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(54) Title: PROCESS FOR PREPARING ZIPRASIDONE

(57) Abstract: The present invention relates to improved process for preparing Ziprasidone and its acid addition salts thereof. The invention particularly provides a method for purifying Ziprasidone base thereby providing substantially pure Ziprasidone and its acid addition salts, hydrates, solvates etc.



WO 2010/073255 A1

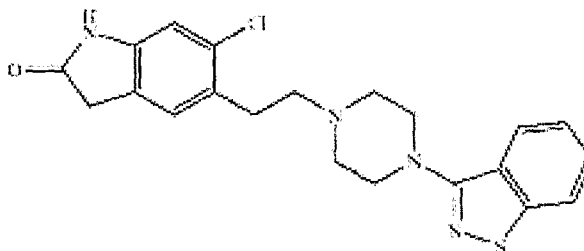
PROCESS FOR PREPARING ZIPRASIDONE**FIELD OF THE INVENTION**

The present invention relates to improved process for preparing Ziprasidone and its acid addition salts thereof. The invention also provides a method for purifying Ziprasidone base thereby providing substantially pure Ziprasidone and its acid addition salts, hydrates, solvates etc.

BACKGROUND OF THE INVENTION:

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary, however, reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Ziprasidone is an antipsychotic agent that is chemically unrelated to phenothiazine or butyrophenone antipsychotic agents. Ziprasidone has the following structure:



The preparation of Ziprasidone base is disclosed in U.S. Pat. No. 4,831,031 (example 16) and U.S. Pat. No. 5,312,925. A process for preparation of Ziprasidone HCl monohydrate having a mean particle size equal to or less than about 85 microns is also disclosed in U.S. Pat. No. 6,150,366 and EP 0 965 343 A2.

Ziprasidone has been marketed under the name GEODON as an oral capsule and as an injectable drug. GEODON capsules contain the monohydrate hydrochloride salt of Ziprasidone, and come in 20, 40, 60 and 80 mg dosage forms. GEODON for injection contains a lyophilized form of Ziprasidone mesylate trihydrate, and contains 20 mg base equivalent of Ziprasidone. The mesylate salts of Ziprasidone, including monohydrate and trihydrate, are disclosed in U.S. Pat. Nos. 6,110,918 and 5,245,765.

Ziprasidone HCl Hemihydrate is disclosed in U.S. Pat. No. 4,831,031, Example 16 (column 13, line 13). Ziprasidone HCl monohydrate is disclosed in U.S. Pat. No. 5,312,925 and EP 0 586 181 A1. The monohydrate is characterized by XRD, IR and

water content. It is reported that the water content of the monohydrate ranges from 3.8 to 4.5% by weight. The Ziprasidone HCl monohydrate is prepared from Ziprasidone base anhydrous.

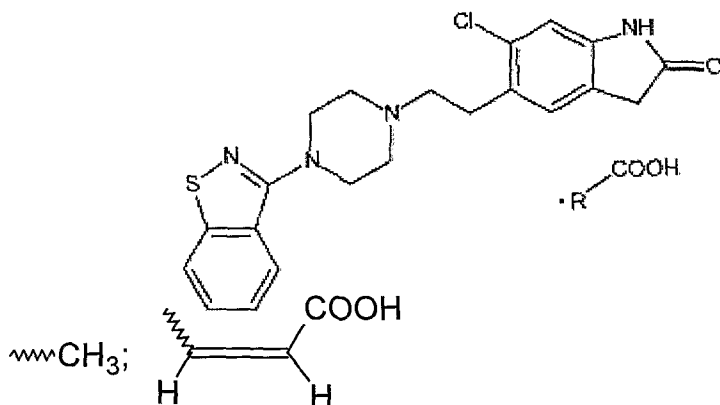
Ziprasidone HCl is usually prepared from Ziprasidone base, and the Ziprasidone base used may affect the quality of the hydrochloride salt. Ziprasidone base in the solid state is disclosed in U.S. Pat. No. 5,338,846. In the '846 patent, Ziprasidone base is characterized by its NMR spectrum. In example 1 of U.S. Pat. No. 5,206,366 Ziprasidone base is also obtained. The base is characterized by NMR, thin layer chromatography and a melting point of 218-220 EC. In WO 03/070246 Ziprasidone base is obtained from tetrahydrofuran. The product is not otherwise characterized. Ziprasidone base is also obtained in U.S. Pat. No. 5,312,925. The Form obtained in the art is labeled herein Form B of Ziprasidone base which is incorporated herein as reference.

Ziprasidone base Form B is characterized by X-ray peaks at 12.1, 15.2, 16.3, 18.4, 25.0 degrees 2 theta and is further characterized by XRD peaks at 5.2, 10.4, 11.3, 13.1, 21.1, 22.1. The Ziprasidone free base has a DSC thermogram in which 17 and 120 J/g endothermic peaks can be seen at 92 and 220°C. The first corresponds to dehydration, the second to melting of the Ziprasidone free base. The water content of the sample of the base is about 1.2% by weight. The Loss on Drying by TGA is about 2.1% by weight.

US 2005/197347 A1 provides a crystalline form of Ziprasidone base having an X-Ray powder diffraction pattern with peaks at 9.4, 13.7, 14.5, 14.9, 18.1, 20.2, 22.8+-0.2 degrees 2 theta, labeled therein as Form B2. In another aspect, the present invention provides a process for preparing the crystalline form B2 comprising:

- a) reacting a salt of Ziprasidone with a base in a reaction mixture containing water, and optionally a water-miscible organic co-solvent, to obtain the crystalline form of Ziprasidone; and
- b) recovering the crystalline form.

WO 2006/034965 A1 provides a process for purification of Ziprasidone Base by reacting crude Ziprasidone Base with maleic acid or acetic acid to obtain an acid addition salt of below general formula



wherein R is WO 2005/108395 A1 discloses new crystalline form of Ziprasidone hydrochloride hemihydrate, process for its preparation, its use for the preparation of Ziprasidone, its pharmaceutical compositions and their use in therapy. Also, US 2005/143396 A1 discloses three crystalline forms of Ziprasidone Hydrochloride Monohydrate viz. Form-I, Form-II and Form-III.

U.S. 2004/152711 provides additional crystalline forms of Ziprasidone HCl and base. The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic.

The polymorphic form may further help in purification of an active pharmaceutical ingredient. In the event of metastability, a metastable polymorphic form may be used to prepare a more stable polymorph. Hence, discovery of new polymorphic forms and new processes help in advancing a formulation scientist in preparation of Ziprasidone as an active pharmaceutical ingredient in a formulation.

Therefore, there is a need to have an improved process, that allows for preparation of highly pure Ziprasidone base in a facile manner on an industrial scale which yields Ziprasidone Hydrochloride Monohydrate with high degree of HPLC purity will all known and unknown impurities less than 0.1% and having organic volatile impurities within their limits.

The inventors of the present invention has found that still there is a need to provide an improved process for purification of Ziprasidone Base resulting in the formation of Crystalline Ziprasidone Base which is then converted to acid addition salt

of Ziprasidone. More particularly, the present invention provides a process for preparation of Ziprasidone Hydrochloride monohydrate via crystalline Form B of Ziprasidone Base.

Objects of Invention:

It is an object of the present invention to overcome or substantially ameliorate one or more of the disadvantages of the prior art or at least to provide a useful alternative.

It is another object of the present invention to provide an improved process for preparing Ziprasidone Base in crystalline form.

Further object of the present invention is to provide a process for preparing Ziprasidone Hydrochloride monohydrate.

It is also an object of the present invention to provide stable Ziprasidone Hydrochloride Monohydrate.

BRIEF DESCRIPTION OF FIGURES:-

A preferred embodiment of the invention will now be described, by way of example only, with reference to the accompanying figures in which:

FIG.1: X-ray diffraction of Crystalline Ziprasidone Base (Form B)

FIG.2: DSC (Differential Scanning calorimetry) of Ziprasidone Base (Form B)

FIG.3: X-ray diffraction of Ziprasidone Hydrochloride Monohydrate

FIG.4: DSC (Differential Scanning calorimetry) of Ziprasidone Hydrochloride Monohydrate

FIG.5: TGA (Thermogravimetric Analysis) of Ziprasidone Hydrochloride Monohydrate

DETAILED DESCRIPTION:

Although the invention has been described with reference to a specific example, it will be appreciated by those skilled in the art that the invention can be embodied in many other forms.

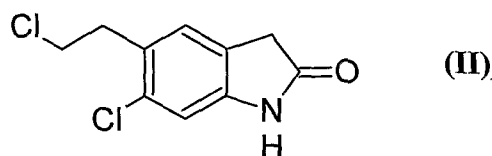
According to embodiment of the present invention, there is provided a process for the preparation of crystalline Ziprasidone base having an X-ray powder diffraction pattern with peaks at 12.3, 15.3, 16.4, 18.5, 25.3 ± 0.2 degrees 2 theta comprises the steps of:

- a) treating Ziprasidone base with a mixture of organic solvent at an elevated temperature to obtain the clear solution;

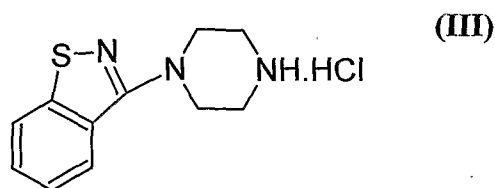
- b) maintaining the reaction mixture at an elevated temperature for sufficient time to complete the reaction;
- c) concentrating the reaction mixture;
- d) cooling the reaction mixture; and
- e) isolating crystalline Ziprasidone base.

According to another embodiment of the present invention, there is provides a process for the preparation of crude Ziprasidone base used for the preparation of crystalline Ziprasidone base, whereby the process comprises of:

- a) reacting substantially pure 6-chloro-5-(2-chloroethyl) oxindole of formula (II)



in 0.3 to 0.7 moles with 3-(1-piperazinyl)-1,2-benzisothiazole or its salts of formula (III)



in 0.3 to 0.7 moles, a base and water at an elevated temperature for sufficient amount of time to complete the reaction;

- b) cooling the reaction mixture to precipitate the product followed by filtration and washing with water;
- c) treating the wet-cake with water, followed by acetic acid to adjust the pH of the reaction mixture from 6.0 to 7.5;
- d) filtering the product followed by treatment with polar organic solvent at a temperature in the range of 50°C to 100°C;
- e) cool the reaction mixture to precipitate the crude Ziprasidone base; and
- f) recover crude Ziprasidone base.

According to third embodiment of the present invention a crystalline Ziprasidone base, wherein the crystalline form is characterized by an X-ray powder diffraction pattern as substantially depicted in **FIG.1**.

The process for preparation of crystalline Ziprasidone base is carried out in the mixture of organic solvents, selected from the group consisting of dimethyl formamide, dimethyl sulfoxide, dioxane, tetrahydrofuran, methanol, ethanol, isopropanol, propanol, preferably dimethyl sulfoxide and tetrahydrofuran at an elevated temperature in the range of about 50°C to about 150°C, preferably from about 75°C to about 125°C, more preferably from about 100°C to about 110°C is also the scope of the present invention.

According to the another aspect of the present invention, there is provided a process for preparation of crude Ziprasidone base wherein 6-chloro-5-(2-chloroethyl) oxindole is reacted from 0.3 to 0.7 moles, preferably 0.4 to 0.5, more preferably of about 0.43 moles with 3-(1-piperazinyl)-1,2-benzisothiazole or its salts is reacted from 0.3 to 0.7 moles, preferably 0.5 to 0.6, more preferably of about 0.52 moles in presence of base and water.

The suitable base is selected from the group consisting of organic amine, an alkoxide, an alkali metal hydroxide, an alkaline earth metal hydroxide, an alkali metal hydride, an alkaline earth metal hydride, an alkali metal carbonate, alkaline earth metal carbonate and hydrogencarbonate.

More preferably, the base can be selected from the group consisting of sodium methoxide, sodium ethoxide, sodium phenoxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, sodium hydride, potassium hydride, calcium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, calcium carbonate, calcium carbonate and basic alumina, most preferably carbonate.

According to the another preferred embodiment of the present invention the process of preparation of crude Ziprasidone base is carried out in the polar organic solvent is selected from the group of C₁-C₄ alcohol like methanol, ethanol, propanol, isopropanol, butanol; ketone like acetone, methyl ethyl ketone, amides like dimethyl formamide, esters like ethyl acetate, methyl acetate, tert-butyl acetate etc., preferably alcohol like isopropanol at temperature in the range of about 50°C to about 100°C, preferably from about 75°C to about 90°C, more preferably from about 75°C to about 85°C.

According to another important aspect of the present invention, there is provided a process for preparation of Ziprasidone acid addition salts or hydrates thereof comprises of:

- a) treating crystalline Ziprasidone base with water at an ambient temperature;

- b) adding source of acid addition salt;
- c) heating the reaction mixture and maintaining at same temperature for a sufficient period of time to prepare Ziprasidone acid addition salt or hydrate thereof;
- d) cooling the reaction mixture;
- e) filtering and washing the solid with isopropanol; and
- f) recovering Ziprasidone acid addition salt or hydrate.

The reaction of step (a) is carried out at an ambient temperature from about 20°C to 35°C followed by addition of source of acid addition salt preferably 3 molar hydrochloric acid solution. The reaction mixture is further heated from about 60°C to about 65°C followed by cooling to recover wet Ziprasidone acid addition salt or hydrate. The solid thus obtained is washed with organic solvent preferably alcohols from C₁-C₄, more preferably isopropanol. The Ziprasidone Hydrochloride Monohydrate thus recovered has the water content intact and thus doesn't allow the degradation of Monohydrate to anhydrous or hemihydrate.

Ziprasidone Hydrochloride Monohydrate is having an X-ray powder diffraction pattern with peaks at 10.8, 14.7, 18.0, 19.0, 19.5, 21.7, 24.3±0.2 degrees 2 theta.

A crystalline Ziprasidone Hydrochloride Monohydrate wherein the crystalline form is characterized by an X-ray powder diffraction pattern as substantially depicted in **FIG.3**. is also the scope of the present invention.

A crystalline Ziprasidone Hydrochloride Monohydrate wherein the crystalline form is characterized by an DSC endotherm substantially as depicted in **FIG.4** is also the scope of the present invention.

A crystalline Ziprasidone Hydrochloride Monohydrate, wherein the crystalline form is characterized by an thermogravimetric analysis as substantially depicted in **FIG.5** and having water content from about 3.8 to about 4.2%.

According to the most preferred embodiment a crystalline Ziprasidone base is crystalline polymorphic Form B of Ziprasidone base.

A crystalline Ziprasidone base and crystalline Ziprasidone Hydrochloride Monohydrate having all single individual impurity less than 0.1% by HPLC is also scope of the present invention.

Use of a crystalline Ziprasidone base for the preparation of Ziprasidone Hydrochloride monohydrate, Ziprasidone Hydrochloride Monohydrate, Ziprasidone Hydrochloride Anhydrous is yet another aspect of the present invention.

The word “Substantially pure” 6-chloro-5-(2-chloroethyl)-oxindole relates to the use of 6-chloro-5-(2-chloroethyl)-oxindole as the key starting material for the preparation of crystalline Ziprasidone base Form B having 6-chloro-5-(2-chloroacetyl)-oxindole and 5-(2-chloroacetyl)-oxindole (deschloro analogue) less than 1500 ppm, preferably less than 1000 ppm, more preferably less than 750 ppm, most preferably less than 500 ppm.

The Impurity Profile Determination of crystalline Ziprasidone hydrochloride comprised testing a sample using HPLC. Typically, the HPLC testing parameters included a column of Phenomenex Luna C8 (Type L7), 5 μ m 4.6*150 mm or equivalent column at a temperature of 40°C and mobile phase is buffer : methanol (550:450). The system equilibrated further for 10 min and a flow rate of 1.0 ml/min. The detector was set for 220 nm. The run time is not less than 20 minutes for assay and not less than 60 minutes for impurity assay. The sample volume was 10 μ L and the diluent was acetonitrile: water 50:50. As commonly known by the skilled artisan, the mobile phase composition and flow rate may be varied in order to achieve the required system suitability.

The sample was prepared by weighing accurately about 50 mg of Ziprasidone Hydrochloride in-house reference standard (dry for 3 hours at 105°C under vacuum oven) and transfer into a 100 mL volumetric flask. Add about 50 mL of mobile phase and sonicate to dissolve the solids. Dilute to volume with mobile phase and mix well. Designate it as stock solution S containing about 500 μ g/mL of Ziprasidone Hydrochloride.

Transfer 5.0 mL of stock solution S to 50 mL volumetric flask. Dilute to volume with mobile phase and mix well. Designate it as standard solution S₁ containing about 50 μ g/mL of Ziprasidone Hydrochloride Monohydrate.

Thereafter, the freshly prepared sample was injected. The sample solutions were injected into the chromatograph and the chromatogram of sample was continued up to the end of the gradient. Thereafter, the areas for each peak in each solution was determined using a suitable integrator. The calculations were obtained using the following formula:

Impurity Profile Determination

$$\% \text{ impurity (known or unknown)} = \frac{R_u \times W_s \times 5 \times 100 \text{ mL} \times \text{RRF} \times \% \text{ purity of Std.}}{R_s \times 100 \text{ mL} \times 50 \times W_T}$$

where R_u = Peak area of individual known/unknown impurity in sample preparation

R_s = Average peak area of Ziprasidone Hydrochloride Monohydrate in the suffix and prefix standard which are injected before and after the sample

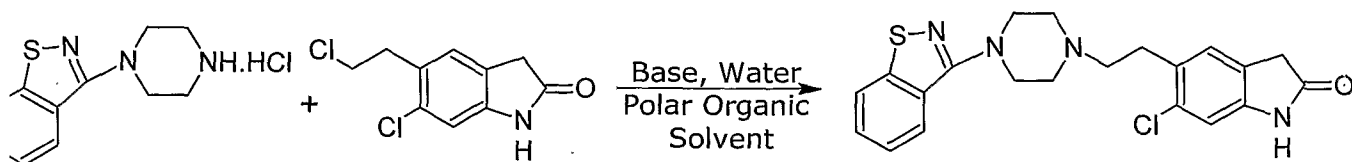
W_s = Weight of Ziprasidone Hydrochloride Monohydrate Standard

W_T = Weight of Ziprasidone Hydrochloride Monohydrate Sample

RRF = Relative Response Factor of individual known impurity.

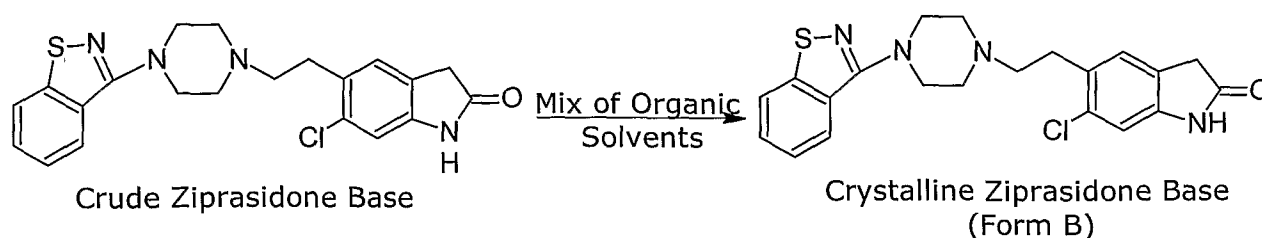
Percentage total impurities = % total known impurities + % total unknown impurities

Example-1: Preparation of Crude Ziprasidone Base



100.0 g of 6-Chloro-5-(2-chloroethyl) oxindole, 133.39 g of 3-(1-Piperazinyl)-1,2-benzisothiazole hydrochloride, 105.94 g of sodium carbonate and 1500 mL of water were taken in round bottom flask and heated to 100°C to 110°C for 24-26 hours. The reaction mixture was cooled and maintained for 30 min. The solid was filtered and washed with water. The wet solid was further slurried with water followed by adjusting the pH of the reaction mass with dilute acetic acid to 6.0 to 7.5 and maintain the reaction mass for 1-2 hours. The solid was filtered and washed with water. The wet solid was treated with isopropanol 1100 mL in round bottom flask and heated at 75°C to 85°C for 2 hours. The reaction mixture was cooled, the obtained solid was filtered and washed with isopropanol. The wet solid was dried at 60°C to 65°C for 8-10 hours to obtain crude Ziprasidone base.

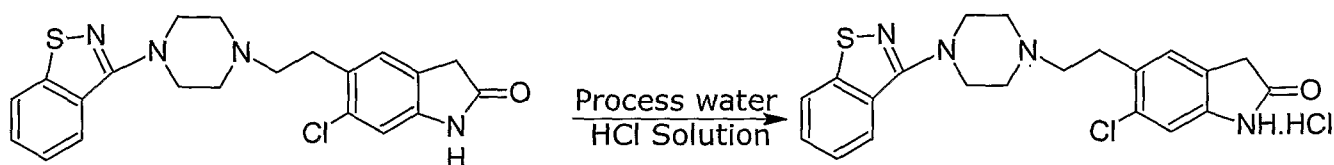
Example-2: Preparation of Crystalline Ziprasidone Base (Form B)



130 g of crude Ziprasidone base, dimethyl sulfoxide 260 mL and tetrahydrofuran 1820 mL were taken in the round bottom flask at room temperature. The reaction mixture was heated to 65°C to 75°C to obtain clear solution. Activated

charcoal 10.4 g was added and reaction mass was maintained for 1 hour. The product was filtered hot and the filtrate was distilled under vacuum below 50°C to remove mixture of dimethyl sulfoxide and tetrahydrofuran to reduce the volume by 70-75%. The reaction mixture was cooled to room temperature. The isolated product was filtered, washed with tetrahydrofuran and suck dried. The product was dried under vacuum at 55°C to 60°C till the LOD is not more than 0.5% to obtain pure crystalline Ziprasidone base Form B.

Example-3: Preparation of Ziprasidone Hydrochloride Monohydrate

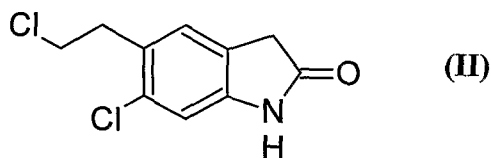


Crystalline Ziprasidone Base (Form B) 100.0 g and water 1500 mL were taken in round bottom flask. 100 mL 3M HCl solution was added to the reaction mass during 30 min. The reaction mixture was heated up to 60°C-65°C for 24 hours. The reaction mixture was cooled and stirred for 1 hour. The solid Ziprasidone hydrochloride monohydrate was filtered, washed with isopropyl alcohol and suck dried. The product was dried at 40°C to 50°C till the water content between 3.8 to 4.5%.

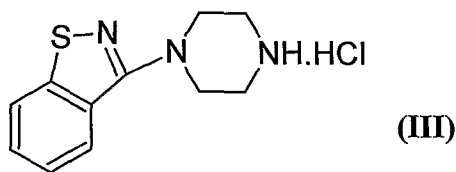
Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art would appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to, limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinary skill in the art and are described in numerous publications.

We Claims:

1. A process for the preparation of crystalline Ziprasidone base having an X-ray powder diffraction pattern with peaks at 12.3, 15.3, 16.4, 18.5, 25.3 ± 0.2 degrees 2 theta which comprises :
 - a) treating Ziprasidone base with a mixture of organic solvent at an elevated temperature to obtain the clear solution;
 - b) maintaining the reaction mixture at an elevated temperature for sufficient time to complete the reaction;
 - c) concentrating the reaction mixture;
 - d) cooling the reaction mixture; and
 - e) isolating crystalline Ziprasidone base.
2. A process as claimed in claim 1 wherein the crude Ziprasidone base is prepared by the process comprises of:
 - a) reacting substantially pure 6-chloro-5-(2-chloroethyl) oxindole of formula (II)



in 0.3 to 0.7 moles with 3-(1-piperazinyl)-1,2-benzisothiazole or its salts of formula (III)

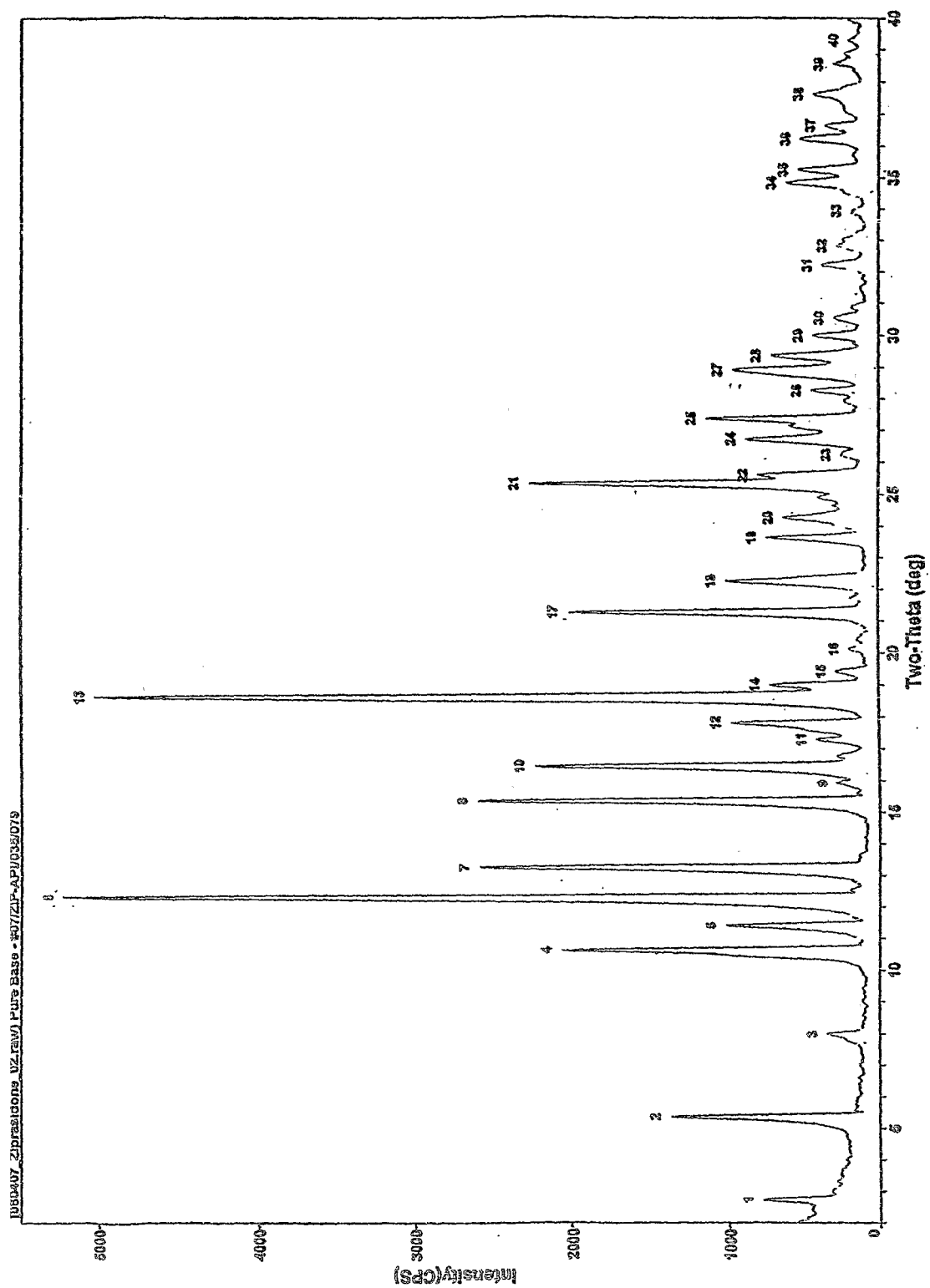


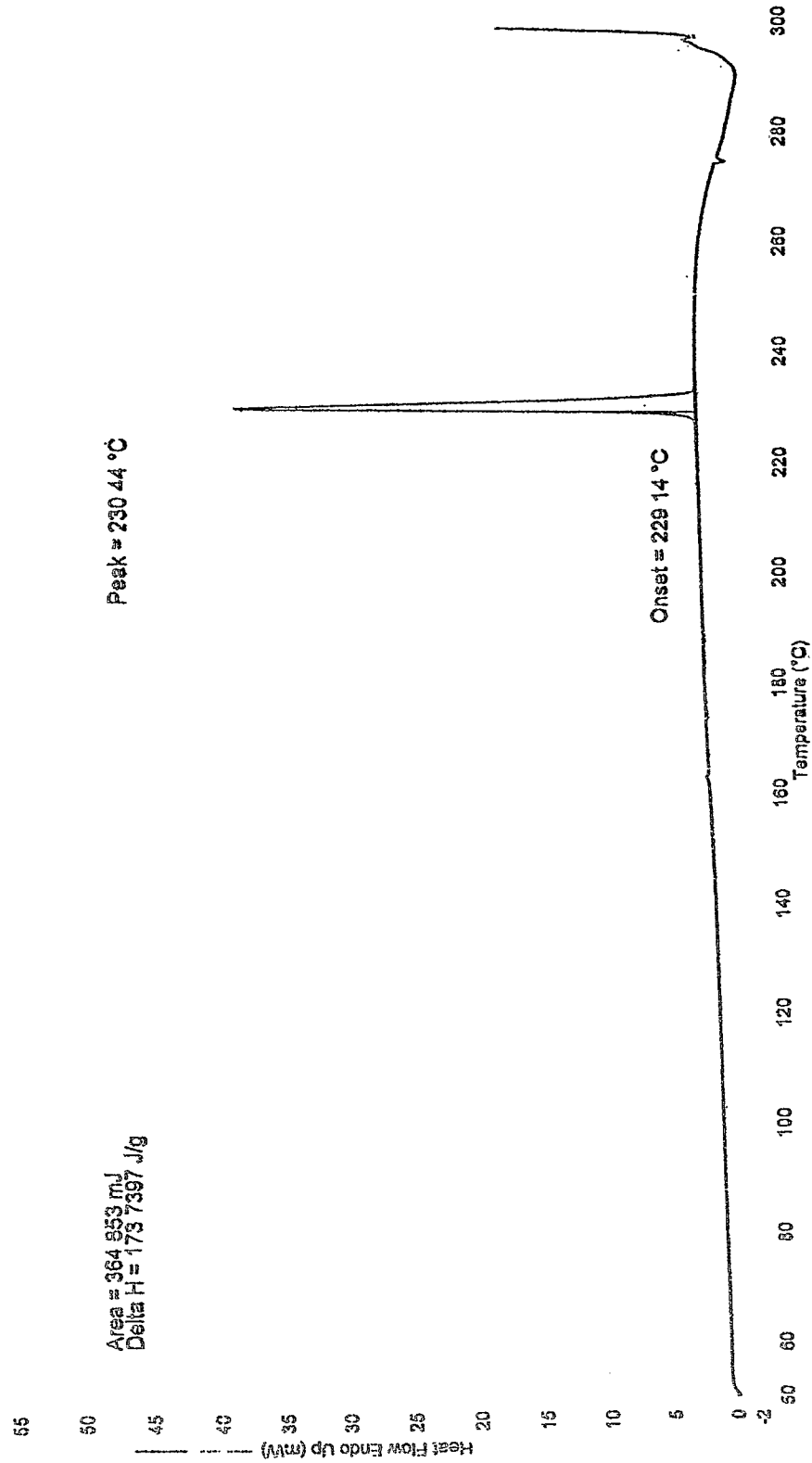
- in 0.3 to 0.7 moles, a base and water at an elevated temperature for sufficient amount of time to complete the reaction;
- b) cooling the reaction mixture to precipitate the product followed by filtration and washing with water;
 - c) treating the wet-cake with water, followed by acetic acid to adjust the pH of the reaction mixture from 6.0 to 7.5;

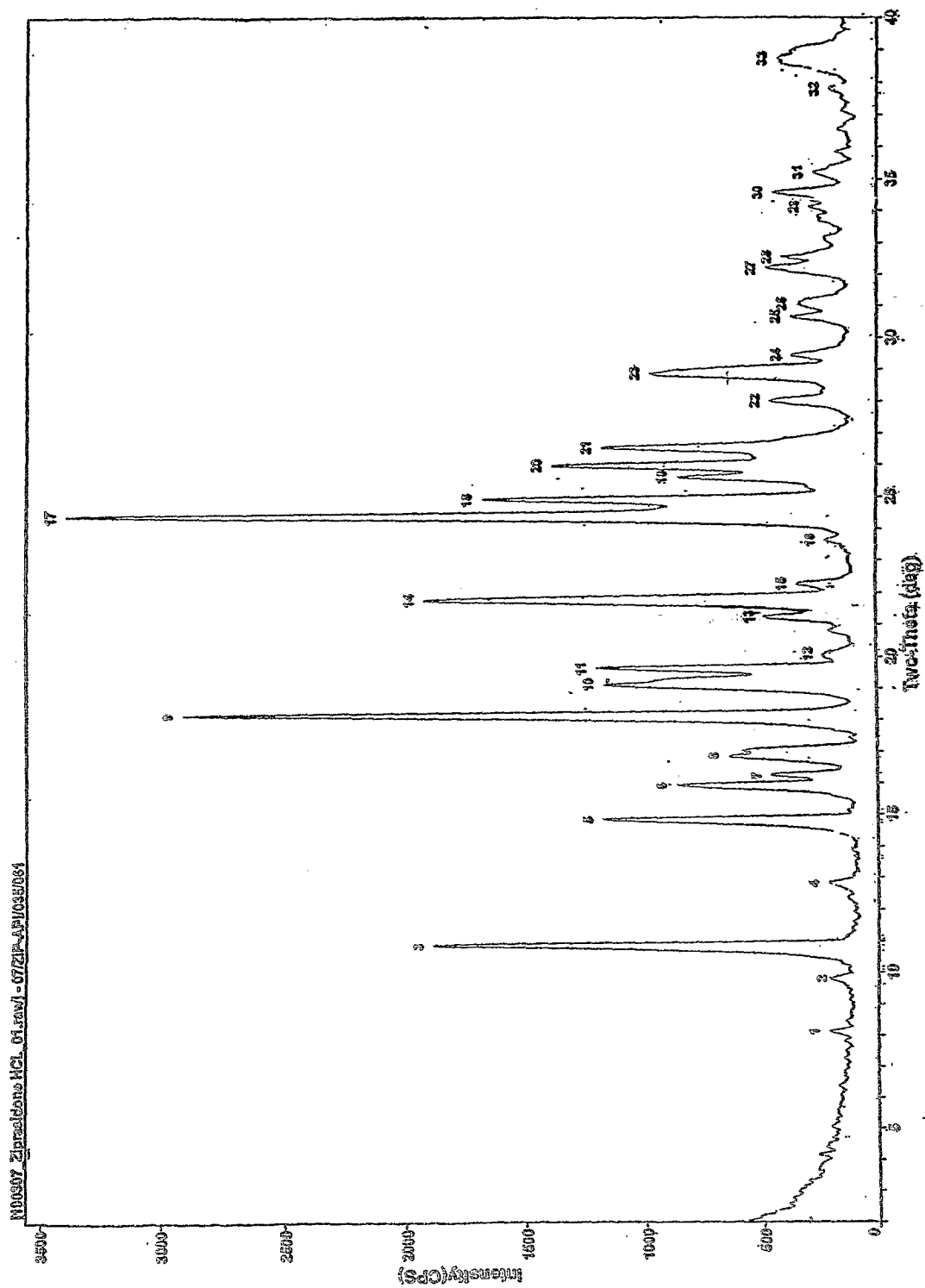
- d) filtering the product followed by treatment with polar organic solvent at a temperature in the range of 50°C to 100°C;
 - e) cooling the reaction mixture to precipitate the crude Ziprasidone base; and
 - f) recovering crude Ziprasidone base.
4. A process as claimed in any preceding claim wherein the mixture of organic solvents is selected from the group consisting of dimethyl formamide, dimethyl sulfoxide, dioxane, tetrahydrofuran, methanol, ethanol, isopropanol, propanol.
 5. A process as claimed in any preceding claim wherein the elevated temperature is in the range of 50°C to 150°C, preferably, from 75°C to 125°C, more preferably from 100°C to 110°C.
 6. A process as claimed in claim 2, wherein 6-chloro-5-(2-chloroethyl) oxindole is reacted in an amount of from 0.3 to 0.7 moles, preferably 0.4 to 0.5, more preferably of about 0.43 moles.
 7. A process as claimed in claim 2, wherein 3-(1-piperazinyl)-1,2-benzisothiazole or its salts is reacted from 0.3 to 0.7 moles, preferably 0.5 to 0.6, more preferably of about 0.52 moles.
 8. A process as claimed in claim 2, wherein the base is selected from the group consisting of organic amine, an alkoxide, an alkali metal hydroxide, an alkaline earth metal hydroxide, an alkali metal hydride, an alkaline earth metal hydride, an alkali metal carbonate, alkaline earth metal carbonate and hydrogencarbonate.
 9. A process as claimed in claim 9, wherein the base is selected from the group consisting of sodium methoxide, sodium ethoxide, sodium phenoxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, sodium hydride, potassium hydride, calcium hydride, sodium carbonate, potassium carbonate, sodium hydrogencarbonate, potassium hydrogencarbonate, calcium carbonate, calcium carbonate and basic alumina.
 10. A process as claimed in claim 9, wherein the base is carbonate.
 11. A process as claimed in claim 2, wherein the polar organic solvent is selected from the group of C₁-C₄ alcohol like methanol, ethanol, propanol, isopropanol, butanol; ketone like acetone, methyl ethyl ketone, amides like dimethyl formamide, esters like ethyl acetate, methyl acetate, tert-butyl acetate etc., preferably alcohol like isopropanol.

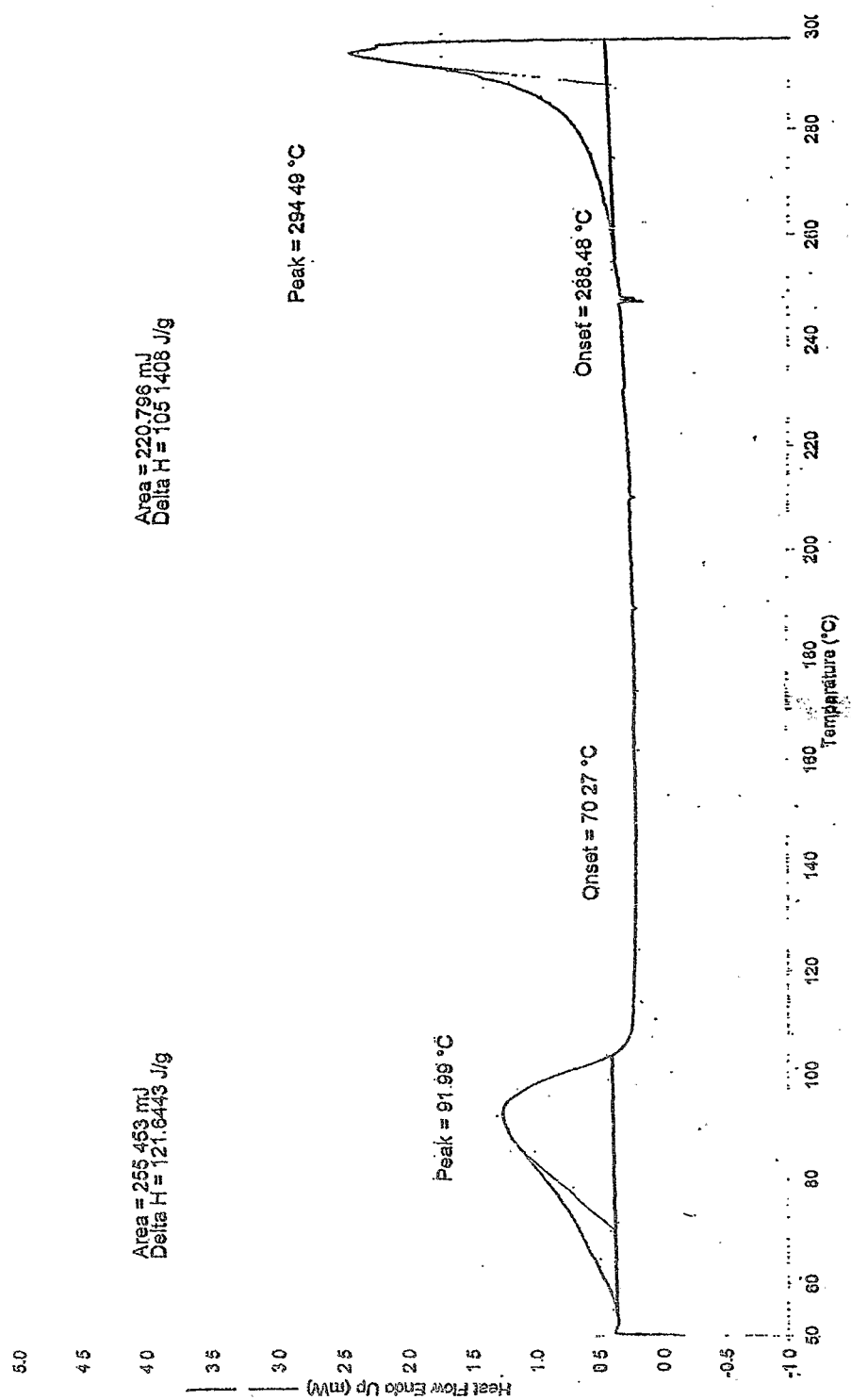
12. A process as claimed in claim 2 (d), wherein the temperature is in the range of 50°C to 100°C, preferably from 75°C to 90°C, more preferably from 75°C to 85°C.
13. A process for preparation of Ziprasidone acid addition salts or hydrates thereof which comprises:
 - a) treating crystalline Ziprasidone base of claim 1 with water at an ambient temperature;
 - b) adding source of acid addition salt;
 - c) heating the reaction mixture and maintaining at same temperature for a sufficient period of time to prepare Ziprasidone acid addition salt or hydrate thereof;
 - d) cooling the reaction mixture;
 - e) filtering and washing the solid with organic solvent; and
 - f) recovering Ziprasidone acid addition salt or hydrate.
14. A process as claimed in claim 13 wherein ambient temperature is from about 20°C to 35°C.
15. A process as claimed in claim 13 or 14 wherein acid addition salt is hydrochloric acid solution.
16. A process as claimed in claim 15, wherein hydrochloric acid solution is of 3 molar concentration.
17. A process as claimed in claim 13 (c), wherein the reaction mixture is heated at a temperature of from 60°C to 65°C.
18. A process of claim 14 (e), wherein the organic solvent is C₁-C₄ alcohols like methanol, ethanol, propanol, isopropanol or butanol, preferably isopropanol.
19. A process of claim 14 (f), wherein Ziprasidone acid addition salt or hydrate is Ziprasidone Hydrochloride Monohydrate.
20. A process of claim 14, wherein Ziprasidone Hydrochloride Monohydrate is having minimum water content that doesn't degrade to anhydrous or hemihydrate forms of Ziprasidone Hydrochloride.
21. A process of claim 21, wherein minimum water content is in the range of 3.5 to 5.0 %, preferably in the range of 3.8 to 4.5 %.
22. A crystalline Ziprasidone base characterized by an X-ray powder diffraction pattern as substantially depicted in **FIG.1**.

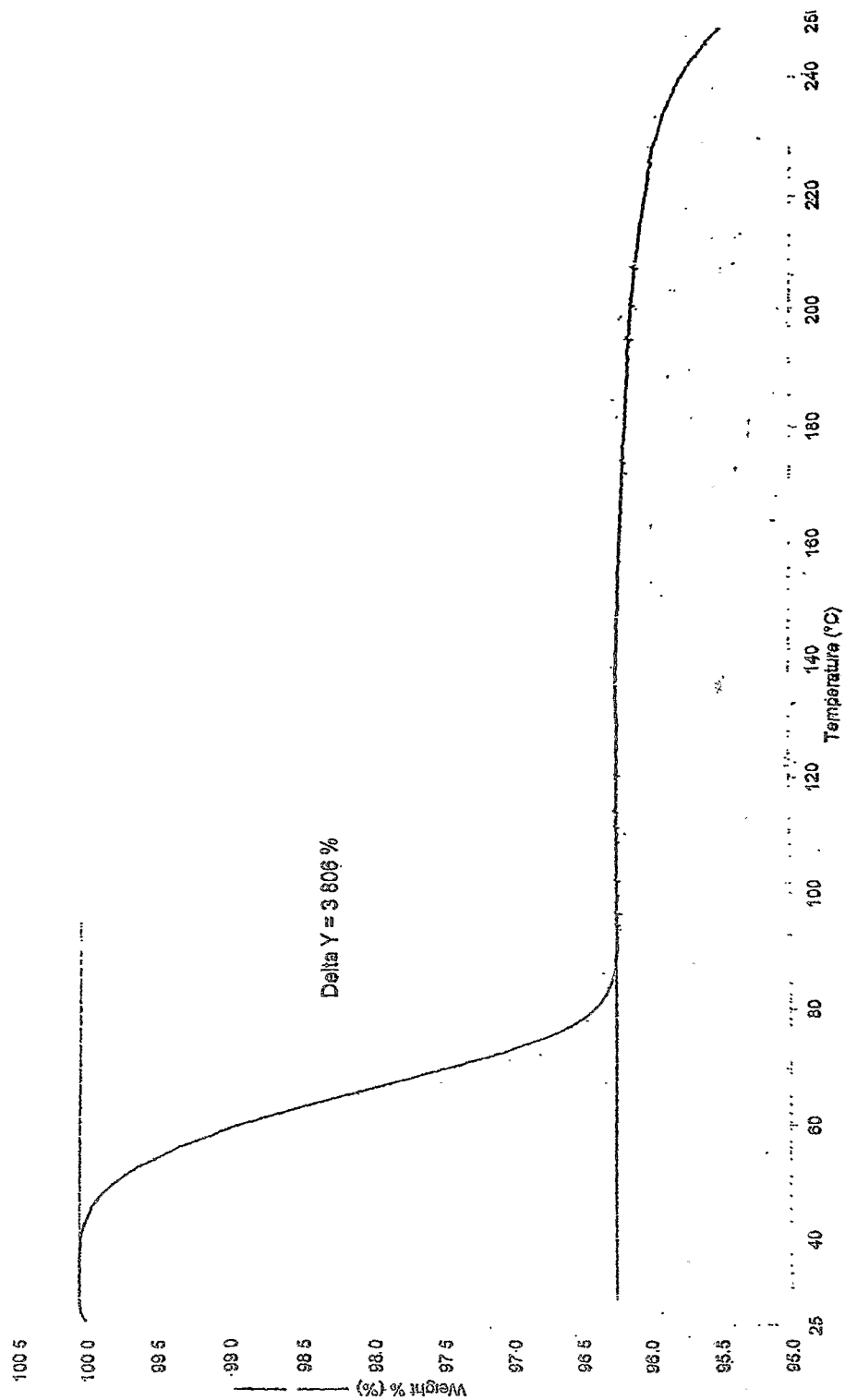
23. Ziprasidone Hydrochloride Monohydrate of claim 14-19, is having an X-ray powder diffraction pattern with peaks at 10.8, 14.7, 18.0, 19.0, 19.5, 21.7, 24.3 ± 0.2 degrees 2 theta.
24. A crystalline Ziprasidone Hydrochloride Monohydrate of claim 20, wherein the crystalline form is characterized by an X-ray powder diffraction pattern as substantially depicted in **FIG.3**.
25. A crystalline Ziprasidone Hydrochloride Monohydrate of claim 20, wherein the crystalline form is characterized by an DSC endotherm substantially as depicted in **FIG.4**.
26. A crystalline Ziprasidone Hydrochloride Monohydrate of claim 20, wherein the crystalline form is characterized by an thermogravimetric analysis as substantially depicted in **FIG.5** and having water content from about 3.8 to about 4.2%.
27. A crystalline Ziprasidone base of claim 1 is polymorphic Form B.
28. A crystalline Ziprasidone base of claim 24, having all single individual impurity less than 0.1% by HPLC.
29. A crystalline Ziprasidone Hydrochloride Monohydrate of claim 20, having all single individual impurity less than 0.1% by HPLC.
30. Use of a crystalline Ziprasidone base for the preparation of Ziprasidone Hydrochloride monohydrate, Ziprasidone Hydrochloride Monohydrate, Ziprasidone Hydrochloride Anhydrous.
31. A process of preparing crystalline Ziprasidone base substantially as herein described with reference to any one of the embodiments of the invention illustrated in the accompanying drawings and/or examples.











INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2008/000858

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D417/04 A61K31/425 A61P25/18
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 practical, 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	WO 2005/061493 A (TEVA PHARMA [IL]; TEVA PHARMA [US]; ARONHIME JUDITH [IL]; MENDELOVICI) 7 July 2005 (2005-07-07) claims 32, 33, 55, the whole document where Form B is mentioned -----	22, 27, 28
X	WO 2005/054235 A (WOCKHARDT LTD [IN]; JAWEED MUKARRAM SIDDIQUI MOHAM [IN]; MERWADE ARAVI) 16 June 2005 (2005-06-16) process on page 6, step b and page 9, example 2 for claims 1, 4, 5, 31; process on page 5, step a) for claim 2; process on page 9, example 3 for claim 13; -----	1, 2, 4, 5, 13, 31
X	EP 0 586 191 A1 (PFIZER [US]) 9 March 1994 (1994-03-09) Fig 1; p. 2, l. 40ff -----	13-21, 23-26, 29, 30



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 June 2010

Date of mailing of the international search report

09/06/2010

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2008/000858

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☒ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 4, 5, 22, 27, 28, 31

Crystalline ziprasidone base and purification of crystalline ziprasidone base

2. claims: 2-12, 31

Crystalline ziprasidone base, its preparation and use

3. claims: 13-21, 23-26, 29, 30

Crystalline hydrochloride monohydrate, its preparation from crystalline ziprasidone base

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2008/000858

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005061493 A	07-07-2005	CA 2550485 A1 CN 1934108 A EP 1592688 A2 JP 2007514001 T	07-07-2005 21-03-2007 09-11-2005 31-05-2007
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EP 0586191 A1	09-03-1994	AU 657231 B2 AU 4600493 A BR 9303014 A CA 2105114 A1 CN 1089607 A CZ 9301789 A3 DE 9312903 U1 EG 20251 A FI 933804 A HU 67023 A2 IL 106777 A JP 2742372 B2 JP 6157521 A NO 933093 A NZ 248543 A PL 300235 A1 PL 174396 B1 RU 2081116 C1 TW 422845 B US 5312925 A ZA 9306394 A	02-03-1995 16-06-1994 15-03-1994 02-03-1994 20-07-1994 13-04-1994 05-01-1994 31-05-1998 02-03-1994 30-01-1995 15-04-1997 22-04-1998 03-06-1994 02-03-1994 26-07-1995 05-04-1994 31-07-1998 10-06-1997 21-02-2001 17-05-1994 28-02-1995