(19) IPOS INTELLECTUAL PROPERTY OFFICE OF SINGAPORE

(11) Publication number: **SG 173692 A1**
(43) Publication date: **29.09.2011**
(51) Int. Cl: ;

(12) Patent Application

(21) Application number: **2011058559**
(22) Date of filing: **09.03.2010**
(30) Priority: **CN 200910047329.2 10.03.2009**

(71) Applicant: **LES LABORATOIRES SERVIER 35, RUE DE VERDUN F-92284 SURESNES CEDEX FR**

(72) Inventor: **SHAN, HANBIN NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN**
ZHANG, PENG NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
YUAN, ZHEDONG NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
JIANG, XUDONG NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
HUANG, YU NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
WANG, HUBO NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
CAO, XUFENG NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
CHENG, XINGDONG NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN
YU, XIONG NO.1320, WEST BEIJING ROAD SHANGHAI 200040 CN

(54) **Title:**
NEW CRYSTALLINE FORM VI OF AGOMELATINE, PREPARATION METHOD AND APPLICATION THEREOF

(57) **Abstract:**
Abstract New Crystalline Form VI of Agomelatine, Preparation and Use thereof The invention provides a new crystalline form of agomelatine, preparation and use thereof. The X-ray powder diffraction diagram of the agomelatine crystalline form shows main peaks at the diffraction angles 20 11.13°, 11.82°, 17.49°, 18.29°, 19.48°, 19.72°, 20.50°, 21.76°, 22.54°, 22.97°, 24.56°, 25.36°, 27.16° and 31 93° Said new crystalline form is characterized by high purity, stability and good reproducibility, and thus is advantageous for the pharmaceutical formulation. In addition, the stability and solubility of said crystalline form are also superior over the several existing crystalline forms.

This PDF First Page has been artificially created from the Singaporian Abstracts

Abstract

New Crystalline Form VI of Agomelatine, Preparation and Use thereof

The invention provides a new crystalline form of agomelatine, preparation and use thereof. The X-ray powder diffraction diagram of the agomelatine crystalline form shows main peaks at the diffraction angles 2θ 11.13°, 11.82°, 17.49°, 18.29°, 19.48°, 19.72°, 20.50°, 21.76°, 22.54°, 22.97°, 24.56°, 25.36°, 27.16° and 31.93°. Said new crystalline form is characterized by high purity, stability and good reproducibility, and thus is advantageous for the pharmaceutical formulation. In addition, the stability and solubility of said crystalline form are also superior over the several existing crystalline forms.

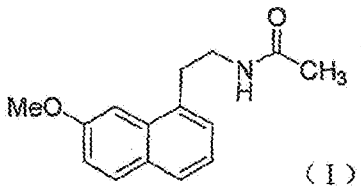
New Crystalline Form VI of Agomelatine, Preparation and Use thereof

Technical field

The invention relates to a crystalline form of agomelatine, N-[2-(7-methoxy-1-naphthyl)]acetamide, its preparation and use thereof.

Technical Background

Agomelatine with chemical name N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide and brand name Valdoxan has the following formula:



(I)

Agomelatine has dual effects by acting as an agonist of melatoninergic system receptors and as an antagonist of the 5HT2C receptor. Its properties allow it to be active in the central nervous system, especially in the treatment of major depression, seasonal affective disorder, sleep disorder, cardiovascular diseases, diseases of the digestive system, insomnia and fatigue caused by jet lag, appetite disturbance and obesity. Agomelatine is the first melatoninergic antidepressant, and is effective for the treatment of depression, the improvement of sleep parameters and the maintenance of sexual function. The preparation and therapeutic use of agomelatine have been reported in the European patent EP0447285.

In view of the pharmaceutical value of agomelatine, it is critical to obtain the said compound in a highly pure, and stable crystalline form as well as with good reproducibility so that it will be advantageous in pharmaceutical formulations and stable enough for long-term storage without specific requirements regarding temperature, light, humidity or oxygen levels.

Chinese Patents CN200510071611.6, CN200610108396.7, CN200610108394.8 and CN200610108395.2 have respectively disclosed the crystalline forms II, III, IV, V of agomelatine and the preparations thereof.

Among these, crystalline form II is prepared by recrystallization from ethanol and water; crystalline form III is prepared by heating agomelatine at 110°C until complete melting occurs and then slowly cooling down until formation of the crystal; crystalline form IV is prepared by heating agomelatine at 110°C until complete melting occurs, followed by rapidly cooling down to 50-70°C and maintaining at 70°C for about 5h until formation of the crystal occurs; crystalline form V is prepared by so-called "high-energy" mechanical grinding of agomelatine.

Description of the Invention

An objective of the invention is to provide a new crystalline form of agomelatine, i.e. crystalline form VI, which exhibits valuable characteristics in the pharmaceutical formulation.

Another objective of the invention is to provide a process for preparing crystalline form VI of agomelatine, which is simple to implement and easily reproducible.

The crystalline form of agomelatine, wherein the X-ray powder diffraction diagram of the crystalline form of agomelatine shows main peaks at the diffraction angles 2θ 11.13°, 11.82°, 17.49°, 18.29°, 19.48°, 19.72°, 20.50°, 21.76°, 22.54°, 22.97°, 24.56°, 25.36°, 27.16° and 31.93°.

The crystalline form of agomelatine, wherein the main peaks at the diffraction angles 2θ in the X-ray powder diffraction diagram of the crystalline form of agomelatine shows the following relative intensity (in percentages):

2θ°	Relative Intensity
11.13	12.4
11.82	17.8
17.49	20.7
18.29	17.9

19.48	66.8
19.72	100
20.50	14.5
21.76	19.7
22.54	22.0
22.97	26.2
24.56	13.1
25.36	16.7
27.16	12.2
31.93	10.1

A process for preparing the crystalline form of agomelatine, wherein agomelatine is firstly dissolved in acetic acid and then added into 0-25°C water to precipitate the crystal.

The process for preparing the crystalline form of agomelatine above, wherein the solution of agomelatine in acetic acid is most preferably added slowly to water with continuous stirring to facilitate the precipitation of the crystal. The said gradual addition to water may be achieved by dropwise addition.

The pharmacological studies with crystalline form VI of agomelatine according to the invention showed that the crystalline form VI of agomelatine may be used in the treatment of diseases of the melatoninergic system, sleep disorder, stress, anxiety, seasonal affective disorder or major depression, cardiovascular diseases, diseases of the digestive system, insomnia and fatigue caused by jet lag, schizophrenia, phobia, depression and the like.

The crystalline form VI of agomelatine provided according to the invention may be formulated together with various pharmaceutically acceptable adjuvants or excipients as various dosage forms for oral or injection administration.

According to the invention, the new crystalline form VI is obtained with high purity, stability and good reproducibility, and is advantageous for the pharmaceutical formulation. In addition, the stability and solubility of said crystalline form are also superior over the several existing crystalline forms.

Brief Description of the Drawing

Fig.1 is an X-ray diffraction diagram of the crystalline form VI obtained from Example 1 of the invention, measured by Bruker D8 ADVANCE instrument under the following settings: Cuka 40Kv 40mA as light source, step length 0.02°, scan speed: 8°/min, scan range: 3°-80°, room temperature.

Specific Embodiments

Example 1

1g of agomelatine was dissolved in 4ml of acetic acid with stirring, then slowly added dropwise to 80ml of water. The mixture was maintained at 0°C with stirring for 3.5h and filtered. The solid was washed with water 8ml×2, dried at 55°C under vacuum until the weight was constant to give 0.91g of white solid. Purity: 99.6%, melting point: 97-98°C.

Example 2

1g of agomelatine was dissolved in 4ml of acetic acid with stirring, then slowly added dropwise to 80ml of water. The mixture was maintained at 5°C with stirring for 3h and filtered. The solid was washed with water 8ml×2, dried at 55°C under vacuum until the weight was constant to give 0.90g of white solid. Purity: 99.6%, melting point: 97-98°C.

Example 3

2g of agomelatine was dissolved in 8ml of acetic acid with stirring, then slowly added dropwise to 160ml of water. The mixture was maintained at 20°C with stirring for 3h and filtered. The solid was washed with water 16ml×2, dried at 55°C under vacuum until the weight was constant to give 1.76g of white solid. Purity: 99.6%, melting point: 97-98°C.

The crystalline form of agomelatine from Example 2 was dried to give a powdery product, whose X-ray diffraction diagram was plotted with interplanar spacing d, Bragg 2θ angle and relative intensity as follows:

2θ°	d(A)	Relative Intensity
11.13	7.942	12.4
11.82	7.481	17.8
17.49	5.066	20.7
18.29	4.846	17.9
19.48	4.553	66.8
19.72	4.498	100
20.50	4.328	14.5
21.76	4.080	19.7
22.54	3.941	22.0
22.97	3.868	26.2
24.56	3.621	13.1
25.36	3.509	16.7
27.16	3.280	12.2
31.93	2.800	10.1

Tests of experimental results

Crystalline forms II, III, IV and VI are respectively placed in a thermostatically controlled container at 40°C for 20 days. The stability of the said crystalline forms is assessed by high performance liquid chromatography.

1. Purity Measurement of the Sample

Chromatographic conditions: octadecylsilane bonded silica as filler; a mixed solution of 10mM/L phosphate buffer (adjusted to pH 7.0 by sodium hydroxide) and acetonitrile in 2:7 by volume as mobile phase; column temperature 40°C; detection wavelength 220nm. The purity is determined using an internal standard method.

The crystalline forms II, III, IV and VI were formulated with the mobile phase as 1mg/mL solution. 10μL of each of the solution was removed and injected into the liquid chromatograph. The chromatograms were recorded.

2. Assay of the Sample

The assay was carried out using an external standard method as described under Purity Measurement of the Sample. The results are as shown in Table I:

Table I

Sample name	Purity of crystalline form II	Purity of crystalline form III	Purity of crystalline form IV	Purity of crystalline form VI
Before storage	99.79%	99.77%	99.82%	99.60%
After storage in the thermostatically controlled containers for 20 days	99.24%	99.10%	99.54%	99.55%

3. Solubility Measurement in Water

The measurement was carried out by HPLC using an external standard method. The results are as shown in Table II:

Table II

Sample name	Purity of crystalline form II	Purity of crystalline form VI
Purity	99.79%	99.77%
Solubility (mg/ml)	1.11	1.24

From the above results, it is seen that the new crystalline form VI of agomelatine is superior over the several existing crystalline forms in terms of stability and solubility. With regard to its preparation, the new crystalline form is also of greater value than the existing crystalline forms III, IV and V in terms of industrial application.

Patent Claims

1. The crystalline form of agomelatine, wherein the X-ray powder diffraction diagram of the crystalline form of agomelatine shows main peaks at the diffraction angles 2θ 11.13°, 11.82°, 17.49°, 18.29°, 19.48°, 19.72°, 20.50°, 21.76°, 22.54°, 22.97°, 24.56°, 25.36°, 27.16° and 31.93°.

2. The crystalline form of agomelatine described in patent claim 1, wherein the main peaks at the diffraction angles 2θ in the X-ray powder diffraction diagram of the crystalline form of agomelatine show the following relative intensities (in percentages):

2θ°	Relative Intensity
11.13	12.4
11.82	17.8
17.49	20.7
18.29	17.9
19.48	66.8
19.72	100
20.50	14.5
21.76	19.7
22.54	22.0
22.97	26.2
24.56	13.1
25.36	16.7
27.16	12.2
31.93	10.1

3. A process for preparing the crystalline form of agomelatine described in patent claims 1 and 2, wherein agomelatine is first dissolved in acetic acid and then added into 0-25°C water to precipitate the crystal.

4. The process for preparing the crystalline form of agomelatine described in patent claim 3, wherein the solution of agomelatine in acetic acid is added slowly to water with continuous stirring to facilitate the precipitation of the crystal.

5. A pharmaceutical composition, wherein the crystalline form VI of agomelatine described in patent claims 1 and 2 may be formulated together with pharmaceutically acceptable adjuvants or excipients.

6. Crystalline form VI of agomelatine described in patent claim 1 and 2 for use in the treatment of diseases of the melatoninergic system, sleep disorder, stress, anxiety, seasonal affective disorder or major depression, cardiovascular diseases, diseases of the digestive system, insomnia and fatigue caused by jet lag, schizophrenia, phobia, depression and the like.

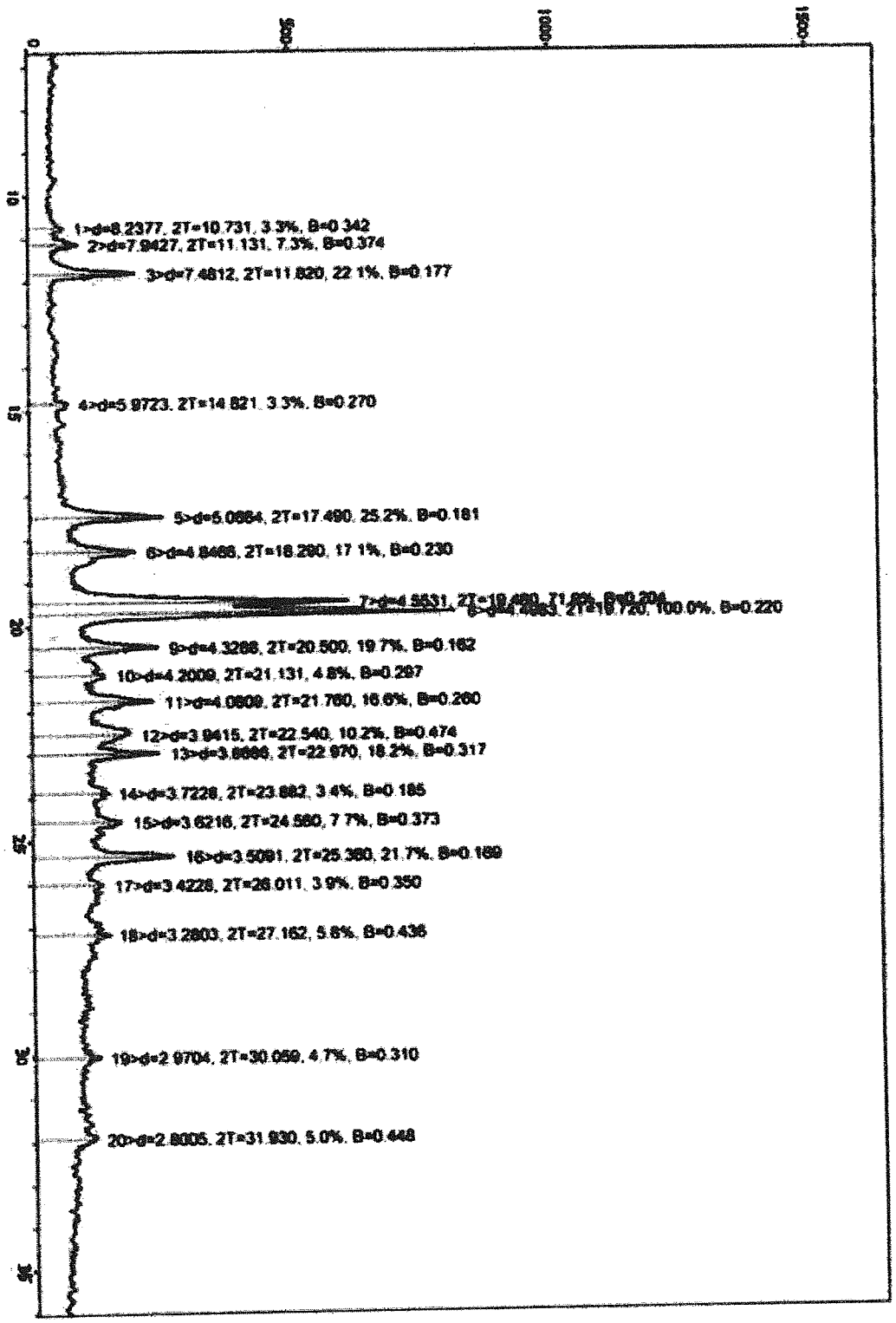

0
5000
10000
15000
10
15
20
25
30
35
1>d=8.2377, 2T=10.731, 3.3%, B=0.342
2>d=7.9427, 2T=11.131, 7.3%, B=0.374
3>d=7.4812, 2T=11.820, 22.1%, B=0.177
4>d=5.9723, 2T=14.821, 3.3%, B=0.270
5>d=5.0664, 2T=17.490, 25.2%, B=0.181
6>d=4.8466, 2T=18.290, 17.1%, B=0.230
7>d=4.8531, 2T=18.480, 71.6%, B=0.204
8>d=4.4983, 2T=19.720, 100.0%, B=0.220
9>d=4.3288, 2T=20.500, 19.7%, B=0.162
10>d=4.2009, 2T=21.131, 4.8%, B=0.297
11>d=4.0809, 2T=21.760, 16.6%, B=0.260
12>d=3.9415, 2T=22.540, 10.2%, B=0.474
13>d=3.8998, 2T=22.970, 18.2%, B=0.317
14>d=3.7228, 2T=23.882, 3.4%, B=0.185
15>d=3.6216, 2T=24.560, 7.7%, B=0.373
16>d=3.5091, 2T=25.360, 21.7%, B=0.169
17>d=3.4228, 2T=26.011, 3.9%, B=0.350
18>d=3.2803, 2T=27.162, 5.8%, B=0.436
19>d=2.9704, 2T=30.059, 4.7%, B=0.310
20>d=2.8005, 2T=31.930, 5.0%, B=0.448

FIG. 1