Description

This invention is concerned with a controlled release formulation for the simultaneous delivery of levodopa and carbidopa in the treatment of parkinsonism whereby the adverse reactions and inadequacies often experienced with the administration of standard carbidopa/levodopa combinations are minimized.

SINEMET^{R} (Merck & Co. Inc., Rahway, N.J.) is the registered trademark for a therapeutic agent useful in the treatment of idiopathic Parkinsonism. It is a combination of levodopa and carbidopa and is provided in tablets of 10 mg carbidopa/100 mg of levodopa; 25 mg of carbidopa/250 mg of levodopa; and 25 mg of carbidopa/100 mg of levodopa. The usual dose is 3 to 4 tablets daily.

Before SINEMET® was introduced to the market in 1975, parkinsonism was treated with levodopa by itself. Large doses of levodopa were necessary to adequately control the Parkinson syndrome and severe adverse reactions, especially emesis, were experienced. To minimize these adverse reactions attempts were made to deliver levodopa in a sustained release fashion. In fact there was a product called Brocadopa Temtabs. Several studies failed to show any advantage of the sustained release formulation over a standard preparation. See Eckstein et al., The Lancet, February 24, 1973, page 431 which states at 432, "for the majority of parkinsonians in our study sustained-release levodopa offered no definite advantage over a standard preparation". Also Curzon et al., The Lancet, April 7, 1973, page 781, states, "These results suggest there is no practical advantage to be gained by the use of an oral sustained-release preparation of levodopa".

Therapy with SINEMET® is widely accepted as the cornerstone in treating idiopathic Parkinson's disease. However, "wearing-off" and "on-off" phenomena have emerged as major problems in the long-term treatment of Parkinson's disease. After two to three years, many patients begin to experience oscillating motor fluctuations which become increasingly disabling. The essential feature is a change from mobility to immobility, which may occur many times a day. Predictable waning of therapeutic effects, following each dose of SINEMET®, is known as "wearing-off" and may first occur during stage II-III of the disease. Such response fluctuations occur in 15 to 40% of patients after two to three years of treatment, and in a greater percentage with longer duration of illness. The fluctuations in levodopa levels which accompany SINEMET® treatment may in themselves contribute to the development of clinical oscillations.

The clinical manifestations of "on-off" include rapid and unpredictable swings from mobility to immobility. "On" periods can usually be correlated with high or rising plasma levodopa levels and are often associated with distinct, abnormal involuntary movements (dose-related dyskinesias), while "off" periods are commonly but not invariably associated with low or falling plasma-levodopa levels. The relation of "off" periods to low plasma levodopa levels and the observation that the administration of apomorphine during an "off" period may restore function suggests that most such periods are due to cerebral dopamine deficiency. Frequent dosage administration helps to alleviate oscillating clinical responses but dyskinesias and bradykinetic episodes may still occur.

Intravenous levodopa has been used to provide stable plasma levels of 2000 to 5000 ng/ml in advanced parkinsonian patients. This procedure reduces motor oscillations, but optimal response in some patients still include either tremor and bradykinesia or mobility with dyskinesia. High protein meals cause a decline in response without affecting plasma levodopa levels, presumably by inhibiting transport of levodopa into the brain.

The above considerations indicate that a dosage preparation of SINEMET® possessing less rapid dissolution properties and providing a more even plasma level profile of levodopa should be efficacious in alleviating some but not all oscillating therapeutic responses.

If the development of clinical fluctuations is promoted by oscillating levodopa levels, a controlled release preparation may also help to prevent the emergence of "wearing-off" and "on-off" phenomena.

Now, with the present invention there is provided a controlled release form of the combination of carbidopa/levodopa designed to obviate or at least alleviate problems associated with the standard combination therapy. Dyskinesias and other central nervous system side effects, and gastrointestinal side effects may be reduced in patients sensitive to high plasma levodopa levels. Patients with oscillating symptoms should respond to the more constant plasma levodopa levels with a more even clinical response. Furthermore, controlled release SINEMET® is expected to represent a more convenient dosage form (i.e., allowing for less frequent medication) for many patients who require standard SINEMET® four or more times a day. A twice-daily dosage regimen may also be feasible in some patients.

The novel controlled release tablet of carbidopa/levodopa of this invention is a matrix or monolithic drug delivery system containing carbidopa and levodopa as active ingredients. The system consists of the two drugs, uniformly dispersed in a polymer vehicle at a concentration that is greater than either drug solubility in the polymer vehicle which is either a single or a combination of polymers.

The novel delivery system provides slow release of both drug components either by erosion or by a diffusion controlled mechanism, depending on the particular polymer vehicle.

Release of drug by erosion occurs by slow disintegration of the tablet surface. Release of drug by diffusion occurs either through the space between the macromolecular polymer chains or through a porous network filled with aqueous medium. Optimum erosion or diffusion conditions can be achieved by controlling the crystalline phase porous structure, degree of swelling, polymer type, polymer ratio, drug concentration and other salient parameters.

Figure 1, is a cross-section of a tablet-shaped homogeneous polymer matrix showing the drug components, 1, homogeneously dispersed in the matrix.

Figure 2, is a schematic representation of the same polymer matrix, 1, after some of the drug has been delivered by diffusion by entry of liquids into the tortuous microporous channels, 2, followed by exit of drug solution through the same tortuous path. This matrix remains essentially intact while delivering its drug content.

Figure 3, is a cross-section of a schematic representation of the polymer matrix, 1, after some of the drug has been delivered by erosion by liquids whereby polymer, 1, and active ingredients, 2, are dispersed in the fluid as solute or suspensoid.

Figure 3a, is a schematic representation of the polymer matrix, 1, after essentially all of the drug, 2, has been delivered by erosion. This matrix completely disintegrates while delivering its drug content.

The polymer vehicle comprises 0-120 mg of Klucel LF®, which is a water soluble hydroxypropyl cellulose polymer; and 0-120 mg of Vinac ASB-516 ®, which is a less water soluble polyvinyl acetate-crotonic acid copolymer; with the proviso that neither polymer is 0 mg.

Other components of the novel formulation are optional dyes and tablet lubricants such as: metallic salts of acids including aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, and zinc stearate; fatty acids, hydrocarbons and fatty alcohols including stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmityl alcohol; fatty acid esters including glyceryl monostearate, glyceryl (mono- and di-) stearate, triglycerides, glyceryl (palmiticstearic) ester, sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, and sodium stearyl fumarate; alkyl sulfates, including sodium lauryl sulfate, and magnesium lauryl sulfate; polymers including polyethylene glycols, polyoxyethylene glycols, and polytetrafluoroethylene (Teflon); and inorganic materials such as talc. The preferred tablet lubricant is magnesium stearate.

In a typical formulation the components thereof are present in the following quantities:

Component	Quantity	
	Range	Preferred Range
Levodopa	20-1200 mg (1)	100-400 mg
Carbidopa	5-300 mg (1)	25-100 mg
Klucel LF ®	0-120 mg (2)	5-25 mg
Vinac ASB-516 ®	0-120 mg (2)	2-50 mg
lubricant	0-25 mg	1-10 mg

(1) The relative amounts of carbidopa to levodopa are preferably from about 1 carbidopa/10 levodopa to 1 carbidopa/4 levodopa.
(2) In a given formulation neither polymer is 0 mg.

A process for preparing the novel formulations comprises mixing levodopa, carbidopa and colorants with a hydroalcoholic or other suitable solvent dispersion of the polymer(s), drying, milling, mixing with the lubricant and compressing into tablets.

Alternatively the formulation can be prepared by mixing levodopa, carbidopa and colorants and adding Klucel LF ® and/or
Vinac ASB-516 ® , either dry or
dispersed in a solvent such as water, alcohol or hydroalcohol. The mixture is dried, mixed with lubricant and compressed into tablets.

Specific examples of the novel controlled release formulation of this invention are as follows:

EXAMPLE 1

Ingredient	Per Tablet
Levodopa USP	200 mg
Carbidopa Hydrous USP	54 mg
Vinac ASB-516® containing about 5% crotonic acid; molar viscosity 15-17 cps(15-17 mPa.s); molecular weight 95,000; available from Air Products and Chemicals, Inc., Box 538, Allentown, PA 18105, U.S.A.	6.5 mg
Klucel LF®, molecular weight, 75,000; viscosity of 5% aqueous solution 75-150 cps(75-150 mPa.s); available from Hercules, Incorporated, Wilmington, Delaware, 19894, U.S.A.	17.0 mg
Magnesium Stearate Impalpable Powder NF	3.0 mg
Red 347 Mapico	0.4 mg
Yellow D & C No. 10 Aluminum Lake HT	1.0 mg

EXAMPLE 2

Ingredient	Per Tablet	
Levodopa USP	200 mg	100 mg.
Carbidopa Hydrous USP	54 mg	27 mg.
Vinac ASB-516 ®	5.0 mg	2.5 mg
Klucel LF ®	17.0 mg	8.5 mg
Magnesium Stearate Impalpable Powder NF	3.0 mg	1.5 mg.
Red 347 Mapico	0.3 mg	0.15 mg.
Yellow D & C No. 10 Aluminum Lake HT	1.1 mg	0.55 mg.

Two controlled release formulations, No. 1 and No. 2 were compared to standard SINEMET® in 20 patients with uncomplicated Parkinson's disease. Mean disability scores were similar over two weeks in patients who received No. 1 or standard SINEMET® and in patients who received No. 2 or standard SINEMET®. (Because of the design of this study, the group of 10 patients which received No. 1 was different from the 10 patients who received No. 2; however, all patients received standard SINEMET®).

Ingredient	Per Tablet (mg)	
	No. 1	No. 2
	CR-2	CR-3
Levodopa	100	200
Carbidopa	50	50
Vinac ASB-516 ®	3	20
Magnesium Stearate	1.7	5.5
Klucel LF ®	10	-

The pharmacokinetic profiles of the sustained release formulations were clearly different from that of standard SINEMET®. Patients on No. 1 achieved peak plasma levodopa concentrations 2.8 ± 1.2 hours after dosing, compared to a T_{max} of 1.1 ± 0.33 hours with standard SINEMET®. For the No. 2 preparation, T_{max} was 3.1 ± 2.2 hours, compared to 1.4 ± 0.5 hours with standard SINEMET®. The eight hour bioavailabilities of No. 1 and No. 2 relative to standard SINEMET® were estimated to be 86% and 75%, respectively.

Although mean peak plasma levodopa concentrations for No. 1 and No. 2 were only about half of those produced by SINEMET®, and the 8 hour levels following No. 1 or No. 2 administration exceeded those with

SINEMET®, indicating sustained release properties for both CR formulations.

Based on these results, and the preferable 1:4 ratio of the No. 2 tablet, four open-label clinical and pharmacokinetic studies of No. 2 were conducted in parkinsonian patients with motor fluctuations. Among 30 such patients (22 with "wearing off" and 8 with unpredictable "on/off"), only a few showed marked improvement with decreased "off" time and smooth response during the day. Many others benefited from nighttime improvement including better sleep and mobility, and improved early morning function. Sustained elevated plasma levodopa levels were achieved, but were associated with unpredictable variability.

The No. 2 formulation proved to be extremely difficult to use because of a marked delay in onset of response after each dosage, a requirement for very high daily dosages (150-400% of standard SINEMET®), and very poor correlation between time of dose and rise in plasma levodopa levels. In fact, nighttime and early morning plasma levels were sometimes higher than daytime levels, although dosing occurred throughout the day and not at night. Severe, sustained, and unpredictable periods of dyskinesias and similarly sustained "off" periods were observed. B.I.D. dosage administration was unsuccessful in 9 of 9 patients with mild to moderate fluctuations. Formulation No. 2 had to be given nearly as frequently as standard SINEMET® in most patients.

The results of these studies strongly indicated that the release rate and bioavailability of the No. 2 tablet were too low in vivo, and probably very sensitive to effects of food and gastric pH. It appeared that in many patients much of the daytime dosage was stored in the stomach and not released until nighttime. A fragmentable matrix with more rapid dissolution characteristics, such as No. 1, had the potential to eliminate some of these problems.

These considerations led to the development of the No. 3 formulation, (Example 2) which has the same in vitro dissolution properties and polymeric matrix as No. 1 but contains 50 mg of carbidopa and 200 mg of levodopa. Fifty patients were enrolled in the No. 3 studies, and preliminary clinical and/or pharmacokinetic data are available from approximately 40 of them.

All four investigators consider the No. 3 formulation to be much easier to use than No. 2, due to 1) predictable onset of response, 2) dosage requirements which are comparable to or slightly higher than standard SINEMET®, and 3) more sustained therapeutic action during the day. Most patients who have completed the initial phase of the No. 3 trails requested long-term treatment because of clinical improvement. In general, dosing frequency can be reduced 25-50% with No. 3 relative to standard SINEMET®. Clinical fluctuations are reduced throughout the day and occasionally eliminated. Patients with mild to moderate fluctuations (especially end-of-dose "wearing-off") benefit most, although half of the more severe patients have also improved. Pharmacokinetic data indicate that plasma levodopa levels are sustained for 3-6 hours following a dose of No. 3, as compared to 1-2 hours with standard SINEMET®.

Onset of response after a single dose of No. 3 is less rapid than with standard SINEMET® and may require 45 minutes. In patients with advanced disease, nighttime and early-morning response with No. 3 is better than with standard SINEMET® but notably less than with No. 2. Plasma L-DOPA levels correlate well with these observations in that early morning L-DOPA levels are moderately higher with No. 3 than standard SINEMET® but much less than with No. 2.

Dyskinesia, mental confusion and psychosis have been observed at higher doses in patients who had similar side effects with standard SINEMET®. Sustained dyskinesias or "off" periods have not been significant problems to date.

Another formulation (Example 1) with dissolution properties intermediate to those of No. 2 and No. 3 has also been developed. This formulation will provide nighttime benefits in severe patients over those seen with No. 3.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A controlled release oral dosage formulation comprising a uniform dispersion of 5-300 mg of carbidopa, 20-1200 mg of levodopa, 0-25 mg of a tablet lubricant and optionally a pharmaceutically acceptable dye, in a polymer vehicle comprising 0-120 mg of a water soluble hydroxypropyl cellulose polymer and 0-120 mg of a less water soluble polyvinyl acetate-crotonic acid copolymer, whereby following administration the carbidopa and levodopa are released slowly and simultaneously from the formulation; characterised in that the water soluble hydroxypropyl cellulose polymer is Klucel LF®, and in that the less water soluble polyvinyl acetate-crotonic acid copolymer is Vinac ASB-516®; with the proviso that neither polymer is 0 mg.

2. The formulation of Claim 1 comprising 200 mg of levodopa and 50 mg of carbidopa or 100 mg of

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SINEMET®, indicating sustained release properties for both CR formulations.

Based on these results, and the preferable 1:4 ratio of the No. 2 tablet, four open-label clinical and pharmacokinetic studies of No. 2 were conducted in parkinsonian patients with motor fluctuations. Among 30 such patients (22 with "wearing off" and 8 with unpredictable "on/off"), only a few showed marked improvement with decreased "off" time and smooth response during the day. Many others benefited from nighttime improvement including better sleep and mobility, and improved early morning function. Sustained elevated plasma levodopa levels were achieved, but were associated with unpredictable variability.

The No. 2 formulation proved to be extremely difficult to use because of a marked delay in onset of response after each dosage, a requirement for very high daily dosages (150-400% of standard SINEMET®), and very poor correlation between time of dose and rise in plasma levodopa levels. In fact, nighttime and early morning plasma levels were sometimes higher than daytime levels, although dosing occurred throughout the day and not at night. Severe, sustained, and unpredictable periods of dyskinesias and similarly sustained "off" periods were observed. B.I.D. dosage administration was unsuccessful in 9 of 9 patients with mild to moderate fluctuations. Formulation No. 2 had to be given nearly as frequently as standard SINEMET® in most patients.

The results of these studies strongly indicated that the release rate and bioavailability of the No. 2 tablet were too low in vivo, and probably very sensitive to effects of food and gastric pH. It appeared that in many patients much of the daytime dosage was stored in the stomach and not released until nighttime. A fragmentable matrix with more rapid dissolution characteristics, such as No. 1, had the potential to eliminate some of these problems.

These considerations led to the development of the No. 3 formulation, (Example 2) which has the same in vitro dissolution properties and polymeric matrix as No. 1 but contains 50 mg of carbidopa and 200 mg of levodopa. Fifty patients were enrolled in the No. 3 studies, and preliminary clinical and/or pharmacokinetic data are available from approximately 40 of them.

All four investigators consider the No. 3 formulation to be much easier to use than No. 2, due to 1) predictable onset of response, 2) dosage requirements which are comparable to or slightly higher than standard SINEMET®, and 3) more sustained therapeutic action during the day. Most patients who have completed the initial phase of the No. 3 trails requested long-term treatment because of clinical improvement. In general, dosing frequency can be reduced 25-50% with No. 3 relative to standard SINEMET®. Clinical fluctuations are reduced throughout the day and occasionally eliminated. Patients with mild to moderate fluctuations (especially end-of-dose "wearing-off") benefit most, although half of the more severe patients have also improved. Pharmacokinetic data indicate that plasma levodopa levels are sustained for 3-6 hours following a dose of No. 3, as compared to 1-2 hours with standard SINEMET®.

Onset of response after a single dose of No. 3 is less rapid than with standard SINEMET® and may require 45 minutes. In patients with advanced disease, nighttime and early-morning response with No. 3 is better than with standard SINEMET® but notably less than with No. 2. Plasma L-DOPA levels correlate well with these observations in that early morning L-DOPA levels are moderately higher with No. 3 than standard SINEMET® but much less than with No. 2.

Dyskinesia, mental confusion and psychosis have been observed at higher doses in patients who had similar side effects with standard SINEMET®. Sustained dyskinesias or "off" periods have not been significant problems to date.

Another formulation (Example 1) with dissolution properties intermediate to those of No. 2 and No. 3 has also been developed. This formulation will provide nighttime benefits in severe patients over those seen with No. 3.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A controlled release oral dosage formulation comprising a uniform dispersion of 5-300 mg of carbidopa, 20-1200 mg of levodopa, 0-25 mg of a tablet lubricant and optionally a pharmaceutically acceptable dye, in a polymer vehicle comprising 0-120 mg of a water soluble hydroxypropyl cellulose polymer and 0-120 mg of a less water soluble polyvinyl acetate-crotonic acid copolymer, whereby following administration the carbidopa and levodopa are released slowly and simultaneously from the formulation; characterised in that the water soluble hydroxypropyl cellulose polymer is Klucel LF®, and in that the less water soluble polyvinyl acetate-crotonic acid copolymer is Vinac ASB-516®; with the proviso that neither polymer is 0 mg.

2. The formulation of Claim 1 comprising 200 mg of levodopa and 50 mg of carbidopa or 100 mg of

levodopa and 25 mg of carbidopa.

3. The controlled release oral dosage formulation of Claim 1 comprising a uniform dispersion of 25-100 mg of carbidopa, 100-400 mg of levodopa, 1-10 mg of a tablet lubricant and optionally a pharmaceutically acceptable dye, in a polymer vehicle comprising 5-25 mg of a water soluble hydroxypropyl cellulose polymer and 2-50 mg of a less water soluble polyvinyl acetate-crotonic acid copolymer, whereby following administration the carbidopa and levodopa are released slowly and simultaneously from the formulation; characterised in that the water soluble hydroxypropyl cellulose polymer is Klucel LF®, and in that the less water soluble polyvinyl acetate-crotonic acid copolymer is Vinac ASB-516®.

4. The formulation of Claim 3 comprising 200 mg of levodopa and 50 mg of carbidopa or 100 mg of levodopa and 25 mg of carbidopa.

Claims for the following Contracting States : ES, GR

1. A process for preparing a controlled release oral dosage formulation comprising a uniform dispersion of 5-300 mg of carbidopa, 20-1200 mg of levodopa, 0-25 mg of a tablet lubricant and optionally a pharmaceutically acceptable dye, in a polymer vehicle comprising 0-120 mg of a water soluble hydroxypropyl cellulose polymer and 0-120 mg of a less water soluble polyvinyl acetate-crotonic acid copolymer, whereby following administration the carbidopa and levodopa are released slowly and simultaneously from the formulation, which process comprises

   A)
   1) mixing levodopa, carbidopa and colorants with a hydroalcoholic or other suitable solvent dispersion of the polymer(s);
   2) drying the mixture previously obtained;
   3) milling the dry mixture obtained;
   4) mixing with the lubricant; and
   5) compressing into tablets;

   or alternatively,

   B)
   1) mixing levodopa, carbidopa and colorants;
   2) adding hydroxypropylcellulose and/or polyvinyl acetate-crotonic acid copolymer, either dry or dispersed in a solvent such as water, alcohol or hydroalcohol;
   3) drying the mixture previously obtained;
   4) mixing with the lubricant; and
   5) compressing into tablets;

   characterized in that the water soluble hydroxypropyl cellulose polymer is Klucel LF®, and in that the less water soluble polyvinyl acetate-crotonic acid copolymer is Vinac ASB-516®, with the proviso that neither polymer is 0 mg.

2. The process of Claim 1 wherein the formulation obtained comprises either 200 mg of levodopa and 50 mg of carbidopa or 100 mg of levodopa and 25 mg of carbidopa.

3. The process of Claim 1, wherein the controlled release oral dosage formulation obtained comprises a uniform dispersion of 25-100 mg of carbidopa, 100-400 mg of levodppa, 1-10 mg of a tablet lubricant and optionally a pharmaceutically acceptable dye, in a polymer vehicle comprising 5-25 mg of a water soluble hydroxypropyl cellulose polymer and 2-50 mg of a less water soluble polyvinyl acetate-crotonic acid copolymer, whereby following administration the carbidopa and levodopa are released slowly and simultaneously from the formulation; characterized in that the water soluble hydroxypropyl cellulose polymer is Klucel LF®, and in that the less water soluble polyvinyl acetate-crotonic acid copolymer is Vinac ASB-516®.

4. The process of Claim 3 wherein the formulation obtained comprises either 200 mg of levodopa and 50 mg of carbidopa or 100 mg of levodopa and 25 mg of carbidopa.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

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1. Formulierung für die gesteuerte Freigabe einer oralen Dosierung umfassend eine gleichmäßige Dispersion von 5 - 300 mg Carbidopa, 20 - 1200 mg Levodopa, 0 - 25 mg eines Tabletten-Gleitmittels und gegebenenfalls einen pharmazeutisch annehmbaren Farbstoff, in einem Polymer-Vehikel umfassend 0 - 120 mg wasserlösliches Kydroxypropylcellulosepolymer und 0 - 120 mg eines weniger wasserlöslichen Polyvinylacetat-CrotonsäureCopolymers, wobei bei folgender Verabreichung Carbidopa und Levodopa langsam und gleichzeitig aus der Formulierung freigegeben werden; **dadurch gekennzeichnet,** daß das wasserlösliche Hydroxypropylcellulosepolymer Klucel LF® ist, und daß das weniger wasserlösliche Polyvinylacetat-CrotonsäureCopolymer Vinac ASB-516® ist, mit der Maßgabe, daß kein Polymer 0 mg beträgt.

2. Formulierung nach Anspruch 1 umfassend 200 mg Levodopa und 50 mg Carbidopa oder 100 mg Levodopa und 25 mg Carbidopa.

3. Formulierung für die gesteuerte Freigabe einer oralen Dosierung nach Anspruch 1, umfassend eine gleichmäßige Dispersion von 25 - 100 mg Carbidopa, 100 - 400 mg Levodopa, 1 - 10 mg eines Tabletten-Gleitmittels und gegebenenfalls einen pharmazeutisch annehmbaren Farbstoff, in einem Polymer-Vehikel umfassend 5 - 25 mg wasserlösliches Hydroxypropylcellulosepolymer und 2 - 50 mg eines weniger wasserlöslichen Polyvinylacetat-Crotonsäure-Copolymer, wobei bei folgender Verabreichung von Carbidopa und Levodopa langsam und gleichzeitig aus der Formulierung freigegeben werden; **dadurch gekennzeichnet,** daß das wasserlösliche Kydroxypropylcellulosepolymer Klucel LF® ist, und daß das weniger wasserlösliche Polyvinylacetat-Crotonsäure-Copolymer Vinac ASB-516® ist.

4. Formulierung nach Anspruch 3 umfassend 200 mg Levodopa und 50 mg Carbidopa oder 100 mg Levodopa und 25 mg Carbidopa.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer Formulierung für die gesteuerte Freigabe einer oralen Dosierung umfassend eine gleichmäßige Dispersion von 5 - 300 mg Carbidopa, 20 - 1200 mg Levodopa, 0 - 25 mg eines Tabletten-Gleitmittels und gegebenenfalls einen pharmazeutisch annehmbaren Farbstoff, in einem Polymer-Vehikel umfassend 0 - 120 mg wasserlösliches Hydroxypropylcellulosepolymer und 0 - 120 mg eines weniger wasserlöslichen Polyvinylacetat-Crotonsäure-Copolymer, wobei bei folgender Verabreichung Carbidopa und Levodopa langsam und gleichzeitig aus der Formulierung freigegeben werden, wobei das Verfahren umfaßt

   A)
   1) Mischen von Levodopa, Carbidopa und Farbstoffen mit einer hydroalkoholischen oder anderen geeigneten Lösungsmitteldispersion des (der) Polymeren;
   2) Trocknen des vorher erhaltenen Gemisches;
   3) Mahlen des erhaltenen trockenen Gemisches;
   4) Mischen mit dem Gleitmittel; und
   5) Pressen in Tabletten;

   oder alternativ

   B)
   1) Mischen von Levodopa, Carbidopa und Farbstoffen;
   2) Hinzugeben von Hydroxypropylcellulose und/oder Polyvinylacetat-Crotonsäure-Copolymer, entweder trocken oder dispergiert in einem Lösungsmittel wie Wasser, Alkohol oder Hydroalkohol;
   3) Trocknen des vorher erhaltenen Gemisches;
   4) Mischen mit dem Gleitmittel; und
   5) Pressen in Tabletten;

   dadurch gekennzeichnet, daß das wasserlösliche Kydroxypropylcellulosepolymer Klucel LF® ist, und daß das weniger wasserlösliche Polyvinylacetat-Crotonsäure-Copolymer Vinac ASB-516® ist, mit der Maßgabe, daß kein Polymer 0 mg beträgt.

2. Verfahren nach Anspruch 1, worin die erhaltene Formulierung entweder 200 mg Levodopa und 50 mg Carbidopa oder 100 mg Levodopa und 25 mg Carbidopa umfaßt.

3. Verfahren nach Anspruch 1 worin die erhaltene Formulierung für die gesteuerte Freigabe einer oralen

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Dosierung umfaßt eine gleichmäßige Dispersion von 25 - 100 mg Carbidopa, 100 - 400 mg Levodopa, 1 - 10 mg eines Tabletten-Gleitmittels und gegebenenfalls einen pharmazeutisch annehmbaren Farbstoff, in einem Polymer-Vehikel umfassend 5 - 25 mg wasserlösliches Hydroxypropylcellulosepolymer und 2 - 50 mg eines weniger wasserlöslichen Polyvinylacetat-Crotonsäure-Copolymer, wobei bei folgender Verabreichung Carbidopa und Levodopa langsam und gleichzeitig aus der Formulierung freigegeben werden; **dadurch gekennzeichnet** daß das wasserlösliche Kydroxypropylcellulosepolymer Klucel LF® ist, und daß das weniger wasserlösliche Polyvinylacetat-Crotonsäure-Copolymer Vinac ASB-516® ist.

4. Verfahren nach Anspruch 3, worin die erhaltene Formulierung entweder 200 mg Levodopa und 50 mg Carbidopa oder 100 mg Levodopa und 25 mg Carbidopa umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Formulation galénique orale à libération prolongée comprenant une dispersion uniforme de 5-300 mg de carbidopa, 20-1200 mg de lévodopa, 0-25 mg d'un lubrifiant pour comprimés et, éventuellement, un colorant pharmaceutiquement acceptable, dans un véhicule polymère comprenant 0-120 mg d'un polymère d'hydroxypropylcellulose soluble dans l'eau et 0-120 mg d'un copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau, par laquelle, après l'administration, le carbidopa et le lévodopa sont libérés lentement et simultanément de la formulation; caractérisée en ce que le polymère d'hydroxypropylcellulose soluble dans l'eau est le Klucel LF® et en ce que le copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau est le Vinac ASB-516®; à condition qu'aucun des polymères ne soit présent à raison de 0 mg.

2. Formulation selon la revendication 1, comprenant 200 mg de lévodopa et 50 mg de carbidopa ou 100 mg de lévodopa et 25 mg de carbidopa.

3. Formulation galénique orale à libération prolongée selon la revendication 1, comprenant une dispersion unifome de 25-100 mg de carbidopa, 100-400 mg de lévodopa, 1-10 mg d'un lubrifiant pour comprimés et, éventuellement, un colorant pharmaceutiquement acceptable, dans un véhicule polymère comprenant 5-25 mg d'un polymère d'hydroxypropylcellulose soluble dans l'eau et 2-50 mg d'un copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau, par laquelle, après l'administration, le carbidopa et le lévodopa sont libérés lentement et simultanément de la formulation; caractérisée en ce que le polymère d'hydroxypropylcellulose soluble dans l'eau est le Klucel LF® et en ce que le copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau est le Vinac ASB-516®.

4. Formulation selon la revendication 3, comprenant 200 mg de lévodopa et 50 mg de carbidopa ou 100 mg de lévodopa et 25 mg de carbidopa.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de préparation d'une formulation galénique orale à libération prolongée comprenant une dispersion uniforme de 5-300 mg de carbidopa, 20-1200 mg de lévodopa, 0-25 mg d'un lubrifiant pour comprimés et, éventuellement, un colorant pharmaceutiquement acceptable, dans un véhicule polymère comprenant 0-120 mg d'un polymère d'hydroxypropylcellulose soluble dans l'eau et 0-120 mg d'un copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau, par laquelle, après l'administration, le carbidopa et le lévodopa sont libérés lentement et simultanément de la formulation, ce procédé comprenant

   A)

   1) le mélange du lévodopa, du carbidopa et des colorants avec une dispersion du ou des polymères dans un solvant hydroalcoolique ou un autre solvant convenable;
   2) le séchage du mélange obtenu ci-dessus;
   3) le broyage du mélange sec obtenu;
   4) le mélange avec le lubrifiant; et
   5) la compression en comprimés;

   ou bien

   B)

   1) le mélange du lévodopa, du carbidopa et des colorants;

* C L M S *

2) l'addition d'hydroxypropylcellulose et/ou de copolymère poly(acétate de vinyle-acide crotonique), sec ou dispersé dans un solvant tel que l'eau, un alcool ou un hydroalcool;
3) le séchage du mélange obtenu ci-dessus;
4) le mélange avec le lubrifiant; et
5) la compression en comprimés;

caractérisé en ce que le polymère d'hydroxypropylcellulose soluble dans l'eau est le Klucel LF® et en ce que le copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau est le Vinac ASB-516®, à condition qu'aucun des polymères ne soit présent à raison de 0 mg.

2. Procédé selon la revendication 1, dans lequel la formulation obtenue comprend 200 mg de lévodopa et 50 mg de carbidopa, ou bien 100 mg de lévodopa et 25 mg de carbidopa.

3. Procédé selon la revendication 1, dans lequel la formulation galénique orale à libération prolongée obtenue comprend une dispersion uniforme de 25-100 mg de carbidopa, 100-400 mg de lévodopa, 1-10 mg d'un lubrifiant pour comprimés et, éventuellement, un colorant pharmaceutiquement acceptable, dans un véhicule polymère comprenant 5-25 mg d'un polymère d'hydroxypropylcellulose soluble dans l'eau et 2-50 mg d'un copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau, par laquelle, après l'administration, le carbidopa et le lévodopa sont libérés lentement et simultanément de la formulation; caractérisé en ce que le polymère d'hydroxypropylcellulose soluble dans l'eau est le Klucel LF® et en ce que le copolymère poly(acétate de vinyle-acide crotonique) moins soluble dans l'eau est le Vinac ASB-516®.

4. Procédé selon la revendication 3, dans lequel la formulation obtenue comprend 200 mg de lévodopa et 50 mg de carbidopa, ou bien 100 mg de lévodopa et 25 mg de carbidopa.