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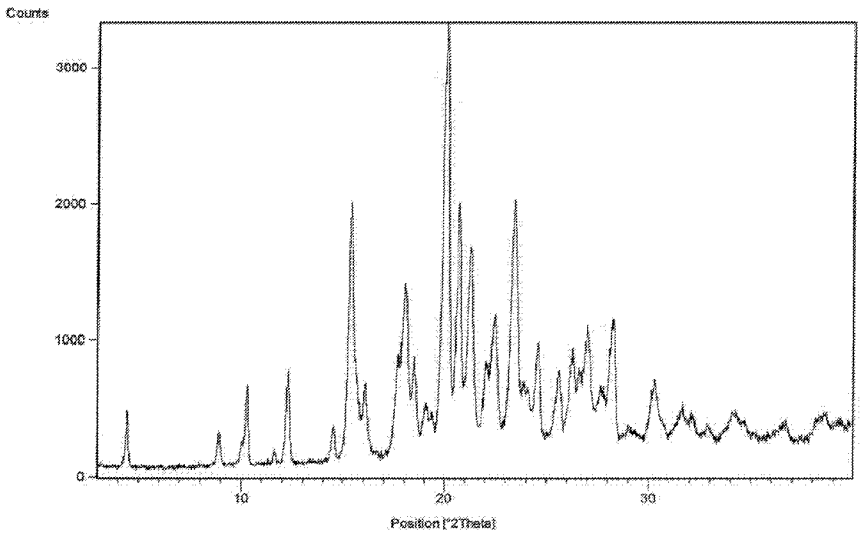
(54) Title: CRYSTALLINE FORM OF MIRABEGRON

FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF THE CRYSTALLINE FORM OF MIRABEGRON



(57) Abstract: The present invention provides a crystalline form of mirabegron, a process for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

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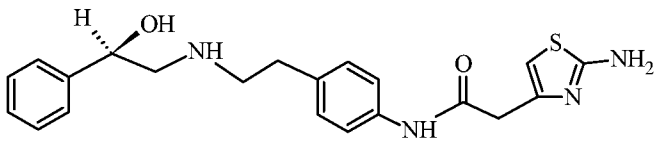
CRYSTALLINE FORM OF MIRABEGRON

Field of the Invention

The present invention provides a crystalline form of mirabegron, a process for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

Background of the Invention

Mirabegron is a beta-3 adrenergic agonist disclosed in U.S. Patent No. 6,346,532. It is chemically designated as 2-(2-aminothiazol-4-yl)-N-[4-[2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide, having the structure depicted by Formula I.



Formula I

Polymorphs of mirabegron are disclosed in U.S. Patent No. 7,342,117; PCT Publication No. WO 2012/156998; and IP.com Disclosure No. IPCOM000228561D.

U.S. Patent No. 7,342,117 discloses α-Form and β-Form of mirabegron; PCT Publication No. WO 2012/156998 discloses an amorphous form of mirabegron; and IPCOM000228561D discloses crystalline forms of mirabegron and mirabegron monohydrochloride.

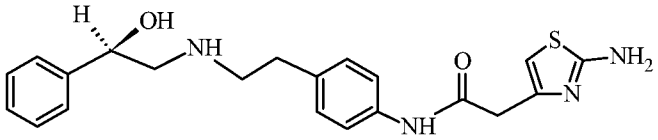
Summary of the Invention

The present invention provides a crystalline form of mirabegron, a process for its preparation, a pharmaceutical composition comprising it, and its use for the treatment of overactive bladder.

The crystalline form of mirabegron of the present invention is highly pure and free-flowing. It is stable towards polymorphic conversion and shows little or no variation in dissolution profile.

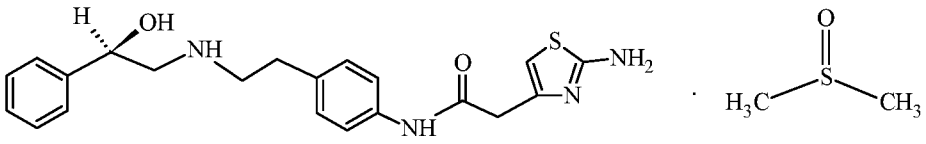
A first aspect of the present invention provides a crystalline form of mirabegron characterized by an X-ray powder diffraction (XRPD) pattern having peaks at d-spacings of 5.74, 4.41, 4.28, 4.16, and 3.80 Å.

A second aspect of the present invention provides a process for the preparation of a crystalline form of mirabegron of Formula I characterized by an XRPD pattern having peaks at d-spacings of 5.74, 4.41, 4.28, 4.16, and 3.80 Å



Formula I

comprising desolvation of the mirabegron dimethyl sulphoxide solvate of Formula II.



Formula II

A third aspect of the present invention provides a pharmaceutical composition comprising a crystalline form of mirabegron characterized by an XRPD pattern having peaks at d-spacings of 5.74, 4.41, 4.28, 4.16, and 3.80 Å and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A fourth aspect of the present invention provides use of a crystalline form of mirabegron, characterized by an X-ray powder diffraction having peaks at d-spacings of about 5.74, 4.41, 4.28, 4.16, and 3.80 Å, for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

Other objects, features, advantages, and aspects of the present invention will become apparent to those skilled in the art from the description provided herein.

Brief Description of the Figures

Figure 1: X-Ray Powder Diffraction (XRPD) pattern of the crystalline form of mirabegron.

Figure 2: Differential Scanning Calorimetry (DSC) thermogram of the crystalline form of mirabegron.

Figure 3: Thermogravimetric Analysis (TGA) of the crystalline form of mirabegron.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term "contacting", as used herein, includes dissolving, mixing, slurrying, stirring, or combinations thereof.

The term "about", as used herein, refers to a variation of up to ±5% in the value of a parameter, such as temperature, stirring time, etc.

The crystalline form of mirabegron is characterized by an XRPD pattern having peaks at d-spacing of 5.74, 4.41, 4.28, 4.16, and 3.80 Å.

The crystalline form of mirabegron is further characterized by an XRPD pattern having peaks at d-spacing of 19.85, 7.17, 4.90, and 3.15 Å.

The crystalline form of mirabegron is further characterized by an XRPD pattern having peaks at 15.44, 20.13, 20.75, 21.36, and 23.44 ± 0.2 degrees 2θ.

The crystalline form of mirabegron is further characterized by an XRPD pattern having peaks at 4.45, 12.34, 18.14, and 28.35 ± 0.2 degrees 2θ.

Table 1 summarizes the d-spacing values in Å, and the corresponding 2θ values of the crystalline form of mirabegron of Formula I.

Table 1: XRPD peaks of a crystalline form of mirabegron

d-spacing [Å]	Pos. [°2Th]	Rel. Int. [%]
19.85	4.45	18.11
9.89	8.94	9.04
8.83	10.01	5.43
8.58	10.31	22.04
7.58	11.67	3.06
7.17	12.34	22.14
6.07	14.58	9.38
5.74	15.44	66.38
5.49	16.15	16.73
5.01	17.71	23.91
4.93	17.98	36.34
4.90	18.14	39.34
4.79	18.52	23.03
4.64	19.12	14.68
4.43	20.02	93.92
4.41	20.13	100.00
4.28	20.75	62.02
4.16	21.36	42.71
4.03	22.06	23.20
3.95	22.52	33.73
3.80	23.44	61.70
3.68	24.15	15.98
3.61	24.64	26.65
3.48	25.62	20.92
3.40	26.28	24.43
3.30	27.04	30.01
3.22	27.72	17.92
3.15	28.35	28.72
3.07	29.10	8.24
2.94	30.36	18.05
2.82	31.67	12.44
2.78	32.25	10.45
2.71	32.97	8.03
2.62	34.18	12.57
2.58	34.76	9.50
2.44	36.78	8.45
2.35	38.30	10.17
2.33	38.72	10.41
2.29	39.36	9.40

The crystalline form of mirabegron is further characterized by a DSC thermogram having endotherms at about 120.28°C and about 142.68°C.

The crystalline form of mirabegron is further characterized by an XRPD pattern, a DSC thermogram, and a TGA as depicted in Figure 1, Figure 2, and Figure 3, respectively.

Mirabegron, which is used for the preparation of mirabegron dimethyl sulphoxide solvate, may be prepared by any method known in the art, such as those described in U.S. Patent No. 7,342,117 or PCT Publication No. WO 2012/156998, which are incorporated herein by reference.

The preparation of the mirabegron dimethyl sulphoxide solvate of Formula II is carried out by contacting mirabegron with dimethyl sulphoxide in the presence of a solvent at a temperature of about 20°C to the reflux temperature of the solvent. The solvent is selected from the group consisting of aromatic hydrocarbons, alkyl acetates, and mixtures thereof. Examples of aromatic hydrocarbons include toluene and xylene. Examples of alkyl acetates include ethyl acetate, propyl acetate, and *t*-butyl acetate. The reaction mixture is stirred at a temperature of about 25°C to about 35°C for about 1 hour to about 4 hours, filtered, washed with the solvent, and dried at a temperature of about 20°C to about 40°C for about 30 minutes to about 20 hours to provide mirabegron dimethyl sulphoxide solvate of Formula II.

The preparation of a crystalline form of mirabegron of Formula I characterized by XRPD peaks at d-spacing values of about 5.74, 4.41, 4.28, 4.16, and 3.80 Å is carried out by drying mirabegron dimethyl sulphoxide solvate of Formula II at about 70°C to about 80°C for about 2 hours to about 8 hours. Any suitable method of drying may be employed, such as drying under reduced pressure, vacuum tray drying, air drying, or combinations thereof.

In one embodiment of the present invention, the crystalline form of mirabegron is prepared by drying mirabegron dimethyl sulphoxide solvate of Formula II at about 70°C to about 75°C in a vacuum tray dryer for about 5 hours to about 6 hours.

In another embodiment of the present invention, the crystalline form of mirabegron is prepared by drying mirabegron dimethyl sulphoxide solvate of Formula II at about 75°C to about 80°C in a vacuum tray dryer for about 2 hours to about 6 hours.

Solvates, pseudomorphs, and hydrates of the crystalline form of the present invention are also included within the scope of the present invention.

The crystalline form of mirabegron of the present invention may be administered as part of a pharmaceutical composition for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency. Accordingly, in a further aspect, there is provided a pharmaceutical composition comprising the crystalline form of mirabegron of the present invention, one or more pharmaceutically acceptable carriers, diluents, or excipients, and optionally other therapeutic ingredients. Pharmaceutical compositions comprising the crystalline form of mirabegron of the present invention may be administered orally, topically, parenterally, by inhalation or spray, rectally, or in the form of injectables. The injectable compositions may include intravenous, intramuscular, subcutaneous, and parenteral injections, as well as the use of infusion techniques.

In the foregoing section, embodiments are described by way of examples to illustrate the processes of invention. However, these are not intended in any way to limit the scope of the present invention. Variants of the examples that would be evident to persons ordinarily skilled in the art are within the scope of the present invention.

EXAMPLES

Example 1: Preparation of mirabegron dimethyl sulphoxide solvate

Mirabegron (9.0 g) was suspended in a mixture of dimethyl sulphoxide (12 mL) and *t*-butyl acetate (100 mL). The reaction mixture was stirred at a temperature of about 25°C to about 35°C for about 3 hours. The solid obtained was filtered, washed with *t*-butyl acetate (50 mL), and suck dried for about 30 minutes, then dried in a vacuum tray dryer at a temperature of about 25°C to about 35°C for about 3 hours to obtain the mirabegron dimethyl sulphoxide solvate.

Yield: 10.1 g

Example 2: Preparation of crystalline form of mirabegron

Method A:

Mirabegron dimethyl sulphoxide solvate (500 mg) was dried at about 73°C to about 75°C under vacuum for about 6 hours to obtain the crystalline form of mirabegron.

Yield: 0.38 g

Method B:

Mirabegron dimethyl sulphoxide solvate (500 mg) was dried at about 78°C to about 80°C under vacuum for about 3 hours to obtain the crystalline form of mirabegron.

Yield: 0.38 g

Method C:

Mirabegron dimethyl sulphoxide solvate (600 mg) was dried at about 80°C under vacuum for about 6 hours to obtain the crystalline form of mirabegron.

Yield: 0.50 g

We claim:

1. A crystalline form of mirabegron characterized by an X-ray powder diffraction (XRPD) pattern having peaks at d-spacing values of 5.74, 4.41, 4.28, 4.16, and 3.80 Å.

2. The crystalline form of mirabegron of claim 1, further characterized by an XRPD pattern having peaks at d-spacing values of 19.85, 7.17, 4.90, and 3.15 Å.

3. The crystalline form of mirabegron of claim 1, further characterized by an XRPD pattern having peaks at values 15.44, 20.13, 20.75, 21.36, and 23.44 ± 0.2 degrees 2θ.

4. The crystalline form of mirabegron of claim 1, further characterized by an XRPD pattern having peaks at 4.45, 12.34, 18.14, and 28.35 ± 0.2 degrees 2θ.

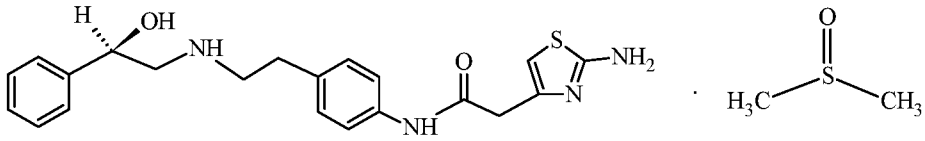
5. The crystalline form of mirabegron of claim 1, characterized by an XRPD pattern substantially as depicted in Figure 1.

6. The crystalline form of mirabegron of claim 1, characterized by a DSC thermogram having endotherms at about 120.28°C and about 142.68°C.

7. The crystalline form of mirabegron of claim 1, characterized by a DSC thermogram substantially as depicted in Figure 2.

8. The crystalline form of mirabegron of claim 1, characterized by a TGA substantially as depicted in Figure 3.

9. A process for the preparation of a crystalline form of mirabegron characterized by an XRPD pattern having peaks at d-spacing values of 5.74, 4.41, 4.28, 4.16, and 3.80 Å, comprising desolvation of the mirabegron dimethyl sulphoxide solvate of Formula II.



Formula II

10. The process according to claim 9, wherein the desolvation of mirabegron dimethyl sulphoxide solvate of Formula II is performed by drying at about 70°C to about 80°C.

11. The process according to claim 10, wherein the drying of the mirabegron dimethyl sulphoxide solvate of Formula II is carried out for about 2 hours to about 8 hours.

12. A pharmaceutical composition comprising a crystalline form of mirabegron characterized by an XRPD pattern having peaks at d-spacing of 5.74, 4.41, 4.28, 4.16, and 3.80 Å and one or more pharmaceutically acceptable carriers, diluents, or excipients.

13. Use of the crystalline form of mirabegron, characterized by an X-ray powder diffraction having peaks at d-spacing values of 5.74, 4.41, 4.28, 4.16, and 3.80 Å, for the

treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.

FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF THE CRYSTALLINE FORM OF MIRABEGRON

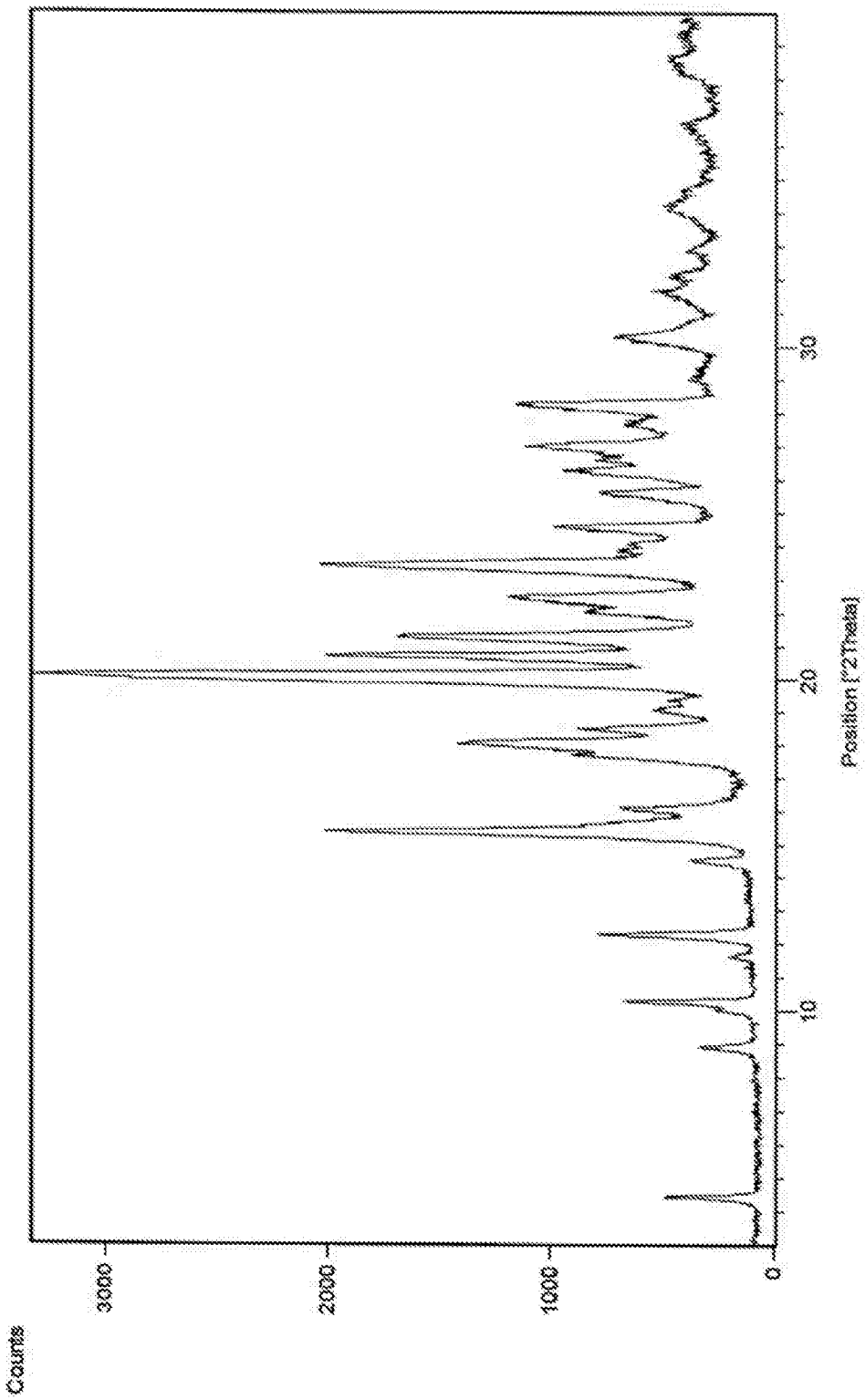


FIGURE 2: DIFFERENTIAL SCANNING CALORIMETRY (DSC) THERMOGRAM OF THE CRYSTALLINE FORM OF MIRABEGRON

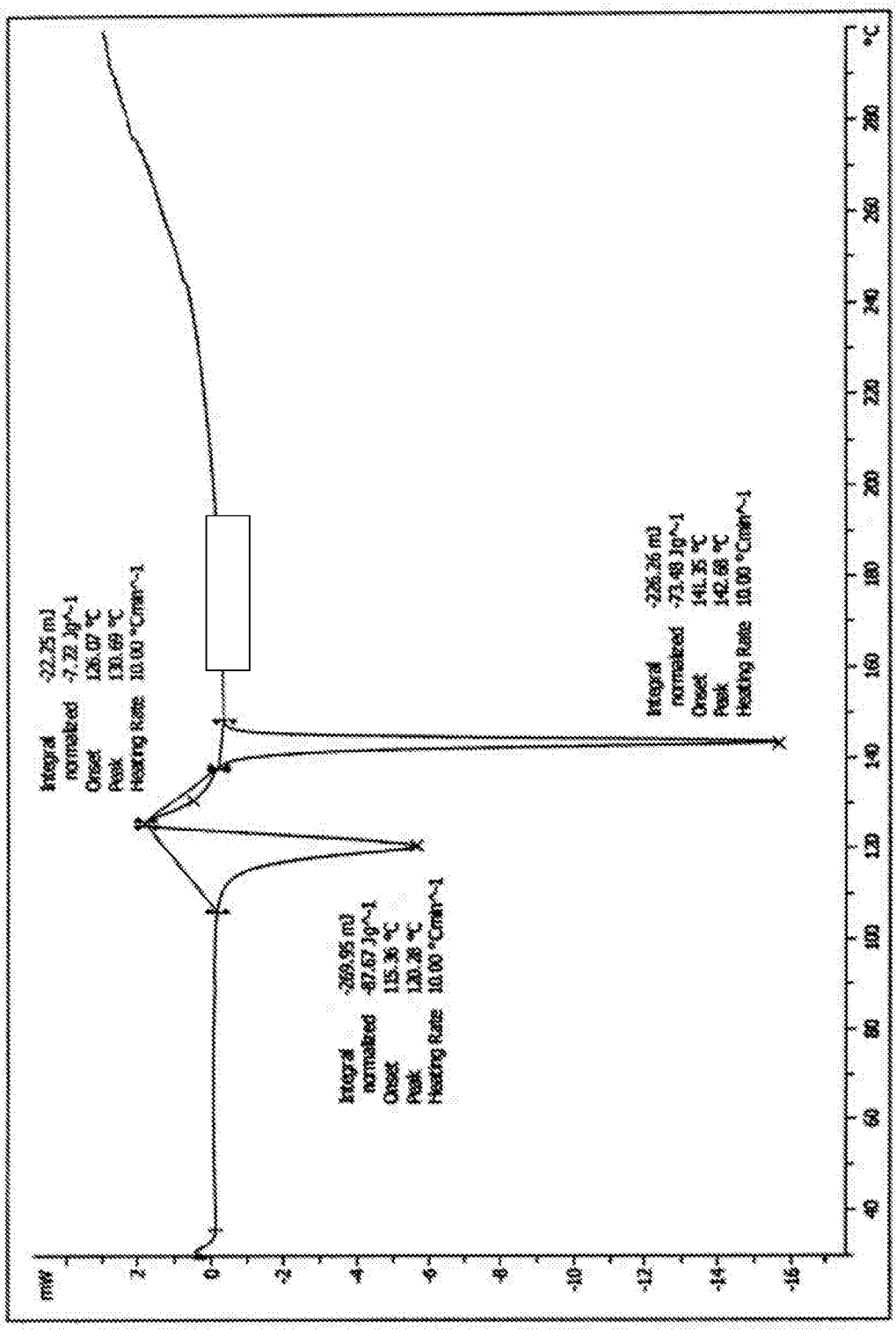
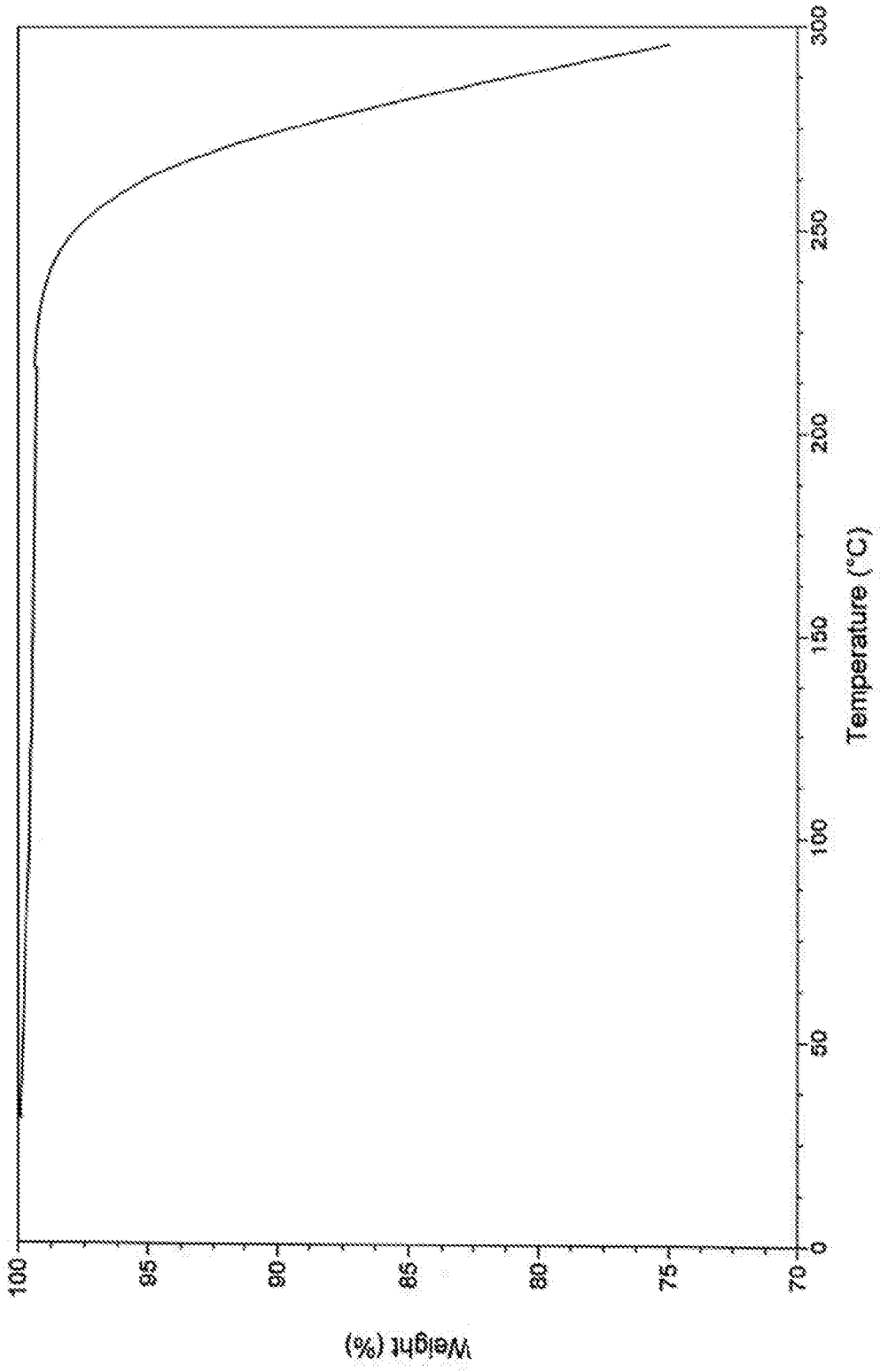


FIGURE 3: THERMOGRAVIMETRIC ANALYSIS (TGA) OF THE CRYSTALLINE FORM OF MIRABEGRON



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/064784

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/40 A61K31/426 A61P3/10
ADD.

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)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"PREPARATION OF MIRABEGRON, IT'S INTERMEDIATES, A CRYSTALLINE FORM OF MIRABEGRON AND A CRYSTALLINE FORM OF MIRABEGRON MONOHYDROCHLO", IP.COM JOURNAL, IP.COM INC., WEST HENRIETTA, NY, US, 19 June 2013 (2013-06-19), XP013157840, ISSN: 1533-0001 cited in the application the whole document -----	1-13
X	EP 1 440 969 A1 (YAMANOUCHI PHARMA CO LTD [JP]) 28 July 2004 (2004-07-28) cited in the application the whole document ----- -/--	1-13

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
25 November 2014	01/12/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gregoire, Ariane

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/064784

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/156998 A2 (REDDYS LAB LTD DR [IN]; PEDDY VISHWESHWAR [IN]; BOGE RAJESHAM [IN]) 22 November 2012 (2012-11-22) cited in the application the whole document	1-13
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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