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(54) Title: IMPROVED PROCESS FOR CRYSTALLIZATION OF BENAZEPRIL HYDROCHLORIDE

(57) Abstract: An improved process for the crystallization of benazepril hydrochloride to obtain in at least 99.8% diastereomeric purity. The process comprises making a concentrated solution of benazepril hydrochloride in ethanol and adding the resulting solution to a non-solvent diisopropyl ether.



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**IMPROVED PROCESS FOR CRYSTALLIZATION OF
BENAZEPRIL HYDROCHLORIDE**

FIELD OF THE INVENTION

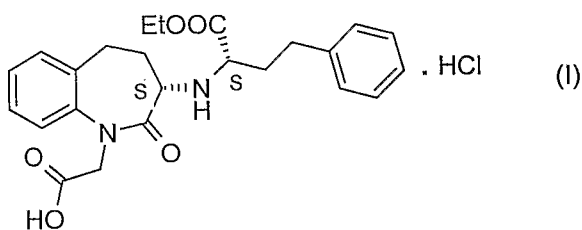
The present invention relates to an improved process for crystallization of Benazepril hydrochloride.

BACKGROUND OF THE INVENTION

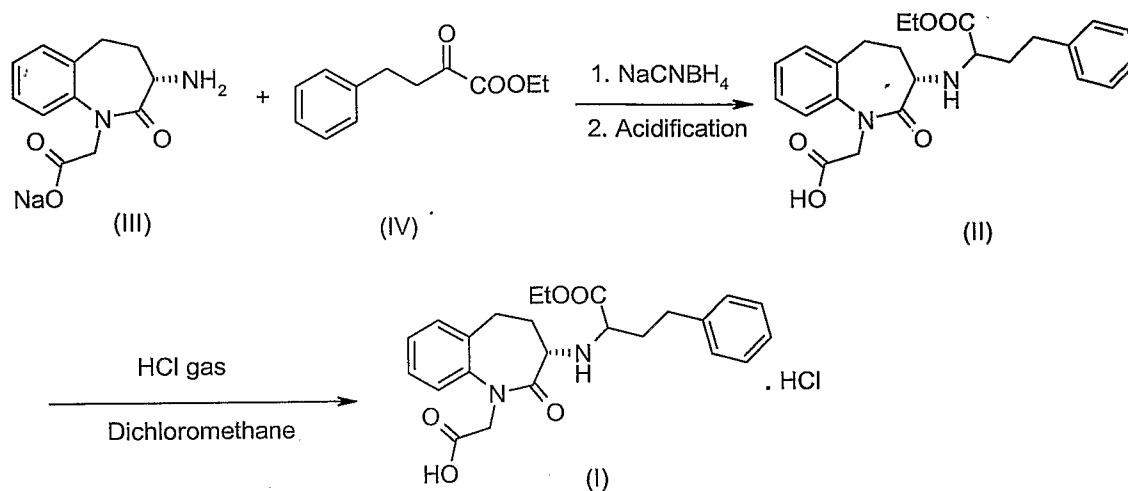
Benazepril (CAS REGISTRY No. 86541-75-5) first disclosed in US 4,410,520 is one of the well-known ACE inhibitors and is used for the treatment of hypertension.

Chemically, Benazepril, is (3S)-1-(carboxymethyl-[[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepine-2-one.

Benazepril is administered orally in the form of hydrochloride salt (CAS REGISTRY No. 86541-74-4) represented by formula (I).



The preparation of benazepril disclosed in US 4,410,520, *J. Med. Chem.* 1985, 28, 1511-1516, and *Helvetica Chimica Acta* (1988) 71, 337-342, as given in scheme 1, involves reductive amination of ethyl 2-oxo-4-phenyl butyrate (IV) with sodium salt of (3S)-3-amino-1-carboxymethyl-2,3,4,5-tetrahydro-1H-benzazepin-2-one (III).



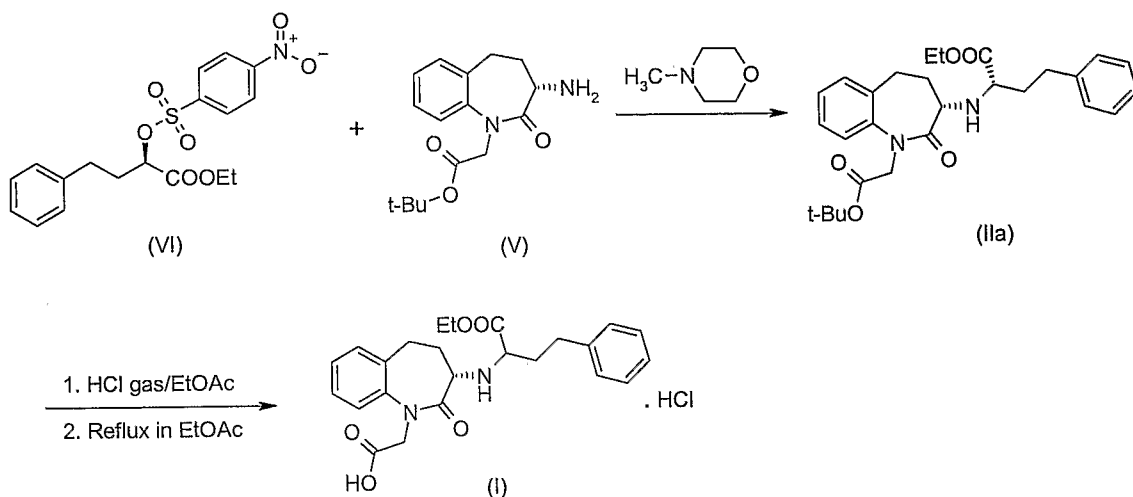
Scheme-1

In example 12 of US 4,410,520, the crude benazepril (II) obtained in a
 5 diastereomeric ratio of SS: SR=70:30 was dissolved in dichloromethane and
 treated with HCl gas to obtain benazepril hydrochloride. The benazepril
 hydrochloride of formula (I) obtained as a foam was crystallized from methyl ethyl
 ketone to obtain in a SS: SR=95:5 diastereomeric ratio. Benazepril hydrochloride
 was further purified by recrystallization from a mixture of 3-pentanone/methanol
 10 (10:1), melting point: 188-190 °C.

Alternatively, in example 27 of US 4,410,520, benazepril hydrochloride was
 purified by refluxing in chloroform, filtering, and washing first with chloroform and
 then with diethyl ether. The melting point of benazepril hydrochloride obtained as
 15 per this example is 184-186 °C.

An alternative process disclosed in US 4,785,089 involves nucleophilic
 substitution of (3S)-3-amino-1-t-butoxycarbonylmethyl-2,3,4,5-tetrahydro-1H-
 benzazepine-2-one (V), using the chiral substrate ethyl (2R)-2-(4-
 20 nitrobenzenesulfonyl)-4-phenyl butyrate (VI) in presence of N-methylmorpholine
 (scheme 2). The benazepril t-butyl ester (IIa) obtained in a diastereomeric ratio of
 SS: SR=96:4 was hydrolyzed to benazepril (II) and converted to hydrochloride

salt by treating with HCl gas in ethyl acetate. The crystalline suspension of benazepril hydrochloride in ethyl acetate was diluted with acetone and filtered to obtain in a diastereomeric ratio of SS: SR=99.1:0.9. Further purification by refluxing in ethyl acetate afforded benazepril hydrochloride in a diastereomeric ratio of SS: SR=99.7:0.3, melting point of 181 °C.



Scheme-2

The above documents do not disclose the crystalline form of benazepril hydrochloride obtained by following the purification processes disclosed in the examples.

The Merck Index., 12th edition reports benazepril hydrochloride crystals obtained from 3-pentanone+methanol (10:1), melting point 188-190 °C

The crystallization methods taught in the prior art does not consistently produce a constant diastereomeric composition of SS:SR diastereomer. This is evident from the variation in the melting points of the benazepril hydrochloride reported in three different working examples, which varies between 181 to 190 °C.

The variation in diastereomeric composition of a pharmaceutical substance is not desirable as it would affect its efficacy. Hence there is a need for a crystallization

process that consistently produce a constant diastereomeric composition of SS diastereomer in greater than 99.8%.

Coming to the crystalline form, it is well known in the art that the solid form of a pharmaceutical substance affect the dissolution rate, solubility and bioavailability. The solid form may be controlled by process employed for the manufacture of the pharmaceutical substance. In particular the process of purification of the solid substance by crystallization is used to control the solid form (*Organic Process Research & Development*, 2003, 7, 958-1027).

It has been found that the crystalline form of benazepril hydrochloride obtained from processes of prior art documents is designated as crystalline Form A as evident from the following documents.

In a monograph published by Al-badar *et al* in *Profiles of Drug Substances, Excipients, and Related Methodology*, Vol. 31, 2004, p117-161; benazepril hydrochloride prepared by the process disclosed in US 4,410,520, and *J. Med. Chem.* 1985, 28, 1511-1516, has been characterized by powder X-ray diffraction pattern having 2 θ peaks at 6.6, 9.9, 11.9, 13.7, 14.0, 14.9, 15.3, 16.4, 17.3, 18.9, 19.6, 20.2, 20.9, 21.5, 22.2, 25.2, 25.5, 26.4, 26.6, 27.1, 27.9, 29.8, 30.4, 31.0, 32.6, 33.3, 33.8, 34.4, 35.5, 38.2, 39.9, 43.9, 48.9.

The major peaks are at 6.6, 9.9, 11.9, 13.7, 14.9, 16.4, 17.3, 18.9, 19.6, 20.2, 20.9, 21.5, 25.2, 25.5, 26.4, 26.6, 27.9, 31.0, and 32.6.

WO 2004/013105 A1 also discloses that by following the processes of the prior art mentioned above, crystalline benazepril hydrochloride is isolated in a form designated as Form A having a powder X-ray diffraction pattern with 2 θ values at 6.7, 10.1, 12.0, 13.8, 15.1, 16.4, 17.4, 19.0, 19.6, 20.2, 20.9, 21.0, 25.3, 25.5, 26.4, 26.6, 27.6, 28.0, 31.0, 32.7.

WO 2004/013105 A1 discloses that benazepril hydrochloride Form A may be prepared from a concentrated solution of the benazepril hydrochloride in a solvent selected from C₁-C₁₀ alcohol, N,N-dimethylformamide, N-methylpyrrolidone by adding an anti-solvent selected from C₄-C₁₂ alkane or C₁-C₁₀ acetate, preferably, hexane or ethyl acetate.

WO 2004/013105 A1 in Example 5 describes a process of making crystalline form A of benazepril hydrochloride by passing HCl gas into a solution of benazepril free base in diethyl ether and filtering the resulting suspension.

10

Similarly, in Example 6, the benazepril hydrochloride was dissolved in water free ethanol and the resulting solution was added to heptane at 20° C to obtain the crystalline Form A.

15 Further, WO 2004/013105 A1, mentions a list of solvents and anti-solvents that can be used to make benazepril hydrochloride crystalline Form A. However, there is no enabling disclosure and the document is silent on the diastereomeric purity of the crystalline form A obtainable by the process disclosed.

20 The processes of crystallization and/or recrystallization disclosed in the prior art do not consistently produce benazepril hydrochloride with constant diastereomeric content as evident from the variation in the melting point of the crystalline benazepril hydrochloride obtained from crystallization from various solvents.

25 The present inventors have now found that use of a mixture of ethanol and diisopropyl ether as a recrystallizing solvent system, benazepril hydrochloride can be consistently obtained in least 99.8% diastereomeric purity.

OBJECT OF THE INVENTION

30 Thus it is an object of the present invention to provide a process consistently provides benazepril hydrochloride with SS diastereomeric content of at least

99.8% and above and simultaneously provides benazepril hydrochloride in crystalline form A.

A further object of the present invention is to provide a process that consistently produces benazepril hydrochloride in crystalline form A with constant diastereomeric content of 99.8% and above by use of a solvent system for crystallization of

SUMMARY OF THE INVENTION

An improved process for the crystallization of benazepril hydrochloride to obtain in at least 99.8% diastereomeric purity, which comprises of (a) making a concentrated solution of benazepril hydrochloride in ethanol (b) adding the resulting solution to a non-solvent diisopropyl ether.

DETAILED DESCRIPTION OF INVENTION

The present inventors have found that use of a mixture of ethanol and diisopropyl ether as a recrystallizing solvent system, benazepril hydrochloride can be consistently obtained in least 99.8% diastereomeric purity and in a solid form having a characteristic X-ray powder diffraction pattern given in Figure 1 with values at 6.7, 10.1, 12.0, 13.8, 15.1, 16.4, 17.4, 19.0, 19.6, 20.2, 20.9, 21.0, 25.3, 25.5, 26.4, 26.6, 27.6, 28.0, 31.0, 32.7.

The ethanol used is preferably water-free., i.e, absolute ethanol.

Accordingly, a concentrated solution of benazepril hydrochloride in absolute ethanol is added to diisopropyl ether with stirring at a temperature between 20-30 °C. The solid obtained was filtered and dried under reduced pressure.

The solid form obtained by the present process is identical to the solid form disclosed in *Profiles of Drug Substances, Excipients, and Related Methodology*, Vol. 31, 2004, p117-161 and WO 2004/013105 A1.

The process of crystallization of present invention is useful to purify the crude benazepril monohydrochloride obtained by any of the processes disclosed in the prior art document.

- 5 The invention is further illustrated by the following non-limiting example.

EXAMPLE

Benazepril hydrochloride (18.8g) was dissolved in absolute ethanol (94ml). Charcoal (0.75g) was added, stirred, and filtered. Filtrate was concentrated to
10 about 1/3 of its original volume at 40° C under reduced pressure. The concentrated solution was added to diisopropyl ether (263 ml) with stirring at about 20-30° C. The solid separated was filtered off and dried under reduced pressure at 45-50 °C for 7h. The benazepril hydrochloride obtained was found to be having a diastereomeric ratio of SS: SR =99.8: 0.2; by HPLC.

- 15 Melting point 187-189° C.

Benazepril hydrochloride obtained by the above process is further characterized by X-ray powder diffraction pattern given in Figure 1 with 2θ values at 6.7, 10.1, 12.0, 13.8, 15.1, 16.4, 17.4, 19.0, 19.6, 20.2, 20.9, 21.0, 25.3, 25.5, 26.4, 26.6,
20 27.6, 28.0, 31.0, 32.7.

CLAIMS

1. An improved process for the crystallization of benazepril hydrochloride to
5 obtain in at least 99.8% diastereomeric purity, which comprises of (a)
making a concentrated solution of benazepril hydrochloride in ethanol (b)
adding the resulting solution to a non-solvent diisopropyl ether.
2. A process according to claim 1 wherein the benazepril hydrochloride is
10 obtained in a crystalline form having a characteristic X-ray powder
diffraction pattern with 2θ values at 6.7, 10.1, 12.0, 13.8, 15.1, 16.4, 17.4,
19.0, 19.6, 20.2, 20.9, 21.0, 25.3, 25.5, 26.4, 26.6, 27.6, 28.0, 31.0, 32.7.
3. A process according to claim 1, wherein the ethanol is absolute ethanol.
- 15 4. A process according to claim 1, wherein the concentrated solution of
benazepril hydrochloride in ethanol is added to diisopropyl ether at
temperature about 10-35° C, preferably 20-30° C.
- 20 5. A process according to claim 1, wherein the crystalline form of benazepril
hydrochloride is isolated by filtration and dried under reduced pressure at
45-50° C.

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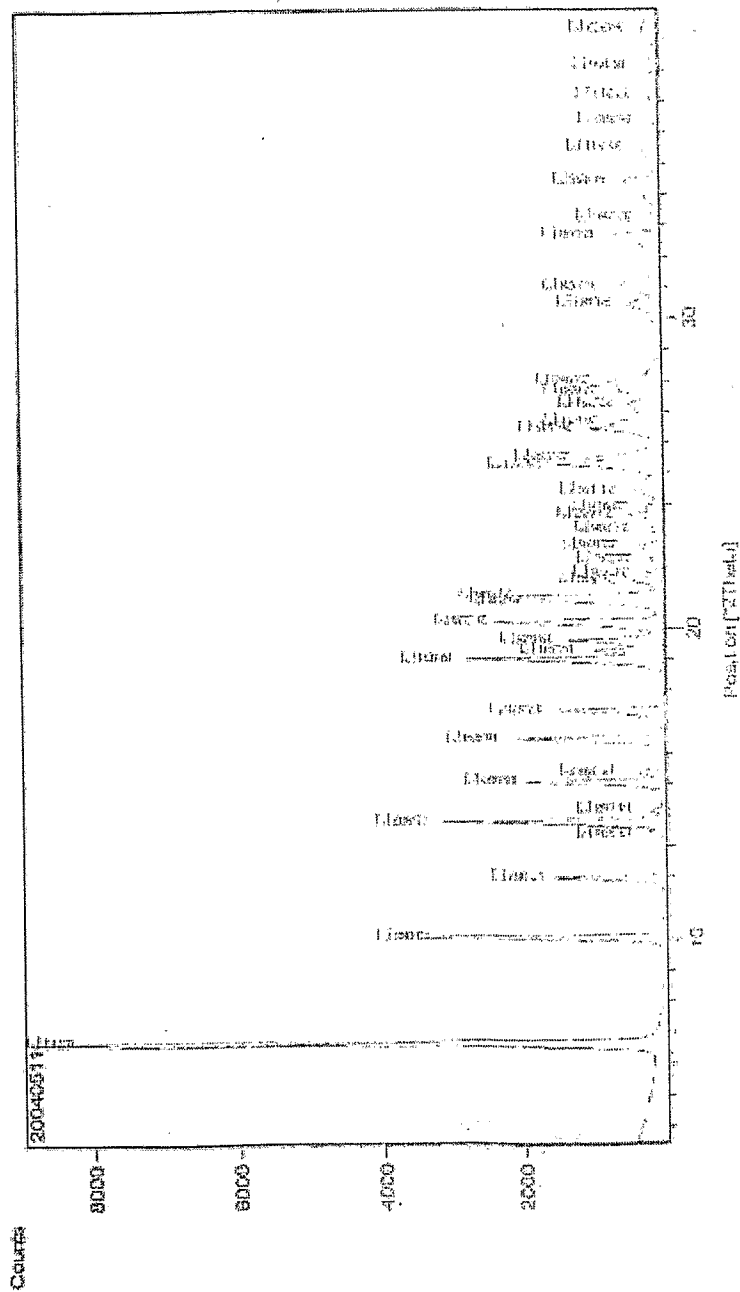


Figure-1