Abstract:
The present invention provides a novel amorphous Form of lurasidone hydrochloride, process for its preparation and pharmaceutical compositions comprising it. In one aspect, the present invention provides an amorphous form of lurasidone hydrochloride. In another aspect, the present invention provides a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises: a) dissolving lurasidone hydrochloride in a mixture of alcoholic solvent and water; and b) subjecting the resulting solution to lyophilization to obtain lurasidone hydrochloride amorphous form.
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NOVEL POLYMORPH OF LURASIDONE HYDROCHLORIDE

This application claims the benefit of Indian Provisional Patent Application No. 893/CHE/2012, filed on March 09, 2012, which is incorporated herein by reference.

Filed of the Invention

The present invention provides a novel amorphous Form of lurasidone hydrochloride, process for its preparation and pharmaceutical compositions comprising it.

Background of the Invention

Lurasidone hydrochloride is chemically, \( (3\alpha?,4\alpha\',7\alpha\',7\alpha\$)-2-[(\alpha?,2\alpha?)-(4-(1,2-benzisothiazol-3-yl)-piperazin-1-yl)methyl]cyclohexyl)methyl]hexahydro-1\( H\)-4,7-methanisoindol-1,3-dione hydrochloride and has the structural formula:

![Structural formula of Lurasidone hydrochloride](image)

Lurasidone hydrochloride is a typical antipsychotic developed by Dainippon Sumitomo Pharma under the trade name Latuda®.

Lurasidone and its salts were disclosed in US patent No. 5,532,372 (‘372 patent).

Polymorphism is defined as "the ability of a substance to exist as two or more crystalline phases that have different arrangement and/or conformations of the molecules in the crystal Lattice. Thus, in the strict sense, polymorphs are different crystalline structures of the same pure substance in which the molecules have different arrangements and/or different configurations of the molecules". Different polymorphs may differ in their physical properties such as melting point, solubility, X-ray diffraction patterns, etc.
Although those differences disappear once the compound is dissolved, they can appreciably influence pharmaceutically relevant properties of the solid form, such as handling properties, dissolution rate and stability. Such properties can significantly influence the processing, shelf life, and commercial acceptance of a polymorph. It is therefore important to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the laboratory by analytical methods such as X-ray diffraction (XRD), Differential Scanning Calorimetry (DSC) and Infrared spectrometry (IR).

Solvent medium and mode of crystallization play very important role in obtaining one polymorphic Form over the other.

Lurasidone and its salts can exist in different polymorphic Forms, which may differ from each other in terms of stability, physical properties, spectral data and methods of preparation.

Process for the preparation of lurasidone hydrochloride was described in '372 patent. According to the patent, crystalline solid of lurasidone hydrochloride was obtained by dissolving crude lurasidone in acetone at 20 to 30°C and then added a solution of hydrogen chloride in 2-propanol, and isolating. The crystalline lurasidone hydrochloride obtained by the process of the prior art is herein after designated as lurasidone hydrochloride crystalline Form I. The powdered x-ray diffractogram (PXRD) of lurasidone hydrochloride crystalline Form I is shown in figure 1. Crystalline Form I is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 11.4, 13.9, 15.1, 15.5, 16.4, 17.1, 19.5, 20.8 and 21.9 ± 0.2 degrees.

Crystalline Form of lurasidone free base was reported in IP.com Journal (2011), 11(4A), 26.

International patent application publication no. WO 2012/063246 ('246 patent) disclosed amorphous Form of lurasidone hydrochloride.

We have found a novel amorphous Form of lurasidone hydrochloride. The novel Form has been found to be stable, reproducible and so, suitable for pharmaceutical preparations.
The novel amorphous Form of lurasidone hydrochloride of the present invention is different from the prior art amorphous Form of lurasidone hydrochloride as disclosed in '246 patent, specifically in the pattern of Powdered X-Ray Diffractogram.

Thus, an object of the present invention is to provide a novel amorphous Form of lurasidone hydrochloride, process for its preparation and pharmaceutical compositions comprising it.

**Summary of the Invention**

In one aspect, the present invention provides an amorphous Form of lurasidone hydrochloride.

In another aspect, the present invention provides a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises:

a) dissolving lurasidone hydrochloride in a mixture of alcoholic solvent and water; and

b) subjecting the resulting solution to lyophilization to obtain lurasidone hydrochloride amorphous Form.

In another aspect, the present invention provides a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises:

a) dissolving lurasidone hydrochloride in an alcoholic solvent, a chlorinated solvent or a mixture thereof; and

b) subjecting the resulting solution to spray drying to obtain lurasidone hydrochloride amorphous Form.

In another aspect, the present invention provides a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises:

a) dissolving lurasidone hydrochloride in a mixture of alcoholic solvent, a chlorinated solvent and an ether solvent; and

b) removing the solvent to obtain lurasidone hydrochloride amorphous Form.

In another aspect, the present invention provides a pharmaceutical composition comprising amorphous Form of lurasidone hydrochloride and pharmaceutically acceptable excipients.
Brief Description of the Drawings

Figure 1 is a n X-ray powder diffraction spectrum of lurasidone hydrochloride crystalline Form I.

Figure 2 is an X-ray powder diffraction spectrum of lurasidone hydrochloride amorphous Form obtained by the example 3 and example 4.

Figure 3 is an X-ray powder diffraction spectrum of lurasidone hydrochloride amorphous Form obtained by the example 7.

Figure 4 is an X-ray powder diffraction spectrum of lurasidone hydrochloride amorphous Form obtained by the example 11.

Figure 5 is an X-ray powder diffraction spectrum of lurasidone hydrochloride amorphous Form obtained by the example 13.

X-ray powder diffraction spectrum was measured on a bruker axs D8 advance X-ray powder diffractometer having a copper-Kα radiation. Approximately 500 mg of sample was gently flattered on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.020 degrees two theta per step and a step time of 10.6 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 KV and current 35 mA.

Detailed Description of the Invention

The term "room temperature" refers to temperature at about 25 to 35°C.

According to one aspect of the present invention, there is provided an amorphous Form of lurasidone hydrochloride. The powdered x-ray diffractogram (PXRD) of lurasidone hydrochloride amorphous Form is shown in figures 2, 3, 4 and 5.

The lurasidone hydrochloride amorphous Form obtained may have water content of up to 20.0% by weight.

According to another aspect of the present invention, there is provided a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises:

a) dissolving lurasidone hydrochloride in a mixture of alcoholic solvent and water; and

b) subjecting the resulting solution to lyophilization to obtain lurasidone hydrochloride amorphous Form.
Lurasidone hydrochloride used in step (a) may preferably be lurasidone hydrochloride obtained by the known process.

The alcoholic solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol and isobutyl alcohol. More preferably the alcoholic solvent is methanol.

The term "Lyophilization" refers to a sublimation process that removes free water or other solvent in the form of solid.

According to another aspect of the present invention, there is provided a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises:

a) dissolving lurasidone hydrochloride in an alcoholic solvent, a chlorinated solvent or a mixture thereof; and

b) subjecting the resulting solution to spray drying to obtain lurasidone hydrochloride amorphous Form.

Lurasidone hydrochloride used in step (a) may preferably be lurasidone hydrochloride obtained by the known process.

The alcoholic solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol and isobutyl alcohol. More preferably the alcoholic solvent is ethanol.

The chlorinated solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from methylene chloride, ethylene chloride, chloroform and carbon tetrachloride, and more preferably the chlorinated solvent is methylene chloride.

The term "Spray drying" refers to is a method of producing a dry powder from a liquid or slurry by rapidly drying with a hot gas.

According to another aspect of the present invention, there is provided a process for the preparation of lurasidone hydrochloride amorphous Form, which comprises:

a) dissolving lurasidone hydrochloride in a mixture of alcoholic solvent, a chlorinated solvent and an ether solvent; and

b) removing the solvent to obtain lurasidone hydrochloride amorphous Form.

Lurasidone hydrochloride used in step (a) may preferably be lurasidone hydrochloride obtained by the known process.
The alcoholic solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol and isobutyl alcohol. More preferably the alcoholic solvent is methanol.

The chlorinated solvent used in step (a) may preferably be a solvent or a mixture of solvents selected from methylene chloride, ethylene chloride, chloroform and carbon tetrachloride, and more preferably the chlorinated solvent is methylene chloride.

The ether solvent used in step (a) may preferably be a solvent or mixture of solvents selected from tetrahydrofuran, 1,4-dioxane, methyl tert-butyl ether and diethyl ether, and more preferably the ether solvent is methyl tert-butyl ether.

The solvent may be removed from the solution in step (b) by known methods, for example, distillation.

The distillation of the solvent may be carried out at atmospheric pressure or at reduced pressure. The distillation may preferably be carried out until the solvent is almost completely distilled off.

As used herein, "reduced pressure" refers to a pressure of less than 100 mmHg.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising amorphous Form of lurasidone hydrochloride and pharmaceutically acceptable excipients, and optionally other therapeutic ingredients. The amorphous Form may preferably be formulated into tablets, capsules, suspensions, dispersions, injectables or other pharmaceutical forms.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

**Examples**

**Example 1:**

**Preparation of lurasidone**

**Stage-I: Preparation of trans-L,2-bis(methanesulfonyloxymethyl)cyclohexane**

Trans-L,2-bis(hydroxymethyl)cyclohexane (50 gm) was dissolved in methylene chloride (1000 ml) and then added triethylamine (136 ml). The contents were then cooled to 0°C and then added methylsulfonyl chloride (51 ml) slowly at 0 to 5°C. The temperature of the reaction mass was raised to room temperature and stirred for 16 hours. Water (500 ml) was added to the reaction mass and stirred for 15 minutes at room
temperature. The layers were separated and the aqueous layer was extracted with methylene chloride. Combined organic layers were dried with sodium sulfate and then concentrated to obtain a residual solid. To the residual solid was added methylene chloride (50 ml) and cyclohexane (250 ml). The contents were stirred for 30 minutes at room temperature, filtered and then dried to obtain 62 gm of trans-1,2-bis(methanesulfonyloxymethyl)cyclohexane.

Stage-II: Preparation of trans-iaJa-octahydrosoindolium-2-spiro-1'-f4'-(L2-benisothiazol-3-yl)piperazine methane sulfonate

Acetonitrile (300 ml) was added to trans-1,2-bis(methanesulfonyloxymethyl)cyclohexane (20 gm) under stirring at room temperature. A mixture of 1-(1,2-benzoisothiazol-3-yl)-piperazine (13.2 gm), sodium carbonate (6.6 gm) and tetrabutyiammonium hydrogen sulfate (200 mg) was added to the solution under stirring. The temperature of the reaction mass was raised to 85°C and then heated to reflux. The reaction mass was maintained for 48 hours at reflux and then cooled to 70°C. The reaction mass was filtered and then concentrated to obtain a residual solid. To the residual solid was added ethyl acetate (40 ml) and stirred for 15 minutes. The separated solid was filtered and then dried to obtain 15 gm of trans-3a,7a-octahydrosoindolium-2-spiro-1'-[4'-(1,2-benisothiazol-3-yl)]piperazine methane sulfonate.

Stage-III: Preparation of lurasidone

Toluene (225 ml) was added to trans-3a,7a-octahydrosoindolium-2-spiro-T-[4'-(1,2-benisothiazol-3-yl)]piperazine methane sulfonate (15 gm) and then added potassium carbonate (7.5 gm) under stirring. To the reaction mixture was added bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (10 gm) and 18-crown ether (1.1 gm). The contents were heated to reflux and maintained for 4 hours. To the reaction mass was added water (500 ml) and then the separated aqueous layer was extracted with toluene. Combined organic layers were dried with sodium sulfate and then concentrated to obtain a residual solid. The residual solid obtained was dissolved in ethyl acetate (45 ml) and stirred for 30 minutes. The separated solid was filtered and then dried to obtain 12 gm of lurasidone.
Example 2:

Preparation of lurasidone hydrochloride crystalline Form I

Lurasidone (4 gm) as obtained in example 1 was dissolved in acetone (200 ml) and stirred for 30 minutes at room temperature to obtain a clear solution. To the solution was added a solution of hydrochloric acid in isopropyl alcohol (4 ml) slowly and then cooled to 0 to 5°C. The contents were maintained for 1 hour at 0 to 5°C and filtered. The solid obtained was dried at 50°C under vacuum for 6 hours to give 3 gm of lurasidone hydrochloride crystalline Form I.

Example 3:

Preparation of lurasidone hydrochloride amorphous Form

Lurasidone hydrochloride crystalline Form I (2.5 gm) as obtained in example 2 was dissolved in methanol (169 ml) and water (955 ml) under stirring. The solution was treated with activated carbon and filtered. The filtrate thus obtained containing 15% of methanol and 85% of water was lyophilized at room temperature for 24 hours to obtain 2.5 gm of lurasidone hydrochloride amorphous Form.

Example 4:

Preparation of lurasidone hydrochloride amorphous Form

Lurasidone hydrochloride (10 gm) was dissolved in methanol (675 ml) and water (3800 ml) under stirring. The solution was treated with activated carbon and filtered. The filtrate thus obtained containing 15% of methanol and 85% of water was lyophilized at room temperature for 24 hours to obtain 9.8 gm of lurasidone hydrochloride amorphous Form.

Example 5:

Preparation of lurasidone hydrochloride amorphous Form

Example 3 was repeated using ethanol solvent instead of methanol solvent to obtain lurasidone hydrochloride amorphous Form.

Example 6:
Preparation of lurasidone hydrochloride amorphous Form

Example 3 was repeated using n-butanol solvent instead of methanol solvent to obtain lurasidone hydrochloride amorphous Form.

Example 7:

Preparation of lurasidone hydrochloride amorphous Form

Lurasidone hydrochloride (10 gm) was dissolved in ethanol (125 ml) and methylene dichloride (125 ml) at room temperature. The solution was treated with carbon and filtered through hi-flow bed. The resulting filtrate was subjected to spray drying at 60 to 65°C to obtain 9.5 gm of lurasidone hydrochloride amorphous Form.

Example 8:

Preparation of lurasidone hydrochloride amorphous Form

Example 7 was repeated using methanol solvent instead of ethanol solvent to obtain lurasidone hydrochloride amorphous Form.

Example 9:

Preparation of lurasidone hydrochloride amorphous Form

Example 7 was repeated using n-butanol solvent instead of ethanol solvent to obtain lurasidone hydrochloride amorphous Form.

Example 10:

Preparation of lurasidone hydrochloride amorphous Form

Example 7 was repeated using ethylene chloride solvent instead of methylene chloride solvent to obtain lurasidone hydrochloride amorphous Form.

Example 11:

Preparation of lurasidone hydrochloride amorphous Form

Lurasidone hydrochloride (10 gm) was dissolved in methanol (675 ml) under stirring at room temperature to obtain a clear solution. The solution was treated with
carbon and filtered through hi-flow bed. The resulting filtrate was subjected to spray drying at 60 to 65°C to obtain 9.5 gm of lurasidone hydrochloride amorphous Form.

Example 12:

5 Preparation of lurasidone hydrochloride amorphous Form
Example 11 was repeated using ethanol solvent instead of methanol solvent to obtain lurasidone hydrochloride amorphous Form.

Example 13:

10 Preparation of lurasidone hydrochloride amorphous Form
To a lurasidone hydrochloride (10 gm) was added methanol (350 ml), methylene chloride (300 ml) and methyl tert-butyl ether (350 ml) at room temperature under stirring to obtain a clear solution. The solution was maintained for 2 hours at room temperature and then treated with carbon. The solution was filtered through h-flow bed and the solvents were distilled off under reduced pressure at below -50°C to obtain a solid. The solid obtained was then dried to obtain 9.5 gm of lurasidone hydrochloride amorphous Form.

Example 14:

20 Preparation of lurasidone hydrochloride amorphous Form
Example 13 was repeated using ethylene chloride solvent instead of methylene chloride solvent to obtain lurasidone hydrochloride amorphous Form.

Example 15:

25 Preparation of lurasidone hydrochloride amorphous Form
Example 13 was repeated using 1,4-dioxane solvent instead of methyl tert-butyl ether solvent to obtain lurasidone hydrochloride amorphous Form.

Example 16:

30 Preparation of lurasidone hydrochloride amorphous Form
Example 13 was repeated using tetrahydrofuran solvent instead of methyl tert-butyl ether solvent to obtain lurasidone hydrochloride amorphous Form.

**Example 17:**

**Preparation of lurasidone hydrochloride amorphous Form**

Example 13 was repeated using ethanol solvent instead of methanol solvent to obtain lurasidone hydrochloride amorphous Form.
We claim:

1. An amorphous Form of lurasidone hydrochloride.
2. The lurasidone hydrochloride amorphous Form of claim 1, having a powder X-ray diffractogram as shown in figures 2, 3, 4 and 5.
3. A process for the preparation of lurasidone hydrochloride amorphous Form of claim 1, which comprises:
   a. dissolving lurasidone hydrochloride in a mixture of alcoholic solvent and water; and
   b. subjecting the resulting solution to lyophilization to obtain lurasidone hydrochloride amorphous Form.
4. The process as claimed in claim 3, wherein the alcoholic solvent used in step (a) is a solvent or a mixture of solvents selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol and isobutyl alcohol.
5. A process for the preparation of lurasidone hydrochloride amorphous Form of claim 1, which comprises:
   a. dissolving lurasidone hydrochloride in an alcoholic solvent, a chlorinated solvent or a mixture thereof; and
   b. subjecting the resulting solution to spray drying to obtain lurasidone hydrochloride amorphous Form.
6. The process as claimed in claim 5, wherein the alcoholic solvent used in step (a) is a solvent or a mixture of solvents selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol and isobutyl alcohol.
7. The process as claimed in claim 5, wherein the chlorinated solvent used in step (a) is a solvent or a mixture of solvents selected from methylene chloride, ethylene chloride, chloroform and carbon tetrachloride.
8. A process for the preparation of lurasidone hydrochloride amorphous Form of claim 1, which comprises:
   a. dissolving lurasidone hydrochloride in a mixture of alcoholic solvent, a chlorinated solvent and an ether solvent; and
   b. removing the solvent to obtain lurasidone hydrochloride amorphous Form.
9. The process as claimed in claim 8, wherein the alcoholic solvent used in step (a) is a solvent or a mixture of solvents selected from methanol, ethanol, isopropyl alcohol, tert-butyl alcohol, n-butanol and isobutyl alcohol.

10. The process as claimed in claim 8, wherein the chlorinated solvent used in step (a) is a solvent or a mixture of solvents selected from methylene chloride, ethylene chloride, chloroform and carbon tetrachloride.

11. The process as claimed in claim 8, wherein the ether solvent used in step (a) is a solvent or mixture of solvents selected from tetrahydrofuran, 1,4-dioxane, methyl tert-butyl ether and diethyl ether.

12. A pharmaceutical composition that comprises amorphous Form of lurasidone hydrochloride and pharmaceutically acceptable excipients, and optionally other therapeutic ingredients.

13. The pharmaceutical composition as claimed in claim 12, wherein the amorphous Form of lurasidone hydrochloride is formulated into tablets, capsules, suspensions, dispersions or injectables.
INTERNATIONAL SEARCH REPORT

International application No. PCT/IN2012/000548

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - G07D 417/14 (2013.01)
USPC - 544/368

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/4035, 31/428, 31/496; C07D 403/14, 417/14 (2013.01)
USPC - 514/252.13, 254.04, 254.09, 544/359, 366, 367, 368, 373

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/4035, 31/428, 31/496; C07D 403/14, 417/14 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Orbit.com, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>Y</td>
<td>US 2010/0093875 A1 (MATSUI et al) 15 April 2010 (15.04.2010) entire document</td>
<td>1, 2, 5-7, 12, 13</td>
</tr>
<tr>
<td>Y</td>
<td>PATTERTSON et al., &quot;The Influence of Thermal and Mechanical Preparative Techniques on the Amorphous state of Four Poorly Soluble Compounds&quot; J. Pharm Sci. 2005, 94(9), Pgs. 1998-2012. entire document</td>
<td>1, 2, 12, 13</td>
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Date of the actual completion of the international search
06 February 2013

Date of mailing of the international search report
08 MAR 2013

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer: Blaine R. Copenhaver

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