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(54) Benævnelse: **KRYSTALFORM AF ARGININSALTET AF PERINDOPRIL, FREMGANGSMÅDE TIL FREMSTILLING DERAF, OG FARMACEUTISKE SAMMENSÆTNINGER, SOM INDEHOLDER DEN**

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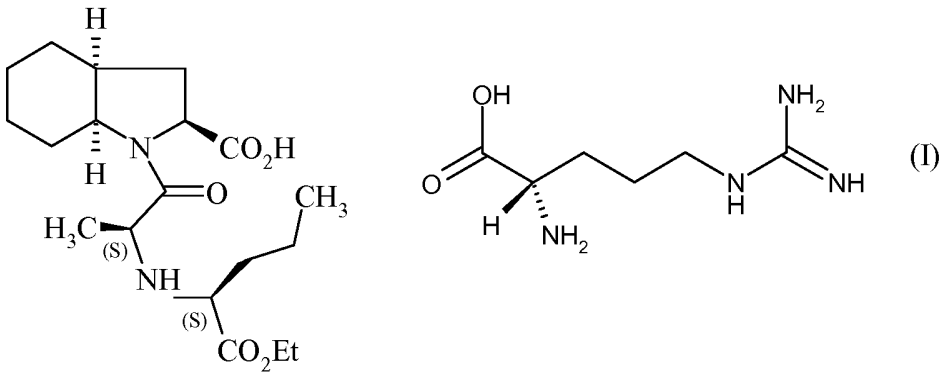
Description

The present invention relates to the α crystalline form of the L-arginine salt of perindopril of formula (I):



(I)

to a process for its preparation and to pharmaceutical compositions containing it.

Perindopril and its pharmaceutically acceptable salts, and more especially its arginine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, impedance of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

Perindopril, its preparation and its use in therapeutics have been described in European Patent specification EP 0 049 658.

The arginine salt of perindopril has been described in European Patent specification EP 1 354 873.

In view of the pharmaceutical value of that compound, it has been of prime importance to obtain it with excellent stability, mainly in terms of hygroscopicity, of processability of the powder, of filtrability of the solid, of grindability, and of solvent retention.

Obtaining a well-defined crystalline form allows those requirements to be met.

Patent specification EP 1 354 873 describes the arginine salt of perindopril. That document does not, however, specify the conditions for obtaining that salt in a well-defined crystalline form.

The Applicant has now found that the arginine salt of perindopril can be obtained in a well-defined crystalline form that, as a result, has valuable characteristics for filtration, drying and ease of formulation.

More specifically, the present invention relates to the α crystalline form of the compound of formula (I), characterised by the following X-ray powder diffraction peaks, measured using a diffractometer with a copper anti-cathode and a Kβ (Ni) filter and expressed in terms of angle 2 theta (°): 4.5, 7.9 and 13.5.

Preferably, the present invention relates to the α crystalline form of the compound of formula (I), characterised by the following X-ray powder diffraction peaks, measured using a diffractometer with a copper anti-cathode and a Kβ (Ni) filter and expressed in terms of angle 2 theta (°): 4.5, 7.9, 13.5, 17.5 and 20.6.

Even more preferably, the present invention relates to the α crystalline form of the compound of formula (I), characterised by the following X-ray powder diffraction diagram measured using a diffractometer (copper anti-cathode and

Kβ (Ni) filter) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, intensity and relative intensity (expressed as a percentage of the most intense line):

Angle 2 theta (°)	**Inter-planar distance d (Å)**	**Intensity**	**Relative intensity (%)**
4.52	19.53	2211	88.7
7.94	11.12	2080	83.5
12.152	7.277	682	27.4
13.480	*6.563*	*2492*	*100.0*
14.029	6.308	422	16.9
14.948	5.922	552	22.1
15.873	5.579	493	19.8
17.531	5.055	1600	64.2
18.787	4.719	363	14.5
19.579	4.530	1078	43.3
20.635	4.301	1794	72.0
22.616	3.928	798	32.0
23.367	3.804	473	19.0
23.807	3.735	362	14.5
24.434	3.640	409	16.4
27.148	3.282	450	18.1
28.214	3.160	417	16.7

The invention relates also to a process for the preparation of the α crystalline form of the compound of formula (I), wherein perindopril is dissolved in water with L-arginine, and then an apolar solvent and a polar solvent are added and the crystals obtained are filtered off, washed and then dried.

Among the apolar solvents there may be mentioned, by way of example, methylcyclohexane, cyclohexane and toluene.

Among the polar solvents there may be mentioned, by way of example, dimethyl sulphoxide, N,N-dimethylformamide, N,N-dimethylacetamide and N-methyl-2-pyrrolidinone.

The crystals so obtained are in a compact form composed of baguettes.

According to one embodiment of the invention, perindopril is dissolved in water with L-arginine and then methylcyclohexane and dimethyl sulfoxide are added and the crystals obtained are filtered off, washed and then dried.

The invention relates also to pharmaceutical compositions comprising as active ingredient the α crystalline form of the compound of formula (I) together with one or more appropriate, inert, non-toxic excipients. Among the pharmaceutical compositions according to the invention there may be mentioned, more especially, those that are suitable for oral, parenteral (intravenous or subcutaneous) or nasal administration, tablets or dragées, sublingual tablets, capsules, lozenges, suppositories, creams, ointments, dermal gels, injectable preparations, drinkable suspensions.
The dosage used can be varied according to the nature and severity of the disorder, the administration route and the age and weight of the patient. It varies from 1 to 500 mg per day in one or more administrations.

The pharmaceutical compositions according to the invention may also contain a diuretic such as indapamide.

The following Examples illustrate the invention.

The X-ray powder diffraction spectrum was measured under the following experimental conditions:

Siemens D5005 diffractometer; scintillation detector;
Copper anti-cathode, voltage 40KV, intensity 30mA;
Mounting θ - θ, fixed specimen;

Temperature: ambient;
Measurement range: 3° to 30°;
Increment between each measurement: 0.04°;
Measurement time per step: 4 s;
Fixed slits: 1.6 mm;
Kβ (Ni) filter;
No internal reference;
Zeroing procedure using Siemens slits;
Experimental data processed using EVA software (version 9.0).

EXAMPLE 1: α crystalline form of perindopril arginine salt

1.5 kg of water, 328 g of perindopril and 155 g of L-arginine are introduced into a reactor at ambient temperature and with stirring. When a clear solution is obtained, 630 g of methylcyclohexane are added, and then 4.7 kg of dimethyl sulphoxide are added slowly. The mixture is then stirred until the temperature of the heterogeneous mixture stabilises at around 20.0°C, after which the mixture is filtered and the solid obtained is washed and dried.

The crystals so obtained are in a compact form composed of baguettes.
The water content of the resulting product is approximately 3.2%, which corresponds to a monohydrate.

X-ray powder diffraction diagram:

The X-ray powder diffraction profile (diffraction angles) of the α form of perindopril arginine salt is given by the significant lines collated in the following table together with the intensity and relative intensity (expressed as a percentage of the most intense line).

Angle 2 theta (°)	Inter-planar distance d (Å)	Intensity	Relative intensity (%)
4.52	19.53	2211	88.7
7.94	11.12	2080	83.5
12.152	7.277	682	27.4
13.480	*6.563*	*2492*	*100.0*
14.029	6.308	422	16.9
14.948	5.922	552	22.1
15.873	5.579	493	19.8
17.531	5.055	1600	64.2
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19.579	4.530	1078	43.3
20.635	4.301	1794	72.0
22.616	3.928	798	32.0
23.367	3.804	473	19.0
23.807	3.735	362	14.5
24.434	3.640	409	16.4
27.148	3.282	450	18.1
28.214	3.160	417	16.7

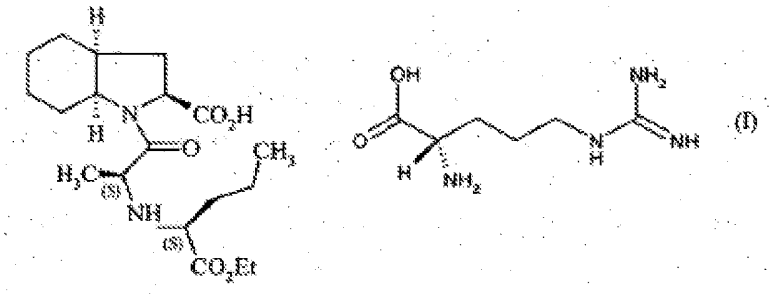
EXAMPLE 2: Pharmaceutical composition

Preparation formula for 1000 tablets each containing 4 mg of active ingredient:

Compound of Example 1	4 g
Hydroxypropylcellulose	2 g
Wheat starch	10 g
Lactose	100 g
Magnesium stearate	3 g
Talc	3 g

Patentkrav

1. α-krystalform af L-argininsaltet af perindopril med formlen (I):



kendetegnet ved følgende røntgenpulverdiffraktionstoppe, målt på et diffraktometer med kobberantikatode og Kβ (Ni)-filter og udtrykt som Bragg 2-theta-vinkel (°): 4,5, 7,9 og 13,5.

2. α-krystalform af forbindelsen med formlen (I) ifølge krav 1, kendetegnet ved følgende røntgenpulverdiffraktionstoppe, målt på et diffraktometer med kobberantikatode og Kβ (Ni)-filter og udtrykt som Bragg 2-theta-vinkel (°): 4,5, 7,9, 13,5, 17,5 og 20,6.

3. α-krystalform af forbindelsen med formlen (I) ifølge krav 1, kendetegnet ved følgende røntgenpulverdiffraktionsdiagram, målt på et diffraktometer (kobberantikatode og Kβ (Ni)-filter) og udtrykt som gitterplanafstande d, Bragg 2-theta-vinkel, intensitet og relativ intensitet (udtrykt i procent i forhold til den mest intense top):

2-theta-vinkel (°)	Gitterplanafstand d (Å)	Intensitet	Relativ intensitet (%)
4,52	19,53	2211	88,7
7,94	11,12	2080	83,5
12,152	7,277	682	27,4
13,480	*6,563*	*2492*	*100,0*
14,029	6,308	422	16,9
14,948	5,922	552	22,1

15,873	5,579	493	19,8
17,531	5,055	1600	64,2
18,787	4,719	363	14,5
19,579	4,530	1078	43,3
20,635	4,301	1794	72,0
22,616	3,928	798	32,0
23,367	3,804	473	19,0
23,807	3,735	362	14,5
24,434	3,640	409	16,4
27,148	3,282	450	18,1
28,214	3,160	417	16,7

4. Fremgangsmåde til fremstilling af α-krystalformen af forbindelsen med formlen (I) ifølge et hvilket som helst af kravene 1-3, hvor perindopril opløses i vand med L-arginin, og der derefter tilsættes et apolært opløsningsmiddel og et polært opløsningsmiddel, og de opnåede krystaller frafiltreres, vaskes og derefter tørres.

5. Fremgangsmåde ifølge krav 4, hvor det apolære opløsningsmiddel er valgt blandt methylcyclohexan, cyclohexan og toluen.

6. Fremgangsmåde ifølge et hvilket som helst af kravene 4 eller 5, hvor det polære opløsningsmiddel er valgt blandt dimethylsulfoxid, N,N-dimethylformamid, N,N-dimethylacetamid og N-methyl-2-pyrrolidinon.

7. Fremgangsmåde ifølge krav 4, hvor det apolære opløsningsmiddel er methylcyclohexan, og det polære opløsningsmiddel er dimethylsulfoxid.

8. Farmaceutisk sammensætning, der som aktiv bestanddel indeholder forbindelsen ifølge et hvilket som helst af kravene 1-3 i kombination med en eller flere inerte, ikke-toksiske og farmaceutisk acceptable bærere.

9. Farmaceutisk sammensætning ifølge krav 8, kendetegnet ved, at den også indeholder et diuretikum.

10. Farmaceutisk sammensætning ifølge krav 9, kendetegnet ved, at diuretikummet er indapamid.

11. Anvendelse af forbindelsen ifølge et hvilket som helst af kravene 1-3 til fremstilling af lægemidler, som er egnede som hæmmer af angiotensin I-konverterende enzym.

12. Anvendelse af forbindelsen ifølge et hvilket som helst af kravene 1-3 til fremstilling af lægemidler, som er egnede til behandling af kardiovaskulære sygdomme.