Composition comprising L-dopa.

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References cited:
EP-A-0 032 562
EP-A-0 080 341
CH-A-0 227 077
FR-A-2 118 266
FR-A-2 373 200
FR-A-2 512 676

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The present invention relates to a multiple-unit-dosage composition comprising as a pharmaceutically active compound L-dopa, i.e., L-3,4-dihydroxyphenylalanine.

The object of the present invention is to obtain a pharmaceutical composition comprising as a pharmaceutically active compound L-dopa, to obtain by means of this in the form of a multiple-unit-dosage a useable L-dopa composition, which gives a high bioavailability, i.e., gives good pharmacologically active plasma levels with administration twice to four times a day.

L-dopa, 1 L-3,4-dihydroxyphenyl alanine, or 3-(3,4-dihydroxyphenyl)-L-alanine, or 3-hydroxy-L-tyrosine, alternatively, is a pharmaceutically active compound, which is active in the inhibition of symptoms of Parkinson's disease, particularly in the inhibition of the tremor related to Parkinson's disease.

However, hitherto has no pharmaceutical composition been developed which gives a satisfactory pharmacological effect, i.e., a pharmaceutically high, even plasma level. This depends on several factors, i.e., that L-dopa is rapidly decomposed by carboxylic elimination. This can, and has been regulated by adding a decarboxylase inhibitor, such as benzerazide or carbidopa, the administration of which means that the L-dopa dose can be considerably reduced. Other problems are that L-dopa is resorbed over a restricted part of the gastro-intestinal tract, i.e., shows a so called absorption window. Hitherto it has been necessary to administer known compositions five to eight times per 24 hrs due to the short half life time of L-dopa. In spite of this the treatment has given high top levels in the plasma which in turn leads to troublesome side-effects.

FR-A 2 116 256 discloses a pharmaceutical composition containing L-dopa as the active ingredient.

Thereby tablets and granules comprising L-dopa is coated with a methacrylic acid or a celluloseacetate phthalate, whereby the tablets or granules do not release L-dopa at a low pH, but release L-dopa rapidly at a higher pH (above pH 5.5).

CH-A 827 077 discloses a pharmaceutical composition containing L-dopa or a derivative thereof, which composition releases the active substance in the intestine during formation of a foam due to the presence of a carbon dioxide generating system. The composition will release its content of L-dopa almost instantaneously when the enteric coating present dissolves in the intestine.

EP-A 0 302 562 discloses composition of diprydiamol in retarded release form, whereby pellets of diprydiamol are enclosed in coatings of different types, such as a mixture of Eudragit SR, and hydroxypropyl methylcellulosephosphatate, ethyelcellulose, Eudragit retard SR, Eudragit SR, and hydroxypropyl methylcellulosephosphatate, or a laminate of ethyelcellulose and hydroxypropyl methylcellulosephosphatate as an inner layer, and celluloseacetate phthalate as an outer layer.

FR-A 2 512 676 discloses a pharmaceutical composition of L-dopa and a decarboxylase inhibitor.

It has now surprisingly been shown possible to solve the abovementioned problem and to obtain a pharmaceutically acceptable composition, which in vivo gives a balanced plasma level, comprising L-dopa as pharmaceutically active compound characterized in that the composition in a release test according to US Pharmacopeia Standards (USP XIX, apparatus 2, 100 rpm) in an artificial gastric juice without enzymes and having a pH of at most 1.2 gives a release of L-dopa of at most 20% by weight during 1 hr, and in accordance with the same standard release method in a phosphate buffer having pH 6.8 releases at least 35% by weight of L-dopa within 1 hr, and at least 80% by weight within 3 hrs, whereby the composition comprises a core having 75–85% by weight of L-dopa, which core is coated with a laminate comprising an inner layer of 3.2–4.5% by weight of the total composition of Pharma-coat® 603 (hydroxypropyl methylcellulose), and 1.2–2.4% by weight of the total composition of ethyl cellulose, and an outer layer of 6.0–9.0% by weight of the total composition of hydroxypropyl methylcellulose phthalate having a pKa of 5.0.

By means of the present invention an even level of active compound has thus been able to be obtained at the administration twice to four times per 24 hrs, simultaneously as the side effects have been reduced.

The present invention further comprises a process for preparing the present multiple-unit-dose pharmaceutical composition, whereby cores comprising L-dopa are coated with at least one anionic polymer having a pKa of 5.0–5.5 to give the release rates given above.

The term anionic polymer having pKa of 5.0–5.5 includes hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, and different Eudragit® qualities, such as S100, whereby these qualities include methylmethacrylate-methylesters.

The present invention will now be described more in detail in the following with reference to a number of examples which all meet the characteristic above. A couple of comparative examples will be shown.

Example 1. and Comparative Examples A to C

An uncoated granulate was prepared from 300 g of L-dopa, 470 g of mannitol, 60 g of Avicel® PH 101 (microcrystalline cellulose), 70 g of L-HPC (low-substituted hydroxypropyl cellulose), and 100 g of ascorbic acid. The granulate present in the form of small spheres having a diameter of 0.5–1.5mm was then coated according to the following.

Example 1.

100 g of uncoated granulate were coated with 9.3g of hydroxypropyl methylcellulose phthalate (HP55, pKa 5.5) to a granulate ready for administration, which was packed in capsules containing the
dose 100mg L-dopa per capsule.

Comparative Example A

100 g of uncoated granulate of above were coated with a laminate consisting of a first inner layer consisting of ethyl cellulose, 3.9 g, and Pharmacoat® 603 (hydroxypropyl methylcellulose), 2.0 g, and a second outer layer consisting of 9.1 g of hydroxypropyl methylcellulose phthalate (HP55) to a granulate ready for administration, which was packed in capsules (100 mg of L-dopa per capsule; about 700 small spheres per capsule).

Comparative Example B

100 g of uncoated granulate of above were coated for comparative reasons with a laminate consisting of a first inner layer of 4.3 g of ethyl cellulose and 2.2 g of Pharmacoat® 603, and a second outer layer of 7.0 g of hydroxypropyl methylcellulose phthalate (HP55) to a granulate ready for administration which was packed in capsules (100 mg of L-dopa per capsule).

Comparative Example C

For comparative reasons 100 g of uncoated granulate of above were coated with 6.7 g of Pharmacoat® 603 to a granulate ready for administration, which was packed in capsules (100 mg of L-dopa per capsule).

The compositions according to Ex. 1 and A–C above were tested by being run in an artificial gastric juice without enzymes, pH 1.2 in accordance with USP Standards (USP XXI, apparatus 2, 100 rpm) and then in a phosphate buffer pH 6.8 according to USP Standard (phosphate buffer: 0.2 M KH2PO4 250 ml, 0.2 M NaOH 112 ml, deionized water to 1000 ml) for the study of the release rates, and in phosphate buffer pH 6.8 alone for the study of the release rates without preexposure in acidic environment. The results are shown in FIG. 1–4 (FIG. 1=Ex. 1; FIG. 2=Ex. A; FIG. 3=Ex. B; FIG. 4=Ex. C).

The compositions according to Ex. 1, and A–C where then tested in a single dose study on 10 healthy test persons each. The composition according to Ex. 1 took part in another study using single dose administration. The results are shown in FIG. 5–9. (FIG. 5, 6=Ex.1; FIG. 7=Ex. A; FIG. 8=Ex. B; FIG. 9=Ex. C).

As evident from FIG. 3 a composition according to Ex. B has too slow release in pH 6.8, and as evident from FIG. 4 a composition according to Ex. C has a total release in pH 1.2 within a short time.

The results evident from FIG. 2, 3 and FIG. 4 are also confirmed by the results according to FIG. 7, 8 and FIG. 9. As evident from FIG. 7 low plasma levels are obtained, and thereby too low a bioavailability; as evident from FIG. 8 no considerable plasma level at all; and as evident from FIG. 9 too a high initial concentration is obtained using a composition according to Ex. C, a concentration which decreases rapidly. As evident from FIG. 5 and 6 a composition according to Ex. 1 gives a considerably more even plasma level and thereby bioavailability. In accordance with FIG. 5 and 6 no strong plasma peaks are obtained.

Example 2–5

An uncoated granulate comprising a high dose of L-dopa was prepared as follows. 850 g of L-dopa were provided with 100 g of Avicel® PH 101 (microcrystalline cellulose), 30 g of Tween 80® polysorbtane ester, and 20 g of Ac-Di-Sol (cross linked Na-carboxymethyl cellulose). The granulate in the form of small spheres, diameter 0.5-1.5 mm, was coated as follows.

Example 2

100 g of the uncoated granulate of above were coated in a fluidized bed with 12.0g of hydroxypropyl methylcellulose phthalate (HP55) to a granulate ready to be administered, which was packed in gelatine capsules (100mg of L-dopa per capsule).

Example 3

100 g of the uncoated granulate of above were coated using a mixture of 9.9 g of hydroxypropyl methylcellulose phthalate (HP55) and 2.1 g of ethyl cellulose to a granulate ready to be administered, which was packed in gelatine capsules (100 mg of L-dopa per capsule).

Example 4

100 g of the uncoated granulate of above were coated with a mixture of 7.2 g of Eudragit® S100 (methyl methacrylate methylesters comprising carboxylic acid groups) and 4.7 g of hydroxypropyl methylcellulose phthalate (HP55) to a granulate ready to be administered, which was packed in capsules (100 mg of L-dopa per capsule).

Example 5

100 g of uncoated granulate of above were coated with a laminate consisting of a first inner layer of 4.2 g of Pharmacoat® 603, and 1.8 g of ethyl cellulose, and a second outer layer of 8.0 g of hydroxypropyl methylcellulose phthalate (HP50, pK 5.0) to a granulate ready to be administered, which was packed in gelatine capsules (100 mg of L-dopa per capsule).

The compositions according to Examples 2-5 were tested with regard to the release rate of L-dopa in artificial gastric juice without enzymes in accordance with USP Standards (USP XXI, apparatus 2, 100 rpm), pH 1.2 for 2 hrs and then in a phosphate buffer pH 6.8. The results are given in FIG. 10–13 (FIG. 10=Ex. 2; FIG. 11=Ex. 3; FIG. 12=Ex. 4; FIG. 13=Ex. 5).
The compositions according to Examples 2 and 5 have also been tested in six healthy test persons each in a single dose study. The results are shown in Fig. 14-15. (Fig. 14=Ex. 2; Fig. 15=Ex. 5).

As evident from Fig. 10-13 the compositions according to Examples 2-5 meet the demands put forward, and as evident from Fig. 14 and 15 the compositions give even plasma levels, completely without interfering peak levels, which also gives good bioavailability.

The composition according to the invention, Example 5 above, has also been tested in patients suffering from Parkinsons disease. The test was also compared with an L-dopa composition present on the market. Fig. 14a and 14b show the blood plasma levels using a composition of Example 5 in two patients, and Fig. 15a and 15b show the blood plasma levels using the composition of the market in the same two patients. The composition according to the invention was administered to patient 1, Fig. 14a, in doses containing 200 mg, 300 mg, and 300 mg per day, while the same patient obtained 250 mg of L-dopa three times a day using the marketed composition. Patient 2, Fig. 14b, and 15b, was given 100 mg of L-dopa of the composition of the invention four times a day, while the patient was given 125 mg of L-dopa of the marketed composition three times a day. Administration points are shown with arrows.

The term multiple-unit-dose above means a dose present in the form of a number of granules, which taken together give the dose size requested. Thus such a multiple-unit-dose can comprise from 100 to 1000 small granules having spherical or other shape.

Using a multiple-unit-dose, which is administered by means of a capsule, normally hard, or in a SAC-HET-bag, or using a measuring spoon or other measuring device, the small units will be distributed in the gastric juice and leak out little by little into the intestinal tract.

Using the present compositions, which are given orally, the pharmaceutically active dose of L-dopa divided into two to four doses per 24 hrs should be 100-1000 mg.

The compositions above can be completed with decarboxylase inhibitors of the above given type, or the compositions can be administered simultaneously with a decarboxylase inhibitor to obtain a better L-dopa effect.

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

1. A multiple-unit-dose composition comprising L-dopa as pharmaceutically active compound characterized in that the composition in a release test according to US Pharmacopea Standards (USP XXI, apparatus 2, 100 rpm) in an artificial gastric juice without enzyme and having a pH of at most 1.2 gives a release of L-dopa of at most 20% by weight during 1 hr, and in accordance with the same standard release method in a phosphate buffer having pH 6.8 releases at least 35% by weight of L-dopa within 1 hr, and at least 90% by weight within 3 hrs, whereby the composition comprises a core having 75-85% by weight of L-dopa, which core is coated with a laminate comprising an inner layer of 3.2-4.5% by weight of the total composition of Pharmacoat® 603 (hydroxypropyl methylcellulose), and 1.2-2.4% by weight of the total composition of ethyl cellulose, and an outer layer of 6.0-9.0% by weight of the total composition of hydroxypropyl methylcellulose phthalate having a Ppk of 5.0.

2. A composition according to claim 1, characterized in that the release rate in artificial gastric juice is at most 10% by weight at pH 1.2 during 2 hrs.

3. A composition according to one or more of the preceding claims, characterized in that it further comprises a decarboxylase inhibitor in the form of benzazepine and/or carbidopa.

Claims for the Contracting State AT

1. Process for the preparation of a multiple-unit-dose composition consisting of a multiple of coated cores comprising L-dopa as pharmaceutically active compound, whereby one prepares a core comprising L-dopa, and coats that core with at least one anionic polymer having a Ppk of 5.0-5.5, characterized in that one produces a core comprising 75-85% by weight of L-dopa, and that one coats this core with a laminate consisting of an inner layer consisting of 3.2-4.5% by weight of the total composition of Pharmacoat® 603 (hydroxypropyl methylcellulose) and 1.2-2.4% by weight of the total composition of ethyl cellulose, and an outer layer of 6.0-9.0% by weight of the total composition of hydroxypropyl methylcellulose phthalate having a Ppk of 5.0, whereby the release rate of L-dopa in a standardized test according to US Pharmacopea Standards (USP XXI, apparatus 2, 100 rpm) in artificial gastric juice containing no enzymes and having a pH of 1.2 is at most 20% by weight during 1 hr, and according to the same test in phosphate buffer of pH 6.8 is at least 35% by weight after 1hr, and at least 80% by weight after 3 hrs.

2. Process according to claim 1, characterized in that the release rate in artificial gastric juice is at most 10% by weight at pH 1.2 during 2 hrs.

3. Process according to claims 1 and 2, characterized in that the composition further comprises a decarboxylase inhibitor in the form of benzazepine and/or carbidopa.

Patentansprüche für die Vertragsstaaten BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE

1. Mehrfachdosis-Dosiszuwachsmethode mit L-Dopa als pharmazeutisch wirksame Verbindung, dadurch gekennzeichnet, daß die Zusammensetzung in einem Freisetzungs test gemäß US-Pharmaco-opea-Standard (USP XXI, Apparat 2, 100 U/min) in einem künstlichen Magensaft ohne Enzyme und mit einem pH-Wert von höchstens 1.2 eine L-Dopa-Freisetzungsrate von mindestens 20 Gew.-% während 1 h und gemäß der gleichen Standardfreisetzungs- methode in einem Phosphatpuffer mit einem pH-Wert von 6.8 und wenigstens 35 Gew.-% L-Dopa innerhalb 1 h und wenigstens 80 Gew.-% innerhalb
von 3h freigibt, wobei die Zusammensetzung einen Kern mit 75 bis 85 Gew.-% L-Dopa besitzt, der mit einem Laminat überzogen ist, welches eine innere Schicht von 3,2 bis 4,5 Gew.-% der Gesamtzusammensetzung an Pharmacoat 603 (Hydroxypropylmethylcellulose) und 1,2 bis 2,4 Gew.-% der Gesamtzusammensetzung an Ethylcellulose und eine Außenschicht von 6,0 bis 9,0 Gew.-% der Gesamtzusammensetzung an Hydroxypropylmethylcellulosephthalat mit einem pHk von 5,0 umfaßt.

2. Zusammensetzung nach Anspruch 1, dadurch gekennzeichnet, daß die Freisetzungsgeschwindigkeit in künstlichem Magensaft höchstens 10 Gew.-% bei pH 1,2 während 2h ist.

3. Zusammensetzung nach einem oder mehreren der vorausgehenden Ansprüche, dadurch gekennzeichnet, daß sie außerdem einen Decarboxylaseinhibitor in der Form von Benzerazid und/oder Cardi-
dopa umfaßt.

Patentansprüche für den Vertragsstaat AT

1. Verfahren zur Herstellung einer Mehrfachinh.-heits-Dosiszusammensetzung, die aus mehreren überzogenen, L-Dopa als pharmazeutisch wirksame Verbindung umfassenden Kernen besteht, wobei man einen L-Dopa umfassenden Kern herstellt und mit wenigstens einem anionischen Polymer mit einem pHk von 5,0 bis 5,5 überzieht, dadurch gekennzeichnet, daß man einen Kern herstellt, der 75 bis 85 Gew.-% L-Dopa umfaßt, und daß man diesen Kern mit einem Laminat überzieht, das aus einer Innenschicht aus 3,2 bis 4,5 Gew.-% der Gesamtzusammensetzung an Pharmacoat 603 (Hydroxypropylmethylcellulose) und 1,2 bis 2,4 Gew.-% der Gesamtzusammensetzung an Ethylcellulose und ei-
er Außenschicht von 6,0 bis 9,0 Gew.-% der Ge-
samtzusammensetzung an Hydroxypropylmethylcellulosephthalat mit einem pHk von 5,0 besteht, wobei die Freisetzungsgeschwindigkeit von L-Dopa in ei-

der standardisierten Test gemäß US-Pharmacopea Standards (USP XXI, Apparatur 2, 100 U/min) in künstlichem Magensaft ohne Enzymgehalt und mit einem pH-Wert von 1,2 höchstens 20 Gew.-% währ-
rend 1h und gemäß dem gleichen Test in Phosphather-
puffer von pH 6,8 wenigstens 35 Gew.-% nach 1h und wenigstens 80 Gew.-% nach 3h beträgt.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die Freisetzungsgeschwindigkeit in künstlichem Magensaft höchstens 10 Gew.-% bei pH 1,2 während 2h ist.

3. Verfahren nach Anspruch 1 und 2, dadurch gekennzeichnet, daß die Zusammensetzung außerdem einen Decarboxylaseinhibitor in der Form von Benzerazid und/oder Cardiodopa umfaßt.

Revisions pour les États contractants BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE

1. Composition en dose unitaire multiple, compren-

nant de la L-Dopa à titre de composé actif du point de vue pharmaceutique, caractérisée en ce que cet-
te composition, au cours d'un test de libération sui-

vant les normes de la US Pharmacoopée (USP XXI,

appareil 2, 100 tours/minute) dans un suc gastrique

artificiel sans enzymes et ayant un pH de 1,2 au plus
donne une libération de L-dopa de 20% au plus en

poids durant 1h, et, suivant la même méthode
de libération normalisée, dans un tampon phosphat-

é ayant un pH de 6,8, elle libère au moins 35% en

poids de L-dopa dans l'heure, et au moins 80% en

poids dans les 3 heures, la composition comprenant

un noyau comportant 75-85% en poids de L-dopa,

celui étant enrobé d'un produit stratifié compren-

ant une couche interne de 3,2-4,5% en poids, par

rapport à la composition totale, de Pharmacoat 603

(hydroxypropyl méthyl cellulose), et 1,2-2,4% en

poids, par rapport à la composition totale, d'éthyl

cellulose, et une couche externe de 6,0 à 9,0% en

poids, par rapport à la composition totale, de phthalate

d'hydroxypropyl méthyl cellulose ayant une valeur

pHk de 5,0.

2. Composition suivant la revendication 1, carac-

térisée en ce que le taux de libération dans le suc

gastrique artificiel est au plus de 10% en poids à un

pH de 1,2 durant 2 heures.

3. Composition suivant l'une ou l'autre des revend-

dications précédentes, caractérisée en ce qu'elle

comprend en outre un inhibiteur de décarboxylase

sous la forme de benzérazide et/ou de cardiodopa.

Revisions pour l'État contractant AT

1. Procédé de préparation d'une composition à do-

se unitaire multiple, comprenant un certain nombre

de noyaux enrobés comportant de la L-dopa à titre

de composé pharmaceutiquement actif, dans lequel

on prépare un noyau comprenant de L-dopa et

enrobe ce noyau par au moins un polymère anioni-

que ayant une valeur pHk de 5,0-5,5, caractérisé en

ce qu'il produit un noyau comprenant 75-85% en

poids de L-dopa, et en ce qu'il enrobe ce noyau

par un produit stratifié comprenant une couche in-

terne consistant en 3,2-4,5% en poids, par rapport

da la composition totale, de Pharmacoat 630

(hydroxypropyl méthyl cellulose) et 1,2-2,4% en

poids, par rapport à la composition totale, d'éthyl

cellulose, et une couche externe de 6,0-9,0% en

poids, par rapport à la composition totale, de phthalate

d'hydroxyphényl méthyl cellulose ayant une valeur

pHk de 5,0, le taux de libération de L-dopa dans

un essai standardisé suivant les normes de la US

Pharmacoopée (USP XXI, appareil 2, 100 tours

minute) dans un suc gastrique artificiel ne con-
tenant pas d'enzymes et présentant un pH de 1,2

étaient au plus de 20% en poids durant 1 heure et, sui-
vant le même essai dans un tampon de phosphat

d'un pH de 6,8, étant d'au moins 35% en poids après

1 heure et d'au moins 85% en poids après 3 heures.

2. Procédé suivant la revendication 1, caractérisé

en ce que le taux de libération dans un suc gastri-

que artificiel est au plus de 10% en poids à un pH de

1,2 durant 2 heures.

3. Procédé suivant les revendications 1 et 2, cara-

ctérisé en ce que la composition comprend en

outre un inhibiteur de décarboxylase sous la forme

de benzérazide et/ou de cardiodopa.
FIG. 10

L-DOPA RELEASED

hrs

pH 1.2  pH 6.8
L-DOPA RELEASED

FIG. 12

hrs

pH 1.2 → pH 6.8
FIG. 15b