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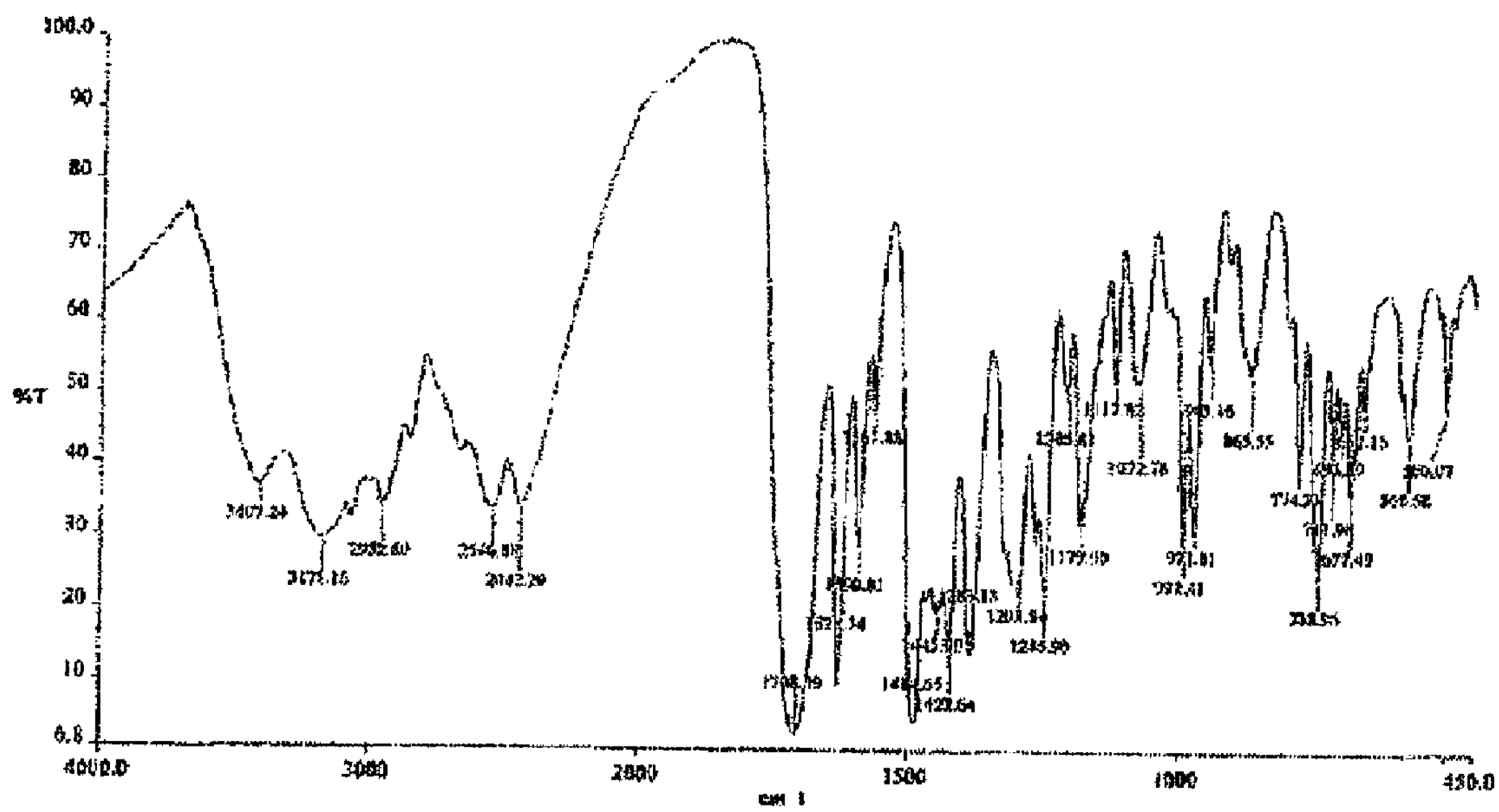
(54) Titre : NOUVEAU CHLORHYDRATE DE ZIPRASIDONE AMORPHE (CHLORHYDRATE DE 5-[2-[4-(1,2-BENZISOTHIAZOL-3-YL)-1-PIPERAZINYL]ETHYL]-6-CHLORO-1,3-DIHYDR O-2H-INDOL-2-ONE) ET PROCEDES POUR SA PRODUCTION

(54) Title: NEW AMORPHOUS ZIPRASIDONE HYDROCHLORIDE (5-[2-[4-(1,2-BENZISOTHIAZOL-3-YL)-1-PIPERAZINYL]ETHYL]-6-CHLORO-1,3-DIHYDRO-2H-INDOL-2-ONE HYDROCHLORIDE) AND PROCESSES TO PRODUCE THE SAME

IR (KBr) of Amorphous Ziprasidone Hydrochloride




(57) Abrégé/Abstract:
The present invention relates to a new and useful amorphous form of ziprasidone hydrochloride (5-(2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride) and preparations thereof.

## ABSTRACT

The present invention relates to a new and useful amorphous form of ziprasidone hydrochloride (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride) and preparations thereof.

## TITLE OF THE INVENTION

New amorphous ziprasidone hydrochloride (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride) and processes to produce the same.

## BACKGROUND OF THE INVENTION

Ziprasidone hydrochloride (5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride) is a potent neuroleptic agent useful in the treatment of various disorders including schizophrenia, anxiety and pain. It is currently marketed under the proprietary name of Geodon. Ziprasidone hydrochloride is known to exist in three crystalline forms; namely, the monohydrate, hemihydrate and anhydrous form as disclosed in U.S. Pat. Nos. 4,831,031 and 5,312,925, both of which are herein incorporated by reference. U.S. Patent 5,312,925 states that ziprasidone hydrochloride monohydrate is hygroscopically stable, thus alleviating potential problems due to weight changes of the active pharmaceutical ingredient during the final formulation process. Nevertheless a very low aqueous solubility is observed for this crystalline form.

Canadian patent 2,252,898 attempts to overcome some of the deficiencies of the prior art, especially the poor aqueous solubility of ziprasidone hydrochloride monohydrate, by formation of various mesylate hydrate salts.

In US patent 6,150,366 the poor aqueous solubility is purportedly increased by controlling, by various methods, the mean particle size of the crystalline ziprasidone free base or ziprasidone hydrochloride to a mean particle size equal to or less than about 85 μm.

US patent 5,935,960 describes another attempt to overcome the poor aqueous solubility of ziprasidone hydrochloride by formation of a pro-drug of ziprasidone, specifically 1-[2-(6-chloro-2,3-dihydro-2-oxo-1H-indol-5-yl)ethyl]-4-[imino(2-mercaptophenyl)methyl]piperazine or one of its pharmaceutically acceptable salts, for instance the dihydrochloride.

Canadian patent 2,245,269 describes numerous compositions comprising of solid spray dried dispersions of sparingly water soluble drugs, including ziprasidone free base, and hydroxypropylmethylcellulose acetate succinate. Again, the form obtained purportedly provides increased aqueous solubility and/or bioavailability.

Therefore, a method which produces an improved form of ziprasidone hydrochloride in high yields and purity, and helps to overcome some of the deficiencies of the known forms is desired.

## SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for the preparation of an improved form of ziprasidone hydrochloride in high yields and purity.

We have surprisingly found that using low-polarity organic solvents such as $C_5$ to $C_{12}$ substituted or unsubstituted cyclic and acyclic hydrocarbons such as hexanes, heptanes, or cyclohexanes; or $C_1$ to $C_3$ chlorinated hydrocarbons such as dichloromethane or chloroform and mixtures thereof to carry out the reaction between ziprasidone free base and anhydrous hydrogen chloride, unexpectedly a novel amorphous form of ziprasidone hydrochloride is obtained. (See Figures 1, 2 and 3 to this specification)

Thus, in accordance to an aspect of the present invention there is provided a process for preparing the novel amorphous form of ziprasidone hydrochloride comprising the steps of:

(i) suspending ziprasidone free base in about 5 to 100 volumes of such low-polarity organic solvent or mixture of solvents at a temperature of from about -10 to about 40°C,

(ii) one of the following steps:

a) bubbling hydrogen chloride gas for a period between 1 and 12 hours

or,

b) exposing the mixture to a suitable pressure of hydrogen chloride

or,

c) adding a solution of hydrogen chloride in a suitable organic solvent,

(iii) stirring the mixture at a temperature between about -10 and 40°C until product is produced,

(iv) filtering and washing the solid at ambient temperature,

(v) if required, stirring the solid with a suitable organic solvent between about -10 and 60°C,

(vi) if required, filtering and washing the solid,

(vii) drying the solid.

Thus according to another aspect of the invention, there is provided a process for producing the novel amorphous form of ziprasidone hydrochloride comprising the steps of:

suspending ziprasidone free base in about 5 to 100 volumes of such low-polarity organic solvent or mixture of solvents at a temperature of from about -10 to about 40°C,

(i) suspending ziprasidone free base preferably in about 5 to 100 volumes of a low-polarity organic solvent or mixture of solvents at a temperature of from about -10 to about 40°C,

(ii) adding hydrogen chloride to the suspension,

(iii) recovering the amorphous ziprasidone hydrochloride.

Examples of low polarity organic solvents, which are useful in the reaction of the present invention include, but are not limited to a $C_5$ to $C_{12}$ substituted or unsubstituted cyclic and acyclic hydrocarbon solvent such as hexanes, heptanes, or cyclohexane; or a $C_1$ to $C_3$ chlorinated hydrocarbon solvent such as dichloromethane or chloroform, and their mixtures thereof. The most preferred solvent is heptanes or dichloromethane.

Examples of suitable organic solvents, which are useful for preparing solutions of anhydrous hydrogen chloride [step (iv)], include but are not limited to, isopropanol, ethanol and ethyl ether.

This novel amorphous form has advantageous properties relative to those of the prior art, for instance, better water solubility and potentially improved bioavailability. It also has the advantage of simplicity in that it avoids the necessity of having to resort to specialized preparation methods. For instance this more aqueous soluble amorphous form does not necessitate the use of a different salt form of ziprasidone as taught in Canadian patent 2,252,898 or a pro-drug of ziprasidone as taught in US patent 5,935,960. Also it avoids the use of specialized spray dried dispersion compositions of ziprasidone free base as taught in Canadian patent 2,245,269 or specialized process equipment to ensure that the mean particle size produced is below 85 μm as taught in US patent 6,150,366.

## DETAILED DESCRIPTION OF THE INVENTION

The following examples illustrate the preparation of ziprasidone hydrochloride anhydrate and amorphous ziprasidone hydrochloride and are not to be construed as limiting the scope of the invention in any manner.

### EXAMPLE 1

Preparation of amorphous 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride.

To a flask equipped with magnetic stirrer, thermometer and a gas bubbling tube was added 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one free base (5.0 g) and heptanes (100 mL) and the suspension was cooled to 0-5°C under nitrogen. Anhydrous hydrogen chloride was bubbled into the suspension for 1-1.5 h. and then the suspension was stirred for about 2.5 h. The product was collected by filtration on a Buchner funnel. The filter cake is rinsed with heptanes at 20-25°C and transferred to a drying oven and dried *in vacuo* at 55-60°C for about 16 h. This afforded 5.38 g (98.9% yield) of amorphous ziprasidone hydrochloride. The, powder X-ray diffractogram, IR (KBr) spectrum and DSC thermogram are consistent with amorphous material. These are shown in figures 1, 2 and 3 respectively.

**EXAMPLE 2**

Preparation of amorphous 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride.

To a flask equipped with magnetic stirrer, thermometer and nitrogen inlet was added 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one free base (5.0 g) and dichloromethane (100 mL) and the suspension was stirred at 20-25°C under nitrogen. A 20.5% anhydrous solution of hydrogen chloride in isopropanol (6.45 g) was added and the mixture was stirred for about 2 h. The product was collected by filtration on a Buchner funnel. The filter cake is rinsed with 3 x 10 mL of dichloromethane at 20-25°C and transferred to a drying oven and dried *in vacuo* at 65-70°C for about 18 h. The crude material was re-slurried at 20-25°C for 10 minutes with heptanes and the suspension was filtered *in vacuo*. The filter cake is rinsed with heptanes at 20-25°C and transferred to a drying oven and dried *in vacuo* at 65-70°C for about 12 h. to afford amorphous ziprasidone hydrochloride having the same PXRD diffractogram, IR and DSC as shown in figures 1 to 3.

**EXAMPLE 3**

Preparation of amorphous 5-[2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]ethyl]-6-chloro-1,3-dihydro-2H-indol-2-one hydrochloride.

To a 1-L pressure reactor equipped with a mechanical stirrer and hydrogen chloride inlet and purge valve was added 5-(2-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl)ethyl)-6-chloro-1,3-dihydro-2H-indol-2-one free base (10.0 g) and heptanes (200 mL) and the suspension was cooled to about 0-5°C and at about 150 rpm The vessel was pressurized to a hydrogen chloride pressure of 30 psi. After about 5 minute, the pressure had dropped to about 20 psi whereupon the pressure was increased to 30 psi. Over the next 10 minutes, the pressure had dropped to about 20 psi and then was stirred for 18 hours. The pressure was still at about 20 psi at which point the pressure was released and the vessel purged with nitrogen. The product was collected by filtration on a Buchner funnel. The filter cake is rinsed with 4 x 40 mL of heptanes and transferred to a drying oven and dried *in vacuo* at 65-70°C for about 5 h to afford amorphous ziprasidone hydrochloride (9.22 g) having the same PXRD diffractogram, IR and DSC as shown in figures 1 to 3.

While the foregoing provides a detailed description of the preferred embodiments of the invention, it is to be understood that the descriptions are illustrative only of the principles of the invention and not limiting. Furthermore, as many changes can be made to the invention without departing from the scope of the invention, it is intended

that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A process for the preparation of substantially amorphous ziprasidone hydrochloride comprising the steps of:

   (i) suspending ziprasidone free base in a low-polarity organic solvent or mixture of solvents;

   (ii) adding hydrogen chloride to the suspension;

   (iii) recovering the amorphous ziprasidone hydrochloride.

2. A process for the preparation of substantially amorphous ziprasidone hydrochloride comprising the steps of:

   (i) mixing ziprasidone free base with a suitable low-polarity organic solvent to prepare a suspension;

   (ii) bubbling anhydrous hydrogen chloride gas;

   (iii) stirring the reaction mixture for a sufficient amount of time to obtain ziprasidone hydrochloride;

(iv) recovering the substantially amorphous ziprasidone hydrochloride and drying the product to suitable residual solvent levels; and

(v) optionally stirring the solid with a suitable organic solvent, filtering and drying.

3. A process for the preparation of substantially amorphous ziprasidone hydrochloride comprising the steps of:

(i) mixing ziprasidone free base with a suitable low-polarity organic solvent to prepare a suspension;

(ii) pressurizing a suitable pressure vessel with hydrogen chloride;

(iii) stirring the reaction mixture for a sufficient amount of time to obtain ziprasidone hydrochloride formation;

(iv) isolating the substantially amorphous ziprasidone hydrochloride and drying to obtain suitable residual solvent levels; and

(v) if required, stirring the solid with a suitable organic solvent, filtering and drying.

4. A process for the preparation of substantially amorphous ziprasidone hydrochloride comprising the steps of:

(i) mixing ziprasidone free base with a suitable low-polarity organic solvent to prepare a suspension;

(ii) adding a solution of hydrogen chloride in a suitable organic solvent,

(iii) stirring the reaction mixture for a sufficient amount of time to obtain ziprasidone hydrochloride formation;

(iv) isolating the substantially amorphous ziprasidone hydrochloride and drying to obtain suitable residual solvent levels; and

(v) if required, stirring the solid with a suitable organic solvent, filtering and drying.

5. The process of claims 1, 2, 3 or 4, wherein the organic solvent for step i is a low-polarity organic solvent.

6. The process of claim 5, wherein the low-polarity organic solvent is a $C_5$ to $C_{12}$ substituted or unsubstituted cyclic and acyclic hydrocarbon.

7. The process of claim 6 wherein the low-polarity organic solvent is selected from hexanes, heptanes, cyclohexanes and mixtures thereof.

8. The process of claim 5, wherein the low-polarity organic solvent is a $C_1$ to $C_3$ chlorinated hydrocarbon solvent such as dichloromethane or chloroform.

9. The process of claim 8 wherein the low-polarity organic solvent is selected from dichloromethane, chloroform and mixtures thereof.

10. The process of claim 1, 2, 3 or 4, wherein the low-polarity organic solvent is dichloromethane.

11. The process of claim 1, 2, 3 or 4, wherein the low-polarity organic solvent is heptanes.

12. A substantially amorphous form of ziprasidone hydrochloride compound.

13. The compound of claim 12 having a PXRD diffractogram as depicted in Figure 1.

14. The compound of claim 12 having an IR spectum as depicted in Figure 2.

15. The compound of claim 12 having a DSC thermogram as depicted in Figure 3.

16. The compound of claim 12 having a PXRD diffractogram as depicted in Figure 1, an IR spectum as depicted in Figure 2, and a DSC thermogram as depicted in Figure 3.

17. The process according to claims 1 to 11 wherein the amount of the organic solvent of step (i) comprises about 5 – 100 volumes of such low-polarity organic solvent or mixture of solvents and the temperature at which step (i) is carried out is between about -10° C to about 40° C.

Figure 1. PXRD Diffractogram of Amorphous Ziprasidone Hydrochloride

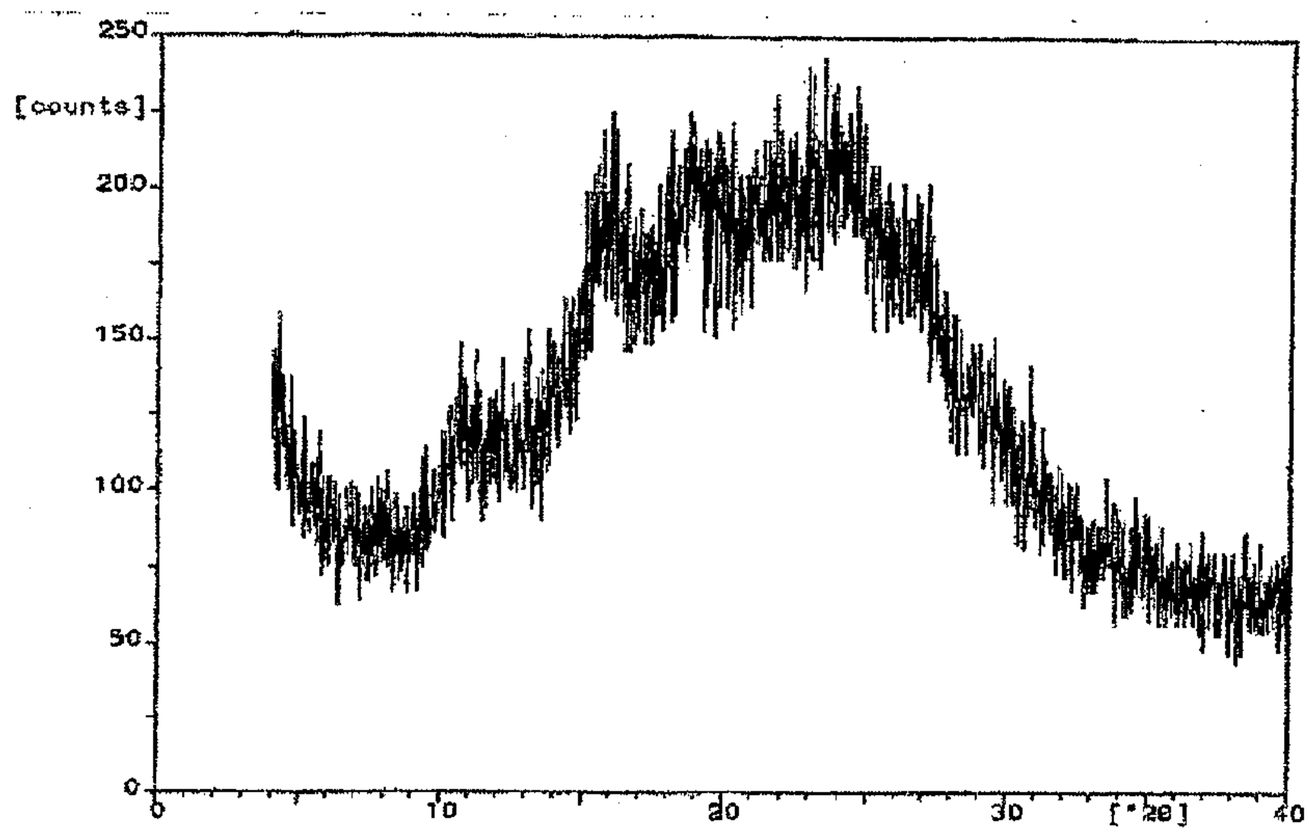



Figure 2. IR (KBr) of Amorphous Ziprasidone Hydrochloride

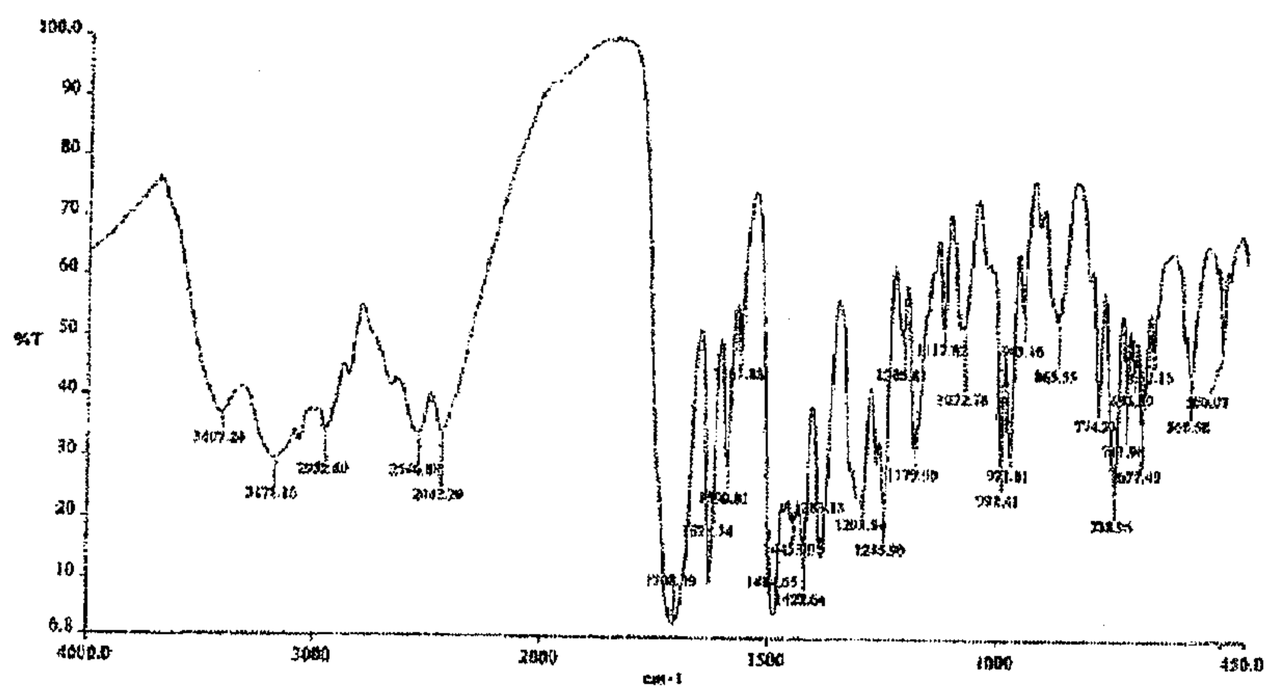
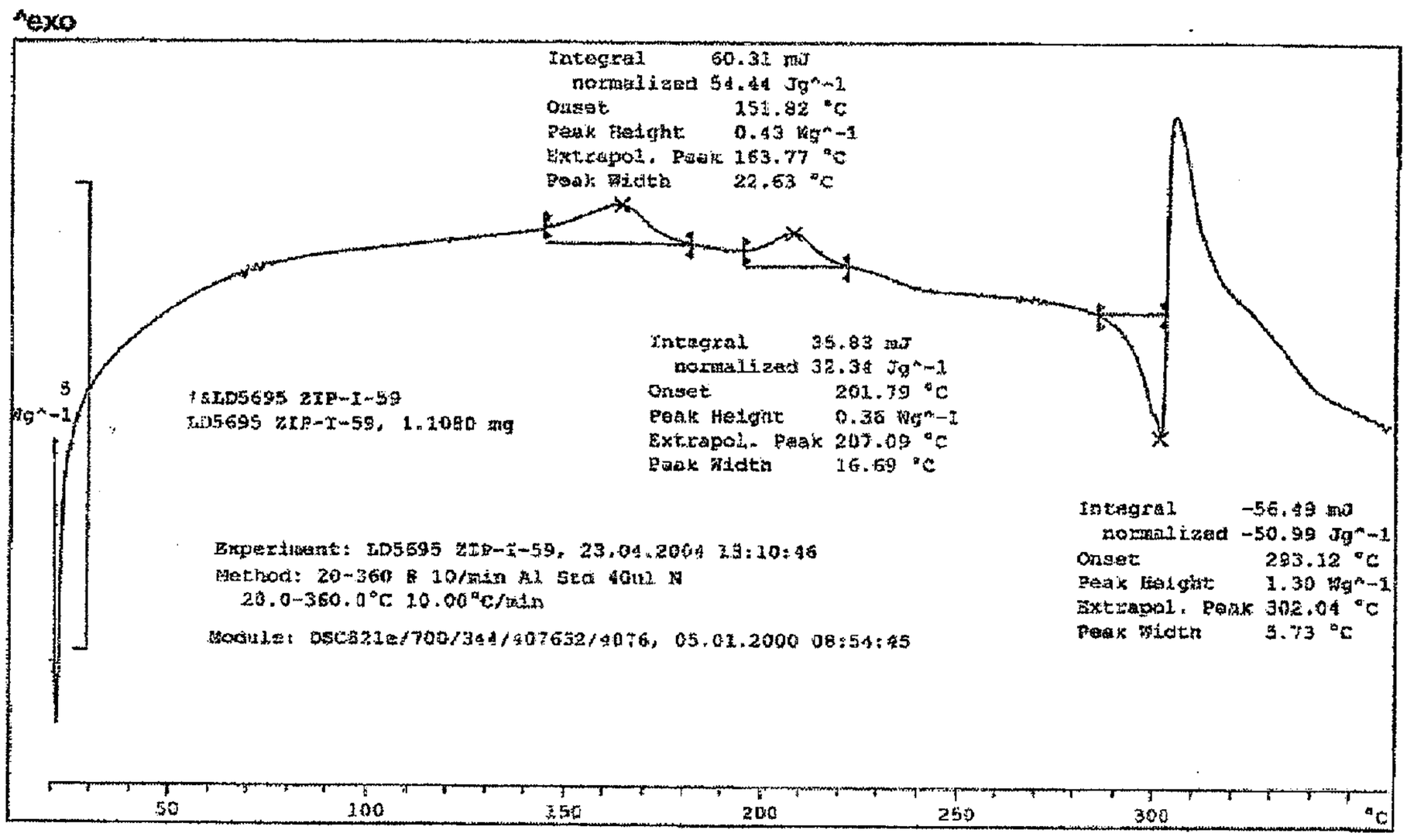
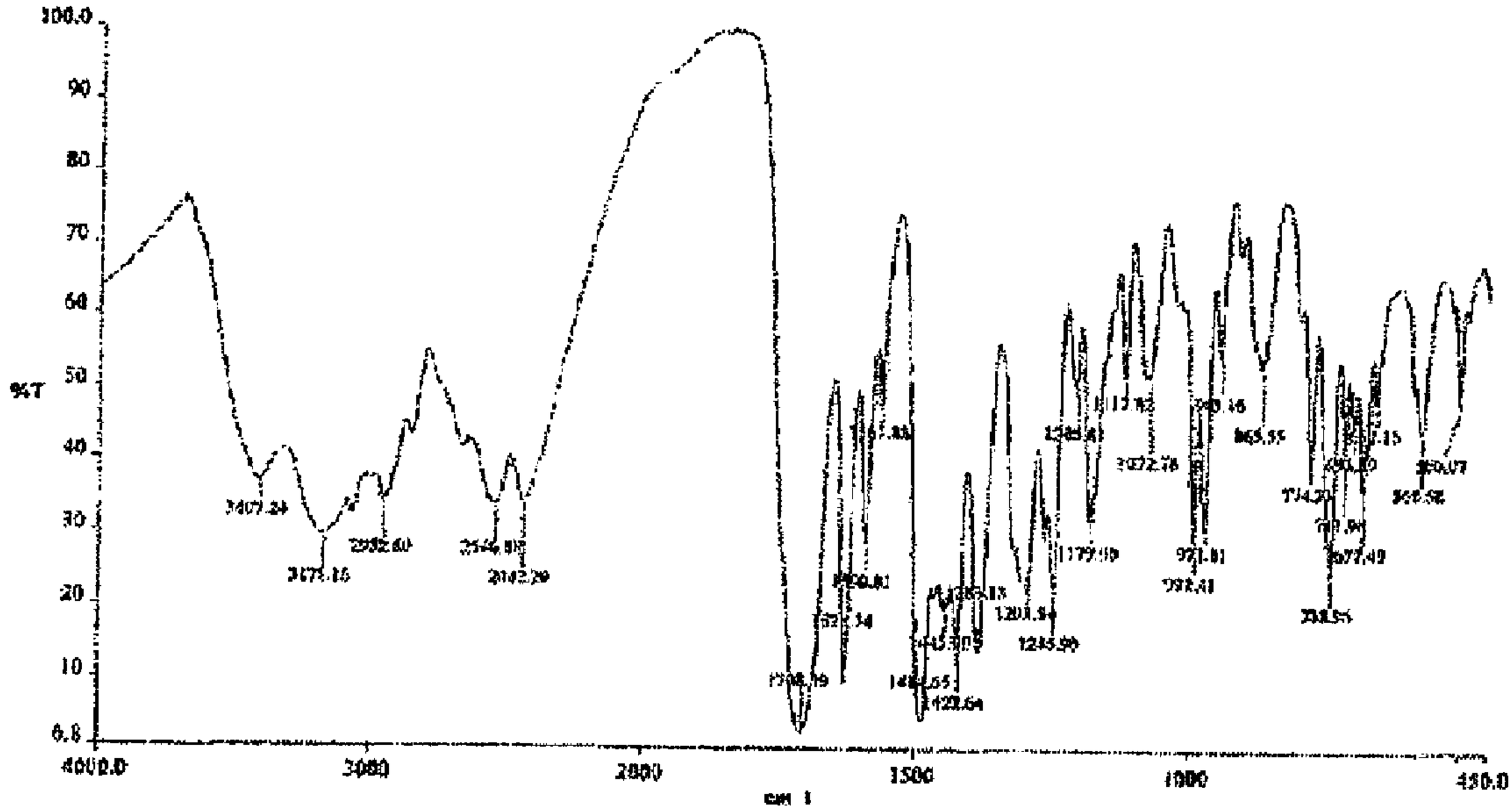


Figure 3. DSC Thermogram of Amorphous Ziprasidone Hydrochloride



# IR (KBr) of Amorphous Ziprasidone Hydrochloride