, definitions of “on” may be based on change from predose measure, and the results analyzed in the standard manner. For example, for the tapping number measure an about 10% change from the average of the predose measurements, may define the time of “on”. For walking time, an about 15%  
10 change may be used.

In accordance with the practice of the invention, the plasma or serum concentration of levodopa comprises: a controlled release oral solid formulation of levodopa having a levodopa plasma or serum concentration profile comprising: a time of administration; a

15 first concentration, and a second concentration. In one embodiment of the method, said first concentration is equal to the maximum concentration of said profile; said second concentration is the minimum concentration occurring at a time later than said first concentration and earlier than or equal to about six hours following the time of administration; and wherein the second concentration is greater than or equal to about  
20 fifty percent of said first concentration. In another embodiment, the second concentration is the minimum concentration occurring between one hour after said time of administration and said second time.

In the method of the invention, the concentration profile may be the median plasma or

25 serum concentration profile. Further, the concentration profile may be the mean plasma or serum concentration profile.

In one embodiment, the concentration profile further comprises a third concentration,

wherein said third concentration is greater than or equal to fifty percent of said first  
30 concentration and said third concentration occurs at a time earlier than said first concentration and within about ninety minutes of said time of administration. In another

embodiment, the third concentration is greater than or equal to sixty percent of said first concentration and said second concentration is greater than or equal to sixty percent of said first concentration.

5 In accordance with the practice of the invention, the disease includes but is not limited to Alzheimer's disease, dystonia, schizophrenia and Parkinson's disease.

The invention further provides methods of providing a therapeutically effective and stable median and/or mean blood plasma level of levodopa in a subject comprising 10 administering to the subject a therapeutically effective amount of any of the formulations of the invention. In one embodiment, the blood plasma level does not fluctuate more than 40% between 0.5 hours after administration and six hours after administration.

#### **ADVANTAGES OF THE INVENTION**

15 Optimally, after administration to a patient suffering from a condition associated with reduced or impaired dopamine levels, a pharmaceutical formulation of the invention releases LD into the plasma of the patient at a steady or near constant level, i.e., with a low peak-to-trough ratio of LD plasma concentration, without any significant decrease or 20 fluctuation for an extended amount of time, for example, mimicking infusion administration; thereby reducing motor fluctuations or the "on-off" effect associated with fluctuations in plasma LD levels caused by currently available oral dosage forms of CD/LD.

25 The pharmaceutical formulations of the invention provide a superior plasma LD profile to a patient than currently available oral pharmaceutical formulations. The formulations of the invention are able to provide a significantly smaller peak-to-trough LD plasma concentration ratio (i.e., narrowing the blood plasma ranges of LD after the initial peak) with e.g., Q6h, dosing. Additionally, some embodiments of the pharmaceutical 30 formulations of the invention provide for improvement by increasing the plasma level of LD. The pharmaceutical formulations of the invention also provide narrow ranges of

plasma LD levels thereby minimizing the “on-off” effect in some patients. The sustained, steady LD plasma profile of this invention is expected to provide a superior and consistent disease control.

5 The following examples are presented to illustrate the present invention and to assist one of ordinary skill in making and using the same. The examples are not intended in any way to otherwise limit the scope of the invention.

10 **EXAMPLE 1: A TABLET OF CARBIDOPA AND LEVODOPA WITH TARTARIC ACID**

15 The bioavailability/pharmacokinetic results of a tablet formulation of the present invention, using 50-200 mg of CD-LD with 215 mg of tartaric acid, were compared to the controlled release version of Sinemet®.

*Preparation of a tablet of CD-LD with tartaric acid (IPX066-B05-07)*

20 CD, LD, and hydroxypropyl were charged into a blender and mixed uniformly. The powder mix was then charged in a high shear granulator and granulated with purified water. Drying of the granules was done overnight in an oven at  $60 \pm 10^\circ\text{C}$ . Dried granules were passed through a 25 mesh screen, then charged and blended with magnesium stearate in a blender.

25 To prepare the tartaric acid final blend, granular tartaric acid was passed through a 20 mesh screen. The tartaric acid, microcrystalline cellulose, and hypromellose were charged and blended in a high shear mixer and granulated with ethyl alcohol. The resultant granules were dried in fluid bed processor at  $55 \pm 10^\circ\text{C}$ . The dry granules were passed through a 25 mesh screen then charged and blended with magnesium stearate in a  
30 blender.

The final CD/LD and tartaric acid blends were compressed into a tablet.

*Resulting Effect of Tartaric Acid on the Pharmacokinetics of Carbidopa-Levodopa 50-200 mg Formulations in Human Subjects*

**Table 1**

Product	Strength (mg)	Dissolution in SGF
IPX066 CD/LD Tablets containing tartaric acid	50-200	Release over 4 hr
IPX066 CD/LD Tablets without tartaric acid	50-200	Release over 6 hr
IPX066 CD/LD Tablets with tartaric acid	50-200	Release over 6 hr
Sinemet® CR Tablets <sup>a</sup>	50-200	Release over 3 hr

5 <sup>a</sup> Merck & Co., Inc., expiration date Aug. 2007

*In vitro* dissolution profiles of study drugs are listed below. Formulation tables for IPX066-B05-07 A, B and C are shown at the end of this example.

10 **Table 2**

Test Formulation		Tartaric Acid (mg)					
A	bi-layer						
B	ER						
C	bi-layer						
Drug release (%); SGF, 50 rpm, USP Apparatus II w/basket sinker							
Test	Compound	30	60	120	180	240	360
A	CDP	16±1.8	30±3.5	55±6.2	73±7.8	86±7.5	97±3.0
	LDP	16±1.8	30±3.6	54±6.3	72±7.9	84±7.5	95±3.0
B	CDP	13±0.6	22±1.3	38±2.5	52±3.5	64±4.3	84±4.7
	LDP	13±0.7	22±1.5	39±2.9	53±4.1	66±5.0	87±5.2
C	CDP	12±0.9	21±2.1	39±4.6	55±6.3	68±6.7	86±5.3
	LDP	12±1.1	21±2.3	39±5.0	55±6.7	68±7.2	87±5.9

*Results and Discussion:* Figure 2 shows a graph illustrating the *in vivo* plasma concentration profiles of three formulations of CD, LD with tartaric acid (referred to herein as IPX066-B05-07 formulations A, B and C) compared to Sinemet® after oral 5 administration.

#### *Pharmacokinetics of IPX066 Test B and Sinemet® CR*

Following administration of one IPX066 Test B tablet, multiple peaks appeared in the LD 10 plasma profiles, with a maximum plasma concentration ( $C_{max}$ ) occurring at approximately 2.5 hours post dose (Figure 2). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 4 hours post dose. Due to extended dissolution rate, IPX066 Test B with the dissolution rate of 6 hours as opposed to the Reference Sinemet® CR with 15 the dissolution rate of 3 hours decreased by 46% in  $C_{max}$  and 44% in AUC of LD, and 38% of  $C_{max}$  and 41% in AUC of CD.

#### *Pharmacokinetics of IPX066 Test C and IPX066 Test B*

Following administration of one IPX066 Test C tablet, multiple peaks also appeared in 20 the LD plasma profiles, with  $C_{max}$  occurring at approximately 3 hours post dose (Figure 2). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 4.5 hours post dose. Even with the extended dissolution rate, IPX066 Test C with the addition of 215 mg of tartaric acid, when compared to IPX066 Test B without the addition of tartaric acid, increased by 50% in  $C_{max}$ , 41% in AUC, 119% in  $C_{6h}$ , and 25 65% in  $C_{8h}$  of LD, and 32% of  $C_{max}$  and 35% in AUC of CD

#### *Pharmacokinetics of IPX066 Test C and IPX066 Test A*

Following administration of one IPX066 Test A tablet, multiple peaks also appeared in 30 the LD plasma profiles, with  $C_{max}$  occurring at approximately 2 hours post dose (Figure 2). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately

4.5 hours post dose. In comparison with IPX066 Test A, IPX066 Test C contained the same amount of tartaric acid and yet a slower dissolution rate by 2 hours. As a result, the LD Cmax, LD AUC, LD C6h, LD C8h, CD Cmax, and CD AUC were reduced by approximately 20%, 14%, 26%, 4%, 22%, and 18%, respectively.

5

*Pharmacokinetics of IPX066 Test A and Sinemet® CR*

Following administration of one IPX066 Test A tablet, multiple peaks also appeared in the LD plasma profiles, with C<sub>max</sub> occurring at approximately 2 hours post dose (Figure 10 2). In contrast, CD was slowly absorbed, with median C<sub>max</sub> occurring at approximately 4.5 hours post dose. BE assessment demonstrated that IPX066 Test A with the dissolution rate of 4 hours and tartaric acid included in formulation is bioequivalent to the Reference Sinemet® CR with the dissolution rate of 3 hours with regard to the C<sub>max</sub> and 15 AUC values for both LD and CD. In addition, the C6h and C8h of LD of IPX066 Test A were lower than those of Reference Sinemet® CR by approximately 25% and 4%, respectively.

The data herein demonstrated that decreasing dissolution rate decreases the exposure of LD and CD, and addition of tartaric acid increases the Cmax and AUC of LD and CD.

20

**IPX066-B05-07 Formulation A**

Ingredients	Per Tablet	
	% (w/w)	Mg
Carbidopa	16.8	54.0
Levodopa	25.47	200.0
Hydroxypropyl cellulose (Klucel-LF)	12.63	99.2
Tartaric Acid	27.38	215.0
Microcrystalline cellulose (Avicel PH101)	21.63	169.8
Hypromellose (Methocel K100LV)	5.48	43.0
Magnesium Stearate	0.53	4.2
Total	100	785.2

Note. 53.09mg CD, USP is equivalent to 50.0 mg CD anhydride

**IPX066-B05-07 Formulation B**

Ingredients	Per Tablet	
	% (w/w)	Mg
Carbidopa	16.8	54.08
Levodopa	62.2	200.00
Hydroxypropyl cellulose	20.0	64.3
Magnesium Stearate	1.0	3.2
Purified water	-	-
Total	100.0	321.5

**5 IPX066-B05-07 Formulation C**

Ingredients	Per Tablet	
	% (w/w)	mg
Carbidopa	6.30	54.0
Levodopa	23.34	200.00
Hydroxypropyl cellulose (Klucel-LF)	19.94	170.9
Tartaric Acid	25.09	215.0
Microcrystalline cellulose (Avicel PH101)	17.82	152.7
Hypromellose (Methocel K100LV)	7.03	60.2
Magnesium Stearate	0.48	4.1
Total	100	856.9

Note. 53.09mg CD, USP is equivalent to 50.0 mg CD anhydride

**EXAMPLE 2**

10

*Preparation of IPX066-B06-02 Formulations A and B*

The following steps were performed to prepare enteric coated pellets containing CD and LD.

CD, LD, and microcrystalline cellulose (Avicel PH-101) were charged and mixed uniformly. The powder mix was charged into a high shear granulator and granulated with purified water. The granulated wet mass was extruded in an extruder with 1.0 mm hole size screen. The extrudate was charged and spheronized in a spheronizer equipped with 3 mm cross-hatch disc. The CD/LD pellets were dried at  $60 \pm 10^\circ\text{C}$  in fluid bed processor. The CD/LD pellets were passed through different size screens. The pellets collected were retained on 18 and 25 mesh screens.

10 The following steps were performed to prepare the enteric coating solution for the CD-LD pellets.

For Formulation IPX066-B06-02 A, Eudragit® S100 and Eudragit® L100 (at the weight ratio of 2:1) and triethyl citrate were dissolved in isopropyl alcohol and acetone solution. 15 The mixture was mixed until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process.

For Formulation IPX066-B06-02 B, Eudragit® S100 and triethyl citrate were dissolved in isopropyl alcohol and acetone solution. The mixture was mixed until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process.

20 For both formulations, the CD/LD pellets were spray-coated using the coating dispersion prepared in Glatt GPCG-1 coater. The coated pellets were dried. The dried, coated CD/LD pellets were screened through a 16 mesh screen. The screened CD/LD pellets were charged and blended with talc in a blender.

The following steps were performed to prepare enteric coated pellets containing tartaric acid (TA).

30

TA was passed through a 20 mesh screen. The screened TA and microcrystalline cellulose (Avicel PH101) were charged in a high shear mixer and granulated with purified water. The granules were extruded in an extruder with 1.0 mm hole size screen. The extrudate was charged and spheronized into a spheronizer equipped with a 3 mm cross hatch disc. The seeds were dried overnight in an oven at  $60 \pm 10^{\circ}\text{C}$ . The dried pellets were passed through 16, 18 and 25 mesh screens. The pellets retained were collected on 18 and 25 mesh screens. A seal coat solution was prepared by charging hypromellose (Pharmacoat 606) and ethylcellulose into an alcoholic solution. The mixture was mixed until dissolved. The dried TA pellets were charged in a coater and spray coated with the seal coat solution prepared. The seal coated CD/LD pellets were dried, and passed through a 14 mesh screen.

The following steps were performed to prepare the enteric coating solution for the TA pellets.

15

For Formulation IPX066-B06-02 A, Eudragit<sup>®</sup> S100 and Eudragit<sup>®</sup> L100 (at the weight ratio of 2:1) and triethyl citrate were dissolved in isopropyl alcohol and acetone solution. The mixture was mixed until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process.

20

For Formulation IPX066-B06-02 B, Eudragit<sup>®</sup> S100 and triethyl citrate were dissolved in isopropyl alcohol and acetone solution. The mixture was mixed until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process.

25

For both formulations, the sealed coated TA pellets were charged in a Glatt GPCG-1 coater and spray coated with the enteric coating solution prepared. The coated TA pellets were dried. The dried, coated TA pellets were passed through a 12 mesh screen. The coated TA pellets were charged and blended with talc in a blender.

30

The following steps were performed to encapsulate the enteric coated drug pellets and enteric coated TA pellets.

5 The coated CD/LD pellets prepared as described above and coated TA pellets prepared as described above were encapsulated into hard gelatin capsules. The filled capsules contained 50 mg carbidopa anhydride, 200 mg LD and 215 mg TA.

*Preparation of IPX066-B06-02 Formulations D and E*

10 The following steps were performed to prepare the carbidopa (CD) and levodopa (LD) final blend.

15 CD, LD, microcrystalline cellulose, and croscarmellose sodium were charged into a blender and mixed uniformly into a powder. Corn starch was dispersed in purified water and stirred for 15 minutes, transferred to boiling water, and stirred continuously until it became starch paste. The spray rate of the peristaltic pump was verified using the starch paste. The powder mix prepared above was charged in a high shear granulator and granulated with starch paste at a flow rate of 50 ~ 1000 g/min. The granules were dried in an oven at  $60 \pm 10^\circ\text{C}$  until LOD was lower than 3.0%. The dried granules were passed 20 through a 25 mesh screen. The screened CD/LD granules, crospovidone and magnesium stearate were charged and blended in a blender.

25 To prepare the TA final blend, granular TA was passed through a 20 mesh screen. The TA and microcrystalline cellulose were charged and blended in a high shear mixer and granulated with purified water. The resulting granules were dried in an oven at  $60 \pm 10^\circ\text{C}$  until L.O.D. measured by a moisture analyzer was lower than 2.0%. The dry granules were passed through a Fitzmill equipped with a 24 mesh screen. The dried TA granules and magnesium stearate were charged and blended in a blender.

30 The final blends were compressed into core tablets as follows.

The CD/LD final blend and TA final blend were weighed, mixed and compressed into a tablet. The tablet contained 50 mg carbidopa anhydride, 200 mg LD and 215 mg TA.

A seal coat was applied to the core tablet by spray coating the core tablet with 5 hypromellose dissolved in the mixture of isopropyl alcohol and purified water solution in Pan Coater. The tablets were dried in the coating pan at  $60 \pm 10^\circ\text{C}$  until the L.O.D. was lower than 3.0%.

The enteric coating solution was prepared as follows.

10

For IPX066-B06-02 Formulation D, Eudragit® S100 and Eudragit® L100 (at the weight ratio of 0.25:1) and triethyl citrate were dissolved in isopropyl alcohol and acetone solution. The mixture was mixed until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process.

15

For IPX066-B06-02 Formulation E, Eudragit® L100 and triethyl citrate were dissolved in isopropyl alcohol and acetone solution. The mixture was mixed until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process.

20

The sealed coated tablet was charged into a Pan Coater and spray coated with the enteric coating solution prepared. The coated tablet was dried in the coating pan at  $40 \pm 10^\circ\text{C}$  for at least 30 minutes.

25 *Resulting Effect of Tartaric Acid and pH of Enteric Coating on the Pharmacokinetics of Carbidopa-Levodopa 50-200 mg Formulations in Human Subjects*

This study shows the effect of acid addition and of various pH of enteric-coating to carbidopa (CD)/levodopa (LD) 50-200 mg formulation on the PK of CD and LD.

30

**Table 3**

Product	Strength (mg)	Enteric pH	Coated
IPX066 CD/LD Capsule with tartaric acid	50-200	6.5	
IPX066 CD/LD Capsule with tartaric acid	50-200	7.0	
Sinemet® CR Tablet <sup>a</sup>	50-200	N/A	
IPX066 CD/LD Tablet with tartaric acid	50-200	6.5	
IPX066 CD/LD Tablet with tartaric acid	50-200	6.0	

<sup>a</sup> Merck & Co., Inc., expiration date Aug. 2007

Formulation information of study drugs are listed below. Formulation tables for IPX066-

5 B06-02 A, B, D and E are shown at the end of this example.

**Table 4**

Test	Formulation	Particle size (μm)	Tartaric Acid (mg)
A	Capsule	D(v,0.9) =36.22 D(v,0.9) =139.48	215
B	Capsule	D(v,0.9) =36.22 D(v,0.9) =139.48	215
D	Tablet	D(v,0.9) =36.22 D(v,0.9) =139.48	215
E	Tablet	D(v,0.9) =36.22 D(v,0.9) =139.48	215

Results and Discussion: Figure 3 show a graph illustrating the *in vivo* plasma

10 concentration profiles of four formulations of CD, LD and TA (referred to herein as IPX066-B06-02 formulations A, B, D and E) compared to Sinemet® after oral administration.

*Pharmacokinetics of IPX066 Test A and Sinemet® CR*

Following administration of one IPX066 Test A capsule, one peak appeared in the LD median plasma profiles, with a maximum plasma concentration ( $C_{max}$ ) occurring at approximately 5.0 hours post dose (Figure 3). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 6.0 hours post dose. Due to delayed dissolution rate (enteric coated pH=6.5), no LD concentration was observed before 1 hr for IPX066 Test A and the LD concentration of IPX066 Test A between 5 and 8 hr was higher than that of the Reference Sinemet® CR based on the median profile suggesting that addition of TA (215 mg) increase the absorption of LD in the later part of intestine. The AUC of LD for IPX066 Test A was only 58% of that of reference Sinemet® CR.

*Pharmacokinetics of IPX066 Test B and Sinemet® CR*

Following administration of one IPX066 Test B capsule, one peak also appeared in the LD median plasma profiles, with delayed and lower  $C_{max}$  occurring at approximately 4.0 hours post dose (Figure 3). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 4.75 hours post dose. No LD concentration was observed before 2 hr for IPX066 Test B. Even with the addition of TA (215 mg), IPX066 Test B did not have higher LD concentration between 5 and 8 hr when compared to Sinemet® CR. This could be due to the dissolution rate of TA is slower than that of LD. The AUC of LD for IPX066 Test B was only 23% of that of reference Sinemet® CR.

*Pharmacokinetics of IPX066 Test D and Sinemet® CR*

Following administration of one IPX066 Test D tablet, one peak also appeared in the LD median plasma profiles, with delayed and lower  $C_{max}$  occurring at approximately 4.25 hours post dose (Figure 3). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 6.0 hours post dose. No LD concentration was observed before 2 hr for IPX066 Test D. Even with the addition of TA (215mg), LD AUC of IPX066 Test D was only 24% of that of Reference Sinemet® CR and LD concentration

between 5 and 8 hr was lower than that of Sinemet® CR. This is due to the highly variable *in vitro* dissolution profile and the faster release rate of TA when compared with that of LD.

5 *Pharmacokinetics of IPX066 Test E and Sinemet® CR*

Following administration of one IPX066 Test E tablet, one peak also appeared in the LD median plasma profiles, with delayed and lower  $C_{max}$  occurring at approximately 4.0 hours post dose (Figure 3). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 5.0 hours post dose. No LD concentration was observed before 2 hr for IPX066 Test E. Even with the addition of tartaric acid (215mg), LD AUC of IPX066 Test E was only 20% of that of Reference Sinemet® CR and LD concentration between 5 and 8 hr was lower than that of Sinemet® CR. This is also due to the highly variable *in vitro* dissolution profile and the faster release rate of TA when compared with that of LD.

The data herein demonstrated that delayed dissolution rate decreases the exposure of LD and CD, and addition of TA which has similar dissolution rate to LD and CD has higher LD concentration between 5 and 8 hr when compared to Sinemet® CR.

20

**IPX066-B06-02 Formulation A**

Ingredients	% (w/w)	Amount (mg)
Carbidopa	14.06	53.98
Levodopa	52.10	200.0
Microcrystalline Cellulose, (Avicel PH-101)	28.36	108.85
Eudragit® L100	1.14	4.39
Eudragit® S100	2.34	8.98
Triethyl Citrate	1.00	3.82
Talc	1.00	3.83
Total	100.0	383.85

Tartaric Acid	57.6	215.0
Microcrystalline Cellulose, NF (Avicel PH-101)	14.4	53.8
Ethylcellulose	6.6	24.8
Hypromellose, Type 2910	1.4	5.1
Eudragit® L100	4.6	17.2
Eudragit® S100	9.4	35.1
Triethyl Citrate	4.0	14.9
Talc	2.0	7.5
Total	100.0	373.4

**IPX066-B06-02 Formulation B**

Ingredients	% (w/w)	Amount (mg)
Carbidopa	12.92	53.98
Levodopa	47.88	200.00
Microcrystalline cellulose (Avicel PH101)	26.06	108.85
Eudragit® S100	8.85	36.95
Triethyl Citrate	2.53	10.55
Talc	1.76	7.37
Total	100.0	417.70

Tartaric Acid	57.6	215.0
Microcrystalline cellulose (Avicel PH101)	14.4	53.8
Ethycellulose	6.6	24.8
Hypromellose,	1.4	5.1
Eudragit® S100	14.0	52.3
Triethyl Citrate	4.0	14.9
Talc	2.0	7.5
Total	100.0	373.4

**IPX066-B06-02 Formulation D**

Ingredients	% (w/w)	mg
Carbidopa	8.57	53.98
Levodopa	31.77	200.00
Microcrystalline cellulose (Avicel PH101)	15.17	95.5
Corn Starch,	1.43	8.98
Croscarmellose Sodium	1.43	8.98
Crospovidone,	0.93	5.88
Magnesium Stearate	1.13	7.11
Tartaric Acid	34.15	215.0
Hypromellose, type 2910	2.93	18.42
Eudragit® L100	1.40	8.82
Eudragit® S 100	0.35	2.20
Triethyl Citrate	0.50	3.15
Talc	0.25	1.57
<b>Total</b>	<b>100.0</b>	<b>629.59</b>

**IPX066-B06-02 Formulation E**

Ingredients	% (w/w)	Amount (mg)
Carbidopa	8.57	53.98
Levodopa	31.77	200.0
Avicel PH-101	15.17	95.5
Corn Starch	1.43	8.98
Croscarmellose Sodium	1.43	8.98
Crospovidone	0.93	5.88
Magnesium Stearate	1.13	7.11
Tartaric Acid	34.15	215.00
Hypromellose, Type 2910	2.93	18.42
Eudragit® L100	1.75	11.02
Triethyl Citrate	0.5	3.15
Talc	0.25	1.57
Total	100.0	629.59

**EXAMPLE 3**5 *Preparation of IPX066-B07-01 Formulations A, B and C*

The following steps were performed to prepare enteric coated pellets containing Carbidopa-Levodopa (CD-LD).

10 CD, LD, and microcrystalline cellulose (Avicel PH-101) were blended together. The mixture was charged into a high shear granulator and granulated with purified water. The granulated wet mass was extruded in an extruder with 1.0 mm hole size screen. The extrudate was charged and spheronized in a spheronizer equipped with 3 mm cross-hatch disc. The spheres obtained from the spheronizer were dried at  $60\pm10^{\circ}\text{C}$  in a Glatt GCPG-15 1 coater. Drying the pellets in the Glatt GPCG-1 eliminated discoloration of the pellets and also reduced the amount of degradation product DHP. The drug-loaded pellets were

screened with 16, 18 and 25 mesh screens and the collected pellets retained on 18 and 25 mesh screens. The core pellets were then coated with hypromellose (Pharmacoat 606) aqueous solution in a Glatt GCPG-1 coater. The coated pellets were screened with an 18 mesh screen after they were dried in GPCG-1.

5

The enteric coating solution was prepared as follows. For formulation IPX066-B07-01 A, Eudragit® S100 and Eudragit® L100 were dispersed separately at the weight ratio of 5:1 into purified water and mixed until a uniform dispersion. 1N NH<sub>4</sub>OH solution was then added drop-wise to both solutions until the pH reached 5.5. The two solutions were 10 combined together and mixed thoroughly. A talc suspension was prepared by dispersing Talc into triethyl citrate solution in purified water and then stirred for 1 hour. The above mixture of L100 and S100 was then combined with the Talc dispersion and mixed thoroughly. The dispersion was screened through a 140 mesh screen before starting the coating process. For IPX066-B07-01 formulation B, the same procedure was followed 15 for formulation A except using only Eudragit® S100 polymer. For IPX066-B07-01 formulation C, the same procedure was followed for formulation A, except using only Eudragit® FS30D polymer.

20 The hypromellose coated seeds were spray coated with the enteric coating dispersion preparation. The coated CD/LD pellets were dried in an oven. The dried CD/LD pellets were passed through a 14 mesh screen. The final blend was prepared by blending the screened CD/LD pellets with talc.

25 The following steps were performed to prepare enteric coated pellets containing TA.

TA was passed through a 20 mesh screen. The screened TA and microcrystalline cellulose (Avicel PH101) was charged in a high shear mixer and granulated with purified water. The wet mass was extruded in an extruder with 1.0 mm hole size screen. The extrudate was charged and spheronized in a spheronizer equipped with a 3 mm cross 30 hatch disc. The pellets obtained were dried overnight in an oven at 60 ± 10°C. The dried pellets were passed through 16, 18 and 25 mesh screens and the collected pellets retained

on 18 and 25 mesh screens. The seal coat solution was prepared by dissolving hypromellose (Pharmacoat 606) and ethylcellulose in alcoholic solution. The seal coat solution was applied to the TA pellets in a Glatt GPCG-1 coater. The pellets were dried in a GPCG-1 and passed through a 14 mesh screen.

5

The enteric coating solution was prepared as follows. For IPX066-B07-01 formulation A, Eudragit® S100 and Eudragit® L100 were dispersed separately at the weight ratio of 5:1 into purified water and mixed until a uniform dispersion. 1N NH<sub>4</sub>OH solution was then added drop-wise to both solutions until pH reached 5.5. The two solutions were combined together and mixed thoroughly. A talc suspension was prepared by dispersing Talc into triethyl citrate solution in purified water and then stirred for 1 hour. The above mixture of L100 and S100 was then combined with the Talc dispersion and mixed thoroughly. The dispersion was screened through a 140 mesh screen before starting the coating process. For IPX066-B07-01 formulation B, the same procedure was followed for formulation A, except using only Eudragit® S100 polymer. For IPX066-B07-01 formulation C, the same procedure was followed for formulation A except using only Eudragit® FS30D polymer. The screened tartaric acid pellets were charged in a Glatt GPCG-1 coater and spray coated with the enteric coating dispersion. The coated seeds were dried in oven. The dried, coated pellets were screened through a 14 mesh screen.

10 20 The final blend was prepared by blending the screened pellets and talc.

The coated CD/LD pellets and coated TA pellets were encapsulated into hard gelatin capsules. The filled capsules contained 50 mg carbidopa anhydride, 200 mg LD and 215 mg TA.

25

*Resulting Effect of Tartaric Acid and pH of Enteric Coating on the Pharmacokinetics of Carbidopa-Levodopa 50-200 mg Formulations in Human Subjects*

Objectives:

5 This study tested the effect of acid addition and of various pH of enteric-coating (Eudragit® S100/L100=5, Eudragit® S100 and Eudragit® FS 30D) to carbidopa (CD)/levodopa (LD) 50-200 mg formulation on the PK of CD and LD.

**Table 5**

Product	Strength (mg)	Enteric Coated Polymer
IPX066 CD/LD Capsule with tartaric acid	50-200	Eudragit® S100/L100=5
IPX066 CD/LD Capsule with tartaric acid	50-200	Eudragit® S100
IPX066 CD/LD Capsule with tartaric acid	50-200	Eudragit® FS 30D
Sinemet® CR Tablet <sup>a</sup>	50-200	N/A

10 <sup>a</sup> Merck & Co., Inc., expiration date 02/2009

Formulation information and in vitro dissolution profiles of study drugs are listed below.

Formulation tables for IPX066-B07-01 A, B and C are shown in the end of this example.

15 **Table 6**

Test	Formulation	Particle size (µm)	Tartaric Acid (mg)
A	Capsule	D(v,0.9) =36.22 D(v,0.9) =139.48	215
B	Capsule	D(v,0.9) =36.22 D(v,0.9) =139.48	215
C	Capsule	D(v,0.9) =36.22 D(v,0.9) =139.48	215

Results and Discussion: Figure 4 shows a graph illustrating the *in vivo* plasma concentration profiles of three formulations of CD, LD and TA (referred to as IPX066-B07-01 formulations A, B and C) compared to Sinemet® after oral administration.

5 *Pharmacokinetics of IPX066 Test A and Sinemet® CR*

Following administration of one IPX066 Test A capsule, one peak appeared in the LD median plasma profiles, with a maximum plasma concentration ( $C_{max}$ ) occurring at approximately 2.75 hours post dose (Figure 4), and the LD concentration remains at the 10 same level from 2.0 to 3.5 hrs. In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 4.0 hours post dose. Due to delayed dissolution rate (enteric coated with Eudragit® S100/L100=5), the absorption of LD (the ascending phase of plasma profile) from IPX066 Test A was slow compared with Sinemet® CR and the LD concentration of IPX066 Test A between 5 and 10 hr was higher than that of the 15 Reference Sinemet® CR based on the median profile suggesting that addition of TA (215 mg) increase the absorption of LD in the lower part of intestine. The AUC of LD for IPX066 Test A was only 87.72% of that of reference Sinemet® CR.

~  
20 *Pharmacokinetics of IPX066 Test B and Sinemet® CR*

Following administration of one IPX066 Test B capsule, one peak also appeared in the LD median plasma profiles, with delayed and lower  $C_{max}$  occurring at approximately 5.0 hours post dose (Figure 4). In contrast, CD was slowly absorbed, with median  $C_{max}$  occurring at approximately 4.5 hours post dose. No LD concentration was observed 25 before 0.75 hr for IPX066 Test B. Because of tartaric acid (215 mg) in the formulation, IPX066 Test B also has higher LD concentration between 5 and 8 hr when compared to Sinemet® CR. However, the AUC of LD for IPX066 Test B was only 56.5% of that of reference Sinemet® CR.

*Pharmacokinetics of IPX066 Test C and Sinemet® CR*

Following administration of one IPX066 Test C tablet, only 4 subjects have detectable LD concentration (Figure 4). This is due to the slow *in vitro* release profile for the  
5 CD/LD core seed.

The data herein demonstrated that delayed dissolution rate decreases the exposure of LD and CD, and addition of TA to LD and CD formulation has higher LD concentration between 5 and 8 hr when compared to Sinemet® CR.

10

**IPX066-B07-01 Formulation A**

Ingredients	% (w/w)	Amount (mg)
Carbidopa	11.24	53.98
Levodopa	41.65	200.0
Microcrystalline cellulose (Avicel PH101)	22.67	108.85
HPMC	3.98	19.10
Eudragit® L100	1.70	8.17
Eudragit® S100	8.51	40.85
Triethyl Citrate	7.13	34.26
Talc	3.04	14.58
Ammonia Solution	0.08	0.38
Total	100.0	480.17

Tartaric Acid	42.27	215.0
Microcrystalline cellulose (Avicel PH101)	10.58	53.8
Ethylcellulose	4.88	24.8
HPMC	1.00	5.1
Eudragit® L100	3.48	17.7
Eudragit® S100	17.36	88.3
Triethyl Citrate	14.57	74.1
Talc	5.70	29.0
Ammonia Solution	0.16	0.8
Total	100.0	508.6

### IPX066-B07-01 Formulation B

Ingredients	% (w/w)	Amount (mg)
Carbidopa	12.65	53.98
Levodopa	46.87	200.0
Microcrystalline cellulose (Avicel PH101)	25.51	108.85
Hypromellose, Type 2910	4.48	19.10
Eudragit® S100	6.42	27.38
Triethyl Citrate	3.21	13.71
Talc	0.80	3.40
Ammonia Solution	0.06	0.27
Total	100.0	426.69

<b>Tartaric Acid</b>	<b>42.38</b>	<b>215.0</b>
Microcrystalline cellulose (Avicel PH101)	10.61	53.8
Ethylcellulose	4.89	24.8
Hypromellose, Type 2910	1.01	5.1
Eudragit® S100	26.01	131.95
Triethyl Citrate	13.01	65.98
Talc	1.81	9.16
Ammonia Solution	0.29	1.46
<b>Total</b>	<b>100.0</b>	<b>507.25</b>

**IPX066-B07-01 Formulation C**

<b>Ingredients</b>	<b>% (w/w)</b>	<b>Amount (mg)</b>
Carbidopa	8.57	53.98
Levodopa	31.74	200.0
Microcrystalline cellulose (Avicel PH-101)	17.28	108.85
Hypromellose, Type 2910	3.03	19.10
Eudragit® FS 30D	30.31	190.97
Triethyl Citrate	0.91	5.71
Talc	8.07	50.86
Ammonia Solution	0.10	0.63
<b>Total</b>	<b>100.0</b>	<b>630.10</b>

<b>Tartaric Acid</b>	<b>38.60</b>	<b>215.0</b>
Microcrystalline cellulose (Avicel PH-101)	9.66	53.8
Ethylcellulose	4.45	24.8
Hypromellose, Type 2910	0.92	5.1
Eudragit® FS 30D	35.75	199.1
Triethyl Citrate	1.08	6.0
Talc	9.44	52.6
Ammonia Solution	0.11	0.6
<b>Total</b>	<b>100.0</b>	<b>557.0</b>

#### EXAMPLE 4

5

The data herein shows the bioavailability/pharmacokinetic results of an enteric coated tablet CD/LD formulations, using 50-200 mg of CD-LD with 0-430 mg of tartaric acid, compared to the controlled release version of Sinemet®.

10 Four formulations of IPX-066-AH1 were evaluated for PK parameters. Information of the study drugs are listed below in Table 7.

Formulation A is a capsule containing IR beads exhibiting a rapid dissolution profile.

15 Formulation B is a capsule containing ER CD/LD beads and ER TA beads. The ER CD/LD beads were formulated by coating the IR beads with Eudragit® polymers (S100:L100 ratio of 2:1). The ER TA beads were coated with a sealed coat and a Eudragit® coat (S100:L100 ratio of 2:1) exhibiting a dissolution profile similar to the CD/LD beads.

20

Formulation C is a capsule containing ER CD/LD beads and ER TA beads. The ER CD/LD beads were formulated by coating the IR beads with Eudragit® polymers

(S100:L100 ratio of 5:1). The ER TA beads were coated with a sealed coat and a Eudragit® coat (S100:L100 ratio of 5:1) exhibiting a dissolution profile similar to the CD/LD beads.

5 Formulation D is similar to formulation B except that the quantity of the TA beads is twice the amount in formulation B.

Formulation E is the reference product, Sinemet® CR 200mg Tablet.

10 **Table 7 IPX066- AH1(A-D)**

Product		CD-LD Strength (mg)	Enteric Coated pH
Formulation A	IPX066 CD/LD IR Capsule	50-200	--
Formulation B	IPX066 CD/LD Capsule with 215 mg tartaric acid	50-200	6.5 (SL2) <sup>b</sup>
Formulation C	IPX066 CD/LD Capsule with 215 mg tartaric acid	50-200	6.5 (SL5) <sup>b</sup>
Formulation D	IPX066 CD/LD Capsule with 430 mg tartaric acid	50-200	6.5 (SL2) <sup>b</sup>
Formulation E (Reference)	Sinemet® CR Tablet <sup>a</sup>	50-200	--

<sup>a</sup> Merck & Co., Inc.; <sup>b</sup>: SL2: Eudragit® S100/L100 is 2:1; SL5: Eudragit® S100/L100 is 5:1.

The qualitative and quantitative compositions for these formulations are summarized

15 below in Table 8.

**Table 8 Qualitative and Quantitative Composition of Formulation**

Ingredients		Formulation				
		A	B	C	D	
<b>mg/capsule</b>						
		Component I	Component II	Component IV	Component II	
Carbidopa, USP		27	27	27	27	
Levodopa, USP		100	100	100	100	
Microcrystalline Cellulose, NF (Avicel PH-101)		18.4	18.4	18.4	18.4	
Lactose Monohydrate, NF		18.4	18.4	18.4	18.4	
Sodium Starch Glycolate, NF		9.2	9.2	9.2	9.2	
Sodium Lauryl Sulfate, NF		9.2	9.2	9.2	9.2	
Povidone, USP		1.84	1.85	1.85	1.85	
Talc, USP		1.95	1.95	4.2	1.95	
Methacrylic acid copolymer, Type A, NF (Eudragit® L100)		---	2.25	2.15	2.25	
Methacrylic acid Copolymer, Type B, NF (Eudragit® S100)		---	4.55	10.75	4.55	
Triethyl Citrate, NF		---	1.95	9.00	1.95	
1N NH <sub>4</sub> OH solution		---	---	0.1	---	
Purified Water, USP		---	---	N/A*	---	
Acetone, NF		N/A*	N/A*	---	N/A*	
Isopropyl Alcohol, USP		N/A*	N/A*	---	N/A*	
		Component III	Component V	Component III	Componen	
Tartaric acid, NF		---	107.5	107.5	215	
Microcrystalline Cellulose, NF (Avicel PH-101)		---	26.95	26.9	53.9	
Ethylcellulose, NF (Ethocel Standard- 10FP Premium)		---	11.2	11.3	22.4	
Hypromellose, USP Type2910 (Pharmacoat 606, 6 cps)		---	20.35	20.25	40.7	
Methacrylic acid copolymer, Type A, NF (Eudragit® L100)		---	9.75	6.1	19.5	
Methacrylic acid Copolymer, Type B, NF (Eudragit® S100)		---	19.3	30.35	38.6	
Triethyl Citrate, NF		---	8.3	25.55	16.6	
Talc, USP		---	5.2	10.3	10.4	
1N NH <sub>4</sub> OH		---	---	0.3	---	
Purified Water, USP		---	---	N/A*	---	
Acetone, NF		N/A*	N/A*	---	N/A*	
Isopropyl Alcohol, USP		N/A*	N/A*	---	N/A*	

Hard Gelatin Capsule		1 unit	1 unit	1 unit	1 unit
<b>Total Capsule Fill Weight</b>		<b>184.97</b>	<b>403.3</b>	<b>448.4</b>	<b>611.85</b>

\* evaporated in drying process

*Manufacture of IPX066- AH1 Formulations*

5 *Four formulations of IPX066- AH1*

*Manufacture of Component I – CD-LD fast release beads*

10 Carbidopa, levodopa, and microcrystalline cellulose, Lactose Monohydrate, Sodium Starch Glycolate, Sodium Lauryl Sulfate, and Povidone were blended and charged in a high shear granulator and granulated with purified water. The granulated wet mass was extruded in an extruder with 1.0 mm hole size screen. The extrudate was charged and spheronized in a spheronizer equipped with 3 mm cross-hatch disc. The spheres obtained from the spheronizer were dried in and the drug-loaded pellets were screened with 16, 18  
15 and 25 mesh screens. The pellets retained on 18 and 25 mesh screens were collected. The final blend was prepared by blending the screened CD/LD pellets with talc.

*Manufacture of Component II – CD-LD fast release beads coated with Eudragit® S100:L100 (2:1)*

20 CD/LD core seeds (also referred to as pellets) were prepared as Component I seeds except that there was no final blend with Talc. The enteric coating solution was prepared by dissolving Eudragit® S100 and Eudragit® L100 at the weight ratio of 2:1 and triethyl citrate in isopropyl alcohol and acetone solution. Talc was then dispersed into the polymer solution and mixed continuously throughout the coating process. The CD/LD pellets were spray coated using the coating dispersion in a coater. The coated pellets were dried and then screened through a 16 mesh screen. The final blend was prepared by blending the screened CD/LD pellets with talc.

*Manufacture of Component III – Tartaric acid fast release beads coated with Eudragit® S100:L100 (2:1)*

Tartaric acid was passed through a 20 mesh screen. Screened tartaric acid and 5 microcrystalline cellulose was charged in a high shear mixer and granulated with purified water. The wet mass was extruded in an extruder with 1.0 mm hole size screen. The extrudate was charged and spheronized in a spheronizer equipped with a 3 mm cross hatch disc and the resulting pellets dried overnight in an oven at 60 ± 10°C. The dried pellets were passed through 16, 18 and 25 mesh screens and the pellets retained on 18 and 10 25 mesh screens were collected.

A seal coat solution was prepared by dissolving hypromellose (Pharmacoat 606) and 15 ethylcellulose in alcoholic solution. The seal coat solution was applied to the tartaric acid pellets in a coater. The pellets were dried and the dried pellets passed through a 14 mesh screen.

An additional seal coat was produced by dissolving hypromellose (Pharmacoat 606) in 20 alcoholic solution. The seal coat solution was applied to the tartaric acid pellet coater, and then the pellets were dried in GPCCG-1. The dried pellets were passed through a 14 mesh screen.

An enteric coating solution was prepared by dissolving Eudragit® S100 and Eudragit® 25 L100 at the weight ratio of 2:1 and triethyl citrate in isopropyl alcohol and acetone solution. Mix until dissolved. Talc was dispersed into the polymer solution and mixed continuously throughout the coating process. The screened tartaric acid pellets were charged in a coater and spray coated with the enteric coating dispersion. The coated seeds were dried, and the dried, coated pellets screened through a 14 mesh screen. The final blend was prepared by blending the screened pellets and talc.

*Manufacture of Component IV – CD-LD fast release beads coated with Eudragit® S100:L100 (5:1)*

Method of manufacture for this component is the same as those of the component II

5 beads, except that the preparation of the enteric coating dispersion was changed. Specifically, the enteric coating dispersion is prepared by charging the required amount of a first portion of purified water in a stainless steel container, and to which while stirring, Methacrylic Acid Copolymer, Type A, NF were charged and dispersed, thereby making a dispersion. The required amount of 1N NH<sub>4</sub>OH solution was added drop wise to the

10 dispersion.

A required amount of a second portion of purified water in a separate stainless steel container was charged. While stirring, Methacrylic Acid Copolymer, Type B, NF were charged and dispersed. Then a required amount of 1N NH<sub>4</sub>OH solution was added drop wise

15 to the dispersion.

A required amount of a third portion of purified water was charged in a separate stainless steel container. Triethyl citrate was charged and dissolved and talc was added to the solution.

20

The first dispersion above was added and mixed to the second dispersion and to which was then added the third dispersion above. The mixed solutions were screened through 140 mesh screen.

25 *Manufacture of Component V – TA fast release beads coated with Eudragit® S100:L100 (5:1)*

Method of manufacture for component V beads is the same as those of the component III beads, except that the preparation of the enteric coating dispersion was changed.

30

Specifically the enteric coating dispersion was prepared by charging the required amount of a first portion of purified water in a stainless steel container and, to which, while stirring, Methacrylic Acid Copolymer, Type A, and NF were charged and dispersed to yield a dispersion; then the required amount of 1N NH<sub>4</sub>OH solution was added drop wise 5 to the above dispersion.

In a separate stainless steel container, the required amount of the second portion of purified water was charged and while stirring, Methacrylic Acid Copolymer, Type B, and NF were charge and dispersed to yield a dispersion; then the required amount of 1N 10 NH<sub>4</sub>OH solution was added to the above dispersion.

In a separate stainless steel container, the required amount of the third portion of purified water was charged and to which triethyl citrate was added and charged; then talc was added to the above solution.

15 The first dispersion above was added and mixed to the second dispersion and to which was then added the third dispersion above. The mixed solutions were screened through 140 mesh screen.

20 *Manufacture of the IPX066 Capsules*

The required amounts of the component beads were filled into hard gelatin capsules according to the specified fill weights in the Table 9 below. The in-process fill weight is controlled at target  $\pm$  10% of the target weights according to Table 9.

**Table 9 Target Fill Weights of IPX066 Capsule Test Formulations**

Components	Formulation			
	IPX066-AH1(A) mg/capsule	IPX066- AH1(B) mg/capsule	IPX066- AH1(C) mg/capsule	IPX066- AH1(D) mg/capsule
Component I Beads	184.97	---	---	---
Component II Beads	---	194.75	---	194.75
Component III Beads	---	208.55	---	417.1
Component IV Beads	---	---	210.25	---
Component V Beads	---	---	238.55	---
<b>Total Capsule Fill weight</b>	<b>403.3</b>	<b>448.8</b>	<b>611.85</b>	

*Pharmacokinetics result for biostudy IPX066- AH1*

5 The Pharmacokinetics parameters of CD and LD for four tested formulations compared to Sinemet® CR after oral administration are summarized in Table 10.

**Table 10 Mean ratio of Ln-transformed  $C_{max}$ , AUC of Levodopa and Carbidopa**

	Parameter	Test/Ref	Ratio (%)
LD	Ln( $C_{max}$ )	A/E	192.54
	Ln( $C_{max}$ )	B/E	127.05
	Ln( $C_{max}$ )	C/E	123.22
	Ln( $C_{max}$ )	D/E	111.99
	Ln(AUC)	A/E	126.53
	Ln(AUC)	B/E	115.03
	Ln(AUC)	C/E	127.15
	Ln(AUC)	D/E	108.74
CD	Ln( $C_{max}$ )	A/E	144.73
	Ln( $C_{max}$ )	B/E	88.97
	Ln( $C_{max}$ )	C/E	124.35
	Ln( $C_{max}$ )	D/E	81.06
	Ln(AUC)	A/E	161.73
	Ln(AUC)	B/E	91.24
	Ln(AUC)	C/E	139.79
	Ln(AUC)	D/E	88.03

*Results and Discussion:*

The data herein demonstrated that formulation A, with the inclusion of water soluble filler such as lactose and a surfactant such as sodium lauryl sulfate, exhibits a rapid LD absorption with a  $t_{max}$  of 30 min. The PK profiles of Formulation B and D are desirable. Both formulations exhibit a significantly higher LD plasma concentration at 6 hours post-dose relative to the Sinemet® CR Tablet. The absorption of LD from formulation B and D are also similar as indicated by a relative AUC of 115% and 109%, respectively. Since the PK profiles of formulation B and D are similar, formulation D with double the quantity of TA beads does not offer any additional benefit over formulation B. Formulation C, with coating consisting of Eudragit® S100:L100 ratio of 5:1, exhibits a PK profile suggesting a faster in-vivo release relative to formulation C and D. This is further supported by an AUC of 127% relative to Sinemet® CR Tablet indicating LD was rapidly released and absorbed in the upper GI tract.

15

**EXAMPLE 5**

The data herein shows the bioavailability/pharmacokinetic results of an enteric coated tablet CD/LD formulations, using 50-300 mg of CD-LD with 0-270 mg of tartaric acid compared to the controlled release version of Sinemet®. Information of study drugs are listed below in Table 11.

IPX066-AH2 Formulation A (IPX066-AH2(A)) is a capsule containing 5 different component beads. Component I is an immediate-release CD/LD bead type. Component II is an ER CD/LD bead type with a fast ER release profile. Component III is an ER CD/LD bead type with a slow ER release profile. Component IV is a TA bead type with a release profile similar to those of Component II. Component V is a TA bead type with a release profile similar to those of Component III.

IPX066-AH2 Formulation B (IPX066-AH2(B)) is a capsule containing ER CD/LD beads formulated with Cremophor RH40 and Poloxamer 188. TA is not included in the formulation.

5 IPX066-AH2 Formulation C (IPX066-AH2(C)) is a capsule containing ER CD/LD beads formulated with Cremophor RH40 and Poloxamer 188, and TA.

IPX066-AH2 Formulation D (IPX066-AH2(D)) is a capsule containing ER CD/LD beads formulated with TA. The capsule does not contain Cremophor RH40 nor Poloxamer 188.

10

The reference product is Sinemet® CR Tablet 200 mg.

**Table 11. IPX066-AH2**

Product		CD-LD Strength (mg)	Enteric Coated pH
A	IPX066 CD/LD Combo Capsule with 270 mg tartaric acid (IR + fast release core +slow release core)	75-300	6.5 (SL2) for fast and slow release core
B	IPX066 CD/LD Capsule with surfactants	50-200	6.5 (SL2)
C	IPX066 CD/LD/tartaric acid Capsule with 215 mg tartaric acid and surfactants	50-200	6.5 (SL2)
D	IPX066 CD/LD/tartaric acid Capsule with 215 mg tartaric acid	50-200	6.5 (SL2)
E	Sinemet® CR Tablet <sup>a</sup>	50-200	--

<sup>a</sup> Merck & Co., Inc.

15

The qualitative and quantitative compositions for these formulations are summarized below in Table 12 and Table 13.

**Table 12. Formulation A (IPX066-AH2(A))**

<b>Ingredients</b>		<b>Formulation A</b>
		<b>mg/capsule</b>
<b>Component I</b>		
Carbidopa USP		6.75
Levodopa USP		25
Microcrystalline Cellulose NF		4.6
Lactose Monohydrate NF		4.5
Sodium Starch Glycolate NF		2.3
Sodium Lauryl Sulfate NF		2.3
Povidone USP		0.46
Talc USP		0.23
Purified Water, USP		N/A*
<b>Component II</b>		
Carbidopa USP		6.75
Levodopa USP		25
Microcrystalline Cellulose NF		4.6
Lactose Monohydrate NF		4.6
Sodium Starch Glycolate NF		2.3
Sodium Lauryl Sulfate NF		2.3
Povidone USP		0.46
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		0.55
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		1.15
Triethyl Citrate NF		0.48
Talc USP		0.49
Acetone, NF		N/A*
Isopropyl Alcohol, USP		N/A*
Purified Water, USP		N/A*
<b>Component III</b>		
Carbidopa USP		26.99
Levodopa USP		100
Microcrystalline Cellulose NF		54.42
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		2.18
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		4.5
Triethyl Citrate NF		1.91
Talc USP		1.91
Acetone, NF		N/A*
Isopropyl Alcohol, USP		N/A*
Purified Water, USP		N/A*
<b>Component IV</b>		

Tartaric acid NF		27
Microcrystalline Cellulose NF		6.79
Ethylcellulose NF		2.81
Hypromellose, Type 2910 USP		5.01
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		2.44
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		4.84
Triethyl Citrate NF		2.08
Talc USP		1.31
Acetone, NF		N/A*
Isopropyl Alcohol, USP		N/A*
Purified Water, USP		N/A*
<b>Component V</b>		
Tartaric acid NF		107.5
Microcrystalline Cellulose NF		26.85
Ethylcellulose NF		12.38
Hypromellose Type 2910 USP		2.63
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		8.62
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		17.5
Triethyl Citrate NF		7.45
Talc USP		4.69
Acetone, NF		N/A*
Isopropyl Alcohol, USP		N/A*
Purified Water, USP		N/A*
Hard Gelatin Capsule		1 unit
<b>Total Capsule Fill weight</b>		<b>526.63</b>

\*evaporated in drying process

**Table 13. Formulation B, C and D (IPX066-AH2(B), IPX066-AH2(C), IPX066-AH2(D))**

Ingredients		Formulation		
		B	C	D
		mg/capsule	mg/capsule	mg/capsule
Carbidopa USP		26.99	26.99	26.99
Levodopa USP		100	100	100
Microcrystalline Cellulose, NF		118.75	65.00	30.00
Lactose Monohydrate NF		53.75	---	---
Mannitol, USP		---	---	50.00
Povidone, USP		17.35	---	---
Talc, USP		23.99	11.11	9.97
Methacrylic acid copolymer, Type A, NF (Eudragit® L100)		48.98	20.13	18.09
Methacrylic acid Copolymer, Type B, NF (Eudragit® S100)		98.19	40.35	36.17
Triethyl Citrate, NF		42.18	17.32	15.55
Poloxamer 188, NF		33.5	33.5	---
Polyoxyl 40 Hydrogenated Castor Oil, NF (Cremophor RH 40)		17.5	17.5	---
Tartaric acid, NF		---	107.5	107.5
Hypromellose, USP Type 2910		---	52.58	47.18
Acetone, NF		N/A*	N/A*	N/A*
Isopropyl Alcohol, USP		N/A*	N/A*	N/A*
Purified Water, USP		N/A*	N/A*	N/A*
Hard Gelatin Capsule		1 unit	1 unit	1 unit
<b>Total Capsule Fill Weight</b>		<b>581.18</b>	<b>491.98</b>	<b>441.45</b>

\*evaporated in drying process

*Manufacture of Formulation A (IPX066-AH2(A))**Manufacture of Component Bead I – CD/LD Fast release beads*

5 Method of manufacture for this component beads is the same as to that for component I beads in IPX066-AH1, as discussed in Example 4 above.

*Manufacture of Component II – CD-LD fast release beads coated with Eudragit® S100:L100 (2:1)*

10 Method of manufacture for this component beads is the same as that for component II beads in IPX066-AH1, as discussed in Example 4 above.

*Manufacture of Component III – CD-LD slow release beads coated with Eudragit®*

15 *S100:L100 (2:1)*

Method of manufacture for this component beads is the same as that for enteric coated CD-LD beads in formulation A tested in IPX066-B06-02, as discussed in Example 2 above.

20 *Manufacture of Component IV – TA fast release beads coated with Eudragit® S100:L100 (2:1)*

25 Method of manufacture for this component beads is the same as that of component III beads in biostudy IPX066-AH1, as discussed in Example 4 above.

*Manufacture of Component V – TA slow release beads coated with Eudragit® S100:L100 (2:1)*

5 Method of manufacture for this component beads is the same as that for enteric coated tartaric acid beads in formulation A tested in IPX066-B06-02 as discussed in Example 2 above.

*Manufacture of the IPX066 Capsules for Formulation A*

10 The required amounts of the component beads were filled into hard gelatin capsules according to the specified target fill weights  $\pm 10\%$ .

**Table 14. Target Fill Weights of IPX066 Capsule Test Formulations.**

Components	IPX066-AH2(A) mg/capsule
Component I Beads	46.2
Component II Beads	48.7
Component III Beads	191.9
Component IV Beads	52.1
Component V Beads	187.7
<b>Total Capsule Fill weight</b>	<b>526.6</b>

15 *Manufacture of Test Formulation B (IPX066-AH2(B))*

To make formulation B, a suitable amount of ethanol and purified water were mixed and to which Cremophor RH40 was dissolved and charged in a first solution; then povidone was charged and mixed in the solution. A separate granulating fluid was prepared by 20 dissolving the required amount of povidone in the required amount of purified water.

Suitable amounts of carbidopa, levodopa, microcrystalline cellulose, lactose monohydrate and poloxamer were charged into a suitable granulator and mixed until a uniform powder is formed.

The mixed powder was granulated by adding the first solution above followed by continued granulation by adding the separate granulating fluid above thereby resulting in a wet mass. The wet mass was extruded through a suitable extruder equipped with a screen size of 1.0 mm. The extrudate was spheronized in a spheronizer at an appropriate speed and the wet extruded beads were dried in a fluidized bed dryer. The dried beads were then passed through a US #16 mesh screen, US #18 mesh screen, US #25 mesh screen and pan. Only the beads that pass through 18 mesh but retained on 25 mesh screen are collected.

10 The enteric coating dispersion was prepared by dispensing and mixing a suitable amount of acetone and isopropyl alcohol and while mixing the solution, triethyl citrate was charged and dissolved in the solution. The mixing was continued until the material was fully dissolved. While mixing, Methacrylic Acid Copolymer, Type A, NF was charged to the solution. The solution was mixed until the material was fully dissolved then again 15 while mixing, Methacrylic Acid Copolymer, Type B, NF was charged to the solution. Mixing continued until the material was fully dissolved. While mixing, talc was charged and dispersed in the solution. Mixing continued throughout the coating process.

20 The collected beads above were charged into a suitable fluidized-bed coater equipped with a Wurster insert and were spray coated using the enteric coating dispersion above. The coated beads were dried, and the dried beads were passed through a US #14 mesh screen. The resulting screened material was charged and a suitable amount of talc was added to it in a suitable blender and mixed until uniform.

25 ***Manufacture of Test Formulation C (IPX066-AH2(C))***

A suitable amount of ethanol and purified water was dispensed and mixed in a stainless steel container to which was charged and dissolved a suitable amount of Cremophor RH40 resulting in a granulating solution.

A suitable amount of carbidopa, levodopa, tartaric acid, microcrystalline cellulose, and poloxamer was charged into a suitable granulator and mixed until uniform. The mixed powder was granulated with the granulating solution above thus creating a wet mass. The wet mass was extruded through a suitable extruder equipped with a screen size of 1.0 mm  
5 and the extrudate was spheronized in a suitable spheronizer at an appropriate speed.

The wet extruded beads were dried in the fluidized bed dryer. The LOD was measured using a Moisture Analyzer and the drying process was stopped when the LOD value was not more than a target value 3%. The dried beads were then passed through a US #16  
10 mesh screen, US #18 mesh screen, US #25 mesh screen and pan. Only the beads retained on 18 mesh and on 25 mesh screen were collected and blended.

The seal coat solution was prepared as follows. An ethanol solution was prepared by mixing the required amount of Alcohol, USP and purified water in a stainless steel  
15 container. A suitable amount hypromellose was charged and dissolved in the ethanol solution.

The collected beads retained on 18 mesh and on 25 mesh screen were charged into a fluidized bed coater equipped with a Wurster insert and spray coated using the seal coat  
20 solution prepared above. The coated beads were dried in the fluidized bed and the dried beads were passed through a US #14 mesh screen. The beads that pass through the screen were collected.

The enteric coating dispersion was prepared as follows. A suitable amount of  
25 Methacrylic Acid Copolymer, Type A, NF, Methacrylic Acid Copolymer, Type B, NF, triethyl citrate and talc were dispensed. A suitable amount of acetone and isopropyl alcohol were mixed well and during the mixing, triethyl citrate was charged and mixed into the solution. Methacrylic Acid Copolymer, Type A, NF was further charged into the solution. Mixing continued until the material was fully dissolved. Methacrylic Acid  
30 Copolymer, Type B, NF was additionally charged into the solution. Mixing continued

until the material was fully dissolved. Talc was then charged and dispersed in the solution. Mixing occurred throughout the process.

The collected beads were coated with the enteric coating dispersion as follows. The  
5 collected beads were charged in a suitable fluidized-bed coater equipped with a Wurster insert and spray coated with the enteric coating dispersion above. The coated beads were then dried and the dried beads passed through a US #14 mesh screen. The screened material was mixed and charged with a suitable amount of talc in a blender.

10 ***Manufacture of Test Formulation D (IPX066-AH2(D))***

A granulating solution was prepared by dissolving polyoxyl in a solution of ethanol and purified water.

15 A suitable amount of carbidopa, levodopa, screened tartaric acid, microcrystalline cellulose, lactose monohydrate and poloxamer were charged and mixed in a granulator. The mixed material was granulated with the granulating solution thereby creating a wet mass. The wet mass was extruded through a suitable extruder equipped with a screen size of 1.0 mm. The resulting extrudates were spheronized in a suitable spheronizer. The wet  
20 extruded beads were dried in a fluidized bed dryer and the LOD was measuring using a Moisture Analyzer. The drying process was stopped when the LOD value is not more than a target value 3%.

The dried beads were passed through a US #16 mesh screen, US #18 mesh screen, US  
25 #25 mesh screen and pan. Only the beads retained on 18 mesh and on 25 mesh screen were collected and retained.

The dried beads were coated with a seal coat. The seal coat may be prepared as follows. An ethanol solution was prepared by mixing the required amount of Alcohol, USP and  
30 purified water in a stainless steel container to which a suitable amount hypromellose was charged. The dried beads were charged into a fluidized bed coater equipped with a

Wurster insert and spray coated using the seal coat solution. The coated beads were then dried in a fluidized bed and the dried coated beads passed through a US #14 mesh screen. The beads that passed through the screen were collected.

5 The collected beads were coated with an enteric coating dispersion. The enteric coating dispersion was prepared as follows. A suitable amount of Methacrylic Acid Copolymer, Type A, NF, Methacrylic Acid Copolymer, Type B, NF, triethyl citrate and talc was dispersed. A suitable amount of acetone and isopropyl alcohol was mixed well. During the mixing, triethyl citrate was charged and dissolved in the acetone and isopropyl alcohol  
10 solution. Then while mixing, Methacrylic Acid Copolymer, Type A, and NF were charged into the solution. Mixing continued until the material was fully dissolved. During the mixing, Methacrylic Acid Copolymer, Type B, and NF were charged into the solution. Mixing continued until the material was fully dissolved. Then talc was charged and dissolved in the solution. Mixing continued throughout the coating process.

15 The seal coated beads were charged into a suitable fluidized-bed coater equipped with a Wurster insert and spray coated using the enteric coating dispersion. The resulting coated beads were dried and the dried beads were passed through a US #14 mesh screen. The screened material were charged and mixed with a suitable amount of talc in a blender  
20 until uniform.

#### ***Pharmacokinetics result for biostudy IPX066-AH2***

25 The Pharmacokinetics parameters of CD and LD for four tested formulations compared to Sinemet® CR after oral administration are summarized in Table 15.

**Table 15. Mean ratio of Ln-transformed  $C_{\max}$ , AUC of Levodopa and Carbidopa**

	Parameter	Test/Ref	Ratio (%)
LD	Ln( $C_{\max}$ )	A/E	80.73
	Ln( $C_{\max}$ )	B/E	16.19
	Ln( $C_{\max}$ )	C/E	18.15
	Ln( $C_{\max}$ )	D/E	16.55
	Ln(AUC)	A/E	108.65
	Ln(AUC)	B/E	10.54
	Ln(AUC)	C/E	15.08
	Ln(AUC)	D/E	15.79
CD	Ln( $C_{\max}$ )	A/E	80.12
	Ln( $C_{\max}$ )	B/E	7.03
	Ln( $C_{\max}$ )	C/E	13.85
	Ln( $C_{\max}$ )	D/E	14.41
	Ln(AUC)	A/E	94.93
	Ln(AUC)	B/E	2.69
	Ln(AUC)	C/E	12.54
	Ln(AUC)	D/E	11.06

### *Results and Discussion*

5 The data herein demonstrated that formulation A achieved a desirable *in vivo* plasma concentration profile. By combining two components of tartaric acid beads (with enteric coating on either fast or slow release core) with three components of CD/LD drug seeds/beads (instant release portion, and enteric coated portion with coating on either fast or slow release core), formulation A showed a significantly flatter plasma concentration profile with a lower  $C_{\max}$  (80.7%) and comparable AUC (109%) relative to the reference drug Sinemet<sup>®</sup> CR.

10

A PK simulation study was conducted to calculate the peak to trough plasma concentration (PT) ratio assuming a three times daily (every 6 hours) dosing regimen.

15 The PT ratio is defined on steady state 18 hours post-dose plasma concentration. The

simulation results are summarized in Table 16, showing that formulation A has a significantly lower, 1.7, PT ratio relative to Sinemet® CR, 3.4.

The addition of surfactants in formulation significantly decreased LD bioavailability.

5 Moreover, it is more advantageous to have separate drug and tartaric acid seeds in formulation, and the incorporation of tartaric acid into same drug seeds significantly decreased LD bioavailability.

**Table 16. Simulation of Steady State Plasma Concentration, AUC, and Peak-to-trough Concentration Ratio.**

Formulation	CD-LD Dose (mg)	<i>C<sub>ss,max</sub></i>	<i>C<sub>ss,18hr</sub></i>	Peak to Trough Plasma Conc ratio
A (IPX066-AH2(A))	75-300	1030	591	1.7
E (reference)	50-200	1212	349	3.4

#### **EXAMPLE 6**

Formulation with separate CD/LD containing surfactant seeds and tartaric acid seeds for

15 IPX-066 was evaluated for PK parameters.

#### ***IPX066-AH3***

Information of study drugs are listed below in Table 17. Formulation A (IPX066-

20 AH3(A)) is a capsule containing ER CD/LD beads formulated with Cremophor RH40 and Poloxamer 188 and ER TA beads with a similar dissolution profile.

**Table 17. IPX066-AH3**

Product		CD-LD Strength (mg)	Enteric Coated pH
A (IPX066-AH3(A))	IPX066 CD/LD containing surfactant Capsule with 215 mg tartaric acid	50-200	6.5 (SL2)
B	Sinemet® CR Tablet <sup>a</sup>	50-200	--

<sup>a</sup> Merck & Co., Inc.

5 The qualitative and quantitative compositions for these formulations are summarized below in Table 18.

**Table 18. Qualitative and Quantitative Composition of Test Formulation**

Ingredients	Formulation A (IPX066-AH3(A))	
	mg/capsule	
		<b>Bead I</b>
Carbidopa, USP	17.99	
Levodopa, USP	66.67	
Microcrystalline Cellulose, NF (Avicel PH-101)	79.17	
Lactose Monohydrate, NF	35.83	
Poloxamer 188, NF (Lutrol F-68, NF)	22.33	
Polyoxyl 40 Hydrogenated Castor Oil, NF (Cremophor RH 40)	11.67	
Povidone, USP	11.57	
Methacrylic acid copolymer, Type A, NF (Eudragit® L100)	32.65	
Methacrylic acid Copolymer, Type B, NF (Eudragit® S100)	65.46	
Triethyl Citrate, NF	28.12	
Talc, USP	15.99	
Acetone, NF	N/A*	
Isopropyl Alcohol, USP	N/A*	
Purified Water, USP	N/A*	
		<b>Bead II</b>
Tartaric acid, NF	71.67	
Microcrystalline Cellulose, NF (Avicel PH-101)	17.93	

Ethylcellulose, NF (Ethocel Standard-10FP Premium)		7.53
Hypromellose, USP Type2910 (Pharmacoat 606, 6 cps)		13.50
Methacrylic acid copolymer, Type A, NF (Eudragit® L100)		14.77
Methacrylic acid Copolymer, Type B, NF (Eudragit® S100)		29.50
Triethyl Citrate, NF		12.63
Talc, USP		7.20
Acetone, NF		N/A*
Isopropyl Alcohol, USP		N/A*
Purified Water, USP		N/A*
Hard Gelatin Capsule		1 unit
<b>Total weight</b>		<b>562.18</b>

\*evaporated in drying process

*Manufacture of Test Formulation*

5 *Manufacture of Component Bead I – CD/LD beads*

Method of manufacture for this component beads is the same as to that for formulation B of IPX066-AH2, as discussed above in Example 5.

*Manufacture of Component Bead II – TA beads*

10 Method of manufacture for this component beads is the same as that of component III beads in IPX066-AH1, except the content for enteric coating is higher in formulation, as discussed in Example 4 above.

*Pharmacokinetics result for IPX066-AH3:*

15 The Pharmacokinetics parameters of CD and LD for tested formulations compared to Sinemet® CR after oral administration are summarized in Table 19.

**Table 19. Mean ratio of Ln-transformed  $C_{max}$ , AUC of Levodopa and Carbidopa**

	Parameter	Test/Ref	Ratio (%)
LD	Ln( $C_{max}$ )	A/B	14.89
	Ln(AUC)	A/B	9.88
CD	Ln( $C_{max}$ )	A/B	4.87
	Ln(AUC)	A/B	7.11

*Results and Discussions*

5 The addition of surfactants in formulation significantly decreased LD bioavailability even when the formulation contains separate drug and tartaric acid seeds.

**EXAMPLE 7**10 ***Formulations for IPX066-AH4***

Four formulations of IPX-066 were evaluated for PK parameters. Information of study drugs are listed below in Table 20.

15 **Table 20. IPX066-AH4**

Formulation	CD-LD (mg)	Dose	Molar Ratio of TA : LD	Amount of Capsule /dose
A (IPX066-AH4(A))		75-300	1.4 :1	2
B (IPX066-AH4(B))		90-360	1.4 :1	3
C (IPX066-AH4(C))		90-360	0.5 :1	2
D (IPX066-AH4(D))		90-360	0.75 :1	2
Sinemet® CR Tablet <sup>a</sup>	50-200		--	--

<sup>a</sup> Merck & Co., Inc.

These formulations contain CD/LD beads and LD beads with different release characteristics. Similar to formulation A of IPX066-AH2, these beads are coated with Eudragit® L100 and S100 polymer in the ratio of 1:2. The quantities of CD/LD and TA in each of the bead type are shown in Table 20.

5

Component I is a CD/LD bead type which exhibits an immediate-release dissolution profile.

10 Component II is a CD/LD bead type which exhibits a faster extended-release dissolution profile.

Component III is a CD/LD bead type which exhibits a slower extended-release dissolution profile.

15 Component IV is a TA bead type which exhibits a dissolution profile which mimics those of component II.

Component V is a TA bead type which exhibits a dissolution profile which mimics those of component III.

20

Component VI is a TA bead type which exhibits an intermediate dissolution profile between those of component II and III.

25

The qualitative and quantitative compositions for these formulations are summarized below in Table 21.

**Table 21. Qualitative and Quantitative Composition of Formulation**

	Formulation A (IPX066- AH4(A))	Formulation B (IPX066- AH4(B))	Formulation C (IPX066- AH4(C))	Formulation D (IPX066- AH4(D))
Ingredients	mg/capsule	mg/capsule	mg/capsule	mg/capsule
<b>Component I</b>				
Carbidopa USP	6.75	6.48	9.72	9.72
Levodopa USP	25	24	36	36
Microcrystalline Cellulose NF	4.6	4.42	6.62	6.62
Lactose Monohydrate NF	4.6	4.42	6.62	6.62
Sodium Starch Glycolate NF	2.3	2.21	3.31	3.31
Sodium Lauryl Sulfate NF	2.3	2.21	3.31	3.31
Povidone USP	0.46	0.44	0.66	0.66
Talc USP	0.23	0.22	0.33	0.33
Purified Water, USP	N/A*	N/A*	N/A*	N/A*
<b>Component II</b>				
Carbidopa USP	6.75	5.4	8.10	8.10
Levodopa USP	25	20	30	30
Microcrystalline Cellulose NF	4.6	3.68	5.52	5.52
Lactose Monohydrate NF	4.6	3.68	5.52	5.52
Sodium Starch Glycolate NF	2.3	1.84	2.76	2.76
Sodium Lauryl Sulfate NF	2.3	1.84	2.76	2.76
Povidone USP	0.46	0.37	0.55	0.55
Methacrylic acid copolymer, Type A NF (Eudragit® L100)	0.56	0.45	0.67	0.67
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)	1.14	0.91	1.36	1.36
Triethyl Citrate NF	0.49	0.39	0.58	0.58
Talc USP	0.49	0.39	0.58	0.58
Acetone, NF	N/A*	N/A*	N/A*	N/A*
Isopropyl Alcohol, USP	N/A*	N/A*	N/A*	N/A*
Purified Water, USP	N/A*	N/A*	N/A*	N/A*
<b>Component III</b>				
Carbidopa USP	26.99	20.51	30.77	30.77
Levodopa USP	100.00	76.00	114.00	114.00
Microcrystalline Cellulose NF	54.43	41.36	62.04	62.04
Methacrylic acid copolymer, Type A NF (Eudragit® L100)	2.19	1.67	2.50	2.50
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)	4.49	3.41	5.12	5.12
Triethyl Citrate NF	1.91	1.45	2.18	2.18
Talc USP	1.92	1.46	2.18	2.18
Acetone, NF	N/A*	N/A*	N/A*	N/A*
Isopropyl Alcohol, USP	N/A*	N/A*	N/A*	N/A*

Purified Water, USP	N/A*	N/A*	N/A*	N/A*
<b>Component IV</b>				
Tartaric acid NF	27.00	21.50	11.40	-
Microcrystalline Cellulose NF	6.74	5.37	2.85	-
Ethylcellulose NF	2.81	2.24	1.19	-
Hypromellose, Type 2910 USP	0.94	0.75	0.40	-
Methacrylic acid copolymer, Type A NF (Eudragit® L100)	2.16	1.72	0.91	
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)	4.41	3.51	1.86	-
Triethyl Citrate NF	1.87	1.49	0.79	-
Talc USP	1.18	0.94	0.50	-
Acetone, NF	N/A*	N/A*	N/A*	-
Isopropyl Alcohol, USP	N/A*	N/A*	N/A*	-
Purified Water, USP	N/A*	N/A*	N/A*	-
<b>Component V</b>				
Tartaric acid NF	107.50	81.70	43.4	-
Microcrystalline Cellulose NF	26.90	20.44	10.86	-
Ethylcellulose NF	12.40	9.42	5.00	-
Hypromellose Type 2910 USP	2.55	1.94	1.03	-
Methacrylic acid copolymer, Type A NF (Eudragit® L100)	8.60	6.54	3.47	-
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)	17.55	13.34	7.09	-
Triethyl Citrate NF	7.45	5.66	3.01	-
Talc USP	4.70	3.57	1.90	-
Acetone, NF	N/A*	N/A*	N/A*	-
Isopropyl Alcohol, USP	N/A*	N/A*	N/A*	-
Purified Water, USP	N/A*	N/A*	N/A*	-
<b>Component VI</b>				
Tartaric acid NF	-	-	-	82.20
Microcrystalline Cellulose NF	-	-	-	20.57
Ethylcellulose NF	-	-	-	9.14
Hypromellose Type 2910 USP	-	-	-	2.29
Methacrylic acid copolymer, Type A NF (Eudragit® L100)				6.58
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)	-	-	-	13.42
Triethyl Citrate NF	-	-	-	5.70
Talc USP	-	-	-	3.59
Acetone, NF	N/A*	N/A*	N/A*	N/A*
Isopropyl Alcohol, USP	N/A*	N/A*	N/A*	N/A*
Purified Water, USP	N/A*	N/A*	N/A*	N/A*
Hard Gelatin Capsule	1 unit	1 unit	1 unit	1 unit
<b>Total Capsule Fill weight</b>	<b>521.62</b>	<b>409.34</b>	<b>439.41</b>	<b>487.25</b>

\* evaporated in drying process

***Manufacture of Test Formulations******Manufacture of Component I – CD-LD fast release beads***

5

Method of manufacture for this component beads is the same as to that for component I beads for formulation A in IPX066-AH2, as discussed in Example 5 above.

***Manufacture of Component II – CD-LD fast release beads coated with Eudragit®***10 *S100:L100 (2:1)*

Method of manufacture for this component beads is the same as to that for component II beads for formulation A in IPX066-AH2, as discussed in Example 5 above.

15 *Manufacture of Component III – CD-LD slow release beads coated with Eudragit® S100:L100 (2:1)*

Method of manufacture for this component beads is the same as to that for component III beads for formulation A in IPX066-AH2, as discussed in Example 5 above.

20

*Manufacture of Component IV – TA fast release beads coated with Eudragit® S100:L100 (2:1)*25 

Method of manufacture for this component beads is the same as to that for component IV beads for formulation A in IPX066-AH2, as discussed in Example 5 above, except no additional seal coat was introduced between seal coating layer and enteric coating layer.

*Manufacture of Component V – TA slow release beads coated with Eudragit® S100:L100 (2:1)*

Method of manufacture for this component beads is the same as to that for component V beads for formulation A in IPX066-AH2, as discussed in Example 5 above.

*Manufacture of Component VI – TA medium release beads coated with Eudragit® S100:L100 (2:1)*

10 Method of manufacture for this component beads is the same as to that for component V beads except the content ratio of ethylcellulose/hypromellose in seal coating is 4/1 instead of 5/1.

*Manufacture of the IPX066 Capsules*

15 The required amounts of the component beads were filled into hard gelatin capsules according to the specified fill weights in the Table 22 below. The in-process fill weight is controlled at target  $\pm$  10% of the target weights according to Table 22.

20 **Table 22. Target Fill Weights of IPX066 Capsule Test Formulations**

Components	Formulation Code			
	IPX066-AH4(A) mg/capsule	IPX066- AH4(B) mg/capsule	IPX066- AH4(C) mg/capsule	IPX066- AH4(D) mg/capsule
Component I Beads	46.24	44.4	66.57	66.57
Component II Beads	48.69	38.95	58.40	58.40
Component III Beads	191.93	145.86	218.79	218.79
Component IV Beads	47.11	37.52	19.89	-
Component V Beads	187.65	142.61	75.76	-
Component VI Beads	-	-	-	143.49
<b>Total Capsule Fill weight</b>	<b>521.62</b>	<b>409.34</b>	<b>439.41</b>	<b>487.25</b>

**Pharmacokinetics result for IPX066-AH4**

The Pharmacokinetics parameters of CD and LD for four tested formulations compared to Sinemet® CR after oral administration are summarized in Table 23.

5

**Table 23. Mean ratio of Ln-transformed  $C_{\max}$ , AUC of Levodopa and Carbidopa**

	Parameter	Test/Ref	Ratio (%)
LD	Ln( $C_{\max}$ )	A/E	92.29
	Ln( $C_{\max}$ )	B/E	119.02
	Ln( $C_{\max}$ )	C/E	132.54
	Ln( $C_{\max}$ )	D/E	133.78
	Ln(AUC)	A/E	105.14
	Ln(AUC)	B/E	136.15
	Ln(AUC)	C/E	143.73
	Ln(AUC)	D/E	154.34
CD	Ln( $C_{\max}$ )	A/E	92.76
	Ln( $C_{\max}$ )	B/E	116.37
	Ln( $C_{\max}$ )	C/E	126.66
	Ln( $C_{\max}$ )	D/E	135.66
	Ln(AUC)	A/E	111.12
	Ln(AUC)	B/E	149.98
	Ln(AUC)	C/E	145.70
	Ln(AUC)	D/E	164.13

*Results and Discussion*

10 Test formulation A (IPX066-AH4(A)) showed a consistent *in vivo* plasma concentration profile as those of formulation A (IPX066-AH2(A)) in IPX066-AH2. Formulation IPX066-AH2(A) and IPX066-AH4(A) differs only in the filler used, i.e. lactose in IPX066-AH2(A) and mannitol in IPX066-AH4(A). The relative AUC (relative to Sinemet® CR Tablet) is 109% and 105% for formulation IPX066-AH2(A) and IPX066-  
15 AH4(A), respectively. The relative  $C_{\max}$  (relative to Sinemet® CR Tablet) is 80.7% and

92.3% for formulation IPX066-AH2(A) and IPX066-AH4(A), respectively. Therefore, the in-vivo performance and bioavailability of the formulation is reproducible and consistent.

5 Based on a simulation study, the steady state peak to trough plasma concentration (PT) ratio was calculated assuming a three times daily, every 6 hours, dosing. The simulated PT ratios, defined as ratio of  $C_{\max}$  and  $C_{ss,18\text{hr}}$ , are summarized in Table 24. The results showed that PT ratio of formulation A (IPX066-AH4(A)), B (IPX066-AH4(B)), C (IPX066-AH4(C)), and D (IPX066-AH4(D)) are 1.8, 2.3, 2.8, and 2.0, respectively. The  
10 PT ratio of Sinemet® CR Tablet is 3.9. Therefore, all IPX066 test formulations have a lower PT ratio relative to the reference, Sinemet® CR Tablet.

The data herein also demonstrated the optimum molar ratio of TA:LD to be 0.75, when comparing PT ratio of formulation B, C, and D.

15 The PK results also indicated that replacing the TA beads of fast and slow release profiles with TA beads with an intermediate release profile in formulation did not change the overall *in vivo* LD plasma profile significantly, as evidenced by the PT ratio.

20 **Table 24. Simulation of Steady State Plasma Concentration, AUC, and Peak-to-trough Concentration Ratio.**

Test Formulation	CD-LD Dose (mg)	TA;LD Molar Ratio	$C_{ss,\max}$	$C_{ss,18\text{hr}}$	$AUC_{ss,24}$	Peak to Trough Plasma Conc ratio
A	75-300	1.4	920	511	13215	1.8
B	90-360	1.4	1238	549	17048	2.3
C	90-360	0.5	1337	477	18204	2.8
D	90-360	0.75	1384	679	19848	2.0
E (reference)	50-200	0	984	254	12348	3.9

**EXAMPLE 8**

IPX066-AH5(A) (47.5mg CD/190 mg LD) was evaluated for PK parameters in a three way cross over PK study using Sinemet® CR (200 mg) as reference. The qualitative and 5 quantitative compositions for this formulation are summarized below.

**Table 25. Quantitative Composition of Formulation IPX066-AH5(A)**

<b>Dosage strength</b>	<b>%</b>	<b>190 mg</b>
<b>Ingredients</b>		<b>mg/capsule</b>
Carbidopa	10.21	51.29*
Levodopa	37.84	190.00
Tartaric acid	17.63	88.52
Microcrystalline Cellulose	19.23	96.55
Mannitol	1.01	5.07
Ethylcellulose	2.03	10.2
Hypromellose, Type2910	0.43	2.16
Sodium Starch Glycolate	0.50	2.53
Sodium Lauryl Sulfate	0.50	2.53
Povidone	0.34	1.73
Talc	1.36	6.84
Methacrylic acid copolymer, Type A (Eudragit® L100)	2.09	10.51
Methacrylic acid Copolymer, Type B (Eudragit® S100)	4.25	21.33
Triethyl Citrate	1.82	9.16
Croscarmellose Sodium	0.69	3.46
Magnesium Stearate	0.05	0.25
Purified water	N/A**	N/A**
Isopropyl alcohol	N/A**	N/A**
Acetone	N/A**	N/A**
Ethyl alcohol	N/A**	N/A**
Total	100.00	502.13
Hard Gelatin Capsules	1 unit (size 00)	

\* Carbidopa is supplied as a monohydrate; the quantity is equivalent to 47.50 mg carbidopa anhydrous accordingly.

10

\*\* Evaporated during drying process.

*Manufacture of Formulation*

Four different component beads were manufactured for formulation IPX066-AH5(A).

5 The qualitative and quantitative compositions for each component seed are summarized in Table 26.

**Table 26. Qualitative and Quantitative Composition for 4 Component Beads in IPX066 Capsule Test Formulation**

10

Ingredients		Formulation
		Formulation Code
		IPX066-AH5(A)
<b>Component I</b>		
Carbidopa USP		9.45*
Levodopa USP		35.00
Croscarmellose Sodium		3.46
Povidone		1.23
Magnesium Stearate		0.25
Purified Water, USP		N/A**
<b>Component II</b>		
Carbidopa USP		7.43*
Levodopa USP		27.50
Microcrystalline Cellulose NF		5.07
Mannitol NF		5.07
Sodium Starch Glycolate NF		2.53
Sodium Lauryl Sulfate NF		2.53
Povidone USP		0.50
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		0.62
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		1.24
Triethyl Citrate NF		0.53
Talc USP		0.54
Acetone, NF		N/A**
Isopropyl Alcohol, USP		N/A**
Purified Water, USP		N/A**
<b>Component III</b>		
Carbidopa USP		34.41*
Levodopa USP		127.50
Microcrystalline Cellulose NF		69.39
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		2.79
Methacrylic acid Copolymer, Type B		5.72

NF (Eudragit® S100)		
Triethyl Citrate NF		2.45
Talc USP		2.44
Acetone, NF		N/A**
Isopropyl Alcohol, USP		N/A**
Purified Water, USP		N/A**
<b>Component IV</b>		
Tartaric acid NF		88.52
Microcrystalline Cellulose NF		22.09
Ethylcellulose NF		10.20
Hypromellose Type 2910 USP		2.16
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		7.10
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		14.37
Triethyl Citrate NF		6.18
Talc USP		3.86
Acetone, NF		N/A**
Isopropyl Alcohol, USP		N/A**
Purified Water, USP		N/A**
Hard Gelatin Capsule		1 unit
<b>Total Capsule Fill weight</b>		<b>502.13</b>

\* Carbidopa is supplied as a monohydrate; the quantity is equivalent to 8.75, 6.88, 31.87 mg carbidopa anhydrous in component I, II, III, respectively.

\*\*evaporated in drying process

##### 5 Manufacture of Component Bead I – CD/LD Ultra Fast release granules

The required amounts of carbidopa, levodopa, croscarmellose sodium, and povidone were charged into a high shear granulator and mix until uniform. The mixed powder was granulated by adding the purified water. The granules were discharged and dried in the oven at  $60 \pm 10^\circ\text{C}$ . The LOD was measured using a Moisture Analyzer and the drying process was stopped when the LOD value is not more than a target value. The granules were crushed by using mortar and pestle. The crushed granules were passed through a US #18 mesh screen, and collect the granules that pass through 18 mesh screen. The collected granules were blended with magnesium stearate.

*Manufacture of Component II – CD-LD fast release beads coated with Eudragit® S100:L100 (2:1)*

Method of manufacture and process flow diagram of this component beads is the same as  
5 those of component 2 beads of formulation A in IPX066-AH4 except that mannitol is replaced by lactose.

*Manufacture of Component III – CD-LD slow release beads coated with Eudragit® S100:L100 (2:1)*

10 Method of manufacture and process flow diagram for this component beads is the same as those of the component 3 beads of formulation A in IPX066-AH4.

*Manufacture of Component IV – TA slow release beads coated with Eudragit® S100:L100 (2:1)*

15 Method of manufacture and process flow diagram for this component beads is the same as those of the component 5 beads of formulation A in IPX066-AH4.

*Manufacture of the IPX066 Capsules for IPX066-AH5(A)*

20 The required amounts of the component beads were filled into hard gelatin capsules according to the specified target fill weights  $\pm 10\%$ .

25 **Table 27. Target Fill Weights of IPX066 Capsule Test Formulation.**

Components	IPX066-AH5(A) mg/capsule
Component I Beads	49.39
Component II Beads	53.56
Component III Beads	244.70
Component IV Beads	154.48
<b>Total Capsule Fill weight</b>	<b>502.13</b>

**EXAMPLE 9**

The example describes the formulations IPX066-AH6(A), and IPX066-AH6(B) and methods for making them.

5

**Table 28**

Formulation	%	IPX066-AH6(A)	IPX066-AH6(B)
Dosage strength		245 mg	195 mg
Ingredients		mg/capsule	mg/capsule
Carbidopa	10.21	66.14*	52.64*
Levodopa	37.84	245.00	195.00
Tartaric acid	17.63	132.53	105.48
Microcrystalline Cellulose	19.23	124.63	99.20
Mannitol	1.01	6.43	5.12
Ethylcellulose	2.03	15.27	12.15
Hypromellose, Type2910	0.43	3.23	2.57
Sodium Starch Glycolate	0.50	3.21	2.55
Sodium Lauryl Sulfate	0.50	3.21	2.55
Povidone	0.34	2.52	2.01
Talc	1.36	9.45	7.52
Methacrylic acid copolymer, Type A (Eudragit® L100)	2.09	14.84	11.81
Methacrylic acid Copolymer, Type B (Eudragit® S100)	4.25	30.11	23.97
Triethyl Citrate	1.82	12.93	10.29
Croscarmellose Sodium	0.69	5.31	4.23
Magnesium Stearate	0.05	0.38	0.30
Purified water	N/A**	N/A**	N/A**
Isopropyl alcohol	N/A**	N/A**	N/A**
Acetone	N/A**	N/A**	N/A**
Ethyl alcohol	N/A**	N/A**	N/A**
Total	100.00	675.19	537.39
Hard Gelatin Capsules		1 unit (size 00)	1 unit (size 0EL)

\* Carbidopa is supplied as a monohydrate; the quantity is equivalent to 61.25 mg, 48.75 mg carbidopa anhydrous accordingly.

\*\* Evaporated during drying process.

*Manufacture of Test Formulation*

5 Four different component beads were manufactured for test formulation IPX066-AH6(A) and AH6(B). The qualitative and quantitative compositions for each component seed are summarized in Table 29.

10 **Table 29. Qualitative and Quantitative Composition for 4 Component Beads in IPX066 Capsule Formulation**

Ingredients		IPX066-AH6(A)	IPX066-AH6(B)
		mg/capsule	mg/capsule
<b>Component I</b>			
Carbidopa USP		14.50*	11.54*
Levodopa USP		53.71	42.75
Croscarmellose Sodium		5.31	4.23
Povidone		1.89	1.50
Magnesium Stearate		0.38	0.30
Purified Water, USP		N/A**	N/A**
<b>Component II</b>			
Carbidopa USP		9.42*	7.50*
Levodopa USP		34.87	27.75
Microcrystalline Cellulose NF		6.43	5.12
Mannitol NF		6.43	5.12
Sodium Starch Glycolate NF		3.21	2.55
Sodium Lauryl Sulfate NF		3.21	2.55
Povidone USP		0.63	0.51
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		0.79	0.63
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		1.57	1.25
Triethyl Citrate NF		0.67	0.53
Talc USP		0.68	0.54
Acetone, NF		N/A**	N/A**
Isopropyl Alcohol, USP		N/A**	N/A**
Purified Water, USP		N/A**	N/A**
<b>Component III</b>			
Carbidopa USP		42.22*	33.60*
Levodopa USP		156.42	124.50
Microcrystalline Cellulose NF		85.13	67.76
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		3.42	2.72

Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		7.02	5.59
Triethyl Citrate NF		3.01	2.39
Talc USP		2.99	2.38
Acetone, NF		N/A**	N/A**
Isopropyl Alcohol, USP		N/A**	N/A**
Purified Water, USP		N/A**	N/A**
<b>Component IV</b>			
Tartaric acid NF		132.53	105.48
Microcrystalline Cellulose NF		33.07	26.32
Ethylcellulose NF		15.27	12.15
Hypromellose Type 2910 USP		3.23	2.57
Methacrylic acid copolymer, Type A NF (Eudragit® L100)		10.63	8.46
Methacrylic acid Copolymer, Type B NF (Eudragit® S100)		21.52	17.13
Triethyl Citrate NF		9.25	7.37
Talc USP		5.78	4.60
Acetone, NF		N/A**	N/A**
Isopropyl Alcohol, USP		N/A**	N/A**
Purified Water, USP		N/A**	N/A**
Hard Gelatin Capsule		1 unit	1 unit
<b>Total Capsule Fill weight</b>		<b>675.19</b>	<b>537.39</b>

\* Carbidopa is supplied as a monohydrate.

\*\*evaporated in drying process

*Manufacture of Component Bead I – CD/LD Ultra Fast release granules*

5 Method of manufacture and process flow diagram of this component beads is the same as those of component 1 beads of formulation A in IPX066-AH5 except that granules were dried by GPCG-1 instead of in an oven, and the granules were milled by Fitzmill instead of crushed by motor and pestle.

*Manufacture of Component II – CD-LD fast release beads coated with Eudragit® S100:L100 (2:1)*

10 Method of manufacture and process flow diagram of this component beads is the same as those of component 2 beads of formulation A in IPX066-AH5.

*Manufacture of Component III – CD-LD slow release beads coated with Eudragit® S100:L100 (2:1)*

Method of manufacture and process flow diagram for this component beads is the same  
5 as those of the component 3 beads of formulation A in IPX066-AH5.

*Manufacture of Component IV – TA slow release beads coated with Eudragit® S100:L100 (2:1)*

10 Method of manufacture and process flow diagram for this component beads is the same as  
those of the component 4 beads of formulation A in IPX066-AH5.

*Manufacture of the IPX066 Capsules for IPX066-AH6(A) and (B)*

15 The required amounts of the component beads were filled into hard gelatin capsules  
according to the specified target fill weights  $\pm 10\%$ .

**Table 30. Target Fill Weights of IPX066 Capsule Test Formulation.**

Components	IPX066-AH6(A) mg/capsule	IPX066-AH6(B) mg/capsule
Component I Beads	75.79	60.32
Component II Beads	67.91	54.05
Component III Beads	300.21	238.94
Component IV Beads	231.28	184.08
<b>Total Capsule Fill weight</b>	<b>675.19</b>	<b>537.39</b>

## CLAIMS

1. A controlled release oral solid formulation of levodopa comprising:
  - a. a controlled release component comprising levodopa, a decarboxylase inhibitor and one or more rate controlling excipients,
  - b. a carboxylic acid component comprising a carboxylic acid that is not levodopa or the decarboxylase inhibitor and one or more rate controlling excipients, and
  - c. an immediate release component comprising levodopa and a decarboxylase inhibitor,

wherein the carboxylic acid component of (b) is a distinct component and is coated with an enteric polymer; and wherein the controlled release component (a), the immediate release component (c) and the carboxylic acid component (b) comprise beads or granules.
2. The controlled release oral solid formulation of claim 1, wherein the carboxylic acid is
  - a. polycarboxylic acid or a dicarboxylic acid,
  - b. is selected from a group consisting of tartaric acid, adipic acid, succinic acid, citric acid, benzoic acid, acetic acid, ascorbic acid, edetic acid, fumaric acid, lactic acid, malic acid, oleic acid, sorbic acid, stearic acid, palmitic acid and boric acid or mixtures thereof,
  - c. tartaric acid.
3. The controlled release oral solid formulation of claim 1 or 2, wherein the decarboxylase inhibitor is carbidopa.
4. The controlled release oral solid formulation of claim 3, wherein
  - the ratio of carbidopa to levodopa is about 1:1 to about 1:10,
  - the ratio of carbidopa to levodopa is about 1:4,
  - the amount of carbidopa is about 48.75 mg and the amount of levodopa is about 195 mg,
  - the amount of carbidopa is about 61.25 mg and the amount of levodopa is about 245 mg, or
  - the amount of carbidopa is about 47.5 mg and the amount of levodopa is about 190 mg.
5. A multiparticulate, controlled release oral solid formulation of levodopa comprising:

- a. a controlled release component comprising levodopa, carbidopa and one or more rate controlling excipients;
- b. an immediate release component comprising levodopa and carbidopa, and
- c. a carboxylic acid component comprising a carboxylic acid that is not levodopa or carbidopa and one or more rate controlling excipients,

wherein the carboxylic acid component of (c) is a distinct component and is coated with an enteric polymer and wherein the controlled release component (a), the immediate release component (b) and the carboxylic acid component (c) comprise beads or granules.

6. The multiparticulate, controlled release oral solid formulation of claim 5, wherein the carboxylic acid component comprises a carboxylic acid selected from the group consisting of tartaric acid, adipic acid, succinic acid, citric acid, benzoic acid, acetic acid, ascorbic acid, edetic acid, fumaric acid, lactic acid, malic acid, oleic acid, sorbic acid, stearic acid, palmitic acid and boric acid or mixtures thereof; or is tartaric acid.
7. The controlled release oral solid formulation of any one of the preceding claims, having a ratio of moles of carboxylic acid to levodopa of greater than 1:4.
8. The controlled release oral solid formulation of any one of the preceding claims, having a ratio of moles of carboxylic acid to levodopa of greater than 1:4 and less than 3:2.
9. The multiparticulate, controlled release oral solid formulation of claim 5 or 6, comprising from about 25 mg to about 1000 mg levodopa.
10. The multiparticulate, controlled release oral solid formulation of claim 9 comprising about 50 to about 600 mg of levodopa.
11. The controlled release oral solid formulation of levodopa of claim 1 or 5 having:
  - a. a levodopa plasma or serum concentration profile comprising:
    - (i) a time of administration,
    - (ii) a first concentration, and
    - (iii) a second concentration,

wherein, said first concentration is equal to the maximum concentration of said profile; said second concentration is the minimum concentration occurring at a time later than said first concentration and earlier than or equal to about six hours following said time of administration; and wherein said second concentration is greater than or equal to about

fifty percent of said first concentration, and the formulation of claim 13, wherein said concentration profile optionally further comprises a third concentration, wherein said third concentration is greater than or equal to fifty percent of said first concentration and said third concentration occurs at a time earlier than said first concentration and within about ninety minutes of said time of administration,

- b. a median levodopa plasma or serum concentration profile comprising:
  - (i) a time of administration;
  - (ii) a first concentration at a first time, that occurs within one hour of said time of administration;
  - (iii) a second concentration at a second time, that occurs after said first time;
  - (iv) a third concentration at a third time, that occurs at least four hours after said second time;

wherein, said second concentration is equal to the maximum concentration of said profile; said first concentration is equal to about fifty percent of said second concentration; said third concentration is equal to about fifty percent of said second concentration,

c. a levodopa plasma or serum concentration profile substantially the same as levodopa formulation IPX066 in Figure 1 for a 380 mg dose of levodopa, or having a levodopa plasma or serum concentration profile substantially proportional to said formulation in Figure 1 for a dose other than 380 mg,

d. a levodopa plasma or serum concentration profile such that the ratio of the maximum concentration of said profile to the concentration at any time between one hour and seven hours after administration of said formulation is less than or equal to 4:1, or

- e. a median levodopa plasma or serum concentration profile comprising:
  - (i) a first concentration at a first time;
  - (ii) a second concentration at a second time, that occurs within about one hour after said first time;
  - (iii) a third concentration at a third time, that occurs at least four hours after said second time; and
  - (iv) a maximum concentration,

wherein, said second concentration is equal to the maximum concentration of said profile; said first concentration is equal to fifty percent of said second concentration; said third concentration is equal to fifty percent of said second concentration.

12. A stable, controlled release oral solid formulation of levodopa of claim 1 comprising levodopa, a decarboxylase inhibitor and a dicarboxylic acid wherein no more than 1% by weight of the degradation product of levodopa is present after being stored for 3 months at 40 degrees Centigrade and 75% relative humidity.
13. The controlled release oral solid formulation of claim 1 or 5, wherein the controlled release component is separately coated with an enteric polymer.
14. The controlled release oral solid formulation of claim 1, wherein the component of (a), (b), or (c) is a bead or granule.
15. The controlled release oral solid formulation of claim 1 or 5, wherein the formulation is a tablet or a caplet.
16. The controlled release oral solid formulation of claim 6 or 14, wherein the bead or granules have immediate release and controlled release components, have a size that pass through 12, 14, 16 or 18 mesh but are retained on 18 or 25 mesh screens.
17. The controlled release oral solid formulation of claim 16, wherein the bead or granules have immediate release and controlled release components, have a size that pass through 18 mesh but are retained on 25 mesh screens.
18. The multiparticulate, controlled release oral solid formulation of claim 5, wherein:
  - the amount of carbidopa is about 48.75 mg and the amount of levodopa is about 195 mg,
  - the amount of carbidopa is about 61.25 mg and the amount of levodopa is about 245 mg,
  - the amount of carbidopa is about 47.5 mg and the amount of levodopa is about 190 mg.
19. The controlled release oral solid formulation of levodopa of claim 1 or 5, wherein the rate controlling excipient is an enteric polymer or a mixture of more than one type of enteric polymer.
20. The controlled release oral solid formulation of levodopa of claim 1 or 5, wherein the controlled release component (a), the immediate release component (c) and the carboxylic

acid component are distinct, separable beads or granules; and wherein the carboxylic acid component (b) comprises a carboxylic acid that is not in (a) and (c).

21. The controlled release oral solid formulation of claim 3 or 6, wherein the ratio of carbidopa to levodopa is about 1:4, and a ratio of moles of carboxylic acid to levodopa is greater than 1:4 and less than 3:2.
22. The controlled release oral solid formulation of claim 1 or 5, wherein the carboxylic acid is physically separated from levodopa and the decarboxylase inhibitor.
23. The multiparticulate, controlled release oral solid formulation of claim 3 or 5, wherein a ratio in weight of levodopa:carbidopa:carboxylic acid component is any of:
  - a. 245.00 mg:61.25 mg:132.53 mg;
  - b. 195.00 mg:48.75 mg:105.48 mg;
  - c. 190.00 mg:47.50 mg:88.52 mg;
  - d. 180.00 mg:45.00 mg:82.20 mg;
  - e. 180.00 mg:45.00 mg:54.80 mg;
  - f. 120.00 mg:30.00 mg:103.20 mg; or
  - g. 150.00 mg:37.50 mg:134.50 mg;

with each value capable of varying by  $\pm 10\%$ .

24. The controlled release oral solid formulation of any one of claims 1 to 6, wherein a ratio of moles of carboxylic acid to levodopa is less than 3:2.
25. The multiparticulate, controlled release oral solid formulation of claim 5, wherein a ratio of moles of carboxylic acid to levodopa is greater than 1:4 and less than 3:2 and wherein the controlled release component and carboxylic acid component are separately coated with an enteric polymer.
26. The controlled release oral solid formulation of levodopa of claim 1, wherein the levodopa and decarboxylase inhibitor of (a) and (c) are not in (b).
27. The multiparticulate, controlled release oral solid formulation of levodopa of claim 7, wherein the levodopa and carbidopa of (a) and (b) are not in (c).
28. A controlled release oral solid formulation of levodopa comprising:

- a. a controlled release component comprising levodopa and a decarboxylase inhibitor, wherein the component is coated with a rate controlling excipient,
- b. a carboxylic acid component coated with a rate controlling excipient, and
- c. an immediate release component comprising levodopa and a decarboxylase inhibitor,

wherein the carboxylic acid component of (b) is a distinct component and wherein the carboxylic acid component (b) comprises a carboxylic acid that is not in (a) and (c).

- 29. The controlled release oral solid formulation of claim 3 or 5, wherein the decarboxylase inhibitor is carbidopa and a ratio in weight of levodopa:carbidopa is any of:
  - a. 245.00 mg:61.25 mg;
  - b. 195.00 mg:48.75 mg;
  - c. 190.00 mg:47.50 mg;
  - d. 180.00 mg:45.00 mg;
  - e. 180.00 mg:45.00 mg;
  - f. 120.00 mg:30.00 mg; or
  - g. 150.00 mg:37.50 mg;with each value capable of varying by  $\pm 10\%$ .
- 30. The controlled release oral solid formulation of claim 1 or 5, wherein the multiparticulate, controlled release oral solid formulation of levodopa is encapsulated in a capsule and the beads or granules therein may be removed from the capsule and sprinkled on food or liquid prior to administration.
- 31. The controlled release oral solid formulation of claim 3 or 5, wherein the controlled release oral solid formulation of levodopa comprises two controlled release components that release carbidopa and levodopa at different rates.
- 32. The controlled release oral solid formulation of claim 3 or 5, wherein the controlled release component comprises a carbidopa bead, or a levodopa bead.
- 33. The controlled release oral solid formulation of claim 3 or 5, wherein the bead or granule is in a tablet or capsule.

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34. The controlled release oral solid formulation of claim 1 or 5, wherein a single dose of the controlled release oral solid formulation administered to a human provides a levodopa plasma concentration profile comprising:
  - a. a time of administration;
  - b. a first peak concentration at a first time that occurs less than or equal to about two hours from said time of administration;
  - c. a second peak concentration at a second time that occurs between about 4 and about 7 hours after said time of administration.
35. The controlled release oral solid formulation of claim 34, wherein the minimum concentration between the first time and the second time is greater than or equal to 50% of the first peak concentration and greater than or equal to 50% of the second peak concentration.
36. The controlled release oral solid formulation of claim 15, wherein the tablet or caplet is a multi-layered or matrix tablet or caplet.
37. The controlled release oral solid formulation of claim 1, wherein the formulation is a multiparticulate.
38. The controlled release oral solid formulation of claim 5 or 37, wherein the multiparticulate formulation is encapsulated or pressed into a tablet.
39. Use of a formulation according to any one of claims 1-38 in the preparation of a medicament for the treatment of reducing motor fluctuations in a patient suffering from Parkinson's disease.
40. Use of a formulation according to any one of claims 1-38 in the preparation of a medicament for the treatment of reducing off time in a patient suffering from Parkinson's disease.
41. Use of a formulation according to any one of claims 1-38 in the preparation of a medicament for the treatment of increasing on time in a patient suffering from Parkinson's disease.

42. Use of a formulation according to any one of claims 1-38 in the preparation of a medicament for the treatment of reducing time to 'on' in a patient suffering from Parkinson's disease.
43. Use of a formulation according to any one of claims 1-38 in the preparation of a medicament for the treatment of enhancing dopamine levels in a subject suffering from a disease associated with reduced or impaired dopamine levels.
44. The use of claim 39, wherein the plasma or serum concentration of levodopa comprises: a controlled release oral solid formulation of levodopa having a levodopa plasma or serum concentration profile comprising:
  - a. a time of administration,
  - b. a first concentration, and
  - c. a second concentration,wherein, said first concentration is equal to the maximum concentration of said profile; said second concentration is the minimum concentration occurring at a time later than said first concentration and earlier than or equal to about six hours following said time of administration; and wherein said second concentration is greater than or equal to about fifty percent of said first concentration.
45. Use of a formulation according to any one of claims 1-38 in the preparation of a medicament for the treatment of providing a therapeutically effective and stable median blood plasma level of levodopa in a subject.
46. The use of claim 45, wherein the blood plasma level does not fluctuate more than 40% between 0.5 hours after administration and six hours after administration.

**Impax Laboratories, Inc.**

**Patent Attorneys for the Applicant/Nominated Person**  
**SPRUSON & FERGUSON**

# IPX066 Plasma Profiles vs. IR or CR

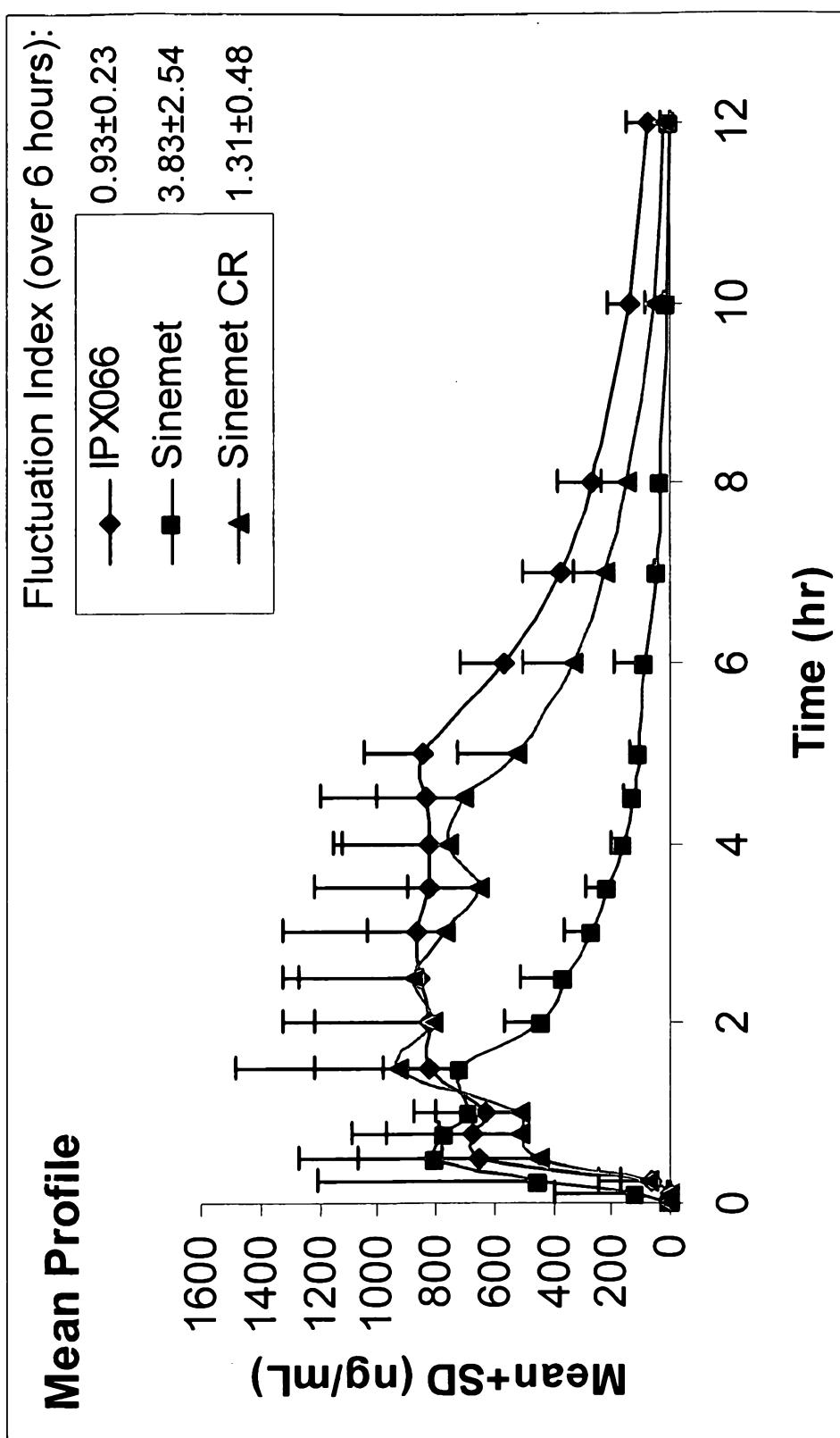
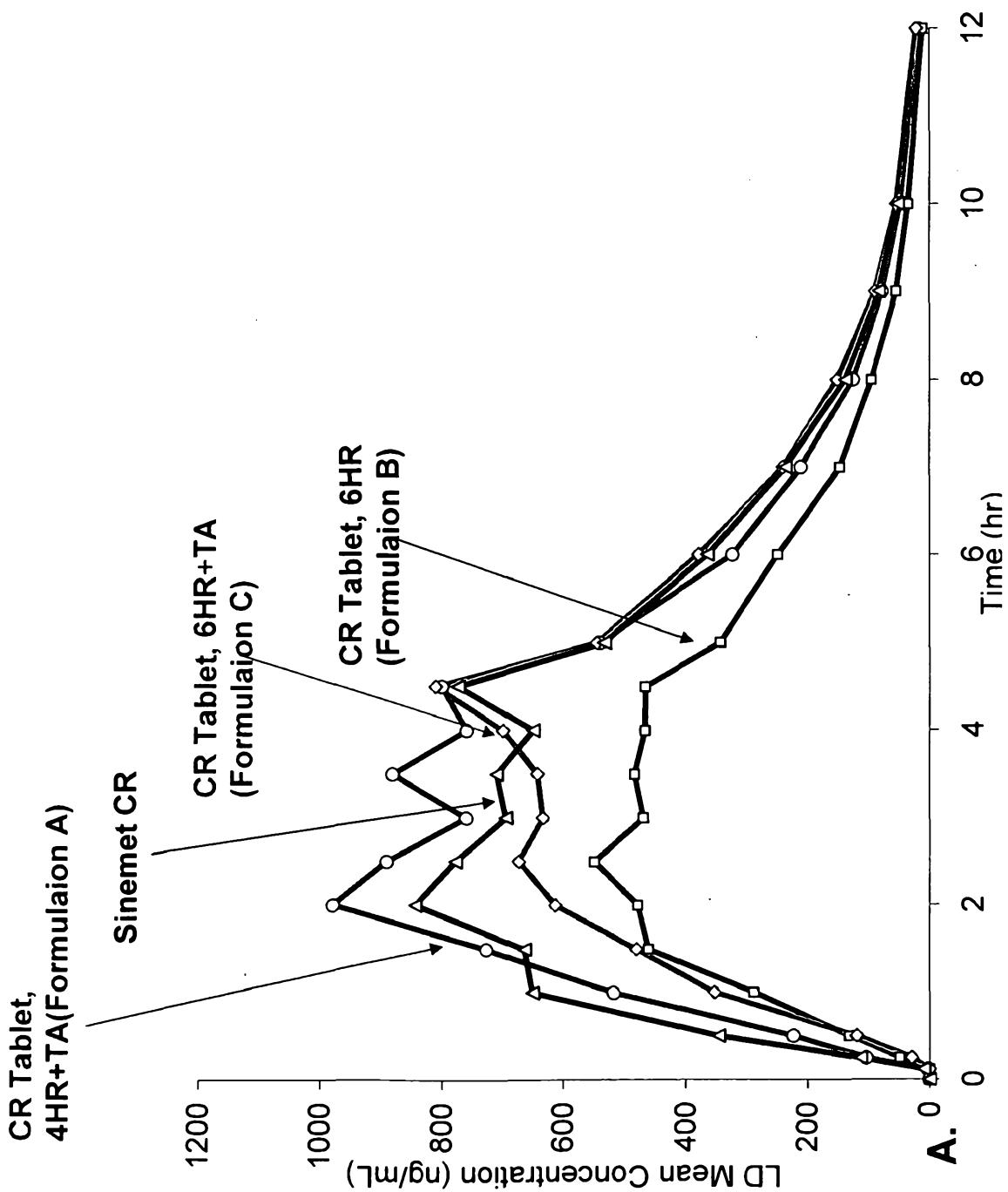
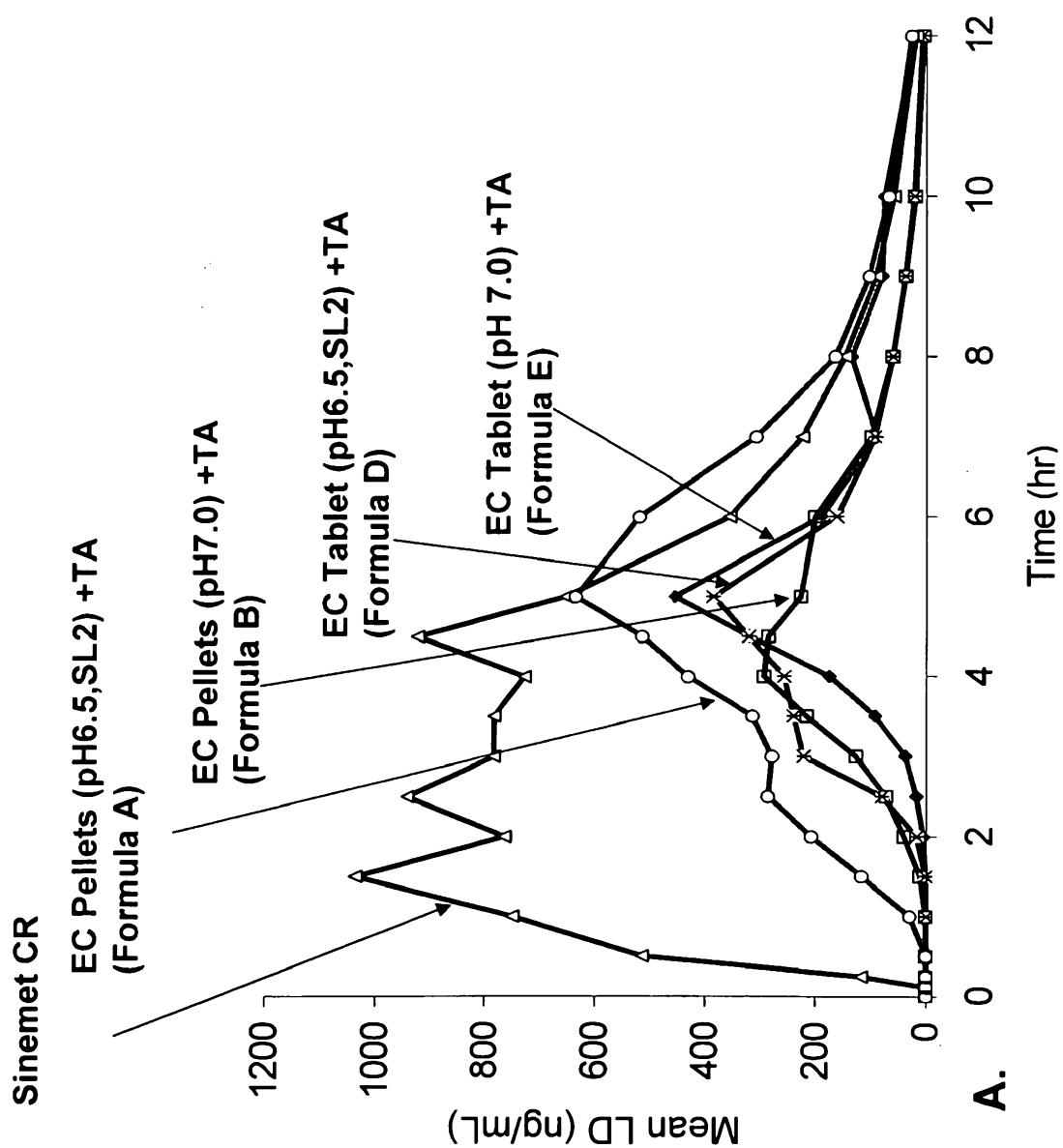


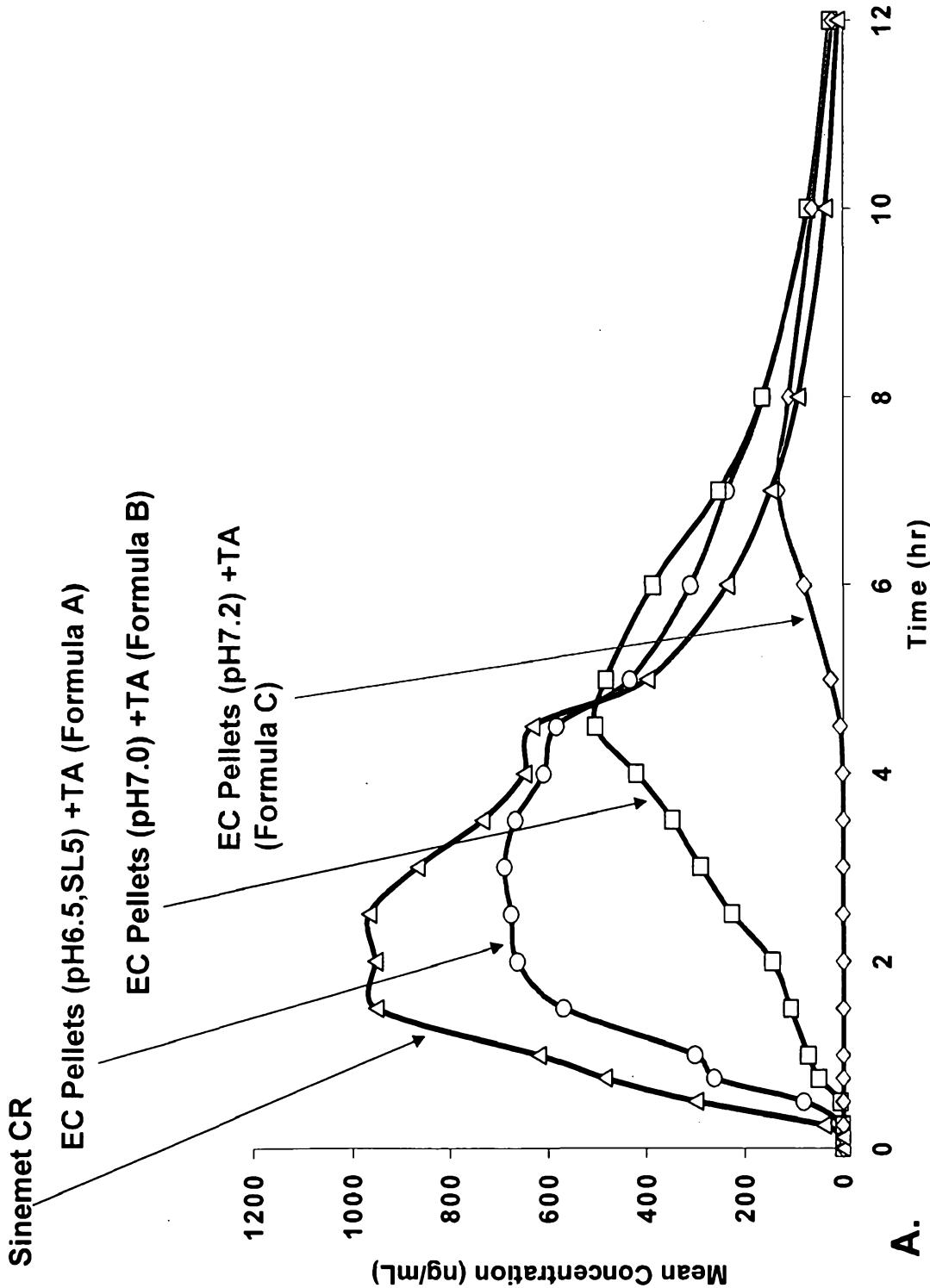
Figure 1

**Figure 2: In-Vivo Plasma Concentration Profiles of PK Study IPX066-B05-07**

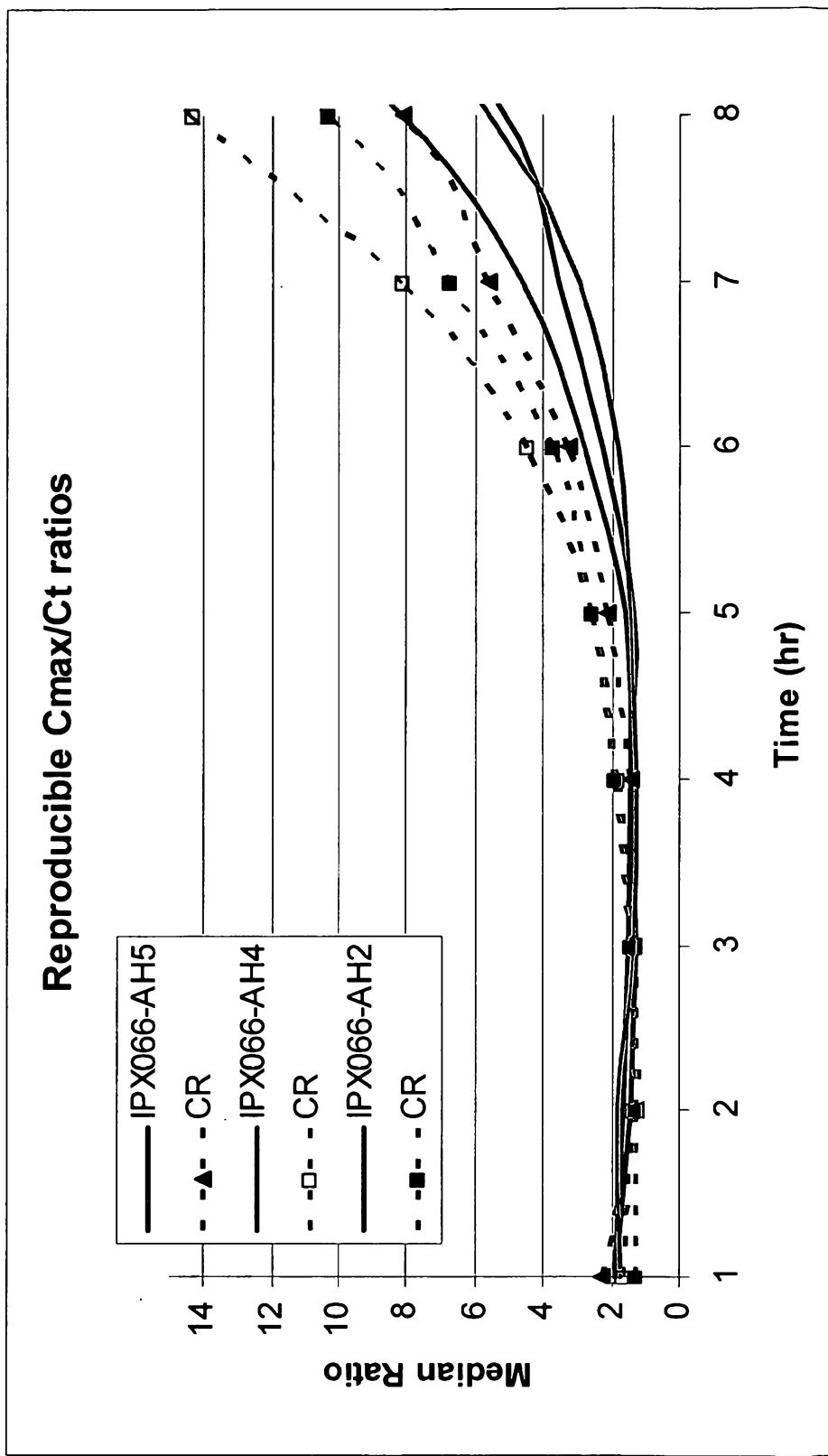
**Figure 3: In-Vivo Plasma Concentration Profiles of PK Study IPX066-B06-02**  
Dissolution



**Figure 4: In-Vivo Plasma Concentration Profiles of PK Study IPX066-B07-01**  
Dissolution



# Three 066 Studies Showed Robust Flat LD Profiles (low $C_{max}/C_t$ Ratios)



**Figure 5**

# Three 066 Studies Showed Robust Lower Intrasubject Variability Than Sinemet CR

Study	N	Population	Infusion	IR Q2-3hr	IPX066	CR
Mouradian	14	Patient	17%	47%		
IPX066-AH2	12	Healthy*			34%	47%
IPX066-AH4	13	Healthy*			35%	46%
IPX066-AH5	15	Healthy*			31%	46%

\*Intrasubject variability was obtained by calculating %CV (=Standard deviation/mean) for LD conc determined from Hour 0.5 to Hour 6 (desired dosing interval) after a single dose for each individual subject. The reported value is the mean variability across study population in each study.

**Figure 6**