Title: LOSARTAN POTASSIUM POLYMORPHS AND PROCESS FOR THE PREPARATION THEREOF

Abstract: Losartan potassium polymorphs, identified as Losartan potassium crystalline hydrate, Losartan potassium amorphous and Losartan potassium modification crystalline III, a process for their preparation, pharmaceutical compositions containing them and their use in therapy.
FIELD OF THE INVENTION

The present invention relates to novel forms of Losartan potassium, in particular to a hydrated crystalline form, the amorphous form and a novel losartan potassium crystalline form, herein referred to as Form III. It also relates to a process for their preparation, pharmaceutical compositions containing them and their use in therapy.

TECHNOLOGICAL BACKGROUND

2-n-Butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1-H-imidazole-5-methanol potassium salt is known as Losartan potassium.

Losartan potassium is a known hormone angiotensin II (All) inhibitor, useful in the treatment of angiotensin-induced hypertension. Losartan potassium is also useful in the treatment of hypercholesterolemia, due to its ability to reduce total cholesterol, and in treating impaired cognitive performance. Furthermore, administration of Losartan potassium in combination with a diuretic, such as furosemide or hydrochlorothiazide, enhances the antihypertensive effect of Losartan potassium, while keeping the antiatherosclerotic and hypocholesterolemizing activities. The administration of Losartan potassium can prevent renal failure sometimes induced by non steroidal anti-inflammatories. US 5,138,069 and WO 93/10106 disclose Losartan potassium and its preparation. Two polymorphic forms of Losartan potassium, referred to as Form I and Form II, were described and characterized in US 5,608,075. WO 03/048135 is directed to several Losartan potassium forms, including a tetrahydrate crystalline form therein defined as Form III. Such known Form III is different from the crystalline form provided by the present invention, also referred to as Form III.
SUMMARY OF THE INVENTION

It has now been found that Losartan potassium can exist, in addition to the known crystalline forms I and II, also in other forms stable at room temperature, in particular in the crystalline hydrated form, in the amorphous form and in a crystalline Form III.

The invention therefore relates to the polymorphic forms, herein referred to as hydrated crystalline form, amorphous form and crystalline Form III, and to a process for their preparation. Two novel processes for the preparation of the crystalline Form II of Losartan potassium, known from US 5,608,075 are also provided.

The invention also relates to a pharmaceutical composition comprising Losartan potassium crystalline Form III, or a mixture thereof with at least one of Losartan potassium crystalline Form I, Losartan potassium crystalline Form II, Losartan potassium crystalline hydrate and amorphous Losartan potassium, as the active ingredient, together with a diluent and/or carrier, and to their use in therapy.

BRIEF DESCRIPTION OF THE FIGURES

The novel forms were characterized using the known techniques DSC (Differential Scanning Calorimetry), XRPD (X-ray powder diffraction), and IR (Infrared Spectroscopy). X-ray diffraction spectra (XRPD) were recorded with an automatic diffractometer T/T for powders and liquids manufactured by Ital-Structures, under the following operative conditions: radiation CuKα (O = 1.5418 Å), scanion with angular step of 0.02° for a time of 3 sec. DSC thermograms were recorded with Perkin Elmer differential scanion calorimeter DSC7, subjecting the sample, placed in an open capsule, to a temperature increase of 10°/min. under nitrogen atmosphere. IR spectra were recorded with a Perkin Elmer spectrophotometer FT-IR System 2000.

Fig. 1A. XRPD (X-ray powder diffraction pattern) of Losartan
potassium crystalline hydrate;

Fig. 1B. XRPD (X-ray powder diffraction pattern) of Losartan potassium amorphous form;

Fig. 1C. XRPD (X-ray powder diffraction pattern) of Losartan potassium crystalline Form III;

Fig. 2A. DSC thermogram of Losartan potassium crystalline hydrate;

Fig. 2B. DSC thermogram of Losartan potassium amorphous form;

Fig. 2C. DSC thermogram of Losartan potassium crystalline Form III;

Fig. 3A. IR (Infrared Spectroscopy) of Losartan potassium crystalline hydrate;

Fig. 3B. IR (Infrared Spectroscopy) of Losartan potassium amorphous form;

Fig. 3C. IR (Infrared Spectroscopy) of Losartan potassium crystalline Form III.

DETAILED DISCLOSURE OF THE INVENTION

A first object of the invention is the hydrated crystalline form of Losartan potassium, typically containing approx. 3 to 14% by weight of water, in particular approx. 11 to 13% by weight of water.

An object of the invention is also the amorphous form of Losartan potassium, which can contain up to 10% by weight of water.

A further object of the invention is the crystalline Form III of Losartan potassium.

A further object of the invention is a novel process for the preparation of Losartan potassium crystalline Form II.

The Losartan potassium solution used to obtain Losartan potassium crystalline hydrate, amorphous Losartan potassium and Losartan potassium crystalline Form III can be prepared according to known methods. For example Losartan can be obtained according to US 5,138,069 and
WO 93/10106. In particular, if Losartan is isolated as free tetrazole (i.e. as free acid), an aqueous solution of Losartan potassium can be prepared by dissolving it in a KOH aqueous solution, in equimolar ratio, and heating to approx. 60°C. The resulting Losartan potassium aqueous solution is used for the preparations described in the following. In a similar way, a Losartan potassium alcoholic solution, for example a methanol or ethanol solution, for use in the preparations indicated in the following, can be prepared.

A. Losartan potassium hydrated crystalline form

According to the process of the invention, a Losartan potassium aqueous solution is concentrated by distillation. The solution is then left to cool spontaneously to room temperature. The resulting solid is filtered and dried in a static dryer to approx. 40-50°C, to give a product identified as Losartan potassium crystalline hydrate. Said hydrate crystalline form has a water content typically ranging from approx. 3 to 14% by weight, in particular approx. from 11 to 13% by weight.

A'. Losartan potassium hydrate crystalline form

Alternatively, the Losartan potassium solution is concentrated by evaporation of the solvent at a temperature ranging from approx. 60 to 100°C. The solution is then left to cool spontaneously to room temperature. The resulting solid is filtered and dried in a static dryer at approx. 40-50°C, to give a product identified as Losartan potassium crystalline hydrate. The resulting hydrate crystalline form has water content typically ranging from approx. 3 to 14% by weight, in particular from approx. 11 to 13% by weight.

The hydrate crystalline form of Losartan potassium, as obtainable by process of the invention, has the following characteristics:

a) X-ray powder diffraction spectrum, Fig. 1A, comprising diffraction peaks at approx. 5.7, 6.9, 8.9, 13.2, 13.9 14.2, 14.9, 15.8, 16.2, 16.3, 17.1, 17.4, 19.9, 20.8, 21.0, 21.6, 21.9, 22.2, 23.3, 23.6, 24.1, 24.8, 25.2, 26.6, 27.5,
28.5 ° 0.2 degrees in 2-theta.

b) DSC thermogram, Fig. 2A, having 3 characteristic peaks: a first endothermal peak at an extrapolated onset temperature of approx. 90°C, corresponding to the release of part of the water, an exothermic peak at an extrapolated onset temperature ranging from 185 to 200°C, corresponding to the transition from the amorphous to crystalline phase here identified at point D, and a second endothermal peak at an extrapolated onset temperature of approx. 272°C, corresponding to complete melting of the product; and

c) IR spectrum, Fig. 3A, which shows a broadened band characteristic of the O-H bond stretching, ranging from the frequencies approx. between 3050 and 3650 cm⁻¹.

B. Losartan potassium amorphous form

This form can be obtained starting from Losartan potassium crystalline hydrate, obtainable as described at points A and A'. Amorphous Losartan potassium is obtained by heating Losartan potassium crystalline hydrate at a temperature of approx. 120-150°C, in a static dryer. After reaching this temperature, the solid is left to cool to room temperature, thereby obtaining amorphous Losartan potassium. The amorphous form can contain water up to approx. 10% by weight.

B'. Losartan potassium amorphous form

Alternatively, Losartan potassium amorphous form can be obtained starting from a Losartan potassium aqueous solution. The solution is first concentrated by distillation of the solvent, then concentrated to a residue under vacuum, while hot. The resulting solid is dried in a static dryer, optionally under vacuum, at approx. 45-50°C, thereby obtaining directly amorphous Losartan potassium. Also this amorphous form can contain water up to approx. 10% by weight.

The Losartan potassium amorphous form obtainable by the process of
the invention has the following characteristics:

a) X-ray powder diffraction spectrum, Fig. 1B, without single diffraction peaks but with the characteristic halo typical of an amorphous substance, having a maximum approx. between 18 and 24° in 2T;

b) DSC thermogram, Fig. 2B, having an exothermic peak at an extrapolated onset temperature ranging from 185 to 200°C, corresponding to the transition from the amorphous to crystalline anhydrous phase identified at point D, and an endothermal peak at an extrapolated onset temperature of approx. 272°C, corresponding to complete melting of the product; and

c) IR spectrum, Fig. 3B, which shows a broadened band characteristic of the O-H bond stretching, ranging from the frequencies approx. between 3050 and 3650 cm⁻¹.

C. Losartan potassium crystalline Form III

A Losartan potassium solution is prepared providing a solution of Losartan potassium in methanol at room temperature. The Losartan potassium methanol solution is heated to approx. 50-60°C and kept at this temperature, under stirring, until complete evaporation of the solvent. The resulting solid is left to dry, for instance in the open air or alternatively in a static dryer at approx. 45-50°C, thereby obtaining crystalline Losartan potassium, identified as Form III.

C', Losartan potassium crystalline Form III

Alternatively, a Losartan potassium crystalline Form III can be prepared starting from losartan free acid, by reacting it with potassium bicarbonate, preferably in 4-5 volumes of methanol. The mixture is stirred at a temperature ranging from 30°C to reflux, preferably at reflux temperature, until complete dissolution of the potassium bicarbonate. The losartan potassium methanol solution, thus obtained, is concentrated, optionally under vacuum, to residue which contains the product and an amount of solvent equal to half the weight
of the product. Under these conditions the polymorph Form III crystallizes. It
can be isolated either by completely distilling off the methanol and subsequent
drying, or by dilution with a non-solvent, for example selected from toluene,
acetone and methyl-tertbutyl ether, followed by filtration and drying, for
instance in the open air or alternatively in a static dryer at approx. 45-50°C.

Losartan potassium crystalline Form III, as obtainable by the process of
the invention, has the following characteristics:

a) X-ray powder diffraction spectrum, Fig. 1C, comprising a very strong
diffraction peak at 7.2 ± 0.2 degrees in 2-theta and diffraction peaks of
average intensity at approx. 7.6, 8.0, 12.5, 13.2, 13.9, 15.3, 16.1, 17.2, 17.8,
18.5, 19.3, 19.6, 20.7, 21.6, 24.2, 24.9, 26.1, 27.8, 28.9, 29.5 ± 0.2 degrees in
2-theta.

b) DSC thermogram, Fig. 2C, having a single endothermal peak at an
extrapolated onset temperature of approx. 271°C, corresponding to complete
melting of the product; and

c) IR spectrum, Fig. 3C, which has two characteristic bands of O-H
bond stretching, at a frequency of approx. 3205 and 3415 cm⁻¹.

D. Losartan crystalline Form II (known from US 5,608,075)

It has been found that Losartan potassium crystalline Form II can be
obtained from amorphous Losartan potassium, as obtainable according to
invention, by heating at a temperature approx. ranging from 220 to 240°C.
Losartan potassium crystalline Form II, prepared according to the process of
the invention, has the following characteristics:

a) X-ray powder diffraction spectrum having the same sequences
angular and peaks intensities as that reported in US 5,608,075 for Losartan
potassium Form II; and

b) DSC thermogram having an endothermal peak at an extrapolated
onset temperature of approx. 271°C, similar to that reported in US 5,608,075
for Losartan potassium Form II.

E. Losartan crystalline Form II

It has also been found that the novel crystalline modification III, when heated to approx. 240°C, is transformed into the known modification II before melting.

The Form II was identified and confirmed by X-rays powder diffraction, whereas thermal analysis gives no indications. In fact the conversion from Form III to Form II is not clearly evidenced in the DSC thermogram of the Form III, Fig. 2C.

The importance of the novel Losartan potassium forms of the invention, resides mainly in their useful application in the pharmaceutical technique, in particular in processes such as filtration, drying, sieving, formulation, and the like.

Losartan potassium crystalline hydrate, amorphous Losartan potassium and Losartan potassium crystalline Form III, according to the invention, can be used in human and veterinary medicine in the treatment of those pathologies which can be treated with Losartan potassium, and with the known crystalline forms Losartan forms I and II. In particular, they can be used in the treatment of hypertension in both humans and warm-blooded animals having homeostatic mechanisms, myocardial infarction and impaired cognitive performance. The treatment, as indicated above, can be also carried out in combination with other medicaments commonly used in the treatment of said pathologies.

The present invention therefore also relates to Losartan potassium crystalline Form III, or a mixture thereof with at least one of Losartan potassium crystalline hydrate and amorphous Losartan potassium, for use as a medicament, in particular in the treatment of hypertension, myocardial infarction and in treating impaired cognitive performance.

The invention also relates to a method for the treatment of hypertension,
myocardial infarction and impaired cognitive performance in a patient in need of said treatment, comprising administering to said patient a therapeutically effective amount of a product selected from Losartan potassium crystalline Form III, or a mixture thereof with at least one of Losartan potassium crystalline hydrate and amorphous Losartan potassium; more preferably Losartan potassium crystalline Form III.

The dosage will depend on the conditions of the patient or animal to be treated, and on other factors such as age, severity of the disease and weight. As a rule, the daily dosage will range approx. from 1 to 500 mg, preferably approx. from 10 to 100 mg, in single or repeated administrations, according to the physician’s indications. Losartan potassium crystalline hydrate, amorphous Losartan and Losartan potassium crystalline Form III can be formulated according to known methods, in a pharmaceutical form suitable for the oral or parenteral use. Examples of said forms are solutions, suspensions and emulsions for the oral or parenteral use, tablets, pills, capsules, mixtures of powders, syrups and suppositories.

The following examples illustrate the invention.

**EXAMPLE 1**

**Preparation of Losartan potassium crystalline hydrate**

A Losartan potassium solution is poured into deionized water in a 50 ml round-bottom flask (33 g; conc. 45.5%). The volume of the solution is halved by distillation. The solution is then left to cool spontaneously to room temperature. The resulting solid is filtered and dried in a static dryer at approx. 45-50°C for about 5 hours, and, after cooling to room temperature, is identified as Losartan potassium crystalline hydrate.

**EXAMPLE 2**

**Preparation of Losartan potassium crystalline hydrate**

A Losartan potassium solution is poured into deionized water in a 50 ml
round-bottom flask (27 g; conc. 37%). The solution is kept under magnetic stirring at 75°C until evaporation of approx. half the solvent. The solution is then left to cool spontaneously to room temperature. The resulting solid is filtered and dried in a static dryer at approx. 45-50°C for about 4 hours, and, after cooling to room temperature, is identified as Losartan potassium crystalline hydrate. Its water content is approx. 11.7% w/w.

**EXAMPLE 3**

**Preparation of amorphous Losartan potassium**

5 g of Losartan potassium crystalline hydrate, obtained as described in Example 1, are placed in a covered Petri dish and heated in a static dryer at 10°C/min. to approx. 120°C. The solid is kept at this temperature for 5 minutes and then left to cool spontaneously to room temperature. The resulting solid was identified as amorphous Losartan potassium. The same preparation of amorphous Losartan potassium can be carried out following the procedure described above, but heating the product in the Petri dish to a temperature of 140°C. Its water content is approx. 4.7% w/w.

**EXAMPLE 4**

**Preparation of amorphous Losartan potassium**

A Losartan potassium solution is poured into deionized water in a 50 ml round-bottom flask (35 g; conc. 42.9%). The solution is concentrated by distilling off approx. 16.0 ml of solvent and then concentrated to a residue under vacuum while still hot. The resulting solid is then dried in a static dryer at 45-50°C for approx. 24 hours, to give, after cooling to room temperature, amorphous Losartan potassium. Its water content is approx. 5.1% w/w.

**EXAMPLE 5**

**Preparation of amorphous Losartan potassium**

Operating analogously to what reported in Example 4, but subjecting the product to drying under vacuum at approx. 45-50°C for about 12 hours,
after cooling to room temperature, amorphous Losartan potassium is obtained having water content lower than 0.5% w/w.

EXAMPLE 6

Preparation of Losartan potassium crystalline Form III

A Losartan potassium methanol solution is prepared adding slowly 2.0 g of Losartan potassium, in a 50 ml round-bottom flask containing 3.3 ml of methanol, under magnetic stirring at room temperature. The resulting solution is kept at 55°C under magnetic stirring until complete evaporation of the solvent. The formed solid is dried in a static dryer at 45-50°C for approx. 3 hours, to give, after cooling to room temperature, Losartan potassium crystalline modification III.

EXAMPLE 7

Preparation of Losartan potassium crystalline Form II starting from amorphous Losartan potassium

3 g of amorphous Losartan potassium, obtained as described in Example 3, are placed in a covered Petri dish and heated in a static dryer at 10°C/min. to approx. 230°C. The solid is kept at this temperature for about 2 minutes and then left to cool spontaneously to room temperature. The obtained solid is identified as Losartan potassium crystalline Form II.

EXAMPLE 8

Preparation of Losartan potassium crystalline Form II starting from Losartan potassium crystalline anhydrous Form III

5 g of Losartan potassium crystalline Form III, obtained as described in Example 6 or Example 9, are placed in a covered Petri dish and heated in a static dryer at 10°C/min. to approx. 240°C. The solid is kept at this temperature for approx. 3 minutes and then left to cool spontaneously to room temperature. The resulting solid is identified as Losartan potassium crystalline Form II.
EXAMPLE 9

Preparation of Losartan potassium crystalline Form III

10 g of Losartan free acid are dissolved in 40 ml of methanol. 2.38 g of potassium bicarbonate are added and the mixture is stirred under reflux until complete dissolution. The resulting solution is kept at 55°C under magnetic stirring until evaporation of 35 ml of the solvent. A precipitate is obtained which is cooled to room temperature, diluted with 25 ml of methyl-tertbutyl ether and filtered. The formed solid is dried in a static dryer at 45-50°C for approx. 3 hours, to give, after cooling to room temperature, 9.9 g of Losartan potassium crystalline modification III.

EXAMPLE 10

Capsules

Capsules for the oral administration are prepared by filling two-piece standard hard gelatine capsules with 100 mg each of powdered active ingredient, 150 mg of lactose, 50 mg of cellulose, and 6 mg of magnesium stearate.
CLAIMS

1. Losartan potassium crystalline Form III characterized by:
   a) X-ray powder diffraction spectrum comprising a very strong diffraction peak at 7.2 ± 0.2 degrees in 2-theta and diffraction peaks of average intensity at approx. 7.6, 8.0, 12.5, 13.2, 13.9, 15.3, 16.1, 17.2, 17.8, 18.5, 19.3, 19.6, 20.7, 21.6, 24.2, 24.9, 26.1, 27.8, 28.9, 29.5 ± 0.2 degrees in 2-theta.
   b) thermogram obtained by differential scanning calorimetry having a single endothermal peak at an extrapolated onset temperature of 271°C; and
   c) IR spectrum which has two characteristic bands at a frequency of 3205 and 3415 cm⁻¹.

2. A process for the preparation of Losartan potassium Form III, as defined in claim 1, comprising heating a Losartan potassium solution in methanol to about 50-60°C, keeping this temperature, under stirring, until evaporation of the solvent and drying the resulting solid.

3. A process according to claim 2, wherein the resulting solid is evaporated in the open air or at a temperature of about 45-50°C.

4. A process for the preparation of Losartan potassium Form III, as defined in claim 1, which comprises concentrating a Losartan potassium methanol solution to residue which contains the product and an amount of solvent equal to half the weight of the product and isolating the thus obtained Form III.

5. A process according to claim 4, where isolation of Form III is obtained either by completely distilling off the solvent or by dilution with a non solvent, followed by filtration and drying.

6. A process for the preparation of Losartan potassium crystalline Form II, comprising heating amorphous Losartan potassium to a temperature ranging
from 220 to 240°C.

7. A process for the preparation of Losartan potassium crystalline Form II, comprising heating Losartan potassium crystalline Form III, as obtainable according to the process of claims 2 or 4, to a temperature of 240°C.

8. A process for the preparation of a Losartan potassium crystalline hydrate form, characterized by:
   a) X-ray powder diffraction spectrum comprising diffraction peaks at approx. 5.7, 6.9, 8.9, 13.2, 13.9, 14.2, 14.9, 15.8, 16.2, 16.3, 17.1, 17.4, 19.9, 20.8, 21.0, 21.6, 21.9, 22.2, 23.3, 23.6, 24.1, 24.8, 25.2, 26.6, 27.5, 28.5 \( \pm 0.2 \) degrees in 2-theta.
   b) thermogram obtained by differential scanning calorimetry having an endothermal peak at an extrapolated onset temperature of 90°C, corresponding to the release of part of the water, an exothermic peak at an extrapolated onset temperature ranging from 185 to 200°C, and a second endothermal peak at an extrapolated onset temperature of 272°C; and
   c) IR spectrum which shows a broadened band ranging from the frequencies between 3050 and 3650 cm\(^{-1}\), which comprises concentrating a Losartan potassium aqueous solution by distillation, cooling spontaneously to room temperature, filtering and drying the resulting solid at 40-50°C.

9. A process, according to claim 8, in which the distillation of the aqueous solution is replaced by evaporation of the solvent at a temperature ranging from 60 to 100°C.

10. A process for the preparation of Losartan potassium amorphous form, which comprises heating Losartan potassium crystalline hydrate, as obtainable according to the process of claims 8 or 9, to a temperature ranging from 120 to 150°C and cooling spontaneously to room temperature.
11. A pharmaceutical composition comprising Losartan potassium crystalline Form III, as defined in claim 1, or a mixture thereof with at least one of Losartan potassium crystalline Form I, Losartan potassium crystalline Form II, Losartan potassium crystalline hydrate and amorphous Losartan potassium, as active ingredient, together with a diluent and/or carrier.