Crystalline form 1 4-[2-[4-[[1-(2-ethoxyethyl)-1H-benzimidazole-2-yl]-1-piperidinyl]ethyl]-α-piperidinyl]-4-α-methyl-benzeneacetic acid (I) is described, procedures for its preparation, pharmaceutical formulae containing crystalline form 1 and the use of crystalline form 1 to treat allergic reactions and pathological processes mediated by histamine in mammals such as man.
POLYMORPH OF 4-[2-[4-[(2-ETHOXYETHYL)-1H-BENZIMIDAZOLE-2-YL]-1-PIPERIDINYL]ETHYL]-α,α-DIMETHYL-BENZENEACETIC ACID

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a Continuation of application Ser. No. 10/511,822 having a filing date under 35 U.S.C. § 371(c) of Mar. 23, 2005, which is presently pending, and which, in turn, is a U.S. National Stage filing under 35 U.S.C. § 371 of International Patent Application No. PCT/ES02/00194 filed Apr. 19, 2002, the priority of which is claimed herein.

AREA OF THE INVENTION

The invention refers to a new crystalline form of 4-[2-[4-[(2-ethoxyethyl)-1H benzimidazole-2-y1]-1-piperidinyl]ethyl]-α,α-dimethyl-benzeneacetic acid (herein referred to as “bilastine”) of formula (I).

From hereon referred to as crystalline form 1, to procedures used to prepare it, to pharmaceutical formulations that contain crystalline form 1 and to the use of crystalline form 1 to treat allergic reactions and pathological processes mediated by histamine in mammals, such as man.

BACKGROUND OF THE INVENTION

U.S. Pat. No. 5,877,187 confers the rights to bilastine, a preparation with antihistaminic properties without sedative or cardiovascular effects. This patent also concerns a procedure to prepare bilastine and the use of this preparation to treat allergic reactions in mammals but it does not include or suggest the possible existence of polymorphic forms of this compound. To prepare pharmaceutical preparations containing bilastine for their administration in mammals and especially in man, in accordance with international health authority specifications, bilastine must be manufactured in the most stable crystalline form possible, especially in a form that has constant physical properties.

SUMMARY OF THE INVENTION

We have found that bilastine can exist in three different crystalline polymorphic forms, each with different physical properties.

The invention refers to crystalline form 1 of bilastine, characterised by X-ray crystallographic analysis, with approximate crystal parameters as follows:

- Crystallographic system: Monoclinic
- Spatial group: P2₁ (1) c
- Crystal size: 0.56 x 0.45 x 0.24 mm
- Cell dimension: a = 23.38 (5) Å; b = 8.829 (17) Å; c = 12.59 (2) Å; α = 90°; β = 90°; γ = 90°
- Volume: 2600 Å³
- Z, calculated density: 4,1184 mg/m³

The crystalline form 1 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide tablet that has the following characteristic absorption bands, expressed in reciprocal centimetres:

- 3430 (s)*; 3057 (w)*; 2970 (s); 2929 (s); 2883 (m)*; 2857 (m); 2797 (w); 1667 (m); 1614 (m); 1567 (w); 1509 (s); 1481 (m); 1459 (vs)*; 1431 (m); 1378 (w); 1346 (m); 1326 (m); 1288 (w); 1254 (m); 1199 (w); 1157 (w); 1121 (vs); 1045 (w); 1020 (w); 991 (w); 973 (w); 945 (w); 829 (w); 742 (s); 723 (w); 630 (w), * where (w)—weak intensity, (m)—medium intensity, (s)—strong intensity, (vs)—very strong intensity.

FIG. 1 represents the infrared spectrum of the crystalline form 1 of bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrum One FTIR spectrophotometer.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows a typical infrared absorption spectrum in potassium bromide of crystalline form 1. (Vertical axis: Transmission (%); Horizontal axis: Wavenumber (cm⁻¹)).

FIG. 2 shows a typical infrared absorption spectrum in potassium bromide of crystalline form 2. (Vertical axis: Transmission (%); Horizontal axis: Wavenumber (cm⁻¹)).

FIG. 3 shows a typical infrared absorption spectrum in potassium bromide of crystalline form 3. (Vertical axis: Transmission (%); Horizontal axis: Wavenumber (cm⁻¹)).

DETAILED DESCRIPTION OF THE INVENTION

We have found that bilastine can exist in three clearly different polymorphic forms called crystalline form 1, crystalline form 2 and crystalline form 3.

The procedure described in U.S. Pat. No. 5,877,187 generates a mixture of crystalline forms 2 and 3. We have discovered experimental conditions and specific solvents to produce clearly different polymorphic forms of bilastine. The crystalline form 1 of pure bilastine is prepared according to the procedures of this invention. The crystalline forms 1 and 2 are stable.

Crystalline form 3 is not very stable and is difficult to obtain in the pure form. Both crystalline form 2 and crystalline form 3 are converted into crystalline form 1 by the procedures of this invention.

Crystalline form 1 of bilastine has a melting point of 200.3⁰ C. Crystalline form 2 has a melting point of 205.2⁰ C. Crystalline form 3 has a melting point of 197.0⁰ C.

The crystalline form 1 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:
(m) = medium intensity, (s) = strong intensity, (vs) = very strong intensity. FIG. 1 represents the infrared spectrum of the crystalline form 1 of bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrometer FTIR spectrophotometer. The crystalline form 2 of bilastine is also characterised by its infrared absorption spectrum in potassium bromide that has the following characteristic absorption bands, expressed in reciprocal centimetres:

\[ \text{Table 1} \]

<table>
<thead>
<tr>
<th>Wavenumber (cm(^{-1}))</th>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>3429 (s); 3053 (w); 2970 (s); 2932 (s); 2868 (s); 2804 (w); 1699 (m); 1614 (m); 1567 (m); 1508 (s); 1461 (vs); 1381 (m); 1351 (s); 1255 (m); 1201 (w); 1156 (m); 1121 (vs); 1048 (w); 995 (w); 823 (w); 767 (w); 744 (s); 724 (w); 630 (w);</td>
<td>( w = ) weak intensity, ( m = ) medium intensity, ( s = ) strong intensity, ( vs = ) very strong intensity</td>
</tr>
</tbody>
</table>

FIG. 2 represents the infrared spectrum of the crystalline form 2 of the bilastine in a potassium bromide tablet recorded in a Perkin Elmer Spectrometer FTIR spectrophotometer.

\[ \text{FIG. 1} \]

We have discovered that, under selected experimental conditions, the mixture of the crystalline forms 2 and 3, obtained according to U.S. Pat. No. 5,877,187, is surprisingly transformed into crystalline form 1. We have also discovered that crystalline form 1 of bilastine is very stable and is not transformed into any of the other polymorphs 2 and 3. Similarly, in the same experimental conditions, the pure crystalline form 2 of bilastine is surprisingly transformed into the pure crystalline form 1. Crystalline form 3, which is the most unstable, undergoes the same transformation under the same conditions.

Crystalline form 1 of bilastine is a very stable polymorph at room temperature and is, therefore, very useful as an active ingredient of a pharmaceutical preparation. Crystalline form 1 is also stable when stored at temperatures above room temperature.

The crystalline form 1 of bilastine is characterised by the following data of its X-ray crystallographic analysis as a monocrystal, with crystal parameters of approximately the following values:

- Crystallographic system: Monoclinic
- Spatial group: \( \text{P2}_1 \) (c)
- Crystal size: \( 0.56 \times 0.45 \times 0.24 \) mm
- Cell dimension:
  - \( a = 23.38 \) Å, \( \alpha = 90^\circ \)
  - \( b = 8.829 \) Å, \( \beta = 90^\circ \)
  - \( c = 12.59 \) Å, \( \gamma = 90^\circ \)
- Volume: \( 2600 \) Å\(^3\)
- \( Z \), calculated density: \( 4, 1.184 \) mg/Å\(^3\)

\[ \text{Table 2} \]

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Preparations</td>
<td>The crystalline form 1 of bilastine can be prepared by the following procedures:</td>
</tr>
<tr>
<td>Preparation 1</td>
<td>Preparing a suspension of bilastine in water, followed by filtration.</td>
</tr>
<tr>
<td>Preparation 2</td>
<td>Preparing a suspension of bilastine in alcohol, followed by drying.</td>
</tr>
</tbody>
</table>

\[ \text{Chemical Reactions} \]

During the development of crystalline form 1 of bilastine for pharmaceutical preparations, elaborated according to correct manufacturing procedures, we have discovered that crystallization of bilastine (prepared according to the description given in U.S. Pat. No. 5,877,187) from isopropyl alcohol and n-butanol, leads to generation of the polymorphic form 1 of bilastine with a high yield. Crystallisation from acetone, dimethylsulfoxide, dimethylformamide, acetonitrile and tetrahydrofuran, or its mixtures thereof also lead to generation of crystalline form 1, although with lower yields. It is, therefore, preferable to use the former solvents.

**Preparation:** The infrared spectrum of crystalline form 1 of bilastine in potassium bromide is characterised by the following bands, absent from polymorphs 2 and 3:

- 2929, 2883, 2857
- 2797, 1667
- 1481
- 1431
- 1356
- 1326
- 1288
- 973
- 945
- 829

**Preparation:** FIG. 1 shows the complete infrared spectrum of crystalline form 1 of bilastine in potassium bromide, recorded with Perkin Elmer Spectrum One spectrophotometer.

**Preparation:** Pharmaceutical preparations of this invention can contain, as well as an effective quantity of crystalline form 1 of bilastine as an active ingredient, an analgesic or anti-inflammatory agent, several pharmaceutically acceptable excipients. The solid pharmaceutical preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid excipient can be one of several substances that act as diluents, aromatising agents, agglutinants or disintegrating agents and an encapsulation material. The powders and tablets preferentially contain from approximately 5 to approximately 20% per cent of the active ingredient. Appropriate solid excipients are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, waxes with low melting point, cocoa butter and similar products. The term "preparations" includes the formulation of the active ingredient with an excipient for encapsulation to produce a capsule in which the active ingredient (with or without other excipients) is surrounded by the excipient by an encapsulation material. Tablets, powders, capsules and capsules can be used as suitable forms for oral administration. The active ingredient can also be incorporated into a chewing gum that contain sweeteners, flavorings and colorings as appropriate.

**Preparation:** To prepare suppositories, a compound with a low melting point, such as a mixture of fatty acid glycerides or cocoa butter, is melted and the active ingredient is mixed well and homogeneously dispersed in the mixture with agitation. The homogeneous melted mixture is placed in the appropriate moulds and left to cool until it solidifies.

**Preparation:** Liquid preparations comprise suspensions that can be made by mixing the finely divided active ingredient in water with suspension agents.

**Preparation:** Also, topical preparations are considered for nasal, ophthalmic and dermal use. Appropriate formulae for nasal administration can correspond to solutions or suspensions. Ophthalmic formulae can be suspensions and ointments. Der-
mal preparations can be suspensions, ointments and creams. Ointments usually contain lipophylic excipients such as mineral oil or vaseline.

[0047] Similarly, a compound is being contemplated for transdermic use, consisting of a therapeutically effective amount of active ingredient incorporated into an excipient that corresponds to a liquid, a gel, a solid matrix or an adhesive patch sensitive to pressure, to be released via a transdermic administration system.

[0048] The effective antiallergic or antihistaminic amount of crystalline form 1 of bilastine for topical administration varies between 0.1 and 5% of the total weight of the pharmaceutical compound. The preferred amount ranges from 0.1 to 2% of the total weight of the pharmaceutical compound.

[0049] The effective antiallergic or antihistaminic amount of crystalline form 1 of bilastine for oral administration varies from 1 to 50 mg/day, with preferably an amount corresponding to approximately 2 to 20 mg/day in a single or fractionated doses.

[0050] Crystalline form 1 of bilastine has antihistaminic properties that have been demonstrated in experimental pharmacological models, such as preventing histamine-induced lethality in the guinea-pig and antagonism against cutaneous capillary permeability induced by histamine in the rat.

[0051] The following examples illustrate but do not limit the scope of the present invention.

EXAMPLE 1

[0052] Preparation of crystalline form 1 of bilastine. Dissolve bilastine (see the U.S. Pat. No. 5,877,187) in isopropyl alcohol heated to reflux for approximately 15-20 minutes under nitrogen while stirring. Cool the solution to 50°C over 6 hours and stop stirring. Let the solution cool to room temperature and stir again for three hours, filter and wash with cold isopropyl alcohol. Dry the solid residue in a vacuum oven at 35-40°C to constant weight.

EXAMPLE 2

[0053] Preparation of crystalline form 1 of bilastine. Heat a suspension of bilastine (see U.S. Pat. No. 5,877,187) in n-butanol and reflux for 3 hours under nitrogen while stirring. Leave the solution to cool down to room temperature, filter off the solid residue and dry it in a vacuum oven at 35-40°C to constant weight.

EXAMPLE 3

[0055] Preparation of crystalline form 1 of bilastine. Treat a mixture of polymorphs 2 and 3 of bilastine for several hours with hot acetone. Let the mixture cool to room temperature and filter off the solid residue. Dry it to constant weight.

EXAMPLE 4

[0057] Preparation of crystalline form 1 of bilastine. Dissolve crystalline form 3 of bilastine in isopropyl alcohol heated to reflux and stir for approximately 15-20 minutes under nitrogen. Let the solution reach room temperature constantly stirring, filtering and washing with cold isopropanol. Dry the solid in a vacuum oven at 35-40°C to constant weight.

EXAMPLE 5

[0059] Preparation of crystalline form 1 of bilastine. Dissolve crystalline form 2 of bilastine in n-butanol heated to reflux while stirring for approximately 3 hours. Let the solution reach room temperature while stirring, filtering and draining. Dry the solid in a vacuum oven at 35-40°C to constant weight.

1. A liquid antihistaminic pharmaceutical composition comprising the crystalline form 1 of bilastine as the active ingredient together with at least one excipient, said crystalline form 1 of bilastine having, upon X-ray crystallography analysis, crystal parameters of substantially the following:

<table>
<thead>
<tr>
<th>Crystallographic system</th>
<th>Monoclinic</th>
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<tbody>
<tr>
<td>Spatial group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.56 x 0.45 x 0.24 mm</td>
</tr>
<tr>
<td>Cell dimension</td>
<td>a = 23.38 (5) ( \AA ), ( \alpha = 90^\circ )</td>
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<tr>
<td></td>
<td>b = 8.829 (17) ( \AA ), ( \beta = 90^\circ )</td>
</tr>
<tr>
<td></td>
<td>c = 12.59 (2) ( \AA ), ( \gamma = 90^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>2600 ( \AA^3 )</td>
</tr>
<tr>
<td>Calculated density</td>
<td>4,1184 mg/m³</td>
</tr>
</tbody>
</table>

an infrared spectrum in potassium bromide with the following bands:

<table>
<thead>
<tr>
<th>Wavenumber (cm(^{-1}))</th>
<th>3057</th>
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<tbody>
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<td>829</td>
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</tbody>
</table>

and an infrared spectrum in potassium bromide which is substantially identical to that shown in FIG. 1.

2. A liquid antihistaminic pharmaceutical composition according to claim 1, wherein said composition is a suspension.

3. A liquid antihistaminic pharmaceutical composition according to claim 1, wherein said composition is an emulsion.

4. A liquid antihistaminic pharmaceutical composition according to claim 1, wherein said composition is a cream.

5. A liquid antihistaminic pharmaceutical composition according to claim 1, wherein said composition is a solution.

6. A liquid antihistaminic pharmaceutical composition according to claim 1, wherein said composition is a lotion.

7. A process for treating allergic diseases in a patient in need thereof, wherein the process comprises administering to said patient a liquid pharmaceutical composition according to claim 1.

8. A process for treating allergic diseases in a patient in need thereof, wherein the process comprises administering to said patient an effective amount of crystalline form 1 of bilastine in a liquid pharmaceutical composition according to claim 1.

* * * * *