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(54) Title: POLYMORPHIC FORMS OF ZIPRASIDONE HCl AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: Provided are various polymorphic forms of ziprasidone HCl and processes for their preparation.

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POLYMORPHIC FORMS OF ZIPRASIDONE HCl AND PROCESSES FOR THEIR PREPARATION

Cross Reference To Related Applications:

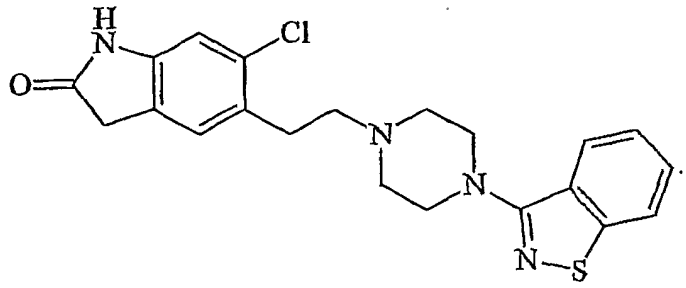
This application claims the benefit of U.S. provisional application Serial No. 60/475,806, filed June 3, 2003; U.S. provisional application Serial No. 60/487,913, filed July 16, 2003; U.S. provisional application Serial No. 60/494,970, filed August 13, 2003; U.S. provisional application Serial No. 60/528,346, filed December 9, 2003, and U.S. provisional application Serial No. 60/571,997, filed May 17, 2004, the contents of all of which are incorporated herein.

Field of the Invention:

The present invention relates to the solid state chemistry of ziprasidone HCl.

Background of the Invention:

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. patent No. 4,831,031 (example 16). Preparation of ziprasidone base is also disclosed in U.S. patent 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 80mg dosage forms. GEODON for injection contains a lyophilized form of ziprasidone mesylate trihydrate, and contains 20mg 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.

The present invention relates to the solid state physical properties of ziprasidone HCl. These properties can be influenced by controlling the conditions under which ziprasidone HCl is obtained in solid form. Solid state physical properties include, for example, the flowability of the milled solid. Flowability affects the ease with which the material is handled during processing into a pharmaceutical product. When particles of the powdered compound do not flow past each other easily, a formulation specialist must take that fact into account in developing a tablet or capsule formulation, which may necessitate the use of glidants such as colloidal silicon dioxide, talc, starch or tribasic calcium phosphate.

Another important solid state property of a pharmaceutical compound is its rate of dissolution in aqueous fluid. The rate of dissolution of an active ingredient in a patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally-administered active ingredient can reach the patient's bloodstream. The rate of dissolution is also a consideration in formulating syrups, elixirs and other liquid medicaments. The solid state form of a compound may also affect its behavior on compaction and its storage stability.

These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. These conformational and orientational factors in turn result in particular intramolecular interactions and intermolecular interactions with adjacent molecules that influence the macroscopic properties of the bulk compound. A particular polymorphic form may give rise to distinct spectroscopic properties that may be detectable by powder X-Ray diffraction, solid state ^{13}C NMR spectrometry and infrared spectrometry. The polymorphic form may also give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior is measured in the laboratory by such techniques as capillary melting point, thermogravimetric analysis

(TGA) and differential scanning calorimetry (DSC) and can be used to distinguish some polymorphic forms from others.

Ziprasidone HCl hemihydrate is disclosed in U.S. Pat. No. 4,831,031, Example 16 (column 13, line 13). A ziprasidone HCl monohydrate (herein designated Form M) is disclosed in U.S. Pat. No. 5,312,925 and EP 0 586 181 A1. Form M is characterized by XRD, IR and water content. It is reported that the water content of Form M ranges from 3.8 to 4.5% by weight. Ziprasidone HCl Form M is prepared from ziprasidone base anhydrous.

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. There is a need in the art for additional polymorphic forms of ziprasidone HCl.

Summary of the Invention

In one aspect, the present invention provides a crystalline form of ziprasidone HCl (Form E), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 7.4, 13.0, 20.7, 23.4, 25.9 ±0.2 degrees 2 theta.

In another aspect, the present invention provides a process for preparing ziprasidone HCl Form E, comprising:

a) combining aqueous HCl with ziprasidone base in the presence of ethyl acetate or acetonitrile to obtain a slurry;

b) maintaining the slurry to obtain ziprasidone HCl; and

c) recovering the ziprasidone HCl.

In another aspect, the present invention provides a crystalline form of ziprasidone HCl, wherein the crystalline form is a trihydrate.

In another aspect, the present invention provides a process for preparing ziprasidone HCl Form E in a mixture with a crystalline ziprasidone HCl having an X-Ray diffraction pattern having peaks at about 10.9, 17.4 and 19.1 ±0.2 degrees 2 theta, comprising:

a) combining aqueous HCl with ziprasidone base in the presence of tetrahydrofuran to obtain a slurry;

b) maintaining the slurry to obtain ziprasidone HCl; and

c) recovering the ziprasidone HCl mixture.

In another aspect, the present invention provides a crystalline form of ziprasidone HCl (Form F), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 11.0, 18.1, 19.5, 21.9 ±0.2 degrees 2 theta.

In another aspect, the present invention provides a process for preparing the ziprasidone HCl Form F, comprising:

a) combining aqueous HCl with ziprasidone base in a solvent selected from the group consisting of methylethylketone, tetrahydrofuran and dimethylacetamide to obtain a slurry;

b) maintaining the slurry to obtain ziprasidone HCl; and

c) recovering the ziprasidone HCl.

In another aspect, the present invention provides a process for preparing the ziprasidone HCl form M, comprising:

a) heating a slurry of ziprasidone HCl in n-butanol or THF, optionally in mixture with water; and

b) recovering the ziprasidone HCl form M.

In another aspect, the present invention provides a process for preparing the ziprasidone HCl form M comprising:

a) combining aqueous HCl with ziprasidone base at a temperature of at least about 40°C in a solvent selected from the group consisting of ethanol, methanol, n-butanol, acetone, ethyl actate, ethyl lactate, dimethyl-carbonate, optionally in a mixtures with water to obtain a slurry,

b) maintaining the slurry to obtain the ziprasidone HCl form M; and

c) recovering the ziprasidone HCl form M.

In another aspect, the present invention provides a process for preparing the ziprasidone HCl form M comprising:

a) contacting gaseous hydrogen chloride with ziprasidone base in methanol to obtain a slurry of ziprasidone hydrochloride in methanol;

b) maintaining the slurry to obtain the ziprasidone HCl form M; and

c) recovering the ziprasidone HCl form M.

In another aspect, the present invention provides a process for preparing the ziprasidone HCl form M substantially free of the crystalline ziprasidone HCl characterized by a powder XRD pattern with peaks at 10.9, 17.4, 19.1, 25.0, 26.0 ±0.2 degrees 2 theta comprising:

a) combining a solution or slurry of ziprasidone base in a solvent with less than one equivalent HCl to obtain a reaction mixture containing ziprasidone HCl;

b) stirring or agitating the reaction mixture;

c) adding additional HCl to obtain additional ziprasidone HCl; and

d) recovering the ziprasidone HCl form M.

In another aspect, the present invention provides for amorphous form of ziprasidone HCl.

In another aspect, the present invention provides a process for preparing amorphous form comprising slurrying ziprasidone base with methyl ethyl ketone or mono-chloro benzene with gaseous hydrochloride.

In another aspect, the present invention provides a crystalline form of ziprasidone HCl (Form G), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 9.0, 20.6, 22.7, 25.0, 27.0 ±0.2 degrees 2 theta.

In another aspect, the present invention provides a process for preparing ziprasidone HCl Form G comprising:

a) combining gaseous HCl with a mixture of ziprasidone base in a solvent selected from the group consisting of carbon tetrachloride, di-isopropyl-ether, ethyl acetate, ethyl lactate and mixtures thereof to obtain a slurry of ziprasidone HCl;

b) maintaining the slurry to obtain ziprasidone HCl Form G; and

c) recovering the ziprasidone HCl.

In another aspect, the present invention provides a process for preparing a mixture of the ziprasidone HCl of Form F and ziprasidone HCl Form G comprising:

a) combining gaseous HCl with a mixture of ziprasidone base in ethyl acetate to obtain a slurry of ziprasidone HCl;

b) maintaining the slurry to obtain ziprasidone HCl; and

c) recovering the mixture.

In another aspect, the present invention provides a crystalline form of ziprasidone HCl (Form I), wherein the crystalline form has an XRD pattern with peaks at 15.8, 16.2, 18.9, 23.8, 27.0 ±0.2 degrees 2 theta,

In another aspect, the present invention provides a crystalline form of ziprasidone HCl (Form J), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 9.1, 19.1, 25.7, 26.3, 26.9 ±0.2 degrees 2 theta.

In another aspect, the present invention provides a process for preparing ziprasidone HCl Form J comprising:

a) combining ziprasidone base with HCl to obtain a slurry of ziprasidone HCl in a C_5 to C_{12} hydrocarbon;

b) maintaining the slurry to obtain the crystalline ziprasidone HCl; and

c) recovering the ziprasidone HCl.

In another aspect, the present invention provides a crystalline form of ziprasidone HCl, wherein the crystalline form has a water content of about 24% by LOD.

In another aspect, the present invention provides a crystalline from of ziprasidone HCl (Form E1), wherein the crystalline form is characterized a powder XRD pattern with peaks at 7.5, 13.0, 21.2, 23.4 and 26.0 ±0.2 degrees 2 theta.

In another aspect, the present invention provides a process for preparing ziprasidone HCl Form E1 comprising drying the ziprasidone HCl Form J.

In another aspect, the present invention provides a crystalline form of ziprasidone, wherein the crystalline form has a water content of about 6% to about 8%.

In another aspect, the present invention provides a pharmaceutical composition and method of treating a patient suffering from schizophrenia.

Figures

Figure 1 is an X-Ray powder diffractogram of amorphous ziprasidone HCl.

Figure 2 is a DSC thermogram of amorphous ziprasidone HCl.

Figure 3 is an IR spectrum of ziprasidone HCl amorphous.

Figure 4 is an X-Ray powder diffractogram of ziprasidone HCl form E.

Figure 5 is a DSC thermogram of ziprasidone HCl form E.

Figure 6 is an IR spectrum of ziprasidone HCl form E.

Figure 7 is an X-Ray powder diffractogram of ziprasidone HCl form F.

Figure 8 is a DSC thermogram of ziprasidone HCl form F.

Figure 9 is an IR spectrum of ziprasidone HCl form F.

Figure 10 is a DSC thermogram of ziprasidone HCl Form M.

Figure 11 is an IR spectrum of ziprasidone HCl Form M.

Figure 12 is an X-Ray powder diffractogram of ziprasidone Base.

Figure 13 is a DSC thermogram of ziprasidone Base.

Figure 14 is an IR spectrum of ziprasidone Base.

Figure 15 is an X-Ray powder diffractogram of ziprasidone HCl Form G.

Figure 16 is an X-Ray powder diffractogram of ziprasidone HCl Form I.

Figure 17 is an X-Ray powder diffractogram of ziprasidone HCl Form J.

Figure 18 is an FTIR spectrum of ziprasidone HCl Form J.

Figure 19 is an FTIR spectrum of ziprasidone HCl Form J.

Figure 20 is an FTIR spectrum of ziprasidone HCl Form J.

Figure 21 is an X-Ray powder diffractogram of ziprasidone HCl Form E1.

Figure 22 is an FTIR spectrum of ziprasidone HCl Form E1.

Figure 23 is an FTIR spectrum of ziprasidone HCl Form E1.

Figure 24 is an FTIR spectrum of ziprasidone HCl Form E1.

Detailed Description of the Invention:

As used herein, the term slurry refers to a heterogeneous mixture.

As used herein, the term reduced pressure refers to a pressure below about 1 atm, more preferably below about 100 mmHg.

The present invention provides for obtaining ziprasidone HCl Form M from ziprasidone base, or other forms of ziprasidone hydrochloride. Ziprasidone base, such as form B, but not limited to this form, is combined with aqueous hydrochloric acid and slurried in solvents such as methanol, ethanol, n-butanol, ethyl acetate, ethyl lactate, acetone, dimethyl carbonate, optionally in mixtures with water. Gaseous hydrogen chloride may be used with methanol. The slurry is then allowed to last for a sufficient amount of time (maintained) to obtain the monohydrate, preferably for about half a day. The slurry process is preferably carried out about room temperature to about reflux temperature of the solvents. Preferred combination of starting bases and solvents include Form B and ethyl acetate/ethanol/methanol/n-butanol. In another embodiment, rather than starting with ziprasidone base, another polymorphic form of ziprasidone HCl is used for the slurry process. Preferred combination of solvents and starting forms include ziprasidone HCl

Form F and THF and ziprasidone HCl Form E and n-butanol, preferably in mixtures with water. Preferably, the slurry is heated for a sufficient amount of time, more preferably to at least about 40°C.

The present invention also provides a process for preparation of Form M, but in a substantially pure form, by slow crystallization from slurry or solution of ziprasidone base in an organic solvent. Preferred solvents are mixtures of THF/AcOH, THF/MeOH, DMA, n-BuOH/AcOH. The temperature of crystallization is more than about 50°C, preferably of about 55 to about 70°C, more preferably about 55 to about 65°C, and most preferably 65± 2°C. The mode of HCl addition is preferably portion-wise.
In one embodiment, a first portion of HCl is added until opalescence is obtained, and the mixture is stirred to induce nucleation, followed by the rest of HCl addition. Typically, opalescence resulting from formation of ziprasidone HCl is observed after adding ~1/10 portion of the HCl. Seeding of ziprasidone base before the HCl addition is ideal.

In one embodiment, A process ziprasidone HCl form M substantially free of the crystalline ziprasidone HCl characterized by a powder XRD pattern with peaks at 10.9, 17.4, 19.1, 25.0, 26.0 ±0.2 degrees 2 theta is prepared by combining a solution or slurry of ziprasidone base in a solvent with less than one equivalent HCl to obtain a reaction mixture containing ziprasidone HCl, stirring or agitating the reaction mixture, adding additional HCl to obtain additional ziprasidone HCl and recovering the ziprasidone HCl form M.

In another aspect, the present invention provides for ziprasidone HCl Form E.
Ziprasidone HCl Form E is characterized by an X-Ray diffraction pattern (Figure 4) with peaks at 7.4, 13.0, 20.7, 23.4, 25.9 ±0.2 degrees 2 theta. Ziprasidone HCl Form E is further characterized by XRD peaks at 13.7, 20.0, 21.3, 25.2 ±0.2 degrees two-theta. The DSC thermogram of ziprasidone HCl Form E (Figure 5) shows endothermic peaks of about 22, 152 and 11 J/g at about 54, 94 and 132°C respectively, which correspond to the desolvation and dehydration of ziprasidone HCl Form E. According to the thermogram, the melting and decomposition of ziprasidone HCl Form E starts at about 280°C. The water content of ziprasidone form E, measured by Karl Fisher, ranges about 9.3% to about 9.6% by weight, and the weight loss measured by TGA is about 19% by weight.

This corresponds approximately to a trihydrate, which may contain solvent approximately as 1 ½ -1 1/3 solvate of acetonitrile, or 2/3-¾ solvate of ethyl acetate.

The FTIR spectrum of ziprasidone HCl form E is shown in Figure 6.

Ziprasidone HCl Form E when exposed to a high relative humidity, such as for about 22 days, transforms to form M. Ziprasidone HCl form E transforms to amorphous form when exposed to about 10% to about 0%, more preferably about 0% relative humidity, for such as 22 days, or after heating at elevated temperature, preferably at about 80°C overnight. Ziprasidone HCl Form E transforms to Form A when exposed to a relative humidity of about 20% to about 60% for about 22 days (see table 1 and 2). Form A is characterized by an X-Ray diffraction pattern having peaks at about 10.9, 17.4 19.1, 25.0 and 26.0 ±0.2 degrees 2 theta.

Ziprasidone HCl novel form E may be prepared by combining ziprasidone base with aqueous HCl in acetonitrile or ethyl acetate to obtain a slurry, and allowing the slurry to last for a sufficient time to obtain Form E. The slurry process is preferably carried out overnight. The combining of HCl with ziprasidone base is preferably carried out at a temperature of about 40°C to about 60°C, with about 50°C being preferred. The slurrying after the combining is preferably carried out at a temperature of about 20°C to about 30°C, more preferably at about room temperature. Ziprasidone Form E may also be obtained as a mixture with Form A by a slurry process that uses tetrahydrofuran as a solvent. Slurrying at room temperature results in the mixture, while slurrying at higher temperatures, such as above about 50°C results substantially in Form A.

Table No. 1

Water uptake (%) and crystal form of ziprasidone HCl form E equilibrated at different relative humidities for 22 days

RH (%)	TGA weight loss (%)	Crystal form
0	5.3	Amorphous
20	7.2	A
40	4.8	A
60	5.0	A

80	9.2	Monohydrate + A
100	51.3	Monohydrate + A+ amorphous

Table No. 2

Crystal form of ziprasidone HCl form E heated at 80-105°C overnight

Original crystal form	Crystal form after heating at 80-105°C overnight
Form E	Amorphous + form F

In another aspect, the present invention provides for ziprasidone HCl Form F. Ziprasidone HCl Form F is characterized by an XRD pattern (Figure 7) with peaks at 11.0, 18.1, 19.5, 21.9 ±0.2 degrees 2 theta. Ziprasidone HCl Form F is further characterized by XRD peaks at 14.9, 24.9, 26.1 ±0.2 degrees 2 theta. Ziprasidone HCl Form F has a DSC thermogram (Figure 8) which shows an about a 71 J/g endothermic peak at about 85°C, corresponding to the dehydration of the ziprasidone HCl Form F. At about 280°C, ziprasidone HCl Form F starts to melt and decompose. The water content and the weight loss by TGA of the sample may range of about 2.6% to about 16% by weight. When ziprasidone HCl Form F is equilibrated at relative humidity of about 0% to about 100%, it retains its crystal form. Ziprasidone HCl Form F, after being heated overnight at about 80°C, has very low water content (0.8%), but still retains its original crystal form (see tables 3 and 4). In the range of relative humidity of about 20% to about 60%, the water content equilibrates around about 4.0% to about 4.5%, which indicates that Form F may be a stable monohydrate when kept in the humidity range of about 20% to about 60% RH.

The IR spectrum of ziprasidone HCl form F in Figure 9 is shown.

Ziprasidone HCl novel Form F may be prepared by combining ziprasidone base with aqueous HCl in tetrahydrofuran, methylethylketone or dimethylacetamide to obtain a slurry, and allowing the slurry to last for a sufficient time to obtain Form F. The slurry may be diluted by addition of water. The combining step is preferably carried out at elevated temperature, more preferably of about 50°C to about 70°C, most preferably at about 60°C. The slurrying after the combining is preferably carried out at a temperature of about 20°C to about 30°C, more preferably at about room temperature. Preferably, when the solvent is dimethylacetamide, a mixture of Form F and Form M is obtained.

Table No. 3

Water uptake (%) and crystal form of ziprasidone HCl form F equilibrated at different relative humidities for 22 days

RH (%)	TGA weight loss (%)	Crystal form
0	2.6	F
20	4.2	F
40	4.0	F
60	4.5	F
80	7.7	F
100	15.8	F

Table No. 4

Crystal form of ziprasidone HCl form F heated at 80-105°C overnight

Original crystal form	Crystal form after heating at 80-105°C overnight	% water content
Form F	Form F	0.8

Form F may be used for the preparation of Form M, by combining ziprasidone HCl Form F, THF and water, heating the slurry to about 50°C, cooling the slurry to room temperature, and maintaining for a sufficient time to obtain Form M.

In another aspect, the present invention provides for amorphous form of ziprasidone HCl. Amorphous ziprasidone HCl has an X-Ray diffraction pattern as substantially depicted in Figure 1, in which reflection peaks are absent (halo-like pattern). Endothermic peaks are absent from the DSC thermogram of amorphous ziprasidone HCl (Figure 2). The FTIR spectrum of amorphous ziprasidone HCl is substantially depicted in Figure 3.

Amorphous form of ziprasidone HCl may be prepared by placing Form E in a dessicator (dry chamber) having low humidity for a sufficient time to obtain amorphous form. In a preferred embodiment, ziprasidone Form E is put in a dessicator having about 0% relative humidity for about 18 days.

Ziprasidone HCl amorphous may be prepared by drying ziprasidone HCl form E at an elevated temperature, preferably of about 80 to about 105°C, for a sufficient period of time, preferably of about 5 to about 30 hours, more preferably overnight (~15 hours). Ziprasidone HCl amorphous may also be prepared by exposing ziprasidone HCl form E to low relative humidity, preferably about 0%, for a sufficient period, preferably a time of about 1 –3 weeks, more preferably for about 3 weeks.
Ziprasidone hydrochloride amorphous may also be prepared by treating the slurry of ziprasidone base in MEK or mono-chlorobenzene with gaseous HCl.

In another aspect, the present invention provides for ziprasidone HCl Form G.
Ziprasidone HCl Form G has an XRPD diffraction pattern with preferred peaks at 9.0, 20.6, 22.7, 25.0, 27.0 ±0.2 degrees 2 theta, and other peaks at 11.3, 12.5, 13.9, 15.6, 21.5, 23.5, 25.8, 28.0, 31.5 ±0.2 degrees two-theta.

Ziprasidone HCl Form G may have a water content of about 5% to about 12%.
Ziprasidone HCl Form G may be a dihydrate (about 7.4% stochiometric value for the dihydrate) or a trihydrate (about 10.7% stochiometric value for the trihydrate).
Ziprasidone HCl Form G is sparingly soluble in methanol, hence the water determination by Karl Fisher is carried out for more than 30 minutes in order to ensure that all the material is dissolved and all the water is analyzed.

Ziprasidone HCl Form G may be prepared by introducing HCl gas into a mixture of ziprasidone base in ethyl acetate, ethyl lactate, carbon tetrachloride, di-isopropyl-ether and mixtures thereof to obtain a slurry of ziprasidone HCl, and allowing the slurry to last for a sufficient time. The slurry is preferably stirred. When ethyl acetate is used in the absence of an ether, the result may be a mixture of Form G with Form F. The resulting wet product may be separated by techniques known in the art such as filtration, and may be dried, preferably at a temperature of about 40°C to about 60°C for about half a day.

In another aspect, the present invention provides for ziprasidone HCl Form I.
Ziprasidone HCl Form I is characterized by an XRD pattern with peaks at 15.8, 16.2, 18.9, 23.8, 27.0 ±0.2 degrees 2 theta, and other peaks at 10.5, 11.3, 21.1, 24.8, 26.0 ±0.2

degrees two-theta. Ziprasidone HCl Form I may be prepared by heating ziprasidone HCl Form G, preferably a ziprasidone Form G obtained from a slurry in di-iso-propyl ether. The heating is preferably carried out at a temperature of about 40°C to about 60°C for about half a day

The polymorphic forms of the present invention are preferably used with particle size up to 100 microns in light of low solubility of ziprasidone HCl in water.

Ziprasidone HCl anhydrous may be prepared by drying ziprasidone HCl Form M, for example by exposing the material to low relative humidity, preferably about 0% relative humidity, for a sufficient period, preferably for about 1 –3 weeks, more preferably for about 3 weeks.

The present invention also provides for ziprasidone HCl form J. Ziprasidone HCl Form J is characterized by XRD peaks at 9.1, 19.1, 25.7, 26.3, 26.9 ±0.2 degrees 2 theta, and other less characteristic peaks at 11.9, 21.4, 23.4, 30.7, 32.2 ±0.2 degrees two-theta. Form J has an FTIR spectrum as substantially depicted in figures 18 to 20. The present invention also provides for ziprasidone HCl Form J with a water content of about 24%.

Ziprasidone HCl Form J may be obtained by slurry of ziprasidone base in a C_5 to C_{12} hydrocarbon, preferably toluene. A few hours of slurrying is sufficient after combining of HCl with ziprasidone base to obtain the slurry. Ziprasidone HCl Form J may then be recovered for example by solvent removal.

The present invention also provides for ziprasidone HCl Form E1. Ziprasidone HCl Form E1 is characterized by XRD peaks at 7.5, 13.0, 21.2, 23.4 and 26.0 ±0.2 degrees 2 theta, and other less characteristic peaks at 10.9, 16.2, 20.8, 25.4, 30.3 and 34.8 ±0.2 degrees two-theta. Ziprasidone HCl Form E1 has an FTIR spectrum as substantially depicted in figures 22 to 24. The present invention also provides for ziprasidone HCl Form E1 with a water content of about 6% to about 8%.

Ziprasidone HCl Form E1 may be prepared by removing solvent from ziprasidone HCl Form J. Such removal may be done by drying Form J at elevated temperature, and/or

under ambient or reduced pressure. A dry nitrogen atmosphere is preferred with a temperature of about 30°C to about 50°C, with about 40°C being preferred.

A slurry is most effective when the solids of the heterogeneous mixture are in substantial contact with the solvent. When the solids settle down, the efficiency of the slurry process often decreases due to a decrease in contact. Thus, one of skill in the art would appreciate that if during the slurry process the solids settle down, a force such as stirring, agitating to disperse the solid. Even when the solids have not settled down, bringing of movement in the solvent may even further increase the efficiency of the slurry process.

One of skill in the art would appreciate that as the slurry is allowed to last for a sufficient time to obtain a particular polymorphic form, the slurry may dry up due to for example evaporation of the solvents. As the examples illustrate, additional amounts of a solvent may be added (same or different solvent), preferably followed by stirring, to obtain a slurry.

The various forms of ziprasidone may be recovered from the slurry by conventional techniques in the art such as decanting, filtration and centrifugation.

Pharmaceutical formulations of the present invention contain crystalline ziprasidone HCl, such as one of those disclosed herein, or ziprasidone HCl amorphous, optionally in mixture with other form(s) of ziprasidone. In addition to the active ingredient(s), the pharmaceutical formulations of the present invention may contain one or more excipients. Excipients are added to the formulation for a variety of purposes.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable

oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

In liquid pharmaceutical compositions of the present invention, ziprasidone and any other solid excipients are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol and cetyl alcohol.

Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth and xanthan gum.

Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

According to the present invention, a liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and losenges, as well as liquid syrups, suspensions and elixirs.

The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

The dosage of GEODON may be used as a guidance. The oral dosage form of the present invention is preferably in the form of an oral capsule having a dosage of about 10 mg to about 160 mg, more preferably of about 20 mg to about 80 mg, and most preferably capsules of 20, 40, 60 and 80 mg.

Instrumentation:

X-Ray powder diffraction data were obtained using by method known in the art using a SCINTAG powder X-Ray diffractometer model X'TRA equipped with a solid state detector. Copper radiation of 1.5418 Å was used. A round aluminum sample holder with round zero background quartz plate, with cavity of 25(diameter)*0.5(dept) mm.

DSC analysis was done using a Mettler 821 Star^e. The weight of the samples was about 5 mg; the samples were scanned at a rate of 10°C/min from 30°C to 320°C. The oven was constantly purged with nitrogen gas at a flow rate of 40 ml/min. Standard 40 µl aluminum crucibles covered by lids with 3 holes were used.

TGA analysis was done using a Mettler M3 meter. The weight of the samples was about 10 mg; the samples were scanned at a rate of 10°C/min from 25°C to 200°C. The oven was constantly purged with nitrogen gas at a flow rate of 40 ml/min. Standard 70 µl alumina crucibles covered by lids with 1 hole were used.

IR analysis was done using a Perkin Elmer SPECTRUM ONE FT-IR spectrometer in DRIFTt mode. The samples in the 4000-400 cm^{-1} interval were scanned 16 times with 4.0 cm^{-1} resolution.

The water content of ziprasidone HCl was measured by the methods known in the art like Karl Fisher or thermogravimetric analysis (TGA). In the case of ziprasidone HCl F, the TGA and Karl Fisher analysis matched, while for ziprasidone HCl form E the TGA analysis exceeded by far that of Karl Fisher, as an indication that a significant quantity of solvent is present.

Ziprasidone base

Ziprasidone free base used for preparations of the crystal forms of ziprasidone HCl 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 like the one shown in Figure 13, 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. The IR spectrum of ziprasidone free base is substantially depicted in Figure 14. The form of ziprasidone is referred to as Form B. One of skill in the art would appreciate that the processes of the present invention may use other forms of ziprasidone base as starting material.

Examples

Example 1- Preparation of Ziprasidone base

Ziprasidone base for the experiments below was prepared according to the procedure "EXPERIMENT" in US Pat. No. 5,312,925, column 4. The water content of the base was 1.2 % (Karl Fisher).

Example 2- Preparation of Ziprasidone base Form B

Ziprasidone base (50g) and toluene (250ml) were charged into a 0.5 L three necked flask. The obtained slurry was heated at 85°C for 2 hours. The hot slurry was filtrated and the solid was washed with methanol. The solid was dried in air-circulated oven at 50°C to afford the dried Ziprasidone base form B (by XRD) (45.39g).

Example 3- Preparation of Ziprasidone HCl form E from Ziprasidone base form B in acetonitrile and aqueous HCl

Aqueous HCl (37%) (10ml) was added to a slurry of ziprasidone base Form B (10g) in acetonitrile (200ml) at reflux. After the addition, the slurry was heated over night. A solid was filtered and washed with acetonitrile. After drying at 50°C for ~16 hours, ziprasidone HCl Form E was obtained (12.71g) (The water content was 9.25% by K.F. and the loss on drying by TGA is 18.8%), as confirmed by XRD.

Example 4- Preparation of Ziprasidone HCl form E from Ziprasidone base form B in ethyl acetate and aqueous HCl

A slurry of ziprasidone base form B (10g) in ethyl acetate (100ml) was heated at reflux without complete dissolution. The slurry was then cooled. When the temperature was about 50°C, aqueous HCl (37%) (10ml) was added, and the slurry was diluted by addition of ethyl acetate (100ml). The slurry was stirred for ~16hours. A solid was filtered and washed with ethyl acetate. The wet solid was ziprasidone HCl Form E, as confirmed by XRD. The wet solid was dried at 50°C. The dried solid had a water content of 9.62% (by K.F.) and a loss on drying of 19% (by TGA). The dried solid was Form E, as confirmed by XRD.

Example 5- Preparation of Ziprasidone HCl form F from Ziprasidone base form B in methylethylketone and aqueous HCl

Aqueous HCl (37%) (10ml) was added drop-wise to a hot slurry of ziprasidone base Form B (10g) in methylethylketone (MEK) (200ml). The slurry was stirred at room temperature over night. A solid was filtered and washed with MEK. The wet solid was ziprasidone HCl Form F. The wet solid was dried at 50°C for two days. The dried product was ziprasidone HCl Form F (10.62g) (The water content was 3.87% by K.F. and the loss on drying is 4.1% by TGA), as confirmed by XRD.

Example 6- Preparation of Ziprasidone HCl form F from Ziprasidone base form B in THF and aqueous HCl

Aqueous hydrochloric acid (37%) (910ml) was added to a hot slurry of ziprasidone base (10g) in tetrahydrofuran (THF) (200ml). The slurry was stirred at room temperature for about 16 hours. A solid was filtered, washed with THF and dried in an oven at 50°C for two days. The wet and the dried solid samples were ziprasidone HCl Form F (The water content was 3.63%), as confirmed by XRD.

Example 7- Preparation of a mixture of Ziprasidone HCl form F and form M from dimethylacetamide/water and aqueous HCl

Ziprasidone base (10g) was dissolved in dimethylacetamide (100ml) at ~95°C. The solution was cooled to 70°C and aqueous HCl (37%) (10ml) was added, resulting in precipitation and formation of a slurry. The slurry was then cooled to room temperature,

followed by addition of water (100 ml). Stirring was continued for 1 hour at room temperature, followed by filtration, and washing of a solid material obtained from filtration with water. The wet solid was dried at 50°C for about 16 hours to a dry solid (7.1g). The wet and the dried solid were ziprasidone HCl Form F in mixture with Form M (The water content of the dried solid is 4.17% by K.F.), as confirmed by XRD.

Example 8- Preparation of Ziprasidone HCl amorphous from form E by drying

Ziprasidone hydrochloride Form E (4.05g) was heated at 80-105°C in an oven for about 16 hours. The solid after heating was ziprasidone HCl amorphous (3.33g) (The water content was 1.21% by K.F.), as confirmed by XRD.

Example 9- Preparation of Ziprasidone HCl Form M in dimethylcarbonate/ methanol from Ziprasidone base form B and aqueous HCl

Ziprasidone base (10g) was taken in dimethylcarbonate (DMC) (100ml) and the mixture was heated at ~90°C. Aqueous HCl (37%) (10ml) was added, resulting in a sticky material. Additional amount of DMC (100ml), and methanol (50ml), were added, resulting in a slurry. The slurry was stirred at room temperature over night. A solid was filtered and washed with DMC, and subsequently dried at 50°C overnight. The wet and the dried solids were ziprasidone HCl monohydrate, as confirmed by XRD. The water content of the dried solid by K.F. is 4.78%.

In all the above examples except example 8, drying was carried out in an air-circulated oven. In example 8, the pressure was atmospheric pressure.

Example 10- Preparation of Ziprasidone HCl Form G from ethyl-lactate/ether/ HCl(g)

Ziprasidone base Form B (10g) was added to ethyl-lactate (50ml) and the slurry obtained was cooled to 5°C. HCl (g) was bubbled through the above slurry and ether (150ml) was added. The slurry was stirred over night at room temperature, filtrated and washed with ether. The wet material was dried at 50°C in an air-circulated oven and ziprasidone HCl Form G was obtained.

Example 11- Preparation of Ziprasidone HCl Form G from carbon-tetrachloride/ HCl(g)

Ziprasidone base Form B (5g) was added to carbon-tetrachloride (50ml) and HCl(g) was bubbled until pH 1 was reached. The temperature rose to ~40°C. The slurry was stirred at room temperature for 3 hours and filtrated. The solid was dried in an air-circulated oven at 50°C for 17 hours. The wet and the dried solid both were ziprasidone HCl Form G.

Example 12- Preparation of Ziprasidone HCl form G from di-isopropyl-ether/ HCl(g)

Ziprasidone base Form B (10g) was added to di-iso-propyl-ether (200ml) and the slurry was stirred at room temperature; through the slurry HCl(g) was bubbled while the temperature rose to ~50°C. The slurry was stirred at room temperature over-night, the solid was filtrated and washed with di-iso-propyl-ether. The wet solid gave ziprasidone HCl Form G. Drying of the wet solid in an air-circulated oven at 50°C for ~16h gave ziprasidone HCl Form I.

Example 13- Preparation of ziprasidone HCl mixture of form G and F from ethyl-acetate/ HCl(g)

Ziprasidone base Form B (10g) was added to ethyl-acetate (200ml) and HCl(g) was bubbled through the slurry; the temperature rose to ~35°C. The slurry was stirred at room temperature for 3 hours and the solid was filtrated, washed with ethyl-acetate and dried for ~16h in an air-circulated oven at 45°C. The wet and dried solids both gave a mixture of ziprasidone HCl Form G and F.

Example 14- Preparation of ziprasidone HCl Form M

A) Preparation of ziprasidone HCl Form M from ziprasidone base in ethyl-lactate/ aq. HCl

Concentrated HCl (37%) was added to the slurry of ziprasidone base (form B) (10g) in ethyl-lactate (200 ml) at 60°C. The reaction mixture was stirred at room temperature for about 16 hours, and a solid was filtrated, washed with ethyl-lactate (20ml) and dried at 50oC for two days. The solid was ziprasidone HCl Form M. (K.F. 4.02%).

B) Preparation of ziprasidone HCl Form M from ziprasidone base in ethanol/aq. HCl

To the slurry of ziprasidone base (Form B) (10g) in ethanol (200ml) at room temperature was added concentrated hydrochloric acid 37% (~5g); the temperature rose to ~30°C during the HCl addition. The slurry was than stirred at room temperature for about 16 hours. A solid was filtrated, washed with ethanol and dried in an air-circulated oven at 50°C. The product was ziprasidone HCl form M. (K.F. 4.37%).

C) Preparation of ziprasidone Form M from ziprasidone base in methanol/HCl(g)

To the slurry of ziprasidone base (Form B) (10g) in methanol (100ml) at ~5°C was bubbled HCl (g); the obtained slurry was then stirred over night at room temperature. A solid was filtrated, washed with methanol and dried at 50°C for about 16 hours. The product was ziprasidone HCl Form M (KF. 4.5%).

D) Preparation of ziprasidone HCl Form M from ziprasidone base in Methanol/aq. HCl

To the slurry of ziprasidone base (Form B) (10g) in methanol (200ml) at 60°C was added concentrated HCl (10ml); the slurry was then stirred at room temperature for about 16 hours. A solid was filtrated, washed with methanol (2x 10ml) and dried at 50°C in an air-circulated oven for 2 days. The product was ziprasidone HCl Form M (K.F. 4.26%).

E) Preparation of ziprasidone HCl Form M from ziprasidone base in n-BuOH/aq. HCl

A slurry of ziprasidone base (Form B) (10g) in n-butanol (250ml) was heated to 60°C While maintaining the temperature, concentrated HCl was added (10ml). The reaction mixture was than stirred at room temperature for about 16 hours. A solid was filtrated, washed with n-butanol (2X20ml) and dried for about 16 hours at 50°C in an air-circulated oven. The dried solid was ziprasidone HCl Form M (K.F. 4.12%).

F) Preparation of ziprasidone HCl Form M from ziprasidone base in acetone/aq. HCl

To the slurry of ziprasidone base (Form B) (10g) in acetone (200ml) at room temperature was added concentrated HCl (10ml); the temperature rose to about 30°C. The reaction mixture was stirred at room temperature for about 16 hours. A solid was filtrated, washed with acetone (2x10ml) and dried for two days in an air-circulated oven at 50°C. The dried solid was ziprasidone HCl Form M (K.F.4.57%).

G) Preparation of ziprasidone HCl Form M from Form F

A slurry of ziprasidone HCl Form F (5g) in THF/ water 95:5 (50ml) was heated at 50°C for two hours. After cooling to room temperature, a solid was filtrated, washed with mixture THF/ water and dried for 18 hours in an air-circulated oven. The dried solid was ziprasidone HCl Form M (K.F. 4.50%).

H) Preparation of ziprasidone HCl Form M from Form E

Ziprasidone HCl Form E (2g) was heated in n-butanol (200ml) and water (40ml) at 85°C; complete dissolution was not obtained. More water was added (20ml) and the slurry was stirred at 90°C for 1.5 hours. A solid was filtrated from the hot slurry, washed with n-butanol/ water (4 ml 3:1) and dried. From the filtrate a solid was obtained upon cooling to 10°C. This material was filtrated, washed and dried in the same conditions. Both dried solids were ziprasidone HCl Form M.

Example 15- Preparation of ziprasidone HCl Form J

Aqueous HCl was drop-wise added over 10 minutes, to a slurry of ziprasidone base (5g) in toluene (100ml) at room temperature. The obtained mixture was stirred at room temperature for 3 hours, and then the solvent was evaporated under vacuum. The solid obtained after the toluene evaporation was ziprasidone HCl Form J.

Example 16- Preparation of ziprasidone HCl Form E1

The above material (ZPR HCl form J form Example 20) was dried by maintaining it at 40oC and under nitrogen atmosphere over night, followed by additional drying with a rotary evaporator. The dried material collected after the two drying stages was ziprasidone HCl Form E1 (water content by K.F. ~6% and ~8% respectively).

Example 17- Preparation of ZPR HCl Form M substantially pure of form A

A) Preparation of ZPR HCl Form M from THF:AcOH

In a 250ml three necked flask were charged Ziprasidone base (5g) and a mixture 9:1 THF:acetic acid. The slurry was heated at 60°C and more solvent was added until complete dissolution was obtained. The total volume of the solvents mixture was 175ml. To the solution 4 drops of 10% hydrochloric acid was added; upon HCl addition a precipitate is formed. The hazy solution was stirred for 1h at 60°C and after this 15 ml 10% HCl was added over 30 minutes. The slurry was than stirred for 2.5h maintaining the temperature at 60°C. The solid was filtrated from the slurry after cooling to room temperature and washed with solvent. The solid obtained after drying at 50°C is ZPR HCl Form M substantially pure of form A. (4.58g). (Water content by K.F.4.04%).

B) Preparation of ZPR HCl Form M from THF:MeOH.

In a 250ml three necked flask were charged Ziprasidone base (5g) and mixture of THF:MeOH 10:3. The mixture was heated at 60°C and diluted with the solvents until the complete dissolution was observed. (the total volume is 240ml.). Hydrochloric acid 10% (2ml) was added and the reaction mixture was stirred for 30 minutes. After this period of time more hydrochloric acid was added to complete the reaction. The stirring was continued for 1h at 60°C; the mixture was than cooled to room temperature and the solid filtrated and washed with solvent. After drying at 50°C the ZPR HCl Form M substantially pure of form A was obtained. (Water content by K.F. 4.08%).

C) Preparation of ZPR HCl Form M from n-Butanol:Acetic Acid.

In a 250ml three necked flask were charged Ziprasidone base (5g) and n-BuOH (100ml) and the slurry was heated at 60°C. Acetic acid was added (10ml) and more n-BuOH (100ml). To the slurry 10% hydrochloric acid (2ml) was added and the mixture was stirred for 1h. After this more HCl was added drop-wise over 30'. The reaction mixture was stirred for 1h at 60°C to complete the reaction. After cooling to the room temperature the solid was filtrated, washed with solvent and dried at 50°C to give ZPR HCl Form M substantially pure of form A (4.25g). (Water content by K.F.4.33%).

D) Preparation of ZPR HCl Form M from N,N-dimethyl- acetamide.

In a 250ml three necked flask were charged Ziprasidone base (5g) and N,N-dimethyl-acetamide (DMA) (100ml) and the mixture has been heated at 60°C. To the obtained solution 32% HCl (3ml) was added and the stirring was continued for 4h. After cooling, the solid was filtrated and then dried to afford ziprasidone HCl Form M substantially pure of form A.

(Water content by K.F. 4.15%).

Example 20- Preparation of ziprasidone Form J and Form E1

To the slurry of ziprasidone base (5g) in toluene (100ml) at room temperature was drop-wise added aqueous HCl over 10 minutes. The obtained mixture was stirred at room temperature for 3 hours, then the solvent was distilled under vacuum. The solid obtained after the toluene distillation was ziprasidone HCl Form J.

The above material (ZPR HCl form J) was dried by maintaining it at 40°C and under nitrogen over night, followed by an additional drying operation on a rotary evaporator. The dried material collected in the two drying stages was ziprasidone HCl Form E1 (water content by K.F. 6% and 7.8% respectively).

Example 21- Preparation of ZPR .HCl amorphous from ZPR base and HCl in methyl-ethyl-ketone

To the chilled slurry of ZPR base (5g) in methylethyl-ketone (MEK) (100ml) (~2oC) Was bubbled hydrogen chloride until the pH 1 was reached. The temperature was in the range 2 to 10°C. The slurry was than stirred at the above temperature for 5 hours, the solid was filtrated and washed with MEK (2x10ml). After drying at 60oC was obtained a solid which is ZPR .HCl amorphous by XRD.

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can 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. Polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Sciences, Volume 95 may be used for guidance. All references mentioned herein are incorporated in their entirety.

What is claimed is:

1. A crystalline form of ziprasidone HCl (Form E), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 7.4, 13.0, 20.7, 23.4, 25.9 ±0.2 degrees 2 theta.
2. The crystalline form of claim 1, wherein the crystalline form is further characterized by peaks at 13.7, 20.0, 21.3, 25.2 ±0.2 degrees two-theta.
3. The crystalline form of claim 2, has an XRD pattern as substantially depicted in Figure 4.
4. A process for preparing ziprasidone HCl of claim 1, comprising:
   a) combining aqueous HCl with ziprasidone base in the presence of ethyl acetate or acetonitrile to obtain a slurry;
   b) maintaining the slurry to obtain ziprasidone HCl; and
   c) recovering the ziprasidone HCl.
5. The process of claim 4, wherein the ziprasidone base is ziprasidone Form B.
6. The process of claim 4, wherein the slurry temperature is at least about 40°C.
7. A crystalline form of ziprasidone HCl, wherein the crystalline form is a trihydrate.
8. The crystalline form of claim 7, wherein the crystalline form is a solvated form of ethyl acetate.
9. The crystalline form of claim 7, wherein the crystalline form is a solvated form of acetonitrile.
10. A process for preparing ziprasidone HCl of claim 1 in a mixture with a crystalline ziprasidone HCl having an X-Ray diffraction pattern having peaks at about 10.9, 17.4 and 19.1 ±0.2 degrees 2 theta, comprising:
    a) combining aqueous HCl with ziprasidone base in the presence of tetrahydrofuran to obtain a slurry;
    b) maintaining the slurry to obtain Ziprasidone HCl; and
    c) recovering the ziprasidone HCl mixture.
11. The process of claim 10, wherein the slurry is at about room temperature.
12. Crystalline form of ziprasidone HCl prepared by the processes of any of claims 4 or 10.
13. A crystalline form of ziprasidone HCl (Form F), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 11.0, 18.1, 19.5, 21.9 ±0.2 degrees 2 theta.

14. The crystalline form of claim 113, wherein the crystalline form is further characterized by peaks at 14.9, 24.9, 26.1 ±0.2 degrees two-theta.

15. The crystalline form of claim 14, wherein the crystalline form is further characterized by an XRD pattern as substantially depicted in Figure 7.

16. A process for preparing the ziprasidone HCl of claim 13, comprising:

a) combining aqueous HCl with ziprasidone base in a solvent selected from the group consisting of methylethylketone, tetrahydrofuran and dimethylacetamide to obtain a slurry;

b) maintaining the slurry to obtain ziprasidone HCl; and

c) recovering the ziprasidone HCl.

17. The process of claim 16, wherein the slurry is diluted by addition of water.

18. The process of claim 16, wherein the ziprasidone base is ziprasidone Form B.

19. The process of claim 16, wherein the slurry is carried out at a temperature of at least about 40°C.

20. Crystalline form of ziprasidone HCl prepared by the process of claim 16.

21. A process for preparing the ziprasidone HCl form M, comprising:

a) heating a slurry of ziprasidone HCl in n-butanol or THF, optionally in mixture with water; and

b) recovering the ziprasidone HCl form M.

22. The process of claim 21, wherein the heating is carried out at a temperature of at least about 40°C.

23. The process of claim 21, wherein the ziprasidone HCl of step (a) is ziprasidone HCl characterized by a powder XRD pattern with peaks at 11.0, 18.1, 19.5, 21.9 ±0.2 degrees 2 theta.

24. The process of claim 21, wherein the ziprasidone HCl of step (a) is ziprasidone HCl characterized by a powder XRD pattern with peaks at 7.4, 13.0, 20.7, 23.4, 25.9 ±0.2 degrees 2 theta.

25. A process for preparing the ziprasidone HCl form M comprising:

a) combining aqueous HCl with ziprasidone base at a temperature of at least about 40°C in a solvent selected from the group consisting of ethanol, methanol, n-butanol, acetone, ethyl actate, ethyl lactate, dimethyl-carbonate, optionally in a mixtures with water to obtain a slurry,

b) maintaining the slurry to obtain the ziprasidone HCl form M; and

c) recovering the ziprasidone HCl form M.

26. A process for preparing the ziprasidone HCl form M comprising:

a) contacting gaseous hydrogen chloride with ziprasidone base in methanol to obtain a slurry of ziprasidone hydrochloride in methanol;

b) maintaining the slurry to obtain the ziprasidone HCl form M; and

c) recovering the ziprasidone HCl form M.

27. A process for preparing the ziprasidone HCl form M substantially free of the crystalline ziprasidone HCl characterized by a powder XRD pattern with peaks at 10.9, 17.4, 19.1, 25.0, 26.0 ±0.2 degrees 2 theta comprising:

a) combining a solution or slurry of ziprasidone base in a solvent with less than one equivalent HCl to obtain a reaction mixture containing ziprasidone HCl;

b) stirring or agitating the reaction mixture;

c) adding additional HCl to obtain additional ziprasidone HCl; and

d) recovering the ziprasidone HCl form M.

28. The process of claim 27, wherein prior to the addition of HCl in step a, the temperature of the solution or the slurry is at least 60^0C.

29. The process of claim 27, wherein the HCl is added slowly.

30. The process of claim 27, wherein the ratio of HCl is step (a) to step (c) is about 1:10 to about 5:10.

31. The process of claim 30, wherein the ratio of HCl is step (a) to step (c) is about 1:10.

32. The process of claim 27, wherein the solvent is a mixture selected from the group consisting of THF/acetic acid, THF/methanol, THF/AcOH di-methyl acetamide, n-butanol/acetic acid and mixtures thereof.

33. The process of claim 27, wherein the precipitation occurs at a temperature of about 55 to about 70°C.

34. The process of claim 33, wherein the temperature is about 55 to about 65°C

35. The process of claim 34, wherein the temperature is within 2 degrees of 65°C.

36. The process of claim 27, further comprising seeding the solution or slurry of ziprasidone base with ziprasidone HCl form M.

37. Crystalline form of ziprasidone HCl prepared by the processes of any of claims 21, 25, 26, or 27.

38. Amorphous form of ziprasidone HCl.

39. The ziprasidone of claim 38, wherein the XRD pattern is that substantially depicted in Figure 1.

40. A process for preparing amorphous form of claim 39, comprising heating the ziprasidone HCl characterized by a powder XRD pattern with peaks at 7.4, 13.0, 20.7, 23.4, 25.9 ±0.2 degrees 2 theta.

41. The process of claim 40, wherein the heating occurs at a temperature of about 80 to about 105°C.

42. A process for preparing amorphous form of claim 38, comprising exposing the ziprasidone HCl characterized by a powder XRD pattern with peaks at 7.4, 13.0, 20.7, 23.4, 25.9 ±0.2 degrees 2 theta to about 10% to about 0% humidity to obtain amorphous form.

43. The process of claim 42, wherein the humidity is about 0%.

44. A process for preparing amorphous form of claim 38, comprising slurrying ziprasidone base with methyl ethyl ketone or mono-chloro benzene with gaseous hydrochloride.

45. Amorphous form of ziprasidone HCl prepared by the processes of any of claims 42, 43 or 44.

46. A crystalline form of ziprasidone HCl (Form G), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 9.0, 20.6, 22.7, 25.0, 27.0 ±0.2 degrees 2 theta.

47. The crystalline form of claim 46, wherein the crystalline form is further characterized by peaks at 11.3, 12.5, 13.9, 15.6, 21.5, 23.5, 25.8, 28.0, 31.5 ±0.2 degrees two-theta.

48. The crystalline form of claim 47, wherein the crystalline form has an XRD pattern as substantially depicted in Figure 15.

49. A process for preparing ziprasidone HCl of claim 46 comprising:

a) combining gaseous HCl with a mixture of ziprasidone base in a solvent selected from the group consisting of carbon tetrachloride, di-isopropyl-ether, ethyl acetate, ethyl lactate and mixtures thereof to obtain a slurry of ziprasidone HCl;

b) maintaining the slurry to obtain ziprasidone HCl of claim of claim 46; and

c) recovering the ziprasidone HCl.

50. The process of claim 49, wherein combining is carried out by bubbling gaseous HCl through a slurry of ziprasidone HCl in the solvent.

51. The process of claim 49, wherein the ziprasidone base is ziprasidone base Form B.

52. A process for preparing a mixture of the ziprasidone HCl of claim 13 or the ziprasidone HCl of claim 46 comprising:

a) combining gaseous HCl with a mixture of ziprasidone base in ethyl acetate to obtain a slurry of ziprasidone HCl;

b) maintaining the slurry to obtain ziprasidone HCl; and

c) recovering the mixture.

53. The process of claim 52, wherein combining is carried out by bubbling gaseous HCl through a slurry of ziprasidone HCl in the solvent.

54. The process of claim 52, wherein the ziprasidone base is ziprasidone base Form B.

55. Crystalline form of ziprasidone HCl prepared by the processes of any of claims 49 or 52.

56. A crystalline form of ziprasidone HCl (Form I), wherein the crystalline form has an XRD pattern with peaks at 15.8, 16.2, 18.9, 23.8, 27.0 ±0.2 degrees 2 theta,

57. The crystalline form of claim 56, wherein the crystalline form has peaks at 10.5, 11.3, 21.1, 24.8, 26.0 ±0.2 degrees two-theta.

58. The crystalline form of claim 57, wherein the crystalline form has an XRD pattern as substantially depicted in Figure 16.

59. A process for preparing crystalline ziprasidone HCl of claim 56, comprising heating the crystalline ziprasidone HCl characterized by a powder XRD pattern with peaks at 9.0, 20.6, 22.7, 25.0, 27.0 ±0.2 degrees 2 theta, wherein the crystalline ziprasidone HCl characterized by a powder XRD pattern with peaks at 9.0, 20.6, 22.7, 25.0, 27.0 ±0.2 degrees 2 theta has been obtained from di-iso-propyl-ether.

60. Crystalline form of ziprasidone HCl prepared by the process of claim 59.

61. A crystalline form of ziprasidone HCl (Form J), wherein the crystalline form is characterized by a powder XRD pattern with peaks at 9.1, 19.1, 25.7, 26.3, 26.9 ±0.2 degrees 2 theta.

62. The crystalline form of claim 61, further characterized by peaks at 11.9, 21.4, 23.4, 30.7, 32.2 ±0.2 degrees two-theta.

63. The crystalline form of claim 62, wherein the crystalline form has an XRD pattern as substantially depicted in Figure 17.

64. A process for preparing ziprasidone HCl of claim 61 comprising:

a) combining ziprasidone base with HCl to obtain a slurry of ziprasidone HCl in a C_5 to C_{12} hydrocarbon;

b) maintaining the slurry to obtain the crystalline ziprasidone HCl; and

c) recovering the ziprasidone HCl of claim 61.

65. The process of claim 64, wherein the hydrocarbon is toluene.

66. A crystalline form of ziprasidone HCl, wherein the crystalline form has a water content of about 24% by LOD.

67. Crystalline form of ziprasidone HCl prepared by the process of claim 64.

68. A crystalline from of ziprasidone HCl (Form E1), wherein the crystalline form is characterized a powder XRD pattern with peaks at 7.5, 13.0, 21.2, 23.4 and 26.0 ±0.2 degrees 2 theta.

69. The crystalline form of claim 68, wherein the crystalline form is further characterized by peaks at 10.9, 16.2, 20.8, 25.4, 30.3 and 34.8 ±0.2 degrees two-theta.

70. A crystalline form of ziprasidone HCl (Form E1), wherein the crystalline form is characterized by an FTIR spectrum as substantially depicted in Figure 22, 23 and 24.

71. A process for preparing ziprasidone HCl of claim 70 comprising drying the ziprasidone HCl characterized by a powder XRD pattern with peaks at 9.1, 19.1, 25.7, 26.3, 26.9 ±0.2 degrees 2 theta.

72. The process of claim 71, wherein drying is carried out by evaporation at a temperature above about 30°C.

73. Crystalline form of ziprasidone HCl prepared by the process claim 72.

74. A crystalline form of ziprasidone, wherein the crystalline form has a water content of about 6% to about 8%.

75. A pharmaceutical composition comprising an effective amount of a the ziprasidone HCl of any one of claims 1, 7,12, 13, 20, 38, 46, 56, 60, 61, 67, 68, 73 or 74, and at least a single pharmaceutically acceptable excipient.

76. A method of treating a patient suffering from schizophrenia comprising administering to the patient the pharmaceutical composition of claim 75.

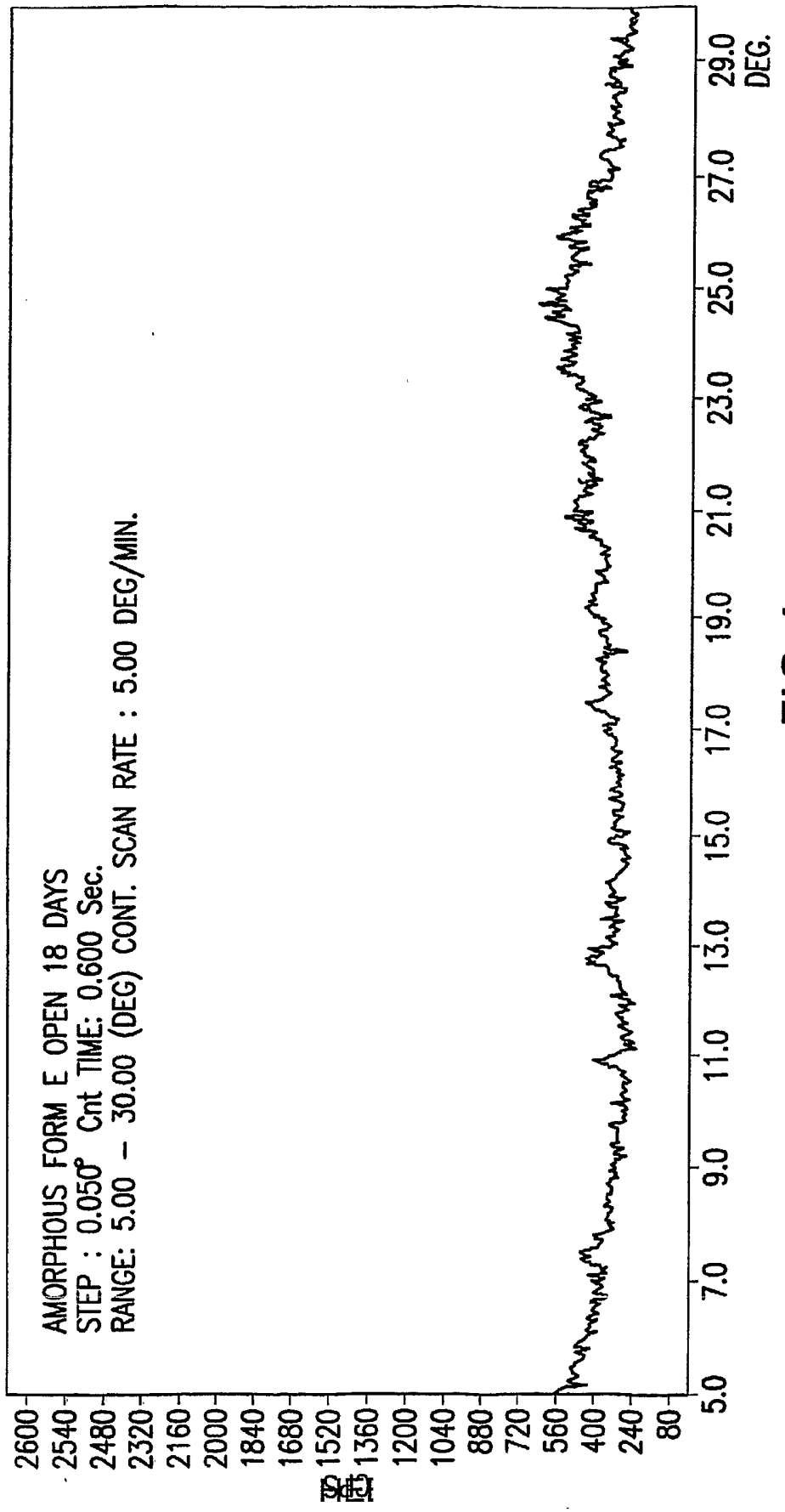

AMORPHOUS FORM E OPEN 18 DAYS
STEP : 0.050° Cnt TIME: 0.600 Sec.
RANGE: 5.00 - 30.00 (DEG) CONT. SCAN RATE : 5.00 DEG/MIN.
2600
2540
2480
2320
2160
2000
1840
1680
1520
1360
1200
1040
880
720
560
400
240
80
5.0
7.0
9.0
11.0
13.0
15.0
17.0
19.0
21.0
23.0
25.0
27.0
29.0
DEG.

FIG. 1

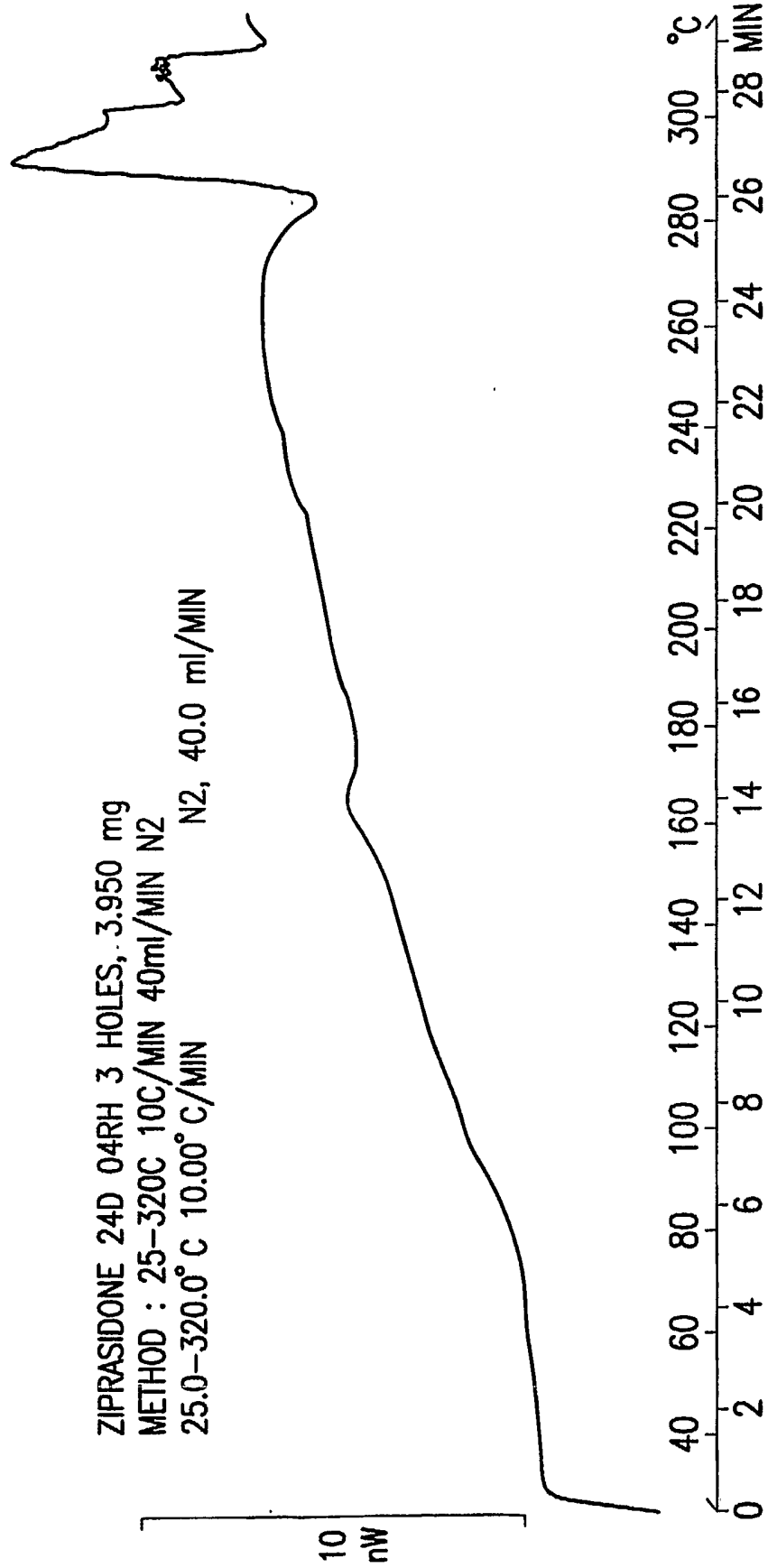

ZIPRASIDONE 24D 04RH 3 HOLES, 3.950 mg
METHOD : 25-320C 10C/MIN 40ml/MIN N2
25.0-320.0°C 10.00°C/MIN
N2, 40.0 ml/MIN
10 mW
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 MIN
40 60 80 100 120 140 160 180 200 220 240 260 280 300 °C

FIG.2

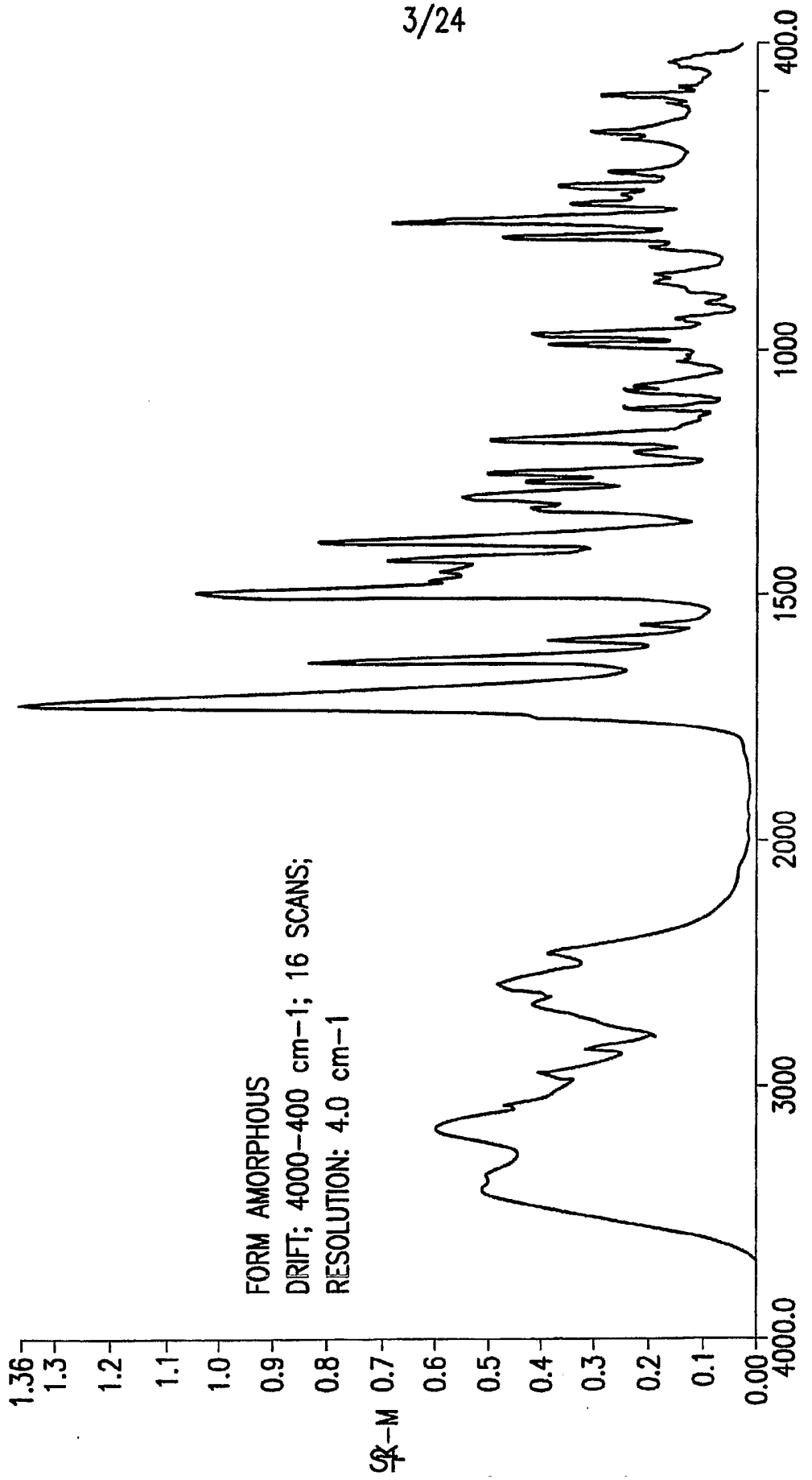

FORM AMORPHOUS
DRIFT; 4000-400 cm-1; 16 SCANS;
RESOLUTION: 4.0 cm-1
1.36
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.00
K-M
4000.0
3000
2000
1500
1000
400.0
cm-1

FIG.3

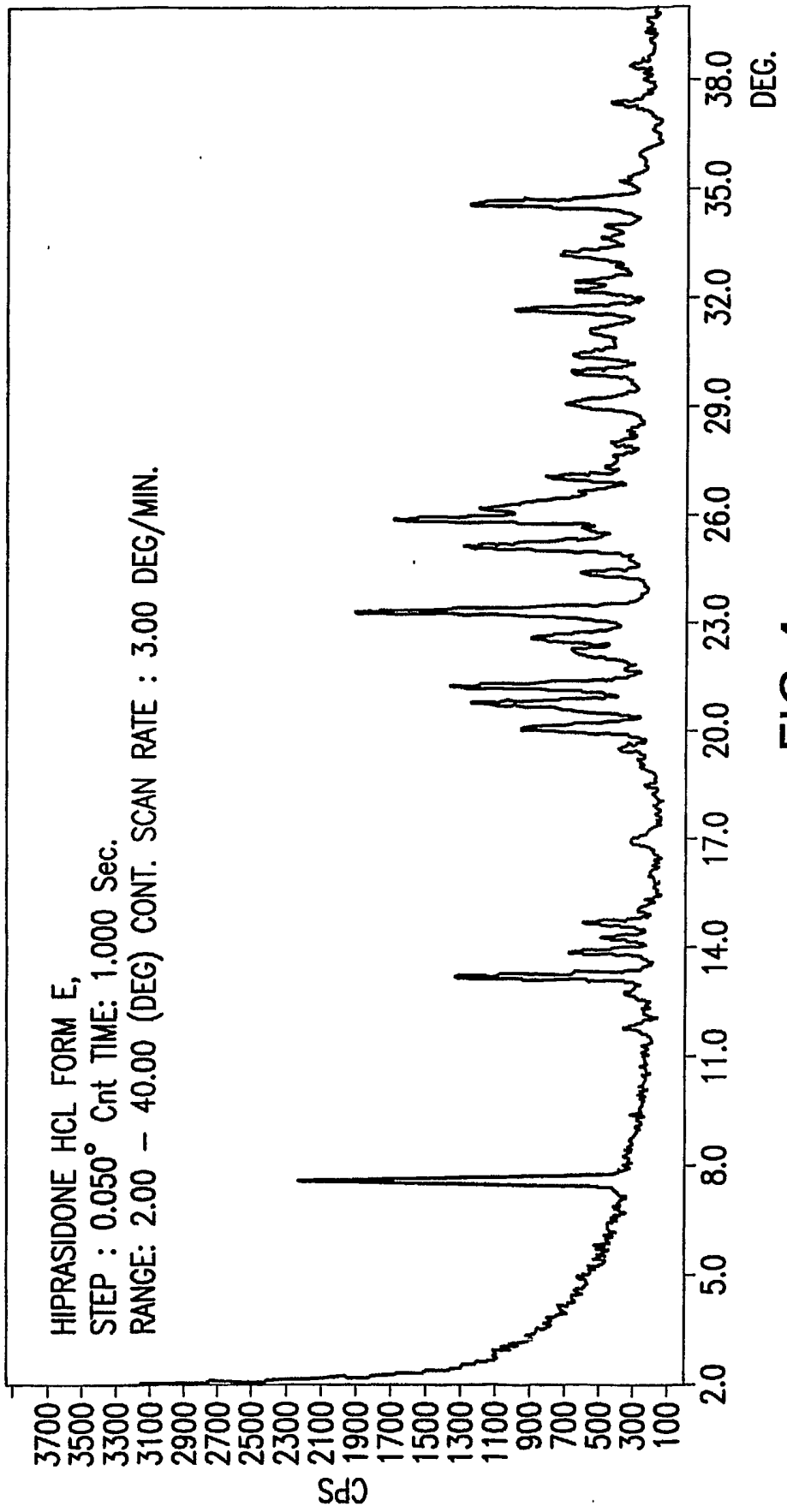

HIPRASIDONE HCL FORM E,
STEP : 0.050° Cnt TIME: 1.000 Sec.
RANGE: 2.00 – 40.00 (DEG) CONT. SCAN RATE : 3.00 DEG/MIN.
CPS
3700
3500
3300
3100
2900
2700
2500
2300
2100
1900
1700
1500
1300
1100
900
700
500
300
100
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG.4

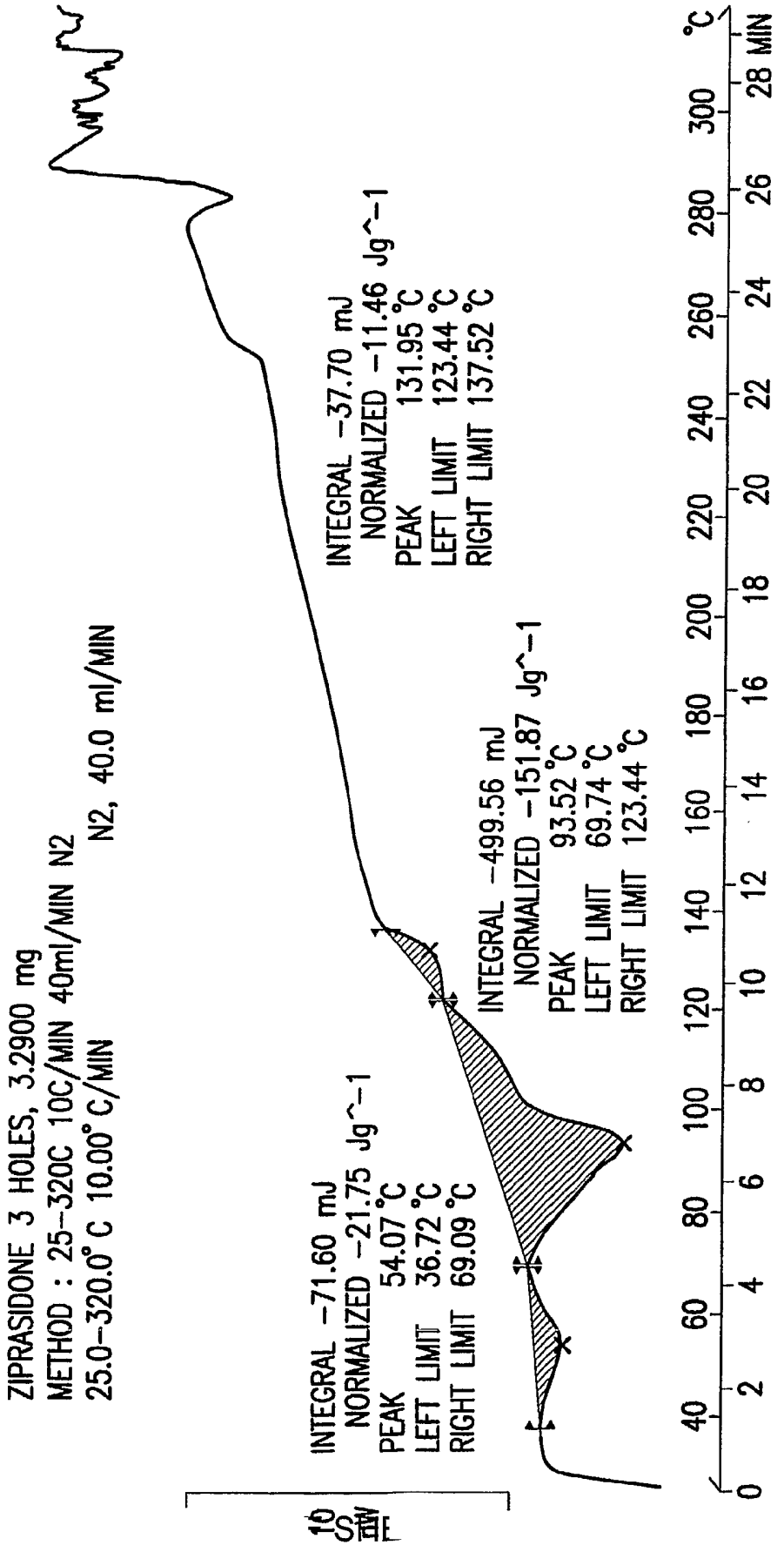

ZIPRASIDONE 3 HOLES, 3.2900 mg
METHOD : 25-320C 10C/MIN 40ml/MIN N2
25.0-320.0°C 10.00°C/MIN N2, 40.0 ml/MIN
INTEGRAL -37.70 mJ
NORMALIZED -11.46 Jg^-1
PEAK 131.95 °C
LEFT LIMIT 123.44 °C
RIGHT LIMIT 137.52 °C
INTEGRAL -499.56 mJ
NORMALIZED -151.87 Jg^-1
PEAK 93.52 °C
LEFT LIMIT 69.74 °C
RIGHT LIMIT 123.44 °C
INTEGRAL -71.60 mJ
NORMALIZED -21.75 Jg^-1
PEAK 54.07 °C
LEFT LIMIT 36.72 °C
RIGHT LIMIT 69.09 °C
10 mW
°C
28 MIN

FIG.5

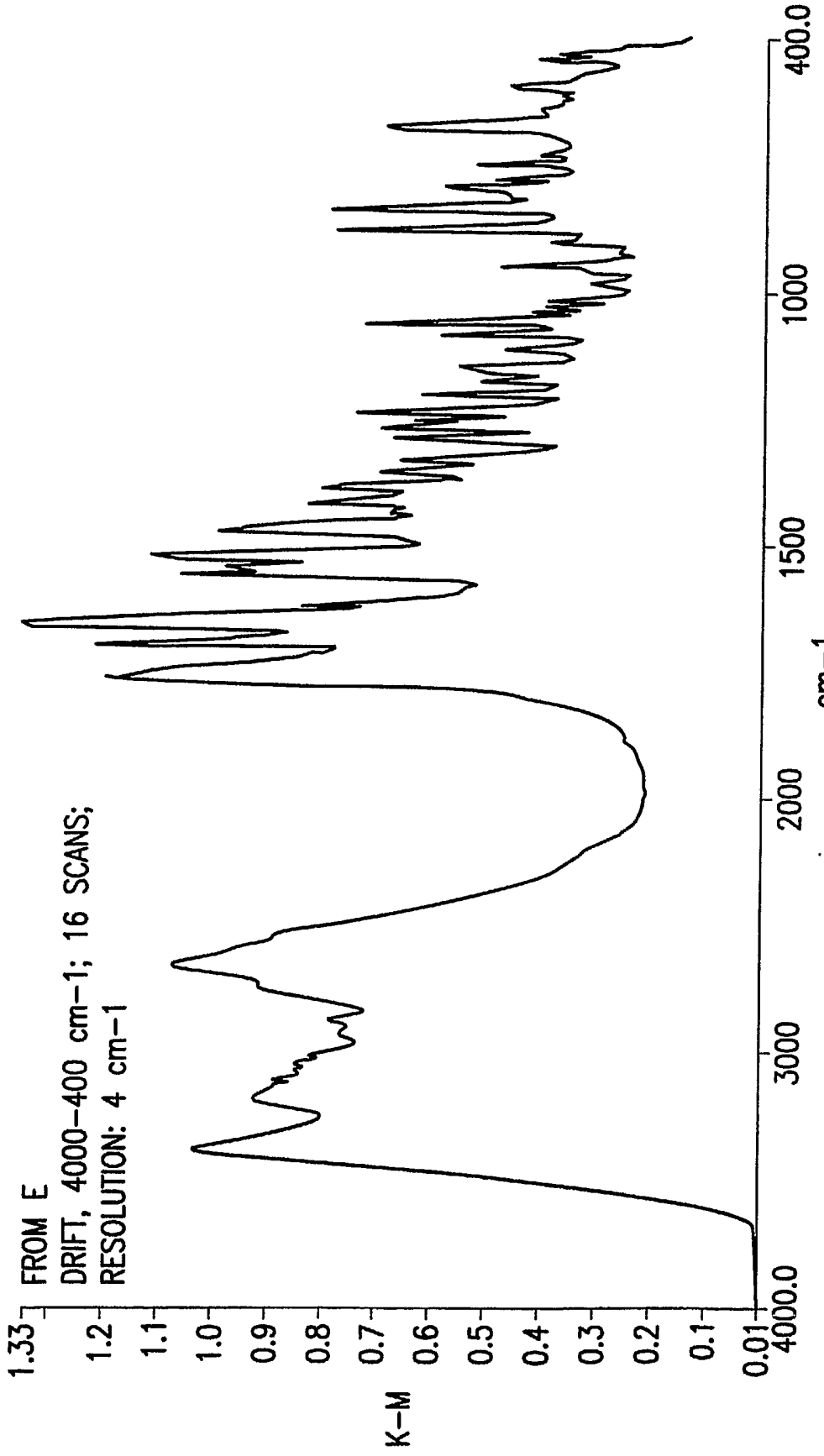

FROM E
DRIFT, 4000–400 cm–1; 16 SCANS;
RESOLUTION: 4 cm–1
K–M
1.33
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.01
4000.0
3000
2000
1500
1000
400.0
cm–1

FIG.6

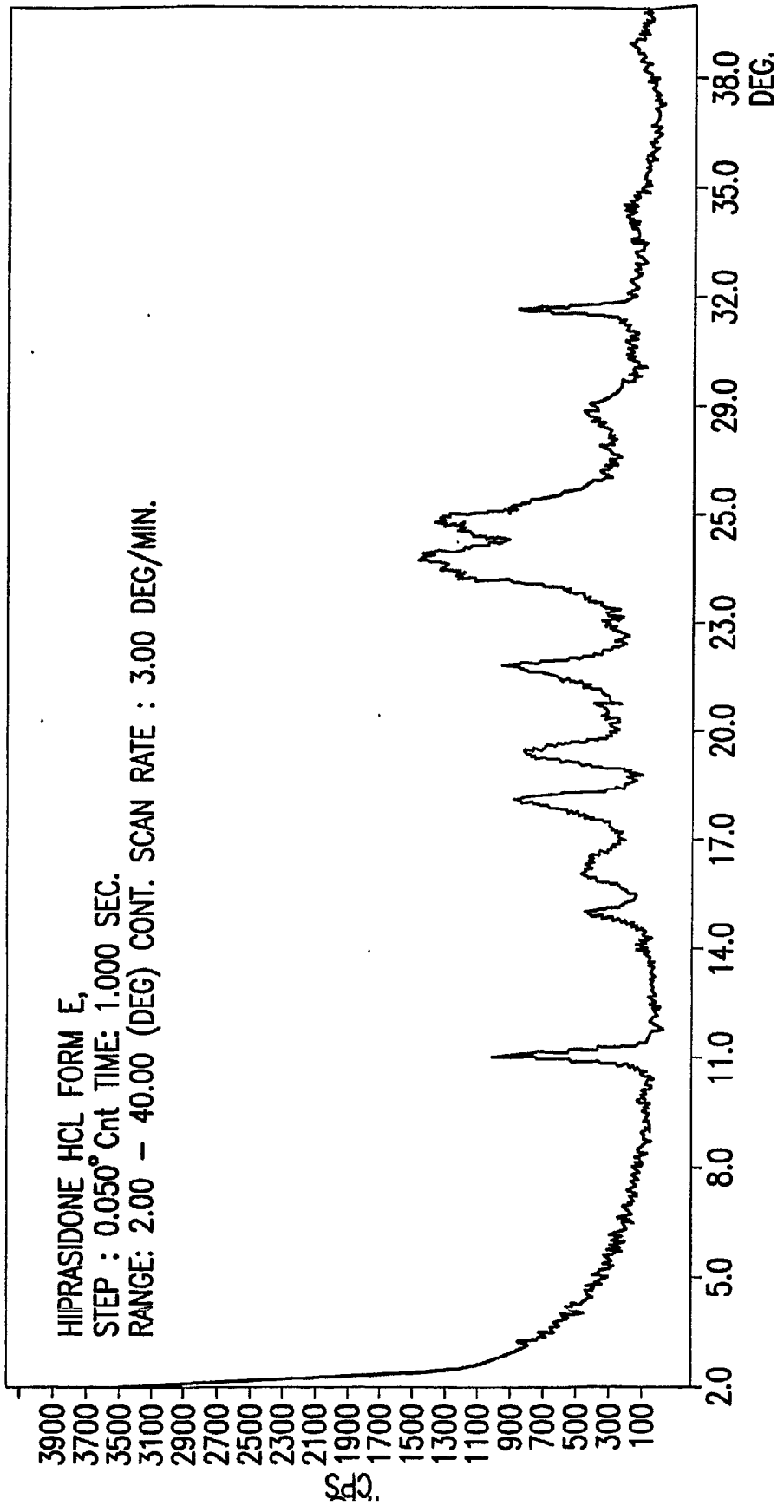

HIPRASIDONE HCL FORM E,
STEP : 0.050° Cnt TIME: 1.000 SEC.
RANGE: 2.00 – 40.00 (DEG) CONT. SCAN RATE : 3.00 DEG/MIN.
CPS
3900
3700
3500
3100
2900
2700
2500
2300
2100
1900
1700
1500
1300
1100
900
700
500
300
100
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
25.0
29.0
32.0
35.0
38.0
DEG.

FIG.7

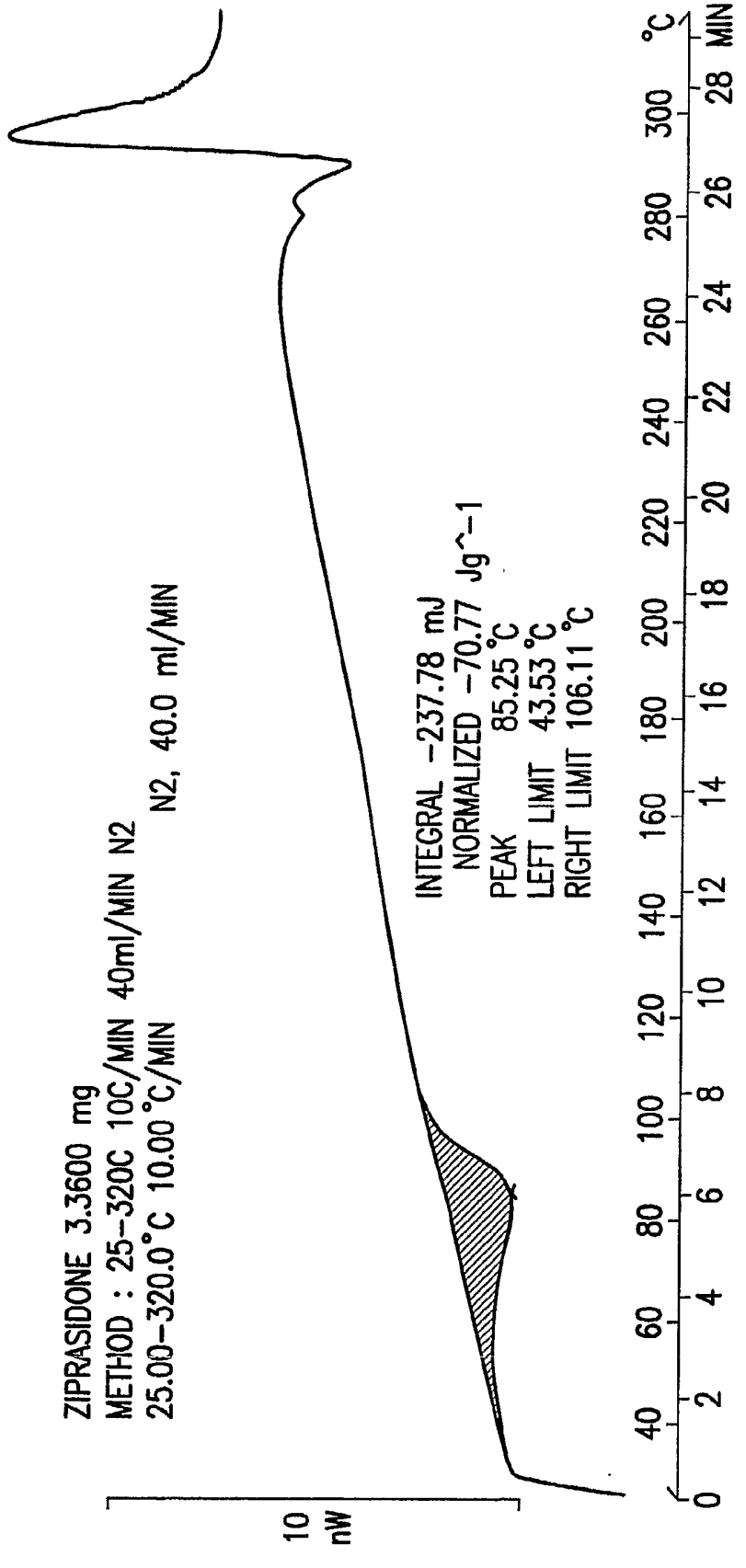

ZIPRASIDONE 3.3600 mg
METHOD : 25-320C 10C/MIN 40ml/MIN N2
25.00-320.0°C 10.00°C/MIN
N2, 40.0 ml/MIN
INTEGRAL -237.78 mJ
NORMALIZED -70.77 Jg^-1
PEAK 85.25 °C
LEFT LIMIT 43.53 °C
RIGHT LIMIT 106.11 °C
10 mW
°C
MIN

FIG.8

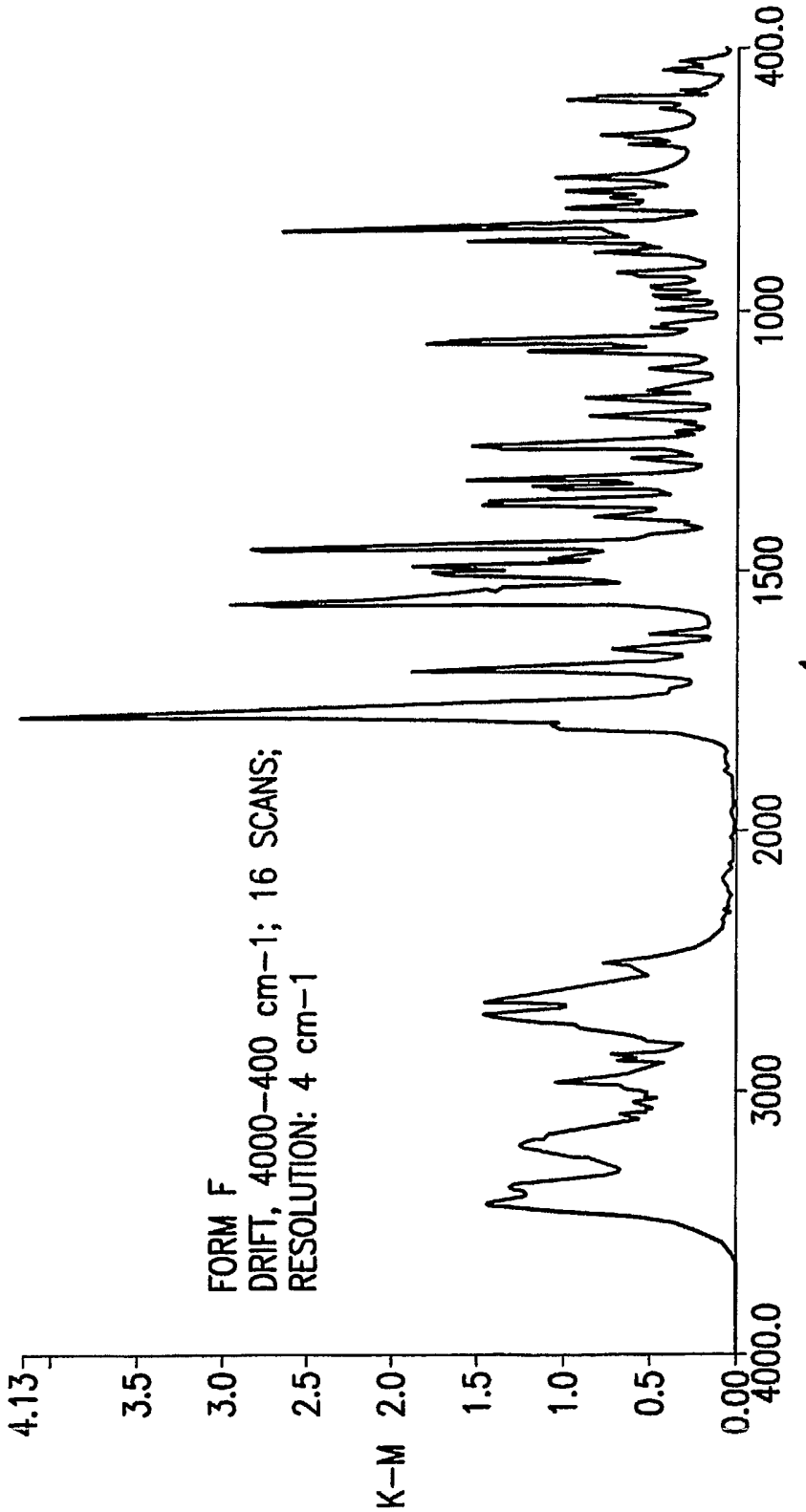

FORM F
DRIFT, 4000–400 cm–1; 16 SCANS;
RESOLUTION: 4 cm–1
K–M
4.13
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.00
4000.0
3000
2000
1500
1000
400.0
cm–1

FIG.9

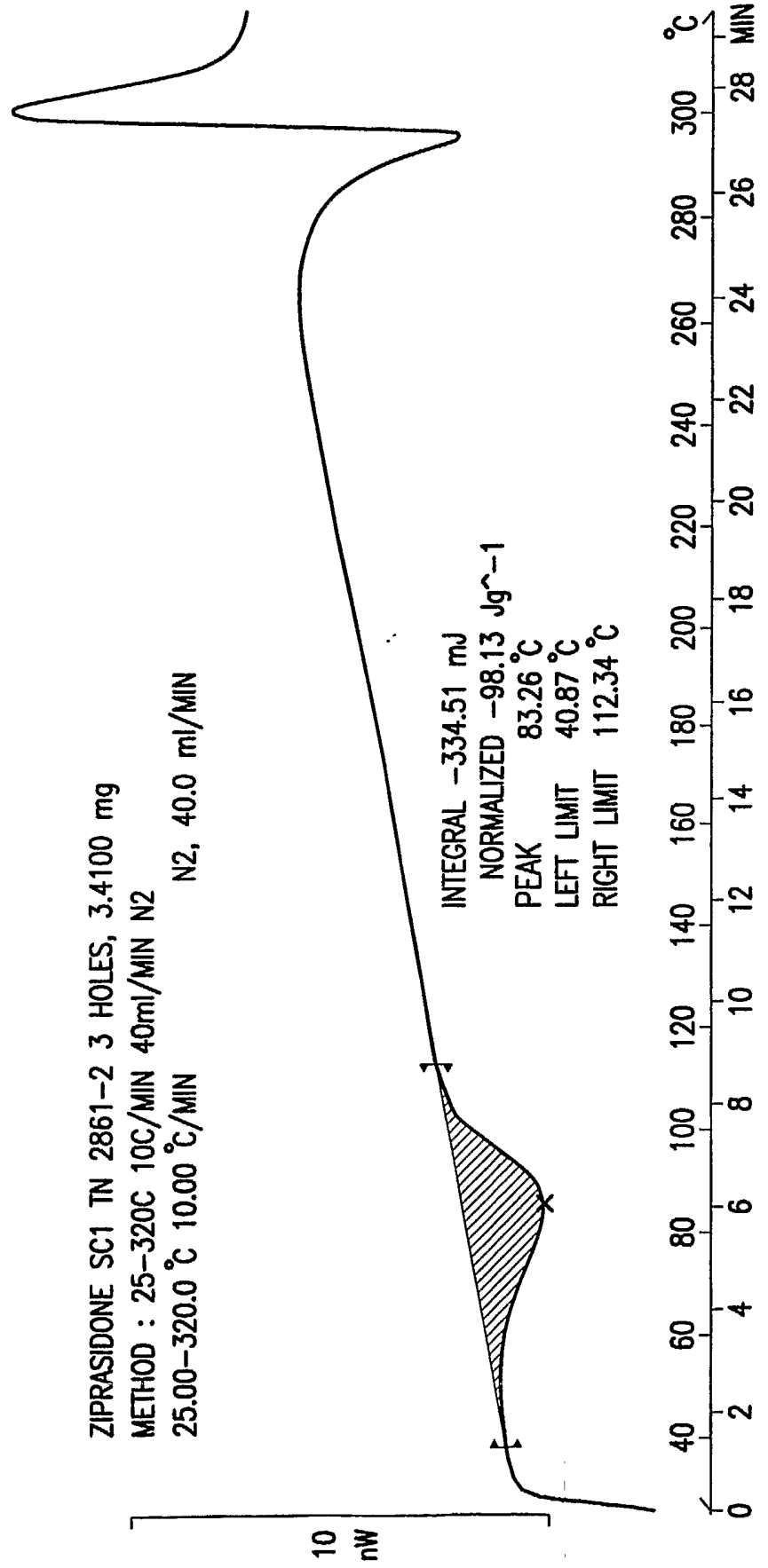

ZIPRASIDONE SC1 TN 2861-2 3 HOLES, 3.4100 mg
METHOD : 25-320C 10C/MIN 40ml/MIN N2
25.00-320.0 °C 10.00 °C/MIN N2, 40.0 ml/MIN
INTEGRAL -334.51 mJ
NORMALIZED -98.13 Jg^-1
PEAK 83.26 °C
LEFT LIMIT 40.87 °C
RIGHT LIMIT 112.34 °C
10 mW
°C
MIN

FIG.10

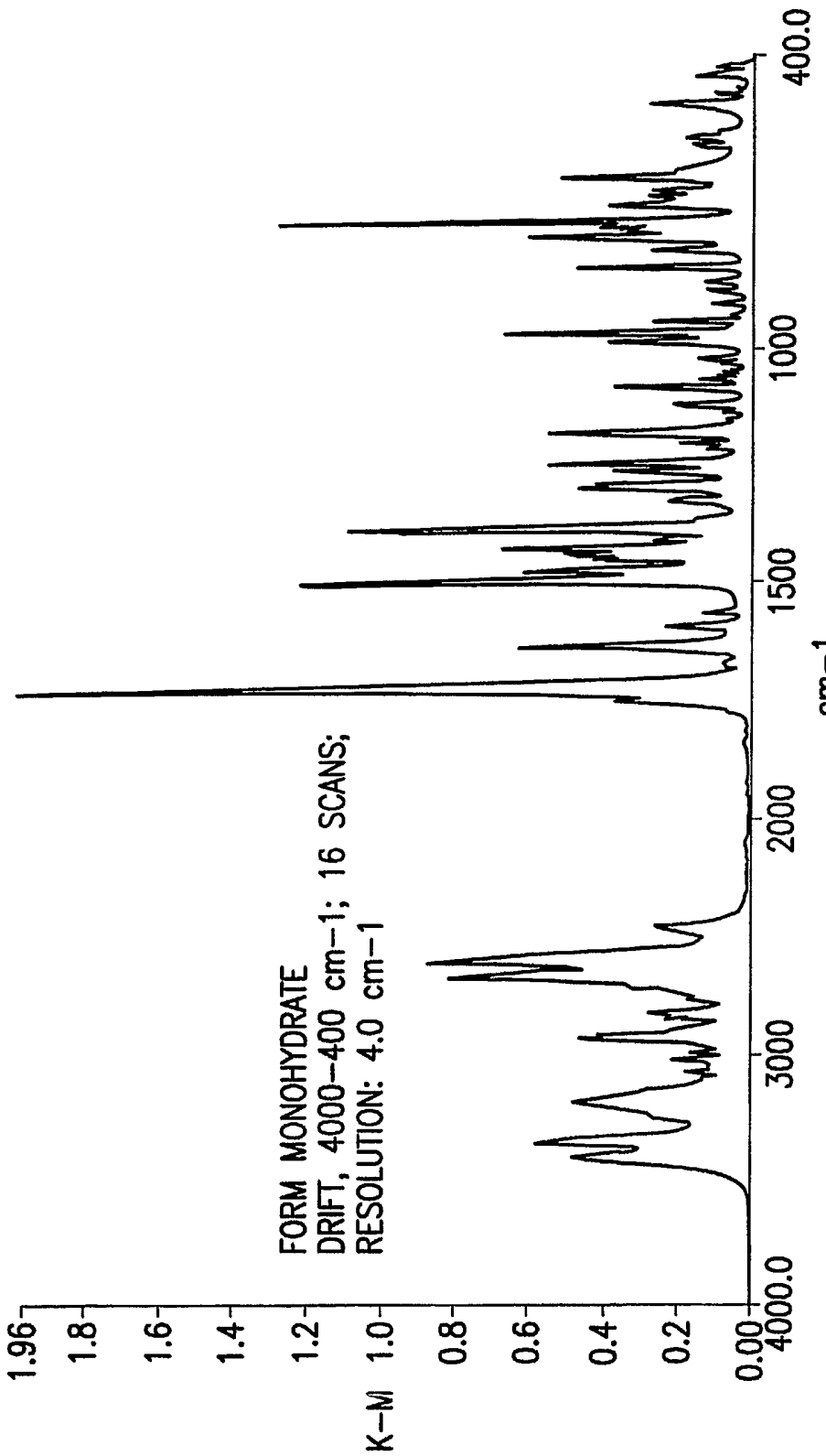

FORM MONOHYDRATE
DRIFT, 4000-400 cm-1; 16 SCANS;
RESOLUTION: 4.0 cm-1
K-M
1.96
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.00
4000.0
3000
2000
1500
1000
400.0
cm-1

FIG.11

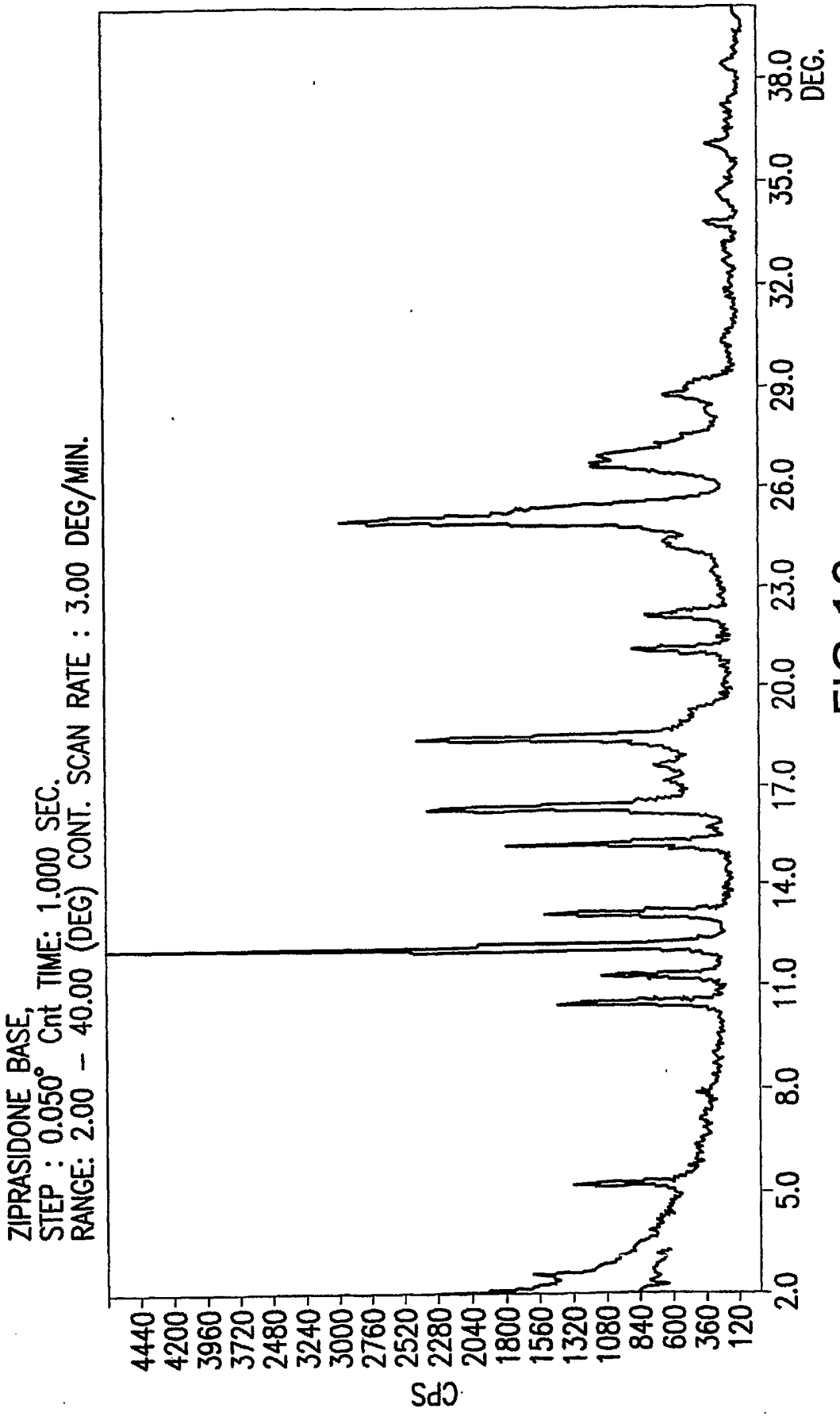

ZIPRASIDONE BASE,
STEP : 0.050° Cnt TIME: 1.000 SEC.
RANGE: 2.00 – 40.00 (DEG) CONT. SCAN RATE : 3.00 DEG/MIN.
CPS
4440
4200
3960
3720
3480
3240
3000
2760
2520
2280
2040
1800
1560
1320
1080
840
600
360
120
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG.12

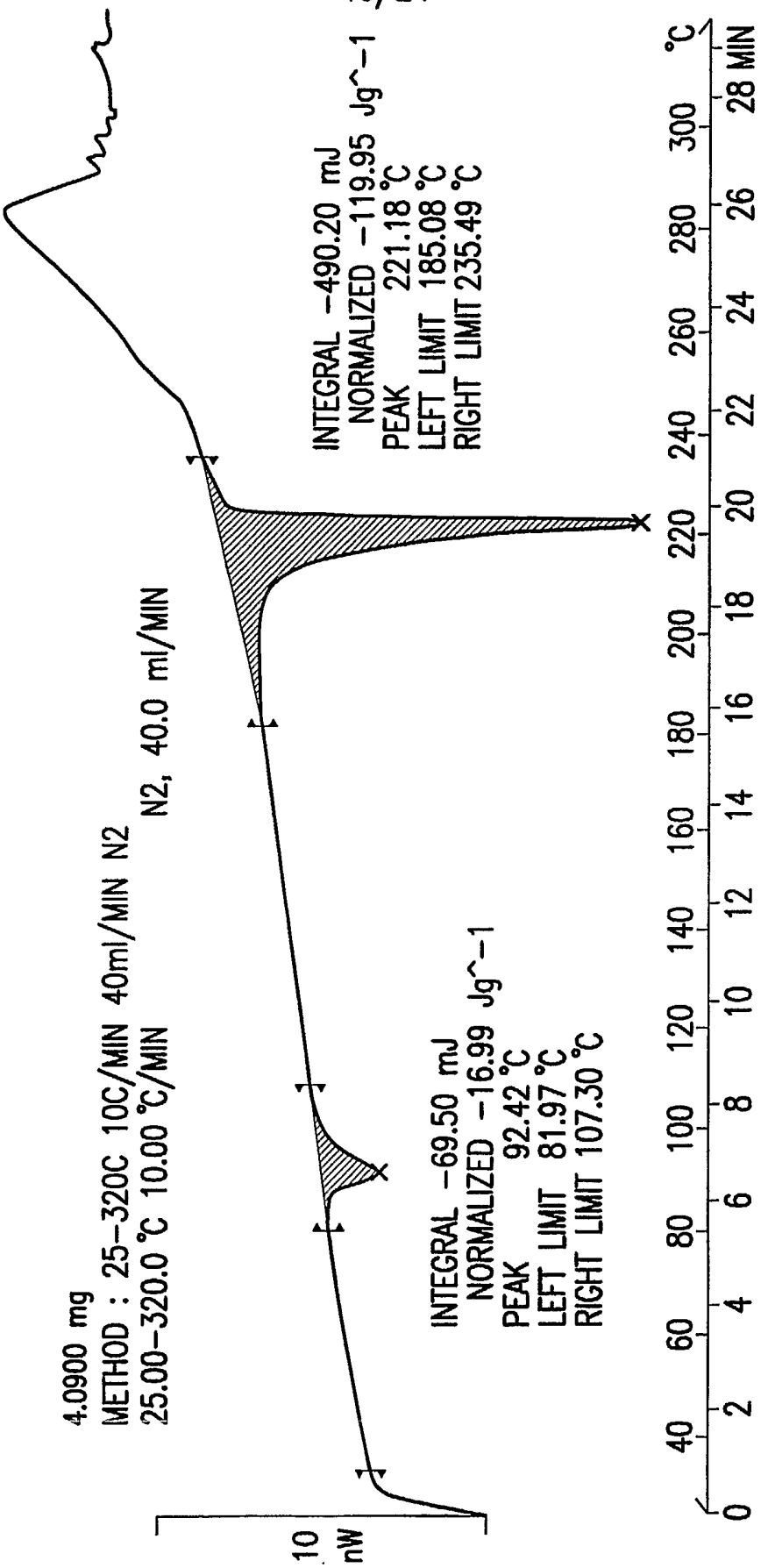

4.0900 mg
METHOD : 25-320C 10C/MIN 40ml/MIN N2
25.00-320.0 °C 10.00 °C/MIN
N2, 40.0 ml/MIN
INTEGRAL -490.20 mJ
NORMALIZED -119.95 Jg^-1
PEAK 221.18 °C
LEFT LIMIT 185.08 °C
RIGHT LIMIT 235.49 °C
INTEGRAL -69.50 mJ
NORMALIZED -16.99 Jg^-1
PEAK 92.42 °C
LEFT LIMIT 81.97 °C
RIGHT LIMIT 107.30 °C
10 mW
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 MIN
40 60 80 100 120 140 160 180 200 220 240 260 280 300 °C

FIG.13

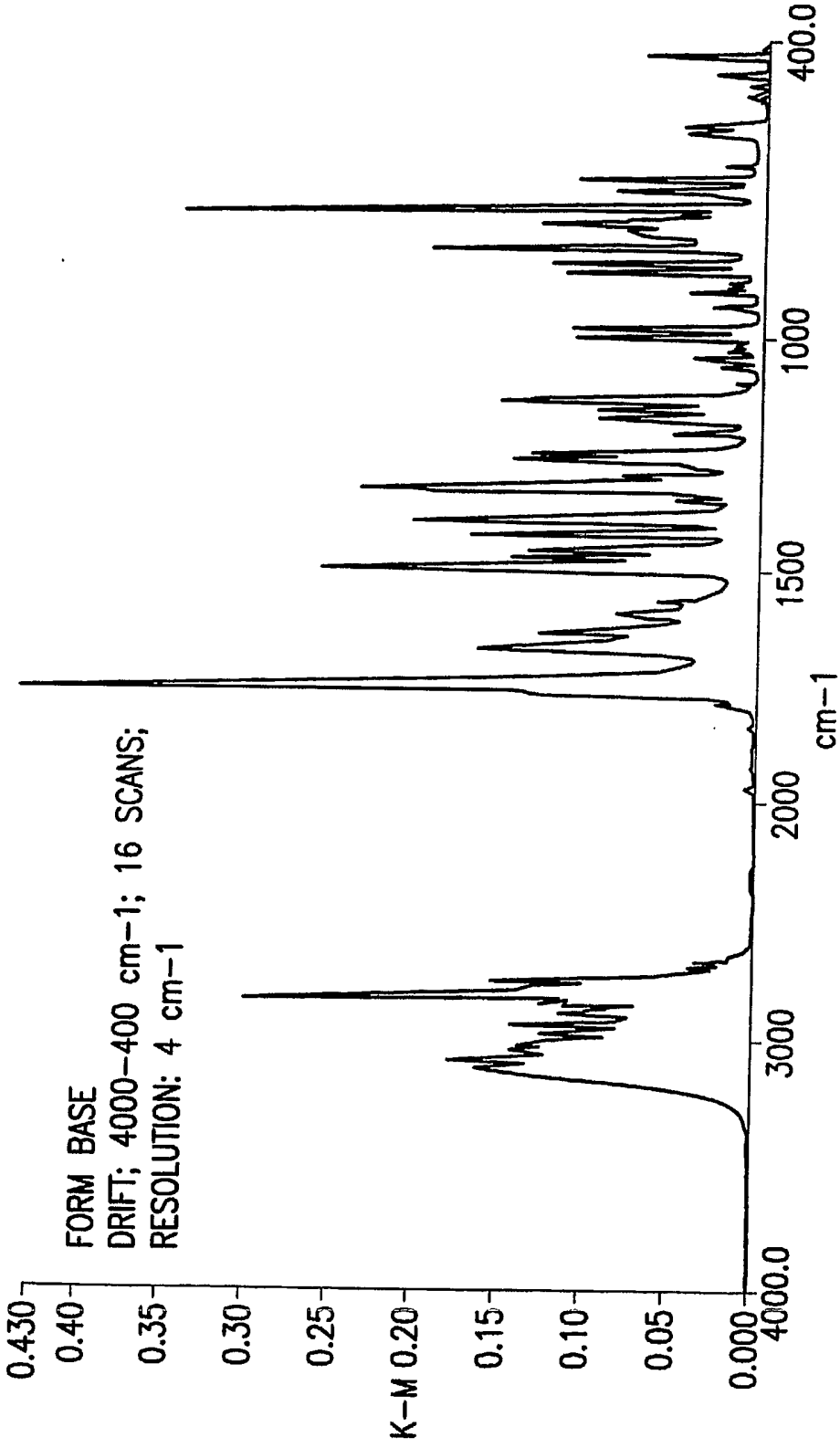

FORM BASE
DRIFT; 4000–400 cm–1; 16 SCANS;
RESOLUTION: 4 cm–1
K–M
0.430
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.000
4000.0
3000
2000
1500
1000
400.0
cm–1

FIG.14

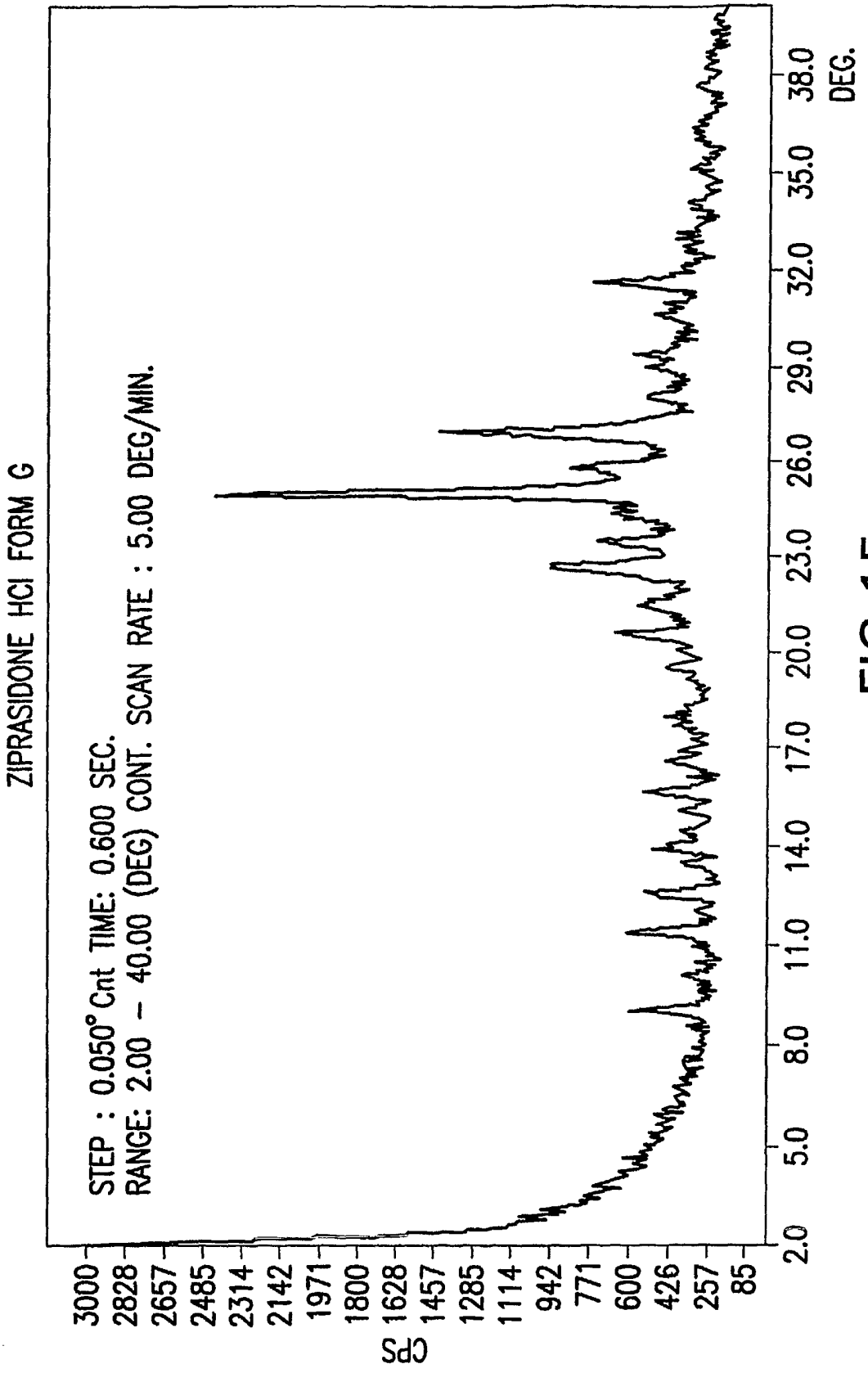

ZIPRASIDONE HCl FORM G
STEP : 0.050° Cnt TIME: 0.600 SEC.
RANGE: 2.00 - 40.00 (DEG) CONT. SCAN RATE : 5.00 DEG/MIN.
CPS
3000
2828
2657
2485
2314
2142
1971
1800
1628
1457
1285
1114
942
771
600
426
257
85
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG.15

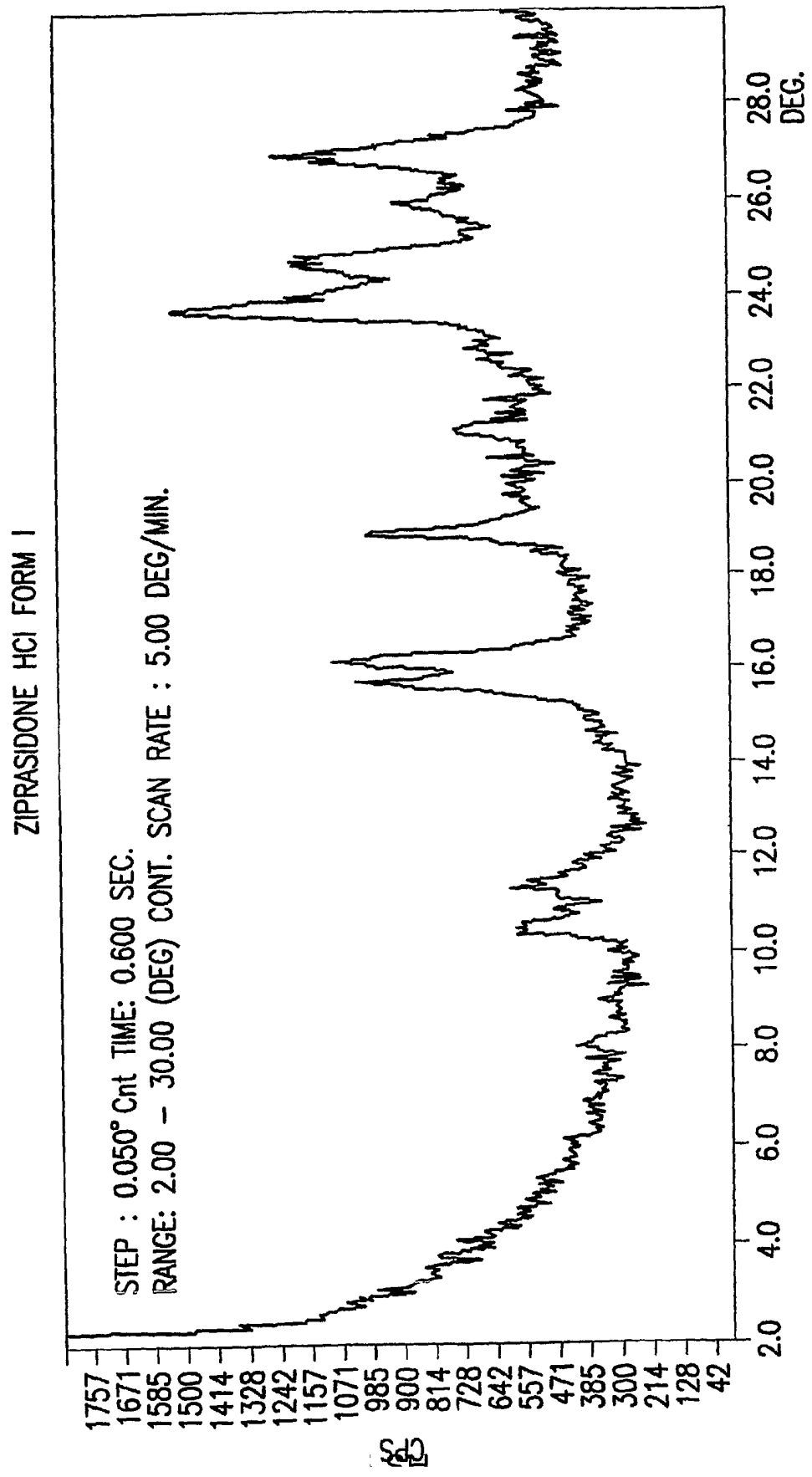

ZIPRASIDONE HCl FORM I
STEP : 0.050° Cnt TIME: 0.600 SEC.
RANGE: 2.00 – 30.00 (DEG) CONT. SCAN RATE : 5.00 DEG/MIN.
CPS
1757
1671
1585
1500
1414
1328
1242
1157
1071
985
900
814
728
642
557
471
385
300
214
128
42
2.0
4.0
6.0
8.0
10.0
12.0
14.0
16.0
18.0
20.0
22.0
24.0
26.0
28.0
DEG.

FIG.16

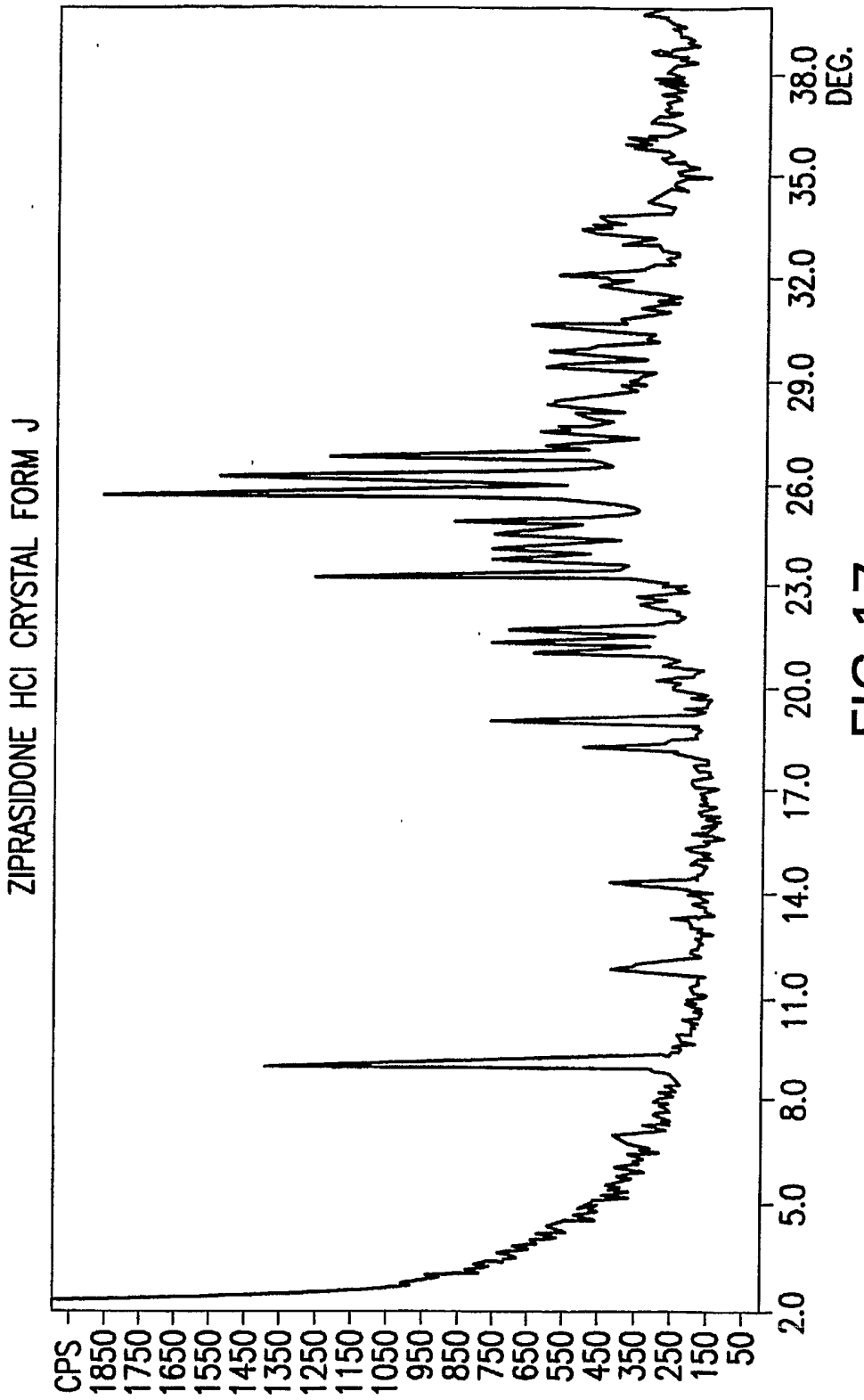

ZIPRASIDONE HCl CRYSTAL FORM J
CPS
1850
1750
1650
1550
1450
1350
1250
1150
1050
950
850
750
650
550
450
350
250
150
50
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG. 17

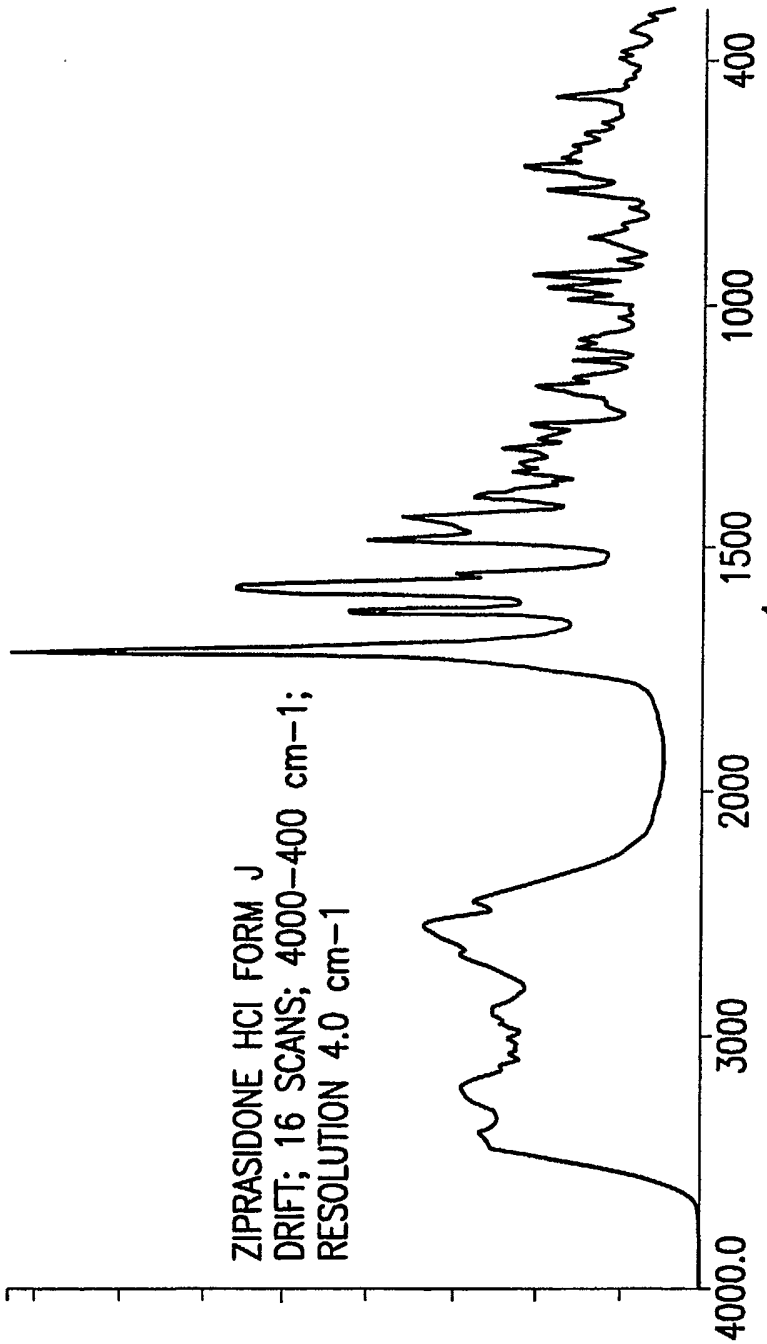

ZIPRASIDONE HCl FORM J
DRIFT; 16 SCANS; 4000–400 cm–1;
RESOLUTION 4.0 cm–1
4000.0
3000
2000
1500
1000
400
cm–1

FIG.18

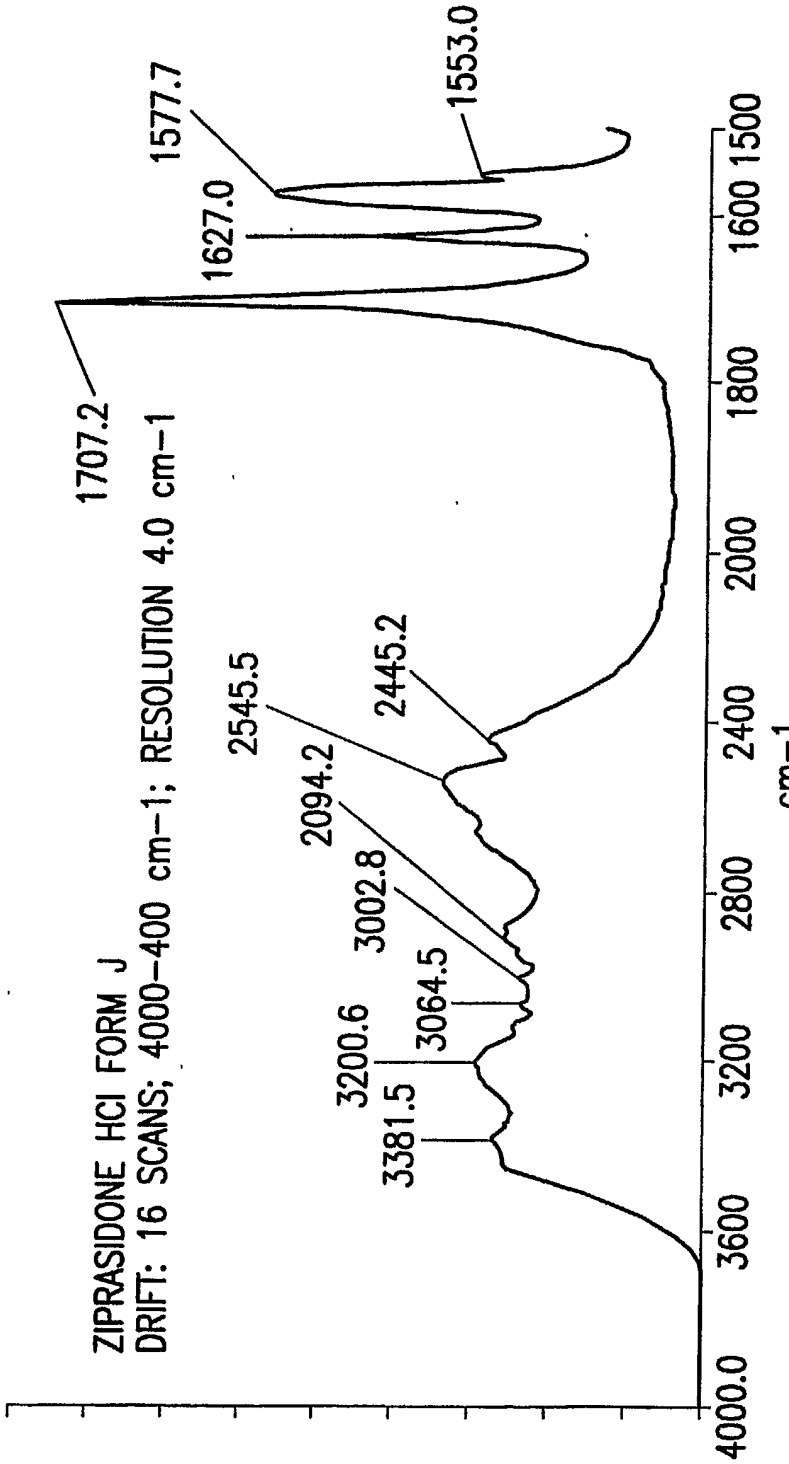

ZIPRASIDONE HCl FORM J
DRIFT: 16 SCANS; 4000-400 cm-1; RESOLUTION 4.0 cm-1
1707.2
1627.0
1577.7
1553.0
2545.5
2445.2
2094.2
3002.8
3200.6
3064.5
3381.5
4000.0
3600
3200
2800
2400
2000
1800
1600
1500
cm-1

FIG.19

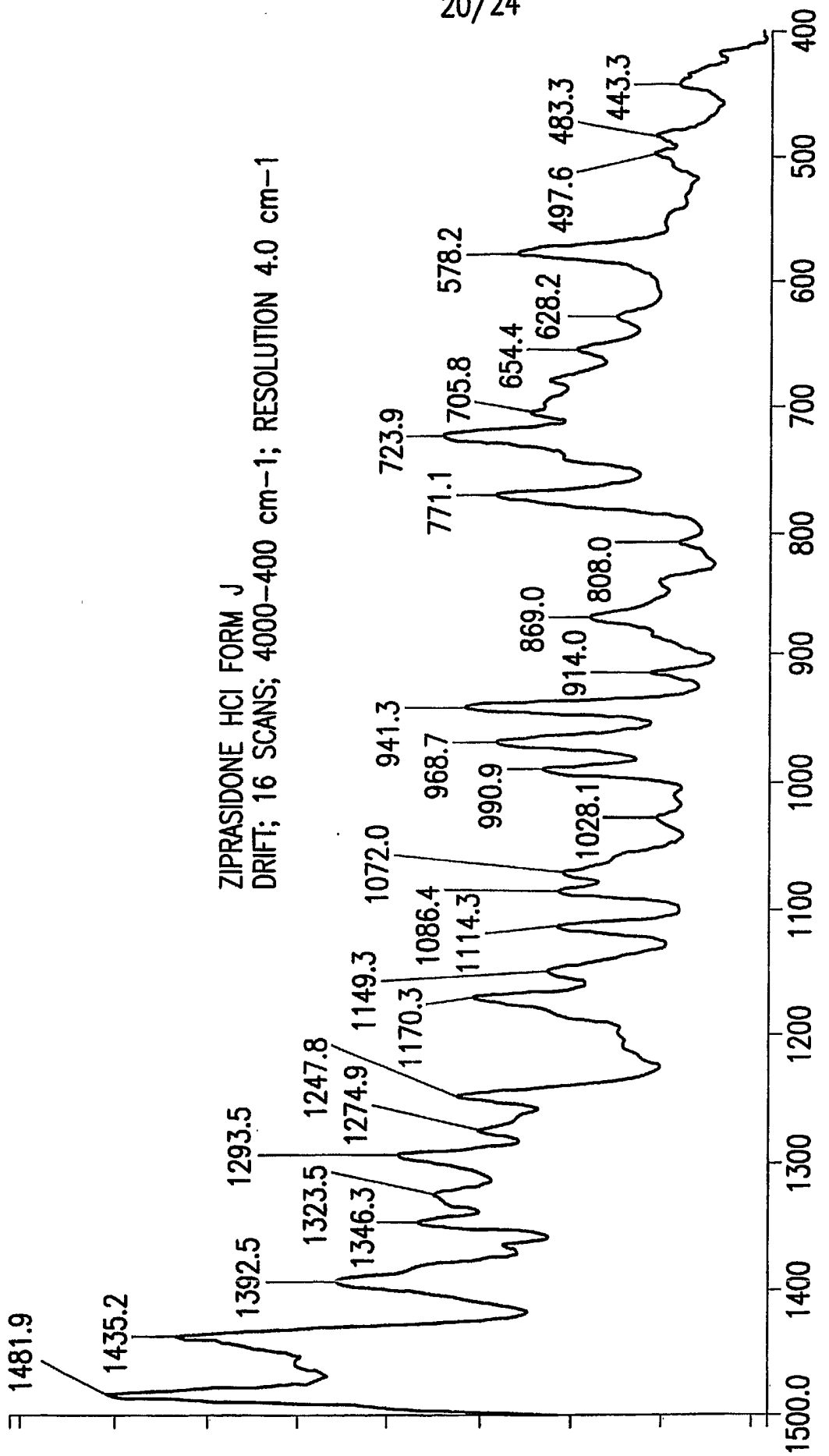

ZIPRASIDONE HCl FORM J
DRIFT; 16 SCANS; 4000–400 cm–1; RESOLUTION 4.0 cm–1
1481.9
1435.2
1392.5
1346.3
1323.5
1293.5
1274.9
1247.8
1170.3
1149.3
1114.3
1086.4
1072.0
1028.1
990.9
968.7
941.3
914.0
869.0
808.0
771.1
723.9
705.8
654.4
628.2
578.2
497.6
483.3
443.3
1500.0
1400
1300
1200
1100
1000
900
800
700
600
500
400
cm–1

FIG.20

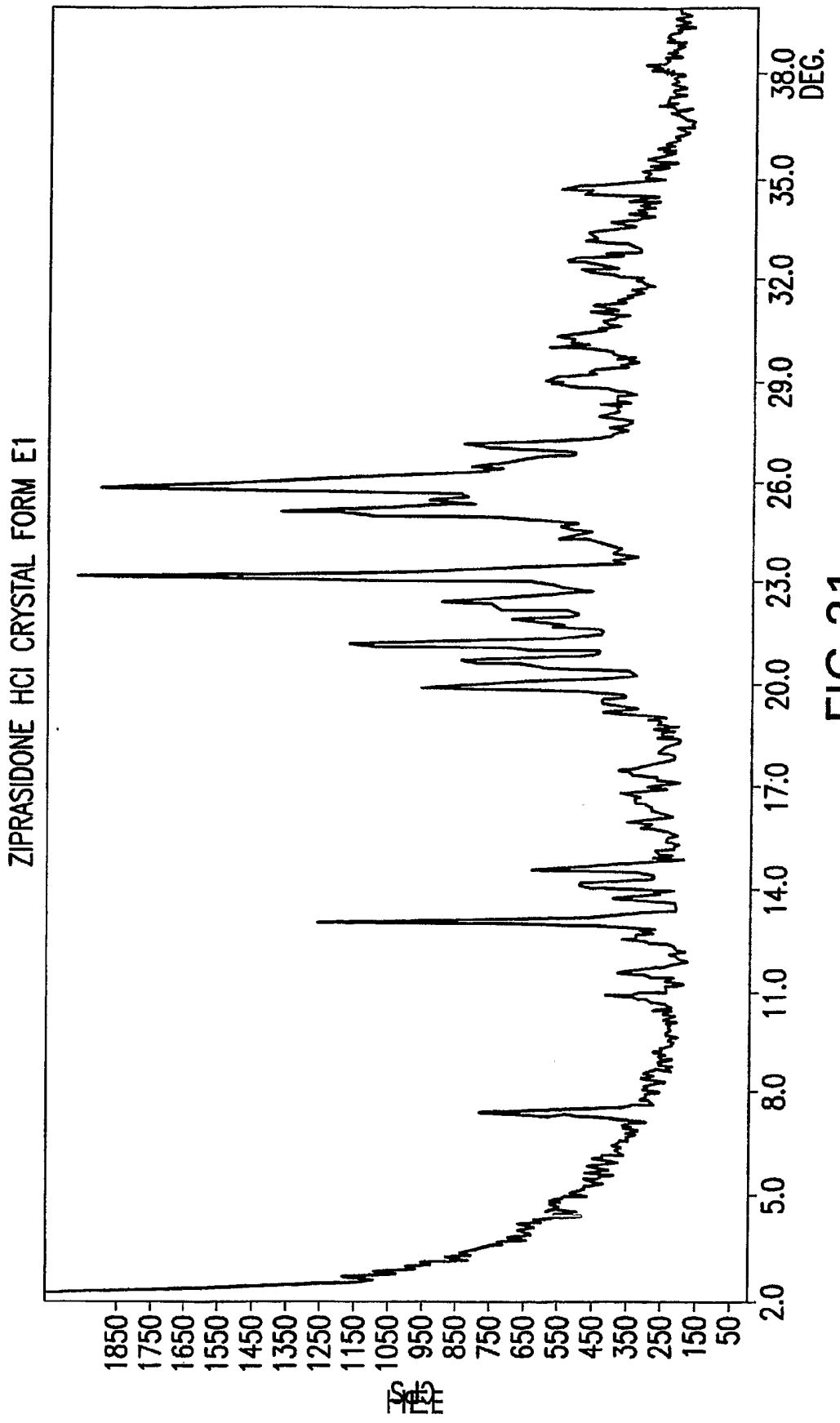

ZIPRASIDONE HCl CRYSTAL FORM E1
1850
1750
1650
1550
1450
1350
1250
1150
1050
950
850
750
650
550
450
350
250
150
50
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
DEG.

FIG.21

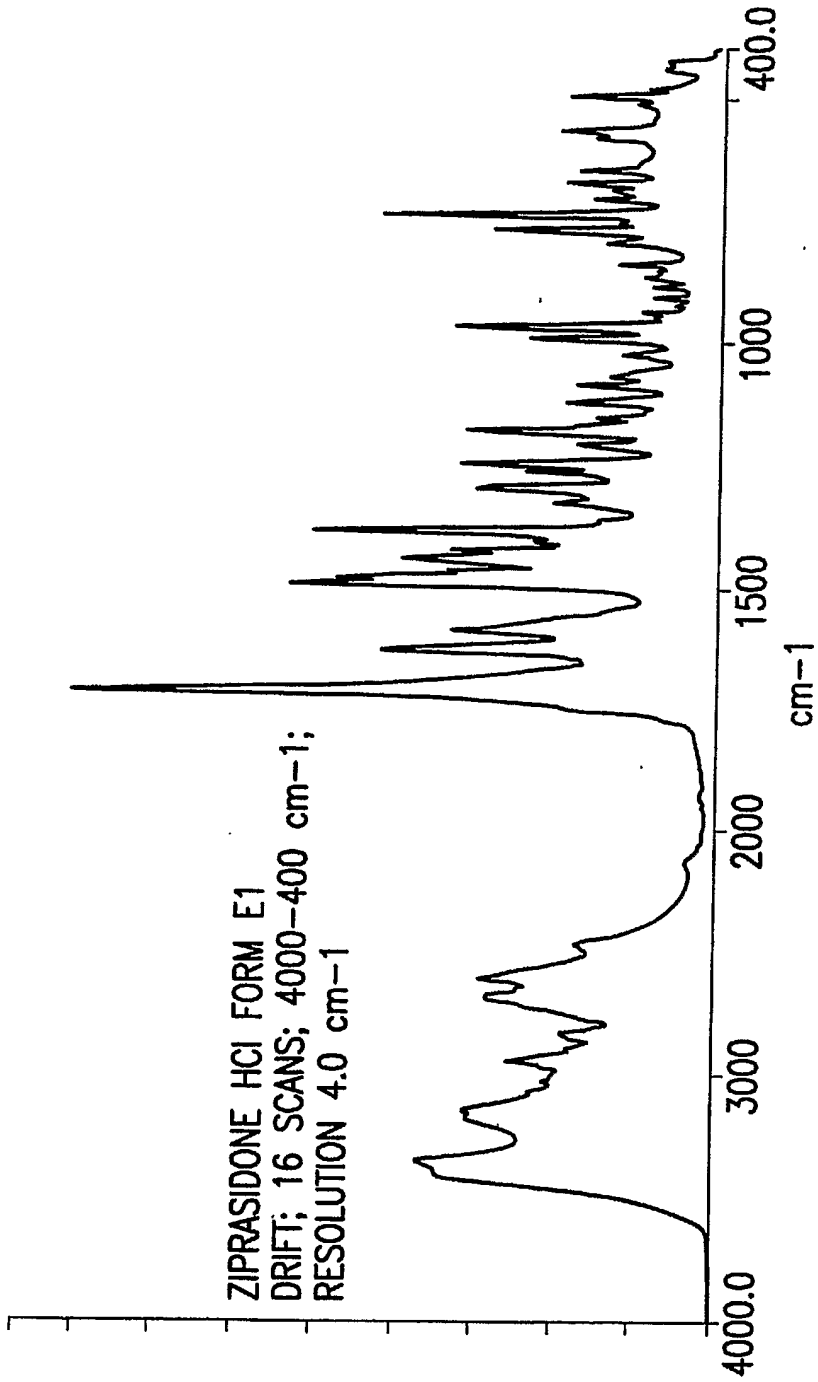

ZIPRASIDONE HCl FORM E1
DRIFT; 16 SCANS; 4000-400 cm-1;
RESOLUTION 4.0 cm-1
4000.0
3000
2000
1500
1000
400.0
cm-1

FIG.22

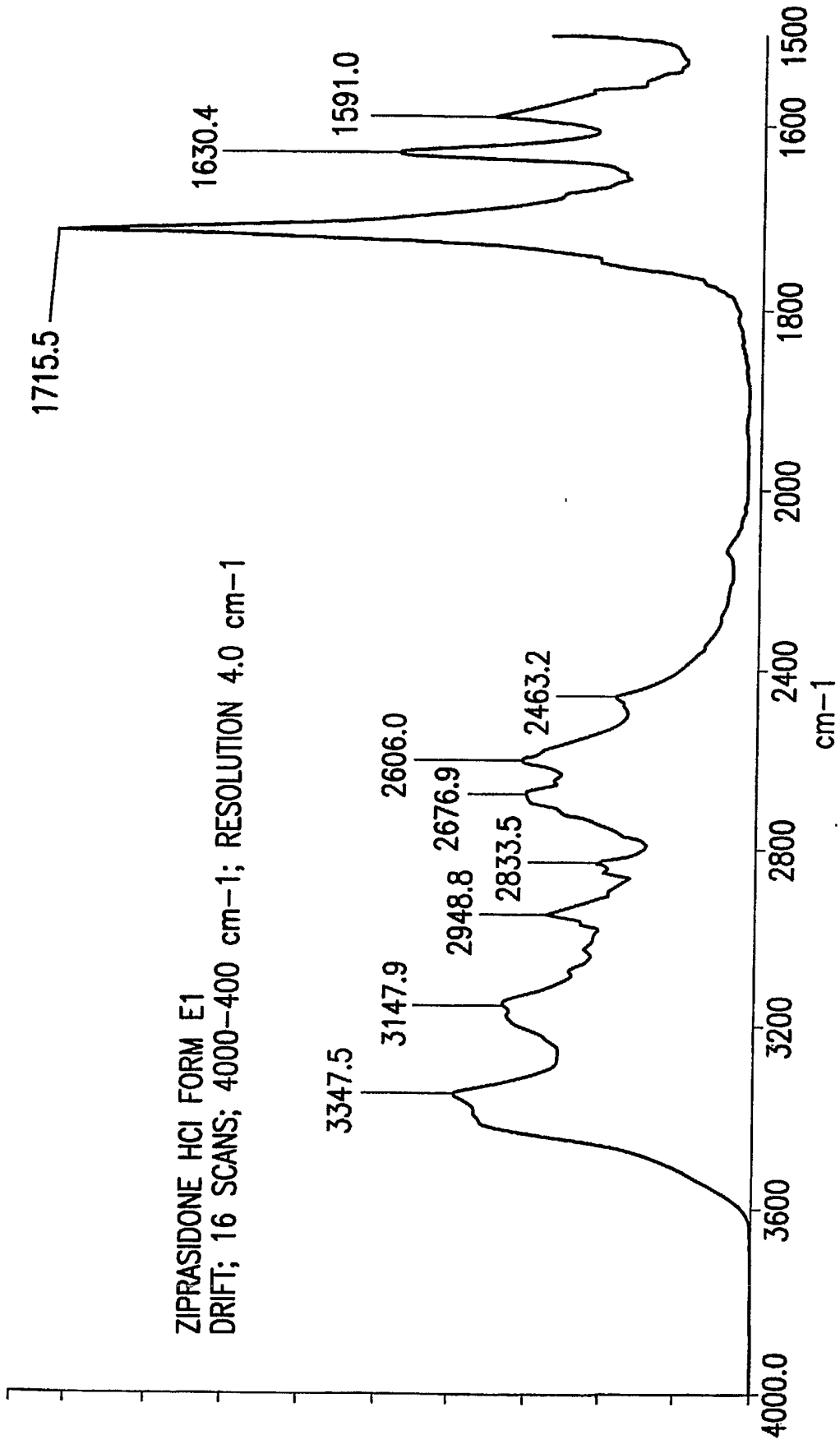

ZIPRASIDONE HCl FORM E1
DRIFT; 16 SCANS; 4000–400 cm–1; RESOLUTION 4.0 cm–1
1715.5
1630.4
1591.0
3347.5
3147.9
2948.8
2833.5
2676.9
2606.0
2463.2
4000.0
3600
3200
2800
2400
2000
1800
1600
1500
cm–1

FIG.23

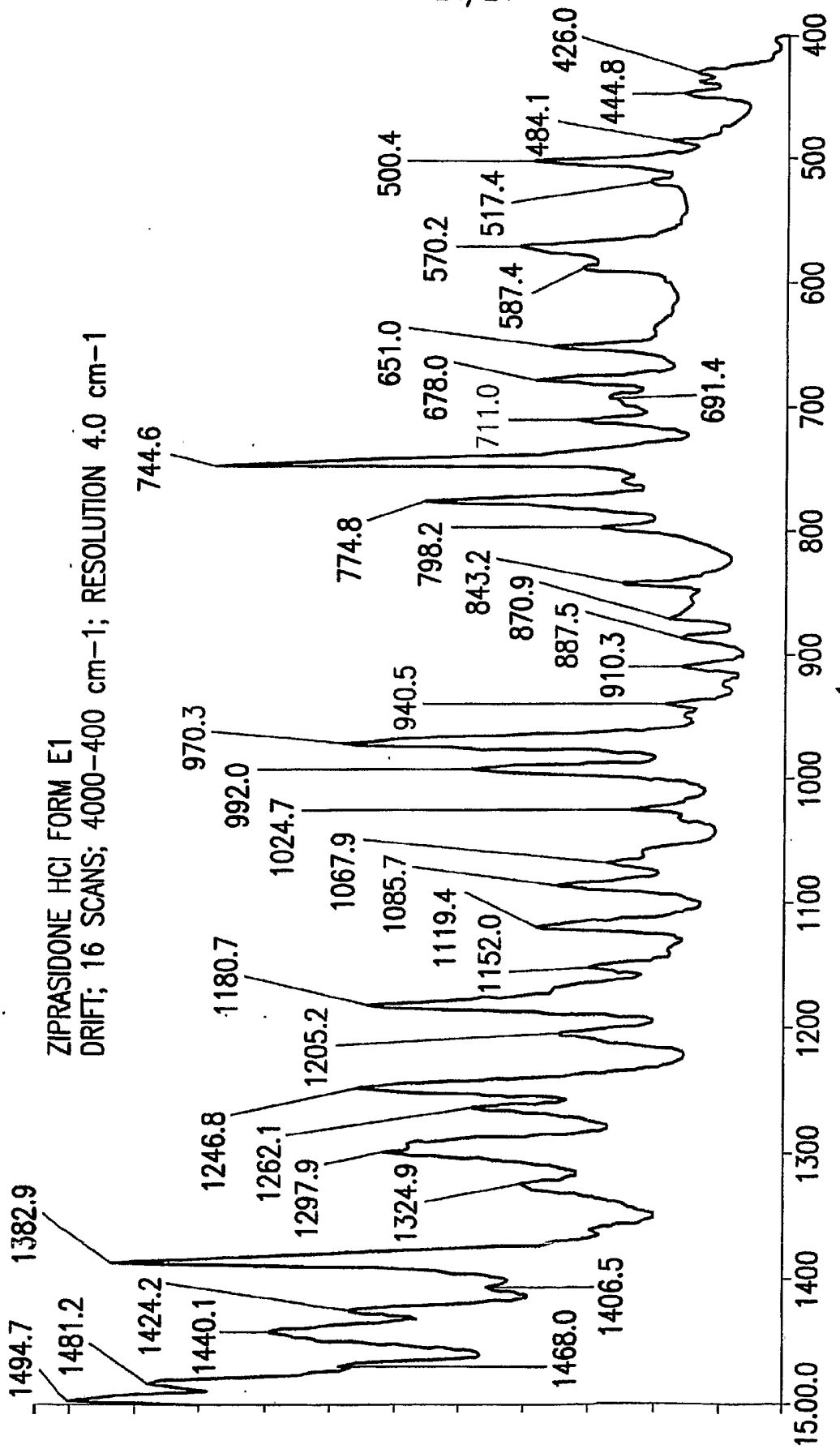

ZIPRASIDONE HCl FORM E1
DRIFT; 16 SCANS; 4000–400 cm–1; RESOLUTION 4.0 cm–1
1494.7
1481.2
1424.2
1440.1
1382.9
1468.0
1406.5
1324.9
1297.9
1262.1
1246.8
1205.2
1180.7
1152.0
1119.4
1085.7
1067.9
1024.7
992.0
970.3
940.5
910.3
887.5
870.9
843.2
798.2
774.8
744.6
711.0
691.4
678.0
651.0
587.4
570.2
517.4
500.4
484.1
444.8
426.0
4000.0
3500
3400
3300
3200
3100
3000
2900
2800
2700
2600
2500
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
cm–1

FIG.24

INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/US2004/018018

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/428 A61P25/18

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 7 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	US 5 312 925 A (ALLEN DOUGLAS J M ET AL) 17 May 1994 (1994-05-17) cited in the application the whole document	1-37, 46-76
X	EP 0 584 903 A (PFIZER) 2 March 1994 (1994-03-02) the whole document	1-37, 46-76

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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	Date of mailing of the international search report
24 January 2005	04. 02. 2005

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Diederen, J

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/US2004/018018

Box 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 76 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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 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 fee, this Authority did not invite payment of any additional fee.

3. [X] 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.:

1-37, 46-74, 75-76 (in part)

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.

[X] 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: 1-12, 75-76 (in part)

   Crystalline form of ziprasidone HCl Form E, its process of preparation and pharmaceutical composition/use

   ---

2. claims: 13-20, 52-55 (in part), 75-76 (in part)

   Crystalline form of ziprasidone HCl Form F, its process of preparation and pharmaceutical composition/use

   ---

3. claims: 21-37, 75-76 (in part)

   Crystalline form of ziprasidone HCl Form M, its process of preparation and pharmaceutical composition/use

   ---

4. claims: 38-45, 75-76 (in part)

   Amorphous form of ziprasidone HCl, its process of preparation and pharmaceutical composition/use

   ---

5. claims: 46-51, 52-55 (in part), 75-76 (in part)

   Crystalline form of ziprasidone HCl Form G, its process of preparation and pharmaceutical composition/use

   ---

6. claims: 56-60, 75-76 (in part)

   Crystalline form of ziprasidone HCl Form I, its process of preparation and pharmaceutical composition/use

   ---

7. claims: 61-67, 75-76 (in part)

   Crystalline form of ziprasidone HCl Form J, its process of preparation and pharmaceutical composition/use

   ---

8. claims: 68-74, 75-76 (in part)

   Crystalline form of ziprasidone HCl Form E1, its process of preparation and pharmaceutical composition/use

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/018018

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