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(54) Title: PROCESS FOR THE PREPARATION OF VILAZODONE HYDROCHLORIDE

(57) Abstract: The present invention provides vilazodone hydrobromide, its process of preparation, pharmaceutical composition, and method of use. The present invention further provides processes of preparation of vilazodone hydrochloride using vilazodone hydrobromide. The present invention further provides crystalline Form A, crystalline Form B and crystalline Form C of vilazodone free base along with their processes of preparation, pharmaceutical compositions, and method of use.



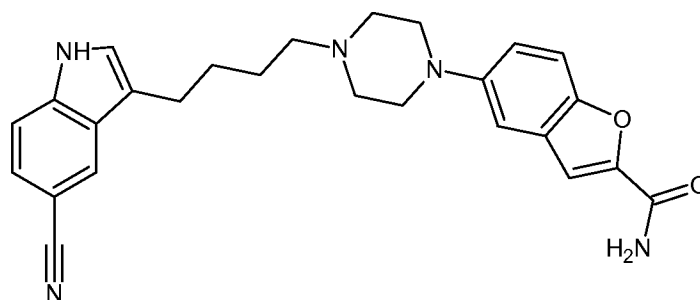
PROCESS FOR THE PREPARATION OF VILAZODONE HYDROCHLORIDE

Field of the Invention

The present invention provides vilazodone hydrobromide, its process of preparation, pharmaceutical composition, and method of use. The present invention further provides processes of preparation of vilazodone hydrochloride using vilazodone hydrobromide. The present invention further provides crystalline Form A, crystalline Form B, and crystalline Form C of vilazodone free base along with their process of preparation, pharmaceutical compositions, and method of use.

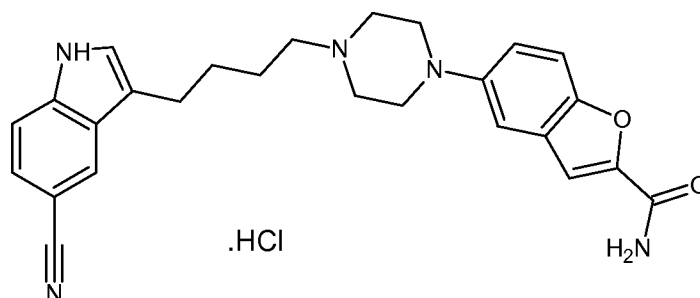
Background of the Invention

Vilazodone free base is chemically described as 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide of Formula I



FORMULA I

Vilazodone hydrochloride is chemically described as 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl}benzofuran-2-carboxamide hydrochloride of Formula II



FORMULA II

Vilazodone hydrochloride is indicated for the treatment of major depressive disorder (MDD).

Processes for the preparation of vilazodone free base, or its hydrochloride salt are described in U.S. Patent Nos. 5,532,241 and 7,834,020.

Summary of the Invention

5 The present invention provides vilazodone hydrobromide, its process of preparation, pharmaceutical composition, and method of use. The present invention further provides processes of preparation of vilazodone hydrochloride using vilazodone hydrobromide. The present invention further provides crystalline Form A, crystalline Form B, and crystalline Form C of vilazodone free base along with their processes of preparation, pharmaceutical compositions, and method of use.

10 Brief Description of the Drawings

Figure 1 depicts the X-ray powder diffraction (XRPD) pattern of the vilazodone hydrobromide obtained according to Example 2.

Figure 1A provides the table of values for the XRPD pattern depicted in Figure 1.

15 Figure 2 depicts the XRPD pattern of crystalline Form B of vilazodone free base obtained according to Example 3.

Figure 2A provides the table of values for the XRPD pattern depicted in Figure 2.

Figure 3 depicts the XRPD pattern of the vilazodone hydrochloride obtained according to Example 4.

Figure 3A provides the table of values for the XRPD pattern depicted in Figure 3.

20 Figure 4 depicts the XRPD pattern of the vilazodone hydrobromide obtained according to Example 6.

Figure 4A provides the table of values for the XRPD pattern depicted in Figure 4.

Figure 5 depicts the XRPD pattern of crystalline Form A of vilazodone free base obtained according to Example 7.

25 Figure 5A provides the table of values for the XRPD pattern depicted in Figure 5.

Figure 6 depicts the XRPD pattern of the vilazodone hydrochloride obtained according to Example 8.

Figure 6A provides the table of values for the XRPD pattern depicted in Figure 6.

Figure 7 depicts the XRPD pattern of crystalline Form C of vilazodone free base obtained according to Example 11.

Figure 7A provides the table of values for the XRPD pattern depicted in Figure 7

Figure 8 depicts the XRPD pattern of the vilazodone hydrochloride obtained
5 according to Example 12.

Figure 8A provides the table of values for the XRPD pattern depicted in Figure 8.

Figure 9 depicts the XRPD pattern of the vilazodone hydrobromide obtained according to Example 14.

Figure 9A provides the table of values for the XRPD pattern depicted in Figure 9.

Figure 10 depicts the XRPD pattern of crystalline Form A of vilazodone free base
10 obtained according to Example 15.

Figure 10A provides the table of values for the XRPD pattern depicted in Figure
10.

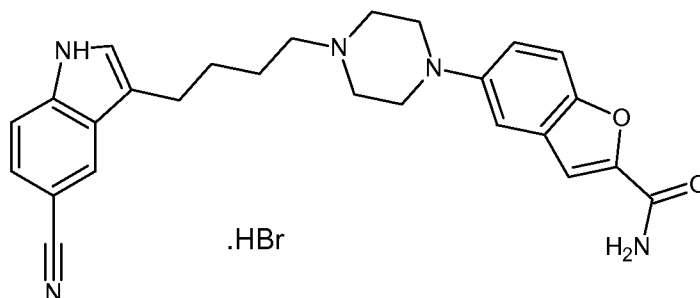
Figure 11 depicts the XRPD pattern of the vilazodone hydrochloride obtained
15 according to Example 16.

Figure 11A provides the table of values for the XRPD pattern depicted in Figure
11.

Detailed Description of the Invention

A first aspect of the present invention provides vilazodone hydrobromide.

20 Vilazodone hydrobromide is chemically described as 5-{4-[4-(5-cyano-1H-indol-3-yl)butyl]piperazin-1-yl} benzofuran-2-carboxamide hydrobromide of Formula III.

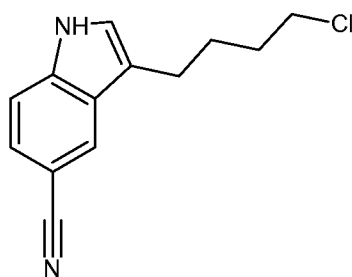


FORMULA III

Vilazodone hydrobromide has substantially the same XRPD pattern as depicted in Figure 1, Figure 4, or Figure 9.

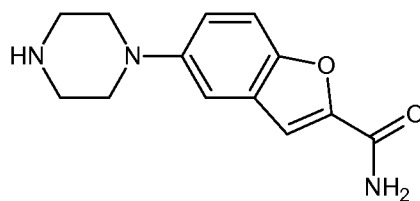
A second aspect of the present invention provides a process for the preparation of vilazodone hydrobromide, which comprises:

- 5 a) reacting 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula IV



FORMULA IV

with 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V,



FORMULA V

- 10 b) treating the reaction mixture obtained in step a) with hydrobromic acid, and
 c) isolating vilazodone hydrobromide from the reaction mixture thereof.

Treatment of the compound of Formula IV with the compound of Formula V may be carried out in the presence of a base and solvent. The solvent may be selected from the group consisting of water, organic solvent, or a mixture thereof. Suitable organic solvents may be selected from the group consisting of alcohols, ketones, nitriles, amides, aromatic or aliphatic hydrocarbons or dimethyl sulfoxide. Suitable amide solvents are N-methylpyrrolidone, and dimethyl formamide. Suitable alcoholic solvents are methanol, 2-propanol or 1-propanol. A suitable nitrile is acetonitrile. Suitable ketonic solvents are acetone and methyl isobutyl ketone. A suitable aromatic hydrocarbon is toluene. A preferred solvent is N-methylpyrrolidone.

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The base may be selected from organic or inorganic bases. Suitable organic base is tributylamine, triethyl amine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylaminopyridine, pyrrolidone or N-methyl morpholine. A preferred organic base is tributylamine. Suitable inorganic base is hydroxides, carbonates, and bicarbonates of alkali or alkaline metal. Suitable carbonates or bicarbonates of alkali or alkaline metal is sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate or potassium bicarbonate. A preferred inorganic base is potassium carbonate. Treatment of the compound of Formula IV with compound of Formula V may be carried out in the presence of alkali metal halides, for example, sodium iodide.

Treatment of the compound of Formula IV with compound of Formula V may be carried out at a temperature of about 5°C to about 140°C, preferably at about 20°C to about 120°C. Treatment of the compound of Formula IV with compound of Formula V may be carried for about 2 hours to about 10 hours, preferably for about 4 hours to about 8 hours.

The reaction mixture obtained in step a) is treated with hydrobromic acid. The hydrobromic acid may be dilute or concentrated. The hydrobromic acid may be used in solution form or gaseous form. The solution of hydrobromic acid may be aqueous or in organic solvent. The organic solvent may be methanol, ethanol or 2-propanol. Treatment of the reaction mixture obtained in step a) with hydrobromic acid may be carried out in the presence of an organic solvent. The organic solvent may be selected from the group consisting of alcoholic solvent, ketones, esters, formamides, water, chlorinated solvents, N-methylpyrrolidone, or a combination thereof. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol, or butanol. Preferred solvents are N-methylpyrrolidone in combination with 2-propanol, methanol or methylated ethanol. Dissolution of the reaction mixture obtained in step a) with hydrobromic acid may be carried out at a temperature of about 10°C to about 40°C, preferably at about 20°C to about 30°C. Dissolution of the reaction mixture obtained in step a) with hydrobromic acid may be carried out for about 5 minutes to about 25 hours, preferably for about 7 hours to about 18 hours.

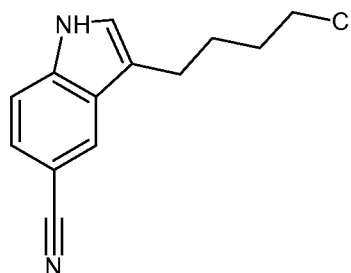
Vilazodone hydrobromide salt may be purified using hydrobromic acid and organic solvent. The hydrobromic acid may be dilute or concentrated. The hydrobromic acid may be used in solution form or gaseous form. The solution of hydrobromic acid

may be aqueous or in organic solvent. Organic solvent may be selected from the group consisting of alcoholic or amide solvent. Suitable amide solvents are N-methylpyrrolidone, and dimethyl formamide. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol or butanol. A preferred solvent is N-methylpyrrolidone in
 5 combination with 2-propanol, methanol or methylated ethanol.

Vilazodone hydrobromide salt may be isolated by filtration, decantation, drying, vacuum drying or a combination thereof.

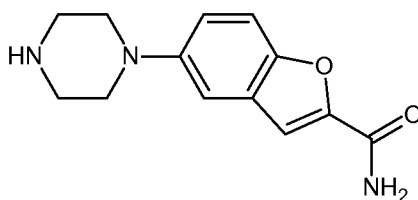
A third aspect of the present invention provides a process for the preparation of vilazodone hydrochloride, which comprises:

- 10 a) reacting 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula IV



FORMULA IV

with 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V,



FORMULA V

15

- b) treating the reaction mixture obtained in step a) with hydrobromic acid;
- c) optionally isolating vilazodone hydrobromide from the reaction mixture thereof;
- d) converting vilazodone hydrobromide to vilazodone free base;
- 20 e) treating vilazodone free base with hydrochloric acid; and
- f) isolating vilazodone hydrochloride from the reaction mixture thereof.

Treatment of the compound of Formula IV with compound of Formula V may be carried out in the presence of a base and solvent. The solvent may be selected the group consisting of water, organic solvent, or a mixture thereof. Suitable organic solvents may be selected from the group consisting of alcohol, ketone, nitrile, amide, aromatic or
5 aliphatic hydrocarbon, or dimethyl sulfoxide. Suitable amide solvents are N-methylpyrrolidone, and dimethyl formamide. Suitable alcoholic solvents are methanol, 2-propanol or 1-propanol. Suitable nitrile solvents are acetonitrile. Suitable ketonic solvents are acetone or methyl isobutyl ketone. Suitable aromatic hydrocarbon solvents are toluene. A preferred solvent is N-methylpyrrolidone.

10 The base may be selected from organic base or inorganic base. Suitable organic bases are tributylamine, triethyl amine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylaminopyridine, pyrrolidone and N-methyl morpholine. A preferred organic base is tributylamine. Suitable inorganic bases are hydroxides, carbonates and bicarbonates of alkali or alkaline metal. Suitable carbonates or bicarbonates of alkali or alkaline metal are
15 sodium carbonate, potassium carbonate, magnesium carbonate, sodium bicarbonate or potassium bicarbonate. A preferred inorganic base is potassium carbonate. Treatment of the compound of Formula IV with compound of Formula V may be carried out in the presence of alkali metal halides, for example, sodium iodide.

Treatment of the compound of Formula IV with a compound of Formula V may be
20 carried out a temperature of about 5°C to about 140°C, preferably at about 20°C to about 120°C. Treatment of the compound of Formula IV with compound of Formula V may be carried for about 2 hours to about 10 hours, preferably for about 4 hours to about 8 hours.

The reaction mixture obtained in step a) is treated with hydrobromic acid. The hydrobromic acid may be dilute or concentrated. The hydrobromic acid may be used in
25 solution form or gaseous form. The solution of hydrobromic acid may be aqueous or in an organic solvent. The organic solvent may be methanol, ethanol, or 2-propanol. The treatment of the reaction mixture obtained in step a) with hydrobromic acid may be carried out in the presence of organic solvent. The organic solvent may be selected from a group consisting of alcoholic solvent, ketones, esters, formamides, water, chlorinated solvents,
30 N-methylpyrrolidone, or a combination thereof. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol or butanol. Preferred solvents are N-methylpyrrolidone in combination with 2-propanol, methanol or methylated ethanol. Dissolution of the reaction

mixture obtained in step a) with hydrobromic acid may be carried out a temperature of about 10°C to about 40°C, preferably at about 20°C to about 30°C. Dissolution of the reaction mixture obtained in step a) with hydrobromic acid may be carried out for about 5 minutes to about 25 hours, preferably for about 7 hours to about 18 hours.

- 5 Vilazodone hydrobromide salt may be purified using hydrobromic acid and organic solvent. The hydrobromic acid may be dilute or concentrated. The hydrobromic acid may be used in solution form or gaseous form. The solution of hydrobromic acid may be aqueous or in organic solvent. The organic solvent may be selected from group consisting of alcoholic or amide solvent. Suitable amide solvents are N-
- 10 methylpyrrolidone, and dimethyl formamide. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol or butanol. Preferred solvents are N-methylpyrrolidone in combination with 2-propanol, methanol or methylated ethanol.

Vilazodone hydrobromide salt may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof.

- 15 Vilazodone hydrobromide may be converted to vilazodone free base. Conversion of vilazodone hydrobromide to vilazodone free base may be carried out in the presence of base and solvent. The base may be selected from organic or inorganic base. The inorganic base may be selected from carbonates, bicarbonates, and hydroxides. A preferred base for the conversion of vilazodone hydrobromide to vilazodone free base is
- 20 sodium bicarbonate. Base used for the conversion of vilazodone hydrobromide to vilazodone free base may be solid or used in the form of an aqueous solution.

- The solvent for the conversion of vilazodone hydrobromide to vilazodone free base may be selected from water, organic solvent, or a combination thereof. The organic solvent may be selected from the group consisting of alcohols, esters, chlorinated solvents, ketones, amides, sulfolanes, or a combination thereof. Suitable alcoholic solvents are
- 25 methanol, ethanol, methylated ethanol, 2-propanol, 1-propanol and butanol. Suitable amide solvents are N-methylpyrrolidone, dimethyl acetamide and dimethyl formamide. A suitable nitrile solvent is acetonitrile. Suitable ketonic solvents are acetone and methyl isobutyl ketone. A suitable chlorinated solvent is dichloromethane. Suitable ester
- 30 solvents are ethyl acetate, methyl acetate and isopropyl acetate. Preferred solvents are water in combination with methanol or ethanol and 2-propanol.

Conversion of vilazodone hydrobromide to vilazodone free base may be carried out at a temperature of about 10°C to about 100°C, preferably at about 20°C to about 85°C. Dissolution of the vilazodone free base in water and alcoholic solvent may be carried out for about 30 minutes to about 6 hours, preferably for about 1 hour to about 4
5 hours.

Vilazodone free base may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof. Vilazodone free base may be crystalline in nature. Vilazodone free base has substantially the same XRPD pattern as depicted in Figure 2, Figure 5, Figure 7, or Figure 10.

10 Vilazodone free base may be treated with hydrochloric acid which may be dilute or concentrated. The hydrochloric acid may be used in solution form or gaseous form. The solution of hydrochloric acid may be aqueous or in an alcoholic solvent. The alcoholic solvent used for the preparation of hydrochloric acid solution is preferably 2-propanol.

Treatment of vilazodone free base with hydrochloric acid may be carried out in
15 water or an organic solvent. The organic solvent may be selected from the group consisting of alcoholic or amide solvents. Suitable amide solvents are N-methylpyrrolidone, and dimethyl formamide, or a combination thereof. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol, butanol, or a combination thereof. Preferred solvents are 2-propanol, either alone or in combination with water or N-
20 methylpyrrolidone. Another preferred solvent is 2-propanol in combination with N-methylpyrrolidone, in the absence of water. Treatment of vilazodone free base with hydrochloric acid may be carried out at a temperature of about 50°C to about 100°C, preferably at about 70°C to about 85°C. Treatment of the reaction mixture obtained in step c) with hydrochloric acid may be carried out for about 30 minutes to about 2 hours,
25 preferably for about 60 minutes to about 2 hours.

The vilazodone hydrochloride salt may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof. The vilazodone hydrochloride salt may be crystalline in nature.

Crystalline vilazodone hydrochloride prepared by the present invention may be
30 characterized using XRPD pattern as depicted in Figure 3, Figure 6, Figure 8, or Figure 11.

A fourth aspect of the present invention provides a process for the preparation of vilazodone hydrochloride, which comprises:

- a) treating vilazodone hydrobromide with hydrochloric acid; and
- b) isolating vilazodone hydrochloride from the reaction mixture thereof.

5 Vilazodone hydrobromide may be converted to vilazodone free base. The conversion of vilazodone hydrobromide to vilazodone free base may be carried out in the presence of base and solvent. The base may be selected from organic or inorganic base. The inorganic base may be selected from carbonates, bicarbonates, or hydroxides. A preferred base for the conversion of vilazodone hydrobromide to vilazodone free base is
10 sodium bicarbonate. The base for the conversion of vilazodone hydrobromide to vilazodone free base may be solid or used in the form of aqueous solution.

The solvent for the conversion of vilazodone hydrobromide to vilazodone free base may be selected from water, organic solvent, or a combination thereof. The organic solvent may be selected from the group consisting of alcoholic solvent, esters, chlorinated
15 solvents, ketones, amides, sulfolanes, or a combination thereof. Suitable alcoholic solvents are methanol, ethanol, methylated ethanol, 2-propanol, 1-propanol or butanol. Suitable amide solvents are N-methylpyrrolidone, dimethyl acetamide and dimethyl formamide. Suitable nitrile solvents are acetonitrile. Suitable ketonic solvents are acetone or methyl isobutyl ketone. Suitable chlorinated solvents are dichloromethane. Suitable
20 ester solvents are ethyl acetate, methyl acetate or isopropyl acetate. Preferred solvents are water in combination with methanol or ethanol and 2-propanol.

Conversion of vilazodone hydrobromide to vilazodone free base may be carried out at a temperature of about 10°C to about 100°C, preferably at about 20°C to about 85°C. Dissolution of vilazodone free base in water and alcoholic solvent may be carried
25 out for about 30 minutes to about 6 hours, preferably for about 1 hour to about 4 hours.

Vilazodone free base may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof. The vilazodone free base may be crystalline in nature. Vilazodone free base has substantially the same XRPD pattern as depicted in Figure 2, Figure 5, Figure 7, or Figure 10.

30 Vilazodone free base may be treated with hydrochloric acid. The hydrochloric acid may be dilute or concentrated. The hydrochloric acid may be used in solution form or

gaseous form. The solution of hydrochloric acid may be aqueous or in an alcoholic solvent. The alcoholic solvent used for the preparation of hydrochloric acid solution is preferably 2-propanol.

Treatment of vilazodone free base with hydrochloric acid may be carried out in water or an organic solvent. The organic solvent may be selected from the group consisting of alcoholic or amide solvent. Suitable amide solvents are N-methylpyrrolidone, and dimethyl formamide or a combination thereof. Suitable alcoholic solvents are methanol, ethanol, 2-propanol, 1-propanol, butanol, or a combination thereof. Preferred solvents are 2-propanol, either alone or in combination with water or N-methylpyrrolidone. Another preferred solvent is 2-propanol in combination with N-methylpyrrolidone, in the absence of water. The treatment of vilazodone free base with hydrochloric acid may be carried out at a temperature of about 50°C to about 100°C, preferably at about 70°C to about 85°C. The treatment of the reaction mixture obtained in step c) with hydrochloric acid may be carried out for about 30 minutes to about 2 hours, preferably for about 60 minutes to about 2 hours.

The vilazodone hydrochloride salt may be isolated by filtration, decantation, drying, vacuum drying or a combination thereof. The vilazodone hydrochloride salt may be crystalline in nature.

Crystalline vilazodone hydrochloride prepared by present invention may be characterized using XRPD pattern as depicted in Figure 3, Figure 6, Figure 8, or Figure 11.

A fifth aspect of the present invention provides crystalline Form A of vilazodone free base. Crystalline Form A of vilazodone free base has substantially the same XRPD pattern as depicted in Figure 5 or Figure 10. The crystalline Form A of vilazodone free base is characterized by an XRPD pattern having interplanar spacing (d) values substantially at 15.19, 5.52, 4.73, 4.27, 4.13, 3.66, and 3.28 ± 0.2 Å. The crystalline Form A of vilazodone free base is further characterized by an XRPD pattern having interplanar spacing (d) values substantially at 15.19, 12.01, 8.03, 6.59, 6.40, 5.52, 5.16, 5.07, 4.73, 4.64, 4.46, 4.27, 4.13, 4.07, 3.81, 3.66, 3.52, 3.49, 3.28, 3.19, 3.13, 3.05, 3.02, 2.97, 2.93, 2.88, 2.79, 2.75, 2.68, 2.50, 2.47, 2.35, and 2.30 ± 0.2 Å.

A sixth aspect of the present invention provides crystalline Form B of vilazodone free base. Crystalline Form B of vilazodone free base has substantially the same XRPD

pattern as depicted in Figure 2. The crystalline Form B of vilazodone free base is characterized by an XRPD pattern having interplanar spacing (d) values substantially at 8.38, 6.17, 5.96, 5.81, 5.01, 4.50, 4.04, 3.68, 3.60, 3.53, and 3.08 ± 0.2 Å. The crystalline Form B of vilazodone free base is further characterized by an XRPD pattern having

5 interplanar spacing (d) values substantially at 17.00, 11.58, 8.38, 6.17, 5.96, 5.81, 5.51, 5.01, 4.79, 4.50, 4.32, 4.24, 4.18, 4.08, 4.04, 3.87, 3.68, 3.60, 3.53, 3.41, 3.28, 3.08, 3.03, 2.99, 2.90, 2.85, 2.71, 2.60, 2.50, 2.46, and 2.41 ± 0.2 Å.

A seventh aspect of the present invention provides crystalline Form C of vilazodone free base. Crystalline Form C of vilazodone free base has substantially the

10 same XRPD pattern as depicted in Figure 7. The crystalline Form C of vilazodone free base is characterized by an XRPD pattern having interplanar spacing (d) values substantially at 14.94, 5.51, 4.71, 4.28, 4.11, 3.65, 3.27, and 3.19 ± 0.2 Å. The crystalline Form C of vilazodone free base is further characterized by an XRPD pattern having interplanar spacing (d) values substantially at 14.94, 7.97, 6.54, 6.38, 5.51, 5.16, 5.05,

15 4.71, 4.45, 4.28, 4.11, 4.05, 3.80, 3.65, 3.51, 3.48, 3.27, 3.19, 3.12, 3.04, 3.01, 2.96, 2.92, 2.87, 2.79, 2.66, 2.50, 2.47, 2.35, and 2.30 ± 0.2 Å.

An eighth aspect of the present invention provides a process of preparing crystalline Form A of vilazodone free base which comprises:

- a) treating vilazodone free base or vilazodone salt with 2-propanol; and
- 20 b) isolating crystalline Form A of vilazodone free base from the reaction mixture thereof.

The vilazodone salt may be vilazodone hydrobromide. Conversion of vilazodone hydrobromide to vilazodone free base may be carried out in the presence of base and solvent. The base may be selected inorganic base, for example, aqueous sodium

25 bicarbonate. Solvent for the conversion of vilazodone hydrobromide to vilazodone free base may be selected from water, 2-propanol, or a combination thereof. Conversion of vilazodone hydrobromide to vilazodone free base may be carried out at a temperature of about 10°C to about 100°C, preferably at about 20°C to about 85°C. Dissolution of vilazodone free base in water and 2-propanol may be carried out for about 30 minutes to

30 about 6 hours, preferably for about 1 hour to about 4 hours. Vilazodone free base may be converted to crystalline Form A of vilazodone free base in the presence of 2-propanol.

The crystalline Form A vilazodone free base may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof.

A ninth aspect of the present invention provides a process of preparing crystalline Form B of vilazodone free base which comprises:

- 5 a) treating vilazodone free base or vilazodone salt with methanol; and
- b) isolating crystalline Form B of vilazodone free base from the reaction mixture thereof.

 The vilazodone salt may be vilazodone hydrobromide. Conversion of vilazodone hydrobromide to vilazodone free base may be carried out in the presence of a base and
10 solvent. The base may be inorganic, for example aqueous sodium bicarbonate. The solvent for the conversion of vilazodone hydrobromide to vilazodone free base may be selected from water, methanol, or a combination thereof. Conversion of vilazodone hydrobromide to vilazodone free base may be carried out at a temperature of about 10°C to about 100°C, preferably at about 20°C to about 85°C. Dissolution of vilazodone free
15 base in water and methanol may be carried out for about 30 minutes to about 6 hours, preferably for about 1 hour to about 4 hours. Vilazodone free base may be converted to crystalline Form B of vilazodone free base in the presence of methanol.

The crystalline Form B vilazodone free base may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof.

20 A tenth aspect of the present invention provides a process of preparing crystalline Form C of vilazodone free base which comprises:

- a) treating vilazodone free base or vilazodone salt with methylated ethanol; and
- b) isolating crystalline Form C of vilazodone free base from the reaction mixture thereof.

25 The vilazodone salt may be vilazodone hydrobromide. Conversion of vilazodone hydrobromide to vilazodone free base may be carried out in the presence of base and solvent. The base may be inorganic, for example aqueous sodium bicarbonate. The solvent for the conversion of vilazodone hydrobromide to vilazodone free base may be selected from water, methylated ethanol or a combination thereof. Conversion of
30 vilazodone hydrobromide to vilazodone free base may be carried out a temperature of about 10°C to about 100°C, preferably at about 20°C to about 85°C. Dissolution of

vilazodone free base in water and methylated ethanol may be carried out for about 30 minutes to about 6 hours, preferably for about 1 hour to about 4 hours. Vilazodone free base may be converted to crystalline Form C of vilazodone free base in the presence of methylated ethanol.

- 5 The crystalline Form C vilazodone free base may be isolated by filtration, decantation, drying, vacuum drying, or a combination thereof.

Crystalline Form A, Form B, or Form C of vilazodone free base of the present invention can be used for the preparation of vilazodone hydrochloride.

- 10 An eleventh aspect of the present invention provides a pharmaceutical composition comprising vilazodone hydrobromide, crystalline Form A of vilazodone free base, crystalline Form B of vilazodone free base, or crystalline Form C of vilazodone free base, and a carrier.

- 15 A twelfth aspect of the present invention provides a method of treating a patient suffering from a depressive disorder, an anxiety disorder, a bipolar disorder, mania, dementia, a substance-related disorder, a sexual dysfunction, an eating disorder, obesity, fibromyalgia, a sleeping disorder, a psychiatric disorder, cerebral infarct, tension, side-effects in the treatment of hypertension, a cerebral disorder, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome, undesired puerperal lactation, or combinations thereof, comprising administering vilazodone hydrobromide, crystalline Form A of vilazodone free base, crystalline Form B of vilazodone free base, or crystalline Form C of vilazodone free base to the said patient.

- 20 XRPD patterns of the samples were determined by using Panalytical X'Pert Pro X-Ray Powder Diffractometer in the range 3-40 degree 2 theta and under tube voltage and current of 45 Kv and 40 mA respectively. Copper radiation of wavelength 1.54 angstrom and Xceletor detector was used.

In the following section, embodiments are described by way of examples to illustrate the process of the invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

EXAMPLES

Example 1: Preparation of Vilazodone Hydrobromide

5-(Piperazin-1-yl)-1-benzofuran-2-carboxamide (50 g) and 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (52.27 g) were added to N-methylpyrrolidone (250 mL) at 28°C. The temperature of the reaction mixture was increased to 120°C and maintained at 115°C to 120°C for 2 hours. Tributylamine (37.75 g) was added to the reaction mixture at 115°C to 120°C and the temperature was maintained at 115°C to 120°C for 6 hours. The reaction mixture was cooled to 30°C. Methanol (500 mL) and concentrated (40% to 48%) hydrobromic acid (37 g) were added to the reaction mixture at 25°C to 30°C. The mixture was stirred at 25°C to 30°C for 16 hours. The reaction mixture was filtered and washed with methanol (50 mL x 4) at 20°C to 30°C.

Yield (Wet): 88 g

Example 2: Preparation of Vilazodone Hydrobromide

Vilazodone hydrobromide (86 g), prepared according to Example 1, was added to N-methylpyrrolidone (250 mL) and conc. hydrobromic acid (5 mL). The reaction mixture was heated to 55°C. Methanol (500 mL) was added to the reaction mixture at 50°C to 55°C and the mixture cooled to 30°C. The reaction mixture was stirred for 2 hours at 25°C to 30°C. The reaction mixture was filtered and washed with methanol (50 mL x 4) at 20°C to 30°C to obtain the title compound having XRPD data as shown in Figure 1.

Yield (Wet): 68 g

Example 3: Preparation of Crystalline Form B of Vilazodone Free Base

Vilazodone hydrobromide (67 g), prepared according to Example 2, was added to a mixture of methanol (1000 mL) and deionized water (500 mL). The reaction mixture was heated to 75°C. Activated carbon (10 g) was added to the reaction mixture at 75°C. The reaction mixture was filtered and washed with a mixture of methanol (100 mL) and deionized water (50 mL). The pH of the reaction mixture was adjusted to 7.02 with sodium bicarbonate solution (150 mL) at 55°C to 60°C. The reaction mixture was cooled to 30°C and stirred for 3 hours. The reaction mixture was filtered and washed with

methanol (50 mL x 3) at 20°C to 30°C. The solid obtained was dried under an air oven at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 2.

Yield: 45.5 g

5

Example 4: Preparation of Vilazodone Hydrochloride

Vilazodone free base (40 g), prepared according to Example 3, was added to 2-propanol (1720 mL) and deionized water (80 mL) at 20°C to 30°C. The temperature of the reaction mixture was raised to 80°C. Activated carbon (4 g) was added at 80°C. The reaction mixture was filtered and washed with 2-propanol (160 mL) at 80°C. 0.1 N 2-propanolic hydrochloride (9.4 g concentrated hydrochloric acid in 904 mL 2-propanol) was added to the reaction mixture over 60 minutes at 78°C to 80°C. The reaction mixture was cooled to 55°C. The reaction mixture was filtered and washed with 2-propanol (40 mL x 2). The reaction mixture was dried under vacuum at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 3.

Yield: 37.5 g

Example 5: Preparation of Vilazodone Hydrobromide

5-(piperazin-1-yl)-1-benzofuran-2-carboxamide (50 g) and 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (52.3 g) were added to N-methylpyrrolidone (250 mL) at 30°C. The temperature of the reaction mixture was increased to 120°C and maintained at 115°C to 120°C for 2 hours. Tributylamine (38 g) was added to the reaction mixture at 115°C to 117°C and the temperature maintained at 115°C to 120°C for 6 hours. The reaction mixture was cooled to 30°C. 2-Propanol (500 mL) and concentrated (40% to 48%) hydrobromic acid (37 g) were added to the reaction mixture at 25°C to 30°C and the reaction mixture was seeded with vilazodone hydrobromide (0.25 g) at 25°C to 30°C. The reaction mixture was stirred at 25°C to 30°C for 6 hours. The reaction mixture was filtered and washed with 2-propanol (50 mL x 4) at 20°C to 30°C.

Yield (Wet): 89 g

30

Example 6: Preparation of Vilazodone Hydrobromide

Vilazodone hydrobromide (88 g), prepared according to Example 5, was added to N-methylpyrrolidone (250 mL) and concentrated hydrobromic acid (5 mL). The reaction mixture was heated to 55°C. 2-Propanol (250 mL) was added to the reaction mixture at 50°C to 55°C and the reaction mixture cooled to 30°C. The reaction mixture was stirred for 1 hour at 25°C to 30°C. The reaction mixture was filtered and washed with 2-propanol (50 mL x 2) at 20°C to 30°C to form title compound having XRPD data as shown in Figure 4.

Yield (Wet): 104 g

10

Example 7: Preparation of Crystalline Form A of Vilazodone Free Base

Vilazodone hydrobromide (102 g), prepared according to Example 6, was added to a mixture of 2-propanol (1000 mL) and deionized water (500 mL). The reaction mixture was heated to 70°C. Activated carbon (10 g) was added to the reaction mixture at 70°C. The reaction mixture was filtered and washed with a mixture of 2-propanol (100 mL) and deionized water (50 mL). The pH of the reaction mixture was adjusted to 7 with sodium bicarbonate solution (~150 mL) at 65°C to 70°C. The reaction mixture was cooled to 30°C and stirred for 30 minutes. The reaction mixture was filtered and washed with 2-propanol (50 mL x 2) at 20°C to 30°C. The solid obtained was dried under an air oven at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 5.

Yield: 42.5 g

Example 8: Preparation of Vilazodone Hydrochloride

Vilazodone free base (40 g) prepared according to Example 7 was added to 2-propanol (1720 mL) at 20°C to 30°C. The temperature of the reaction mixture was raised to 82°C and deionized water (80 mL) was added at 78°C to 80°C. Activated carbon (2 g) was added at 80°C and the temperature was maintained for 30 minutes. The reaction mixture was filtered and washed with 2-propanol (200 mL) at 80°C. 0.1 N 2-propanolic hydrochloride (9.4 g concentrated hydrochloric acid in 904 mL 2-propanol) was added to the reaction mixture over 60 minutes at 78°C to 80°C. The reaction mixture was cooled to

30

55°C. The reaction mixture was filtered and washed with 2-propanol (80 ml) at 55°C. The reaction mixture was dried under vacuum at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 6.

Wet weight: 43 g

5 Dry weight: 39.5 g

Example 9: Preparation of Vilazodone Hydrobromide

5-(Piperazin-1-yl)-1-benzofuran-2-carboxamide (50 g) and 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (52.3 g) were added to N-methylpyrrolidone (250 mL) at 20°C to 30°C. The temperature of the reaction mixture was increased to 120°C and maintained at 110°C to 120°C for 2 hours. Tributylamine (37.8 g) was added to the reaction mixture at 110°C to 120°C and the temperature was maintained at 110°C to 120°C for 6 hours. The reaction mixture was cooled to 30°C. Methylated ethanol (500 mL) and aqueous (40% to 48%) hydrobromic acid (38 g) were added to the reaction mixture. The reaction mixture was stirred at 20°C to 30°C for 15 hours. The solid was filtered and washed with methylated ethanol (4 x 50 mL) at 20°C to 30°C.

Yield (Wet): 119 g

Example 10: Preparation of Vilazodone Hydrobromide

Vilazodone hydrobromide (118 g), prepared according to Example 9, was added to N-methylpyrrolidone (250 mL) and the mixture was heated to 75°C. A mixture of methylated ethanol (500 ml) and deionized water (50 mL) was added to the reaction mixture at 70°C to 75°C. The reaction mixture was heated to 84°C and cooled to 30°C. The reaction mixture was stirred for 1 hour at 25°C to 30°C. The solid was filtered and washed with methylated ethanol (2 x 50 mL) at 25°C to 30°C to form the title compound.

25 Yield (Wet): 63.7 g

Example 11: Preparation of Crystalline Form C of Vilazodone Free Base

Vilazodone hydrobromide (63.7 g), prepared according to Example 10, was added to a mixture of methylated ethanol (1000 mL) and deionized water (500 mL). The mixture was heated to 82°C. Activated carbon (10 g) was added to the reaction mixture and stirred

under reflux for 30 minutes. The mixture was filtered and washed with a mixture of methylated ethanol (100 mL) and deionized water (50 mL) at 80°C. The pH of the reaction mixture was adjusted to 8 with sodium bicarbonate solution (290 mL) at 50°C to 60°C. The reaction mixture was cooled to 28°C and stirred for 1 hour. The solid was
5 filtered and washed with methylated ethanol (2 x 50 mL) at 25°C to 30°C. The solid obtained was dried under an air oven at 50°C to 55°C for 8 hours to obtain the title compound having XRPD data as shown in Figure 7.

Yield: 44.1 g

10 Example 12: Preparation of Vilazodone Hydrochloride

Vilazodone free base (42 g), prepared according to Example 11, was added to 2-propanol (1680 mL) at 20°C to 30°C. The temperature was raised to 82°C. Deionized water (84 mL) was added at 82°C and stir for 20 minutes at 82°C. Activated carbon (2.1 g) was added and the temperature was maintained for 30 minutes under reflux. The
15 reaction mixture was filtered and washed with 2-propanol (126 mL) at 82°C. The reaction mixture was heated to 82°C. A mixture of hydrochloric acid (9.91 g concentrated hydrochloric acid, diluted to 952 mL with 2-propanol) was added to the reaction mixture at 82°C over 60 minutes. The reaction mixture was cooled to 54°C and stirred for 30 minutes at 50°C to 55°C. The solid was filtered and washed with 2-propanol (2 x 42 mL)
20 at 50°C to 55°C. The reaction mixture was dried under vacuum at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 8.

Yield: 41.1 g

Example 13: Preparation of Vilazodone Hydrobromide

25 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide (50 g) and 3-(4-chlorobutyl)-1H-indole-5-carbonitrile (52.27 g) were added to N-methylpyrrolidone (250 mL) at 26°C. The temperature of the reaction mixture was increased to 120°C and maintained at 110°C to 120°C for 2 hours. Tributylamine (37.75 g) was added to the reaction mixture at 117°C to 118°C and the temperature was maintained at 115°C to 118°C for 6 hours. The reaction
30 mixture was cooled to 30°C. 2-Propanol (500 mL) and concentrated (40% to 48%) hydrobromic acid (27 mL) were added to the reaction mixture at 25°C to 30°C and the

reaction mixture was seeded with vilazodone hydrobromide (0.25 g) at 25°C to 30°C. The reaction mixture was stirred at 25°C to 30°C for 16 hours. The reaction mixture was filtered and washed with 2-propanol (50 mL x 4) at 25°C to 30°C.

Yield (Wet): 130 g

5

Example 14: Preparation of Vilazodone Hydrobromide

Vilazodone hydrobromide (129 g), prepared according to Example 13, was added to N-methylpyrrolidone (250 mL) and concentrated hydrobromic acid (5 mL) at 55°C. 2-Propanol (500 mL) was added to the reaction mixture at 50°C to 55°C and the mixture was cooled to 30°C. The reaction mixture was stirred for 2 hours at 25°C to 30°C. The reaction mixture was filtered and washed with 2-propanol (50 mL x 3) at 20°C to 30°C to obtain the title compound having XRPD data as shown in Figure 9.

Yield (Wet): 170 g

15 Example 15: Preparation of Crystalline Form A of Vilazodone Free Base

Vilazodone hydrobromide (169 g), prepared according to Example 14, was added to a mixture of 2-propanol (1000 mL) and deionized water (500 mL). The reaction mixture was heated to 80°C. Activated carbon (10 g) was added to the reaction mixture at 79°C to 80°C and the mixture stirred for 60 minutes at 78°C to 80°C. The reaction mixture was filtered and washed with a mixture of 2-propanol (100 mL) and deionized water (50 mL) at 80°C. The pH of the reaction mixture was adjusted to 7.01 with sodium bicarbonate solution (150 mL) at 60°C to 65°C. The reaction mixture was cooled to 30°C and stirred at 25°C to 30°C for 3 hours. The solid was filtered and washed with 2-propanol (50 mL x 3) at 20°C to 30°C. The solid obtained was dried in an air oven at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 10.

Yield: 47 g

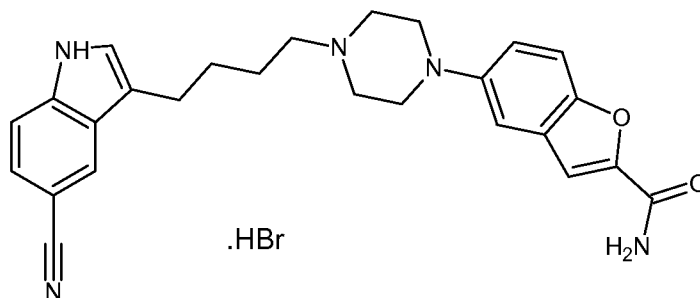
Example 16: Preparation of Vilazodone Hydrochloride

Vilazodone free base (45 g) prepared according to Example 15 was added to 2-propanol (1935 mL) at 30°C. The temperature of the reaction mixture was raised to 80°C. N-Methylpyrrolidone (90 mL) was added at 78°C to 80°C. Activated carbon (2.25 g) was
5 added at 78°C and maintained at 78°C to 80°C for 60 minutes. The reaction mixture was filtered and washed with 2-propanol (135 mL) at 78°C to 80°C. 0.1 N 2-propanolic hydrochloride (1020 mL) was added to the reaction mixture over 60 minutes at 78°C to 80°C. The reaction mixture was cooled to 55°C. The reaction mixture was filtered and
10 washed with 2-propanol (135 mL) at 55°C. The reaction mixture was dried under vacuum at 50°C to 55°C for 16 hours to obtain the title compound having XRPD data as shown in Figure 11.

Yield: 43 g

We claim:

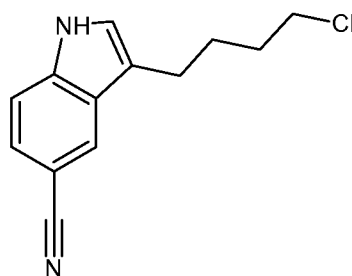
1. Vilazodone hydrobromide of Formula III.



FORMULA III

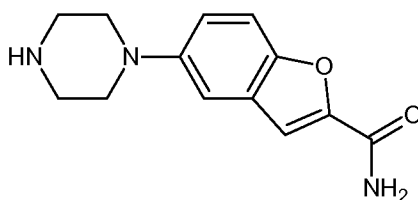
2. A process for the preparation of vilazodone hydrobromide, which comprises:

- a) reacting 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula IV



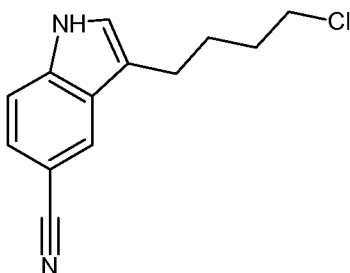
FORMULA IV

with 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V;



FORMULA V

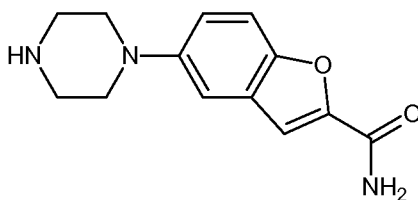
- b) treating the reaction mixture obtained in step a) with hydrobromic acid; and
- c) isolating vilazodone hydrobromide from the reaction mixture thereof.
3. A process for the preparation of vilazodone hydrochloride, which comprises:
- a) reacting 3-(4-chlorobutyl)-1H-indole-5-carbonitrile of Formula IV



3
4
5

FORMULA IV

with 5-(piperazin-1-yl)-1-benzofuran-2-carboxamide of Formula V;



6
7

FORMULA V

- 8 b) treating the reaction mixture obtained in step a) with hydrobromic acid;
- 9 c) optionally isolating vilazodone hydrobromide from the reaction mixture
- 10 thereof;
- 11 d) converting vilazodone hydrobromide to vilazodone free base;
- 12 e) treating vilazodone free base with hydrochloric acid; and
- 13 f) isolating vilazodone hydrochloride from the reaction mixture thereof.

1 4. A process for the preparation of vilazodone hydrochloride, which comprises:

- 2 a) treating vilazodone hydrobromide with hydrochloric acid; and
- 3 b) isolating vilazodone hydrochloride from the reaction mixture thereof.

1 5. The process according to claims 2 and 3, wherein the reaction of the compound of

2 Formula IV and the compound of Formula V may be carried out in the presence of a base

3 and solvent.

1 6. The process according to claim 5, wherein the solvent is selected from the group

2 consisting of water, organic solvent, or a mixture thereof.

- 1 7. The process according to claim 6, wherein the organic solvent is selected from the
2 group consisting of alcohol, ketone, nitrile, amide, aromatic or aliphatic hydrocarbon or
3 dimethyl sulfoxide.
- 1 8. The process according to claim 5, wherein the solvent is N-methylpyrrolidone.
- 1 9. The process according to claim 5, wherein the base is selected from organic base or
2 inorganic base.
- 1 10. The process according to claim 9, wherein the organic base is tributylamine,
2 triethyl amine, diisopropyl amine, diisopropyl ethylamine, 4-dimethylaminopyridine,
3 pyrrolidone or N-methyl morpholine.
- 1 11. The process according to claim 9, wherein the inorganic base is hydroxides,
2 carbonates or bicarbonates of alkali or alkaline metal.
- 1 12. The process according to claim 3, wherein the hydrobromic acid used in step b) is
2 in solution form or gaseous form.
- 1 13. The process according to claim 12, wherein solution of the hydrobromic acid is in
2 an aqueous or organic solvent.
- 1 14. The process according to claim 3, wherein the conversion of vilazodone
2 hydrobromide to vilazodone free base in step d) is carried out in the presence of a base and
3 solvent.
- 1 15. The process according to claim 4, wherein vilazodone hydrobromide is converted
2 to vilazodone free base in the presence of a base and solvent.
- 1 16. The process according to claim 14 or 15, wherein the base is sodium bicarbonate.
- 1 17. The process according to claim 14 or 15, wherein the solvent is water, organic
2 solvent, or a combination thereof.
- 1 18. The process according to claim 17, wherein the organic solvent is selected from the
2 group consisting of alcoholic solvent, esters, chlorinated solvents, ketones, amides,
3 sulfolanes, or a combination thereof.
- 1 19. The process according to claim 15, wherein vilazodone free base is further
2 converted to vilazodone hydrochloride in a solvent selected from water, alcoholic or amide
3 solvent.

- 1 20. The process according to claim 3, wherein the treatment of vilazodone free base
2 with hydrochloric acid is carried out in a solvent selected from water, alcoholic or amide
3 solvent.
- 1 21. The process according to claims 19 and 20, wherein the treatment of vilazodone
2 free base with hydrochloric acid is carried out in 2-propanol in combination with N-
3 methylpyrrolidone in the absence of water.
- 1 22. The process according to claims 19 and 20, wherein the treatment of vilazodone
2 free base with hydrochloric acid is carried out in 2-propanol, either alone or in
3 combination with water or N-methylpyrrolidone.
- 1 23. Crystalline Form A of vilazodone free base having an XRPD pattern substantially
2 the same as depicted in Figure 5 or Figure 10.
- 1 24. Crystalline Form A of vilazodone free base characterized by an XRPD pattern
2 having interplanar spacing (d) values substantially at 15.19, 5.52, 4.73, 4.27, 4.13, 3.66,
3 and $3.28 \pm 0.2 \text{ \AA}$.
- 1 25. The crystalline Form A of vilazodone free base according to claim 24 which is
2 further characterized by an XRPD pattern having interplanar spacing (d) values
3 substantially at 15.19, 12.01, 8.03, 6.59, 6.40, 5.52, 5.16, 5.07, 4.73, 4.64, 4.46, 4.27, 4.13,
4 4.07, 3.81, 3.66, 3.52, 3.49, 3.28, 3.19, 3.13, 3.05, 3.02, 2.97, 2.93, 2.88, 2.79, 2.75, 2.68,
5 2.50, 2.47, 2.35, and $2.30 \pm 0.2 \text{ \AA}$.
- 1 26. Crystalline Form B of vilazodone free base an XRPD pattern substantially the
2 same as depicted in Figure 2.
- 1 27. Crystalline Form B of vilazodone free base is characterized by an XRPD pattern
2 having interplanar spacing (d) values substantially at 8.38, 6.17, 5.96, 5.81, 5.01, 4.50,
3 4.04, 3.68, 3.60, 3.53, and $3.08 \pm 0.2 \text{ \AA}$.
- 1 28. The crystalline Form B of vilazodone free base according to claim 27 which is
2 further characterized by an XRPD pattern having interplanar spacing (d) values
3 substantially at 17.00, 11.58, 8.38, 6.17, 5.96, 5.81, 5.51, 5.01, 4.79, 4.50, 4.32, 4.24, 4.18,
4 4.08, 4.04, 3.87, 3.68, 3.60, 3.53, 3.41, 3.28, 3.08, 3.03, 2.99, 2.90, 2.85, 2.71, 2.60, 2.50,
5 2.46, and $2.41 \pm 0.2 \text{ \AA}$.
- 1 29. Crystalline Form C of vilazodone free base having an XRPD pattern substantially
2 the same as depicted in Figure 7.

- 1 30. Crystalline Form C of vilazodone free base is characterized by an XRPD pattern
2 having interplanar spacing (d) values substantially at 14.94, 5.51, 4.71, 4.28, 4.11, 3.65,
3 3.27, and 3.19 ± 0.2 Å.
- 1 31. The crystalline Form C of vilazodone free base according to claim 30 which is
2 further characterized by an XRPD pattern having interplanar spacing (d) values
3 substantially at 14.94, 7.97, 6.54, 6.38, 5.51, 5.16, 5.05, 4.71, 4.45, 4.28, 4.11, 4.05, 3.80,
4 3.65, 3.51, 3.48, 3.27, 3.19, 3.12, 3.04, 3.01, 2.96, 2.92, 2.87, 2.79, 2.66, 2.50, 2.47, 2.35,
5 and 2.30 ± 0.2 Å.
- 1 32. A process of preparing crystalline Form A of vilazodone free base which
2 comprises:
- 3 a) treating vilazodone free base or vilazodone salt with 2-propanol; and
4 b) isolating crystalline Form A of vilazodone free base from the reaction
5 mixture thereof.
- 1 33. A process of preparing crystalline Form B of vilazodone free base which
2 comprises:
- 3 a) treating vilazodone free base or vilazodone salt with methanol; and
4 b) isolating crystalline Form B of vilazodone free base from the reaction
5 mixture thereof.
- 1 34. A process of preparing crystalline Form C of vilazodone free base which
2 comprises:
- 3 a) treating vilazodone free base or vilazodone salt with methylated ethanol; and
4 b) isolating crystalline Form C of vilazodone free base from the reaction
5 mixture thereof.
- 1 35. Use of crystalline Form A, Form B, or Form C of vilazodone free base according
2 to claims 23, 26, or 29 for the preparation of vilazodone hydrochloride.
- 1 36. A pharmaceutical composition comprising vilazodone hydrobromide, crystalline
2 Form A of vilazodone free base, crystalline Form B of vilazodone free base, or crystalline
3 Form C of vilazodone free base and a carrier.
- 1 37. A method of treating a patient suffering from a depressive disorder, an anxiety
2 disorder, a bipolar disorder, mania, dementia, a substance-related disorder, a sexual

3 dysfunction, an eating disorder, obesity, fibromyalgia, a sleeping disorder, a psychiatric
4 disorder, cerebral infarct, tension, side-effects in the treatment of hypertension, a cerebral
5 disorder, chronic pain, acromegaly, hypogonadism, secondary amenorrhea, premenstrual
6 syndrome, undesired puerperal lactation, or combinations thereof, comprising
7 administering vilazodone hydrobromide, crystalline Form A of vilazodone free base,
8 crystalline Form B of vilazodone free base, or crystalline Form C of vilazodone free base
9 to the said patient.

FIGURE 1: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF THE VILAZODONE HYDROBROMIDE OBTAINED ACCORDING TO EXAMPLE 2.

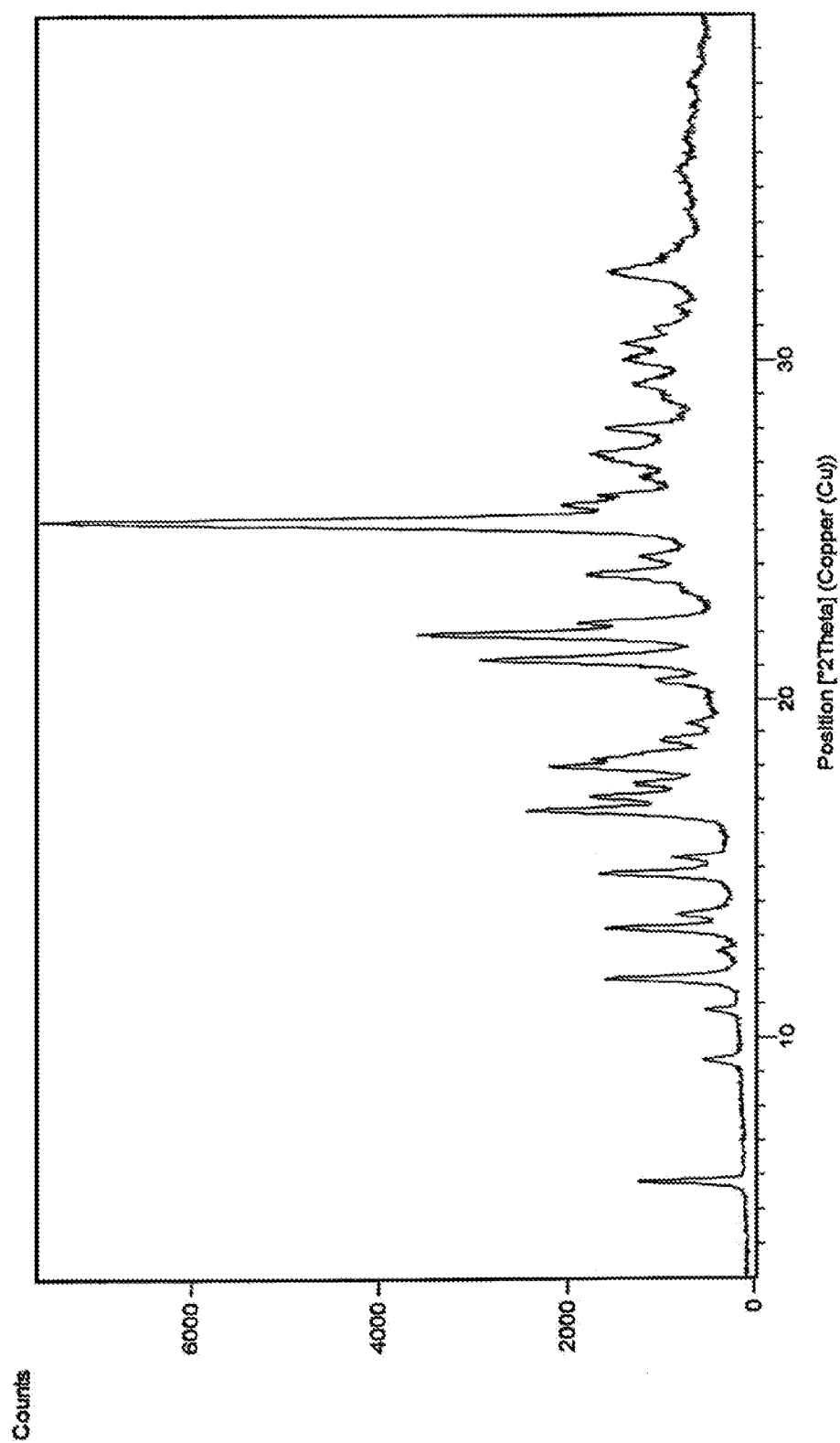


FIGURE 1A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 1.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.82	15.20	15.91
9.35	9.46	5.51
10.82	8.17	4.95
11.73	7.54	19.71
12.56	7.04	2.25
13.24	6.69	19.21
13.66	6.48	8.13
14.84	5.97	20.06
15.32	5.78	7.52
16.71	5.30	30.25
17.11	5.18	21.12
17.49	5.07	14.08
17.99	4.93	26.04
18.22	4.87	19.43
18.79	4.72	10.01
19.30	4.60	5.67
20.54	4.32	10.35
21.21	4.19	35.06
21.96	4.05	45.88
22.27	3.99	21.79
23.71	3.75	20.49
24.23	3.67	12.12
25.29	3.52	100.00
25.79	3.45	22.27
26.06	3.42	16.49
27.26	3.27	18.70
28.04	3.18	16.29
29.27	3.05	11.87
29.97	2.98	12.85
30.50	2.93	13.66
32.58	2.749	15.25
35.44	2.53	4.54
38.10	2.36	2.18

FIGURE 2: X-RAY POWDER DIFFRACTION (XRPD) PATTERN OF CRYSTALLINE FORM B OF VILAZODONE FREE BASE OBTAINED ACCORDING TO EXAMPLE 3.

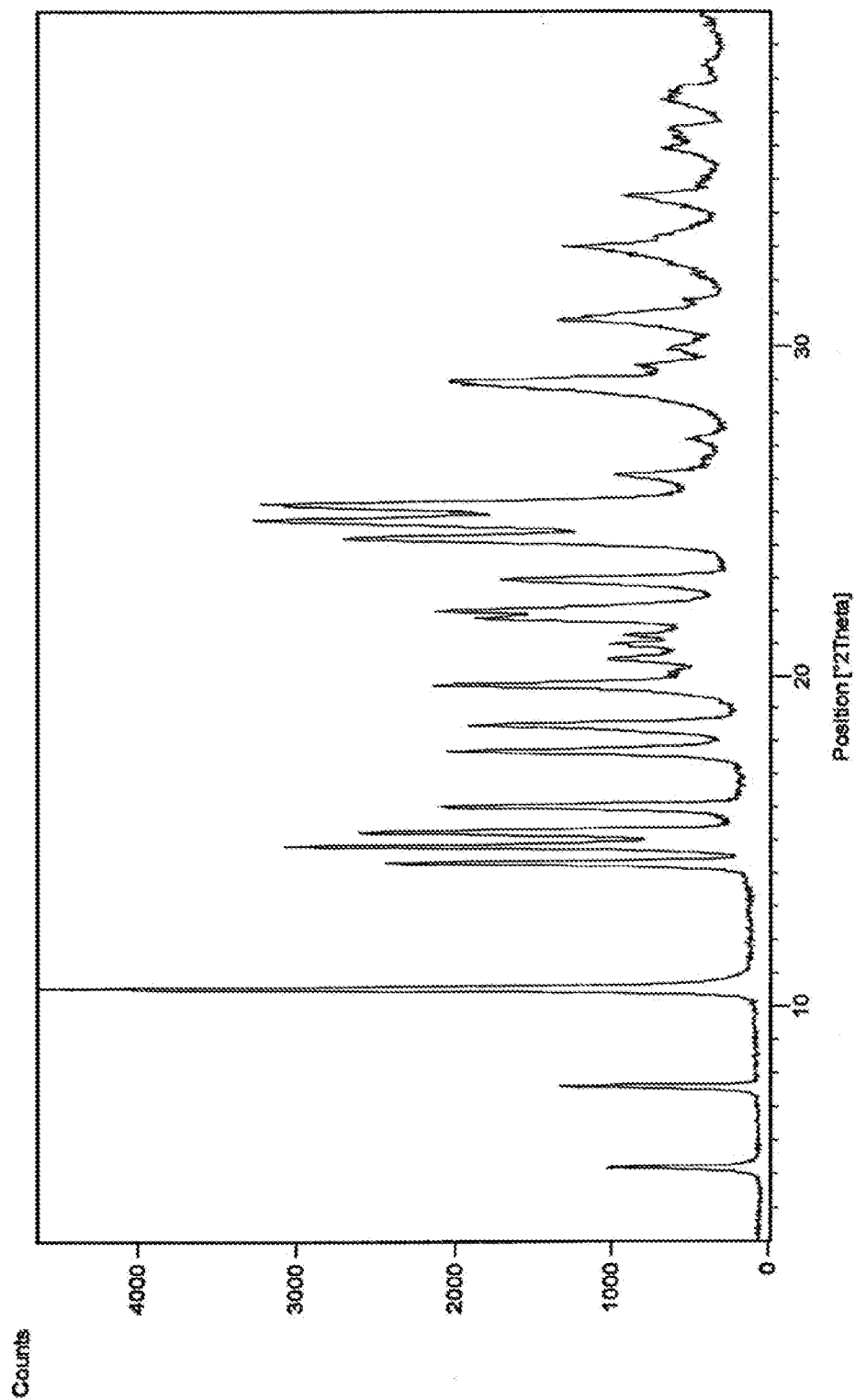


FIGURE 2A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 2.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.20	17.00	20.82
7.63	11.58	24.70
10.56	8.38	100.00
14.35	6.17	48.58
14.86	5.96	64.35
15.25	5.81	53.65
16.08	5.51	38.96
17.71	5.01	41.93
18.52	4.79	37.72
19.72	4.50	42.31
20.55	4.32	17.96
20.94	4.24	17.83
21.23	4.18	15.59
21.76	4.08	37.50
22.00	4.04	41.25
22.96	3.87	33.73
24.19	3.68	54.09
24.76	3.60	68.00
25.25	3.53	65.16
26.12	3.41	16.35
27.21	3.28	5.58
28.97	3.08	40.12
29.43	3.03	11.80
29.92	2.99	8.70
30.78	2.90	24.52
31.38	2.85	5.94
32.99	2.71	23.41
34.51	2.60	13.18
35.92	2.50	7.95
36.53	2.46	7.44
37.35	2.41	7.58

FIGURE 3: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF THE VILAZODONE HYDROCHLORIDE OBTAINED ACCORDING TO EXAMPLE 4.

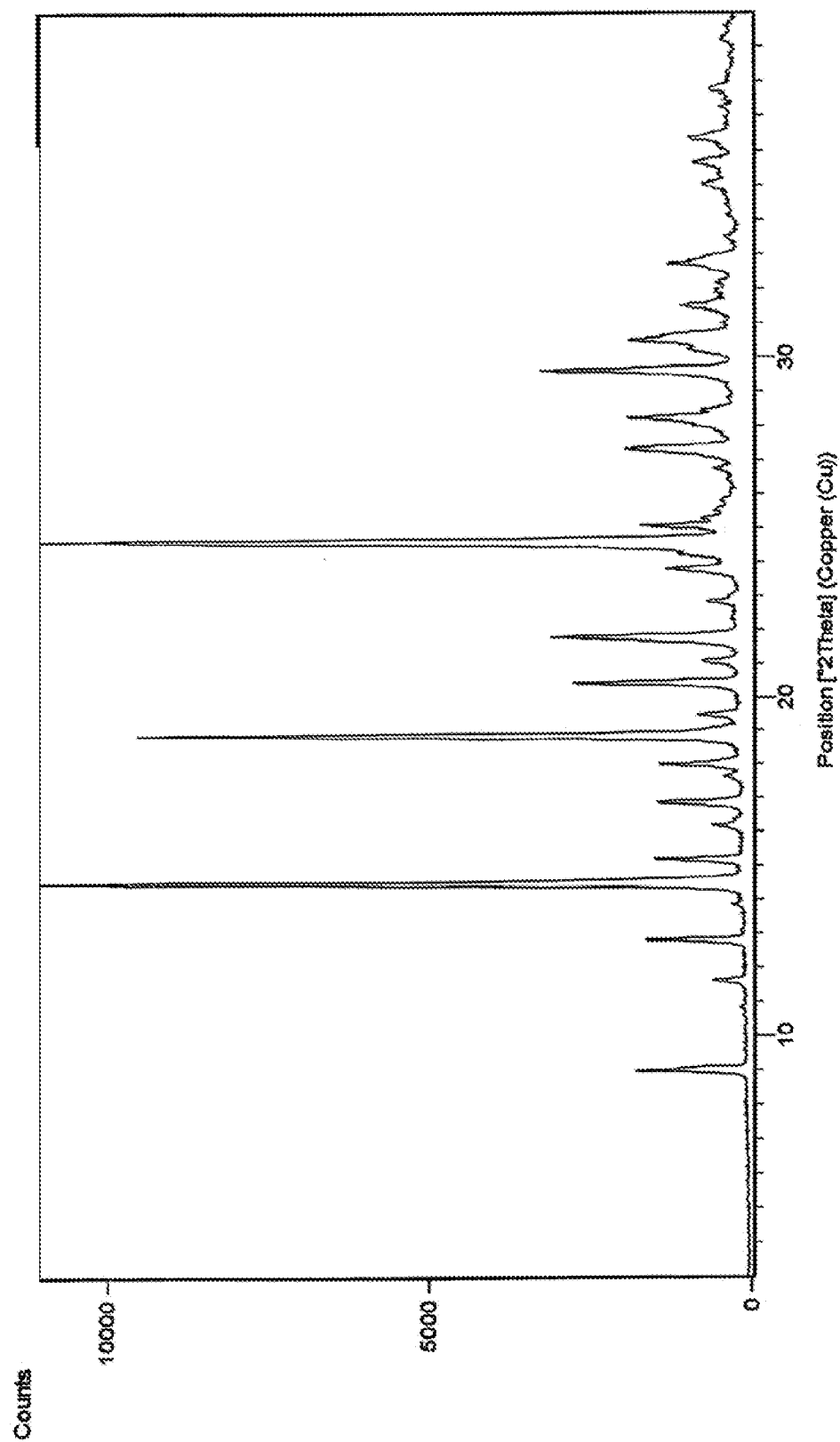


FIGURE 3A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 3.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
8.98	9.85	15.45
9.08	9.74	8.71
11.64	7.60	4.44
12.83	6.90	14.34
14.52	6.10	100.00
15.21	5.82	13.11
16.20	5.47	4.91
16.89	5.25	12.73
17.98	4.93	12.43
18.87	4.70	86.70
19.47	4.56	7.05
20.43	4.35	24.83
21.08	4.21	6.57
21.78	4.08	28.46
22.82	3.90	5.75
23.79	3.74	11.44
24.20	3.68	9.04
24.64	3.61	98.82
25.06	3.55	14.74
25.54	3.49	4.49
25.81	3.45	3.71
26.72	3.34	4.68
27.32	3.26	17.35
28.23	3.16	17.03
28.48	3.13	6.32
29.62	3.02	29.80
30.19	2.96	7.67
30.50	2.93	16.48
31.54	2.84	8.46
32.73	2.74	11.24
33.49	2.67	3.22
35.00	2.56	6.36
35.67	2.52	7.47
36.35	2.47	8.17
37.24	2.41	3.53
37.78	2.38	5.39
39.23	2.30	3.58

FIGURE 4: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF THE VILAZODONE HYDROBROMIDE OBTAINED ACCORDING TO EXAMPLE 6.

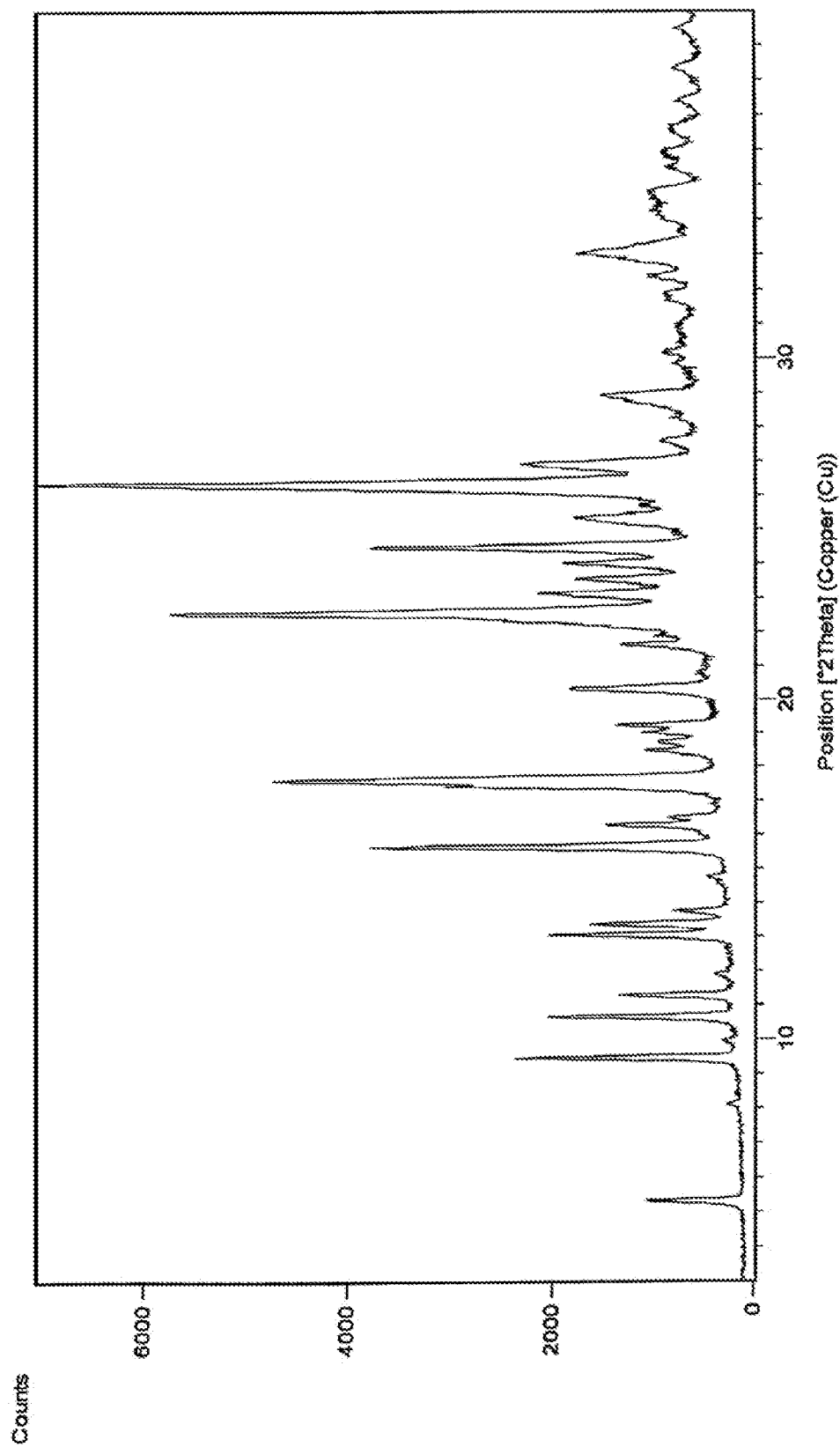


FIGURE 4A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 4.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.33	16.58	13.88
9.48	9.33	32.61
10.68	8.28	25.79
11.32	7.82	18.29
13.08	6.77	28.33
13.40	6.61	22.19
15.69	5.65	51.31
16.29	5.44	19.60
16.52	5.36	10.42
17.43	5.09	41.41
17.63	5.03	66.05
18.47	4.80	14.05
18.75	4.73	12.36
19.03	4.66	14.87
19.24	4.61	18.49
20.33	4.37	25.37
21.62	4.11	17.42
22.57	3.94	81.82
23.13	3.84	30.07
23.55	3.78	24.74
24.02	3.70	26.50
24.51	3.63	53.73
25.35	3.51	24.92
26.38	3.38	100.00
26.94	3.31	31.19
27.62	3.23	11.44
28.93	3.09	21.02
30.16	2.96	11.23
31.82	2.81	11.29
32.37	2.77	13.51
33.07	2.71	23.81
34.04	2.63	11.88
34.87	2.57	13.55
35.47	2.53	10.69
36.00	2.49	11.48
36.60	2.45	10.60
37.43	2.40	9.46
38.36	2.35	9.99
39.48	2.28	9.75

FIGURE 5: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF CRYSTALLINE FORM A OF VILAZODONE FREE BASE OBTAINED ACCORDING TO EXAMPLE 7.

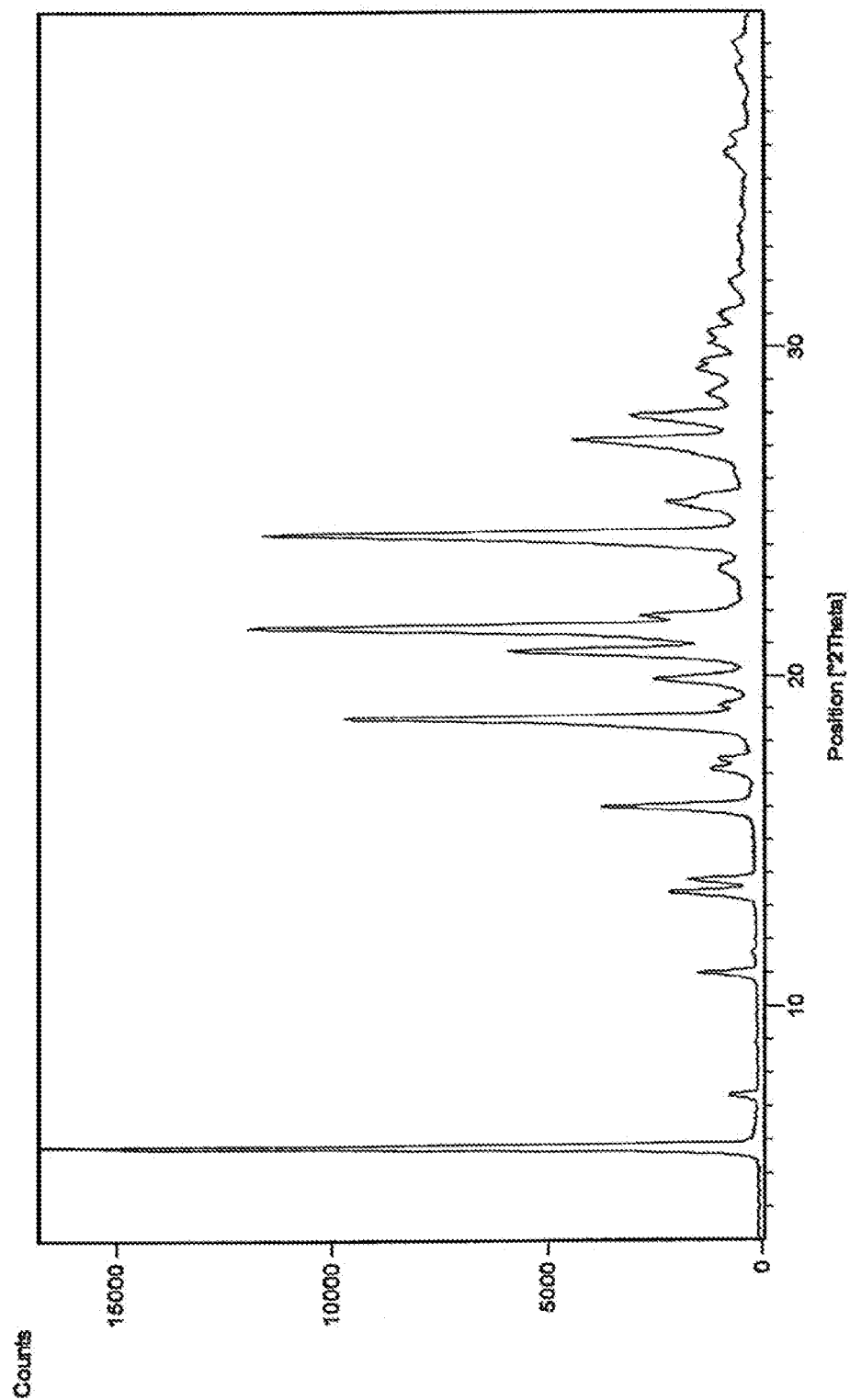


FIGURE 5A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 5.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.82	15.19	100.00
7.36	12.01	4.05
11.01	8.03	7.70
13.44	6.59	12.62
13.83	6.40	9.73
16.06	5.52	21.15
17.19	5.16	6.62
17.49	5.07	5.16
18.75	4.73	55.71
19.12	4.64	5.12
19.88	4.46	14.53
20.79	4.27	33.01
21.52	4.13	66.41
21.84	4.07	16.25
23.35	3.81	5.21
24.33	3.66	68.54
25.30	3.52	12.81
25.52	3.49	7.80
27.19	3.28	26.11
27.97	3.19	16.69
28.55	3.13	6.75
29.30	3.05	8.31
29.59	3.02	7.70
30.11	2.97	6.73
30.50	2.93	6.59
31.09	2.88	4.75
32.04	2.79	3.63
32.56	2.75	2.32
33.42	2.68	2.28
35.86	2.50	4.24
36.36	2.47	3.46
38.26	2.35	2.66
39.09	2.30	2.94

FIGURE 6: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF THE VILAZODONE HYDROCHLORIDE OBTAINED ACCORDING TO EXAMPLE 8.

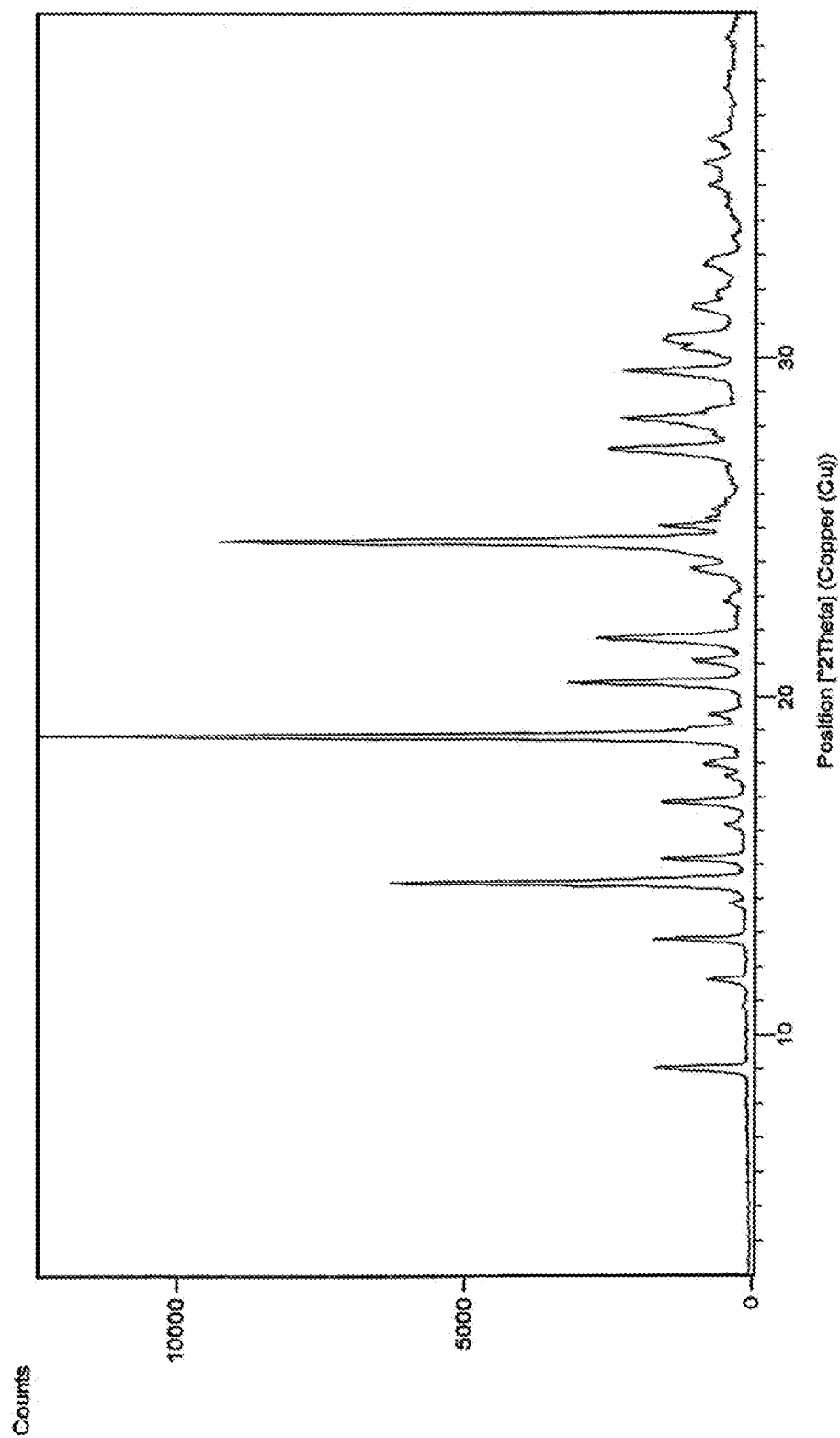


FIGURE 6A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 6.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
9.08	9.74	12.76
11.64	7.60	5.81
12.83	6.90	13.35
13.89	6.37	2.68
14.52	6.10	51.44
15.21	5.83	12.08
16.21	5.47	3.32
16.88	5.25	12.43
17.65	5.02	3.19
17.98	4.93	6.40
18.11	4.90	5.52
18.87	4.70	100.00
19.08	4.65	8.29
19.46	4.56	5.65
20.44	4.34	26.08
21.08	4.21	7.84
21.76	4.08	21.27
22.81	3.90	3.43
23.80	3.74	8.52
24.64	3.61	74.96
25.06	3.55	12.95
25.55	3.49	5.11
27.34	3.26	20.33
28.24	3.16	18.26
29.62	3.02	18.20
30.24	2.95	9.76
30.67	2.91	10.91
31.52	2.84	8.15
31.96	2.80	4.59
32.72	2.74	6.27
32.94	2.72	5.15
35.01	2.56	5.80
35.65	2.52	6.54
36.35	2.47	5.74
37.77	2.38	3.54
39.24	2.30	3.14

FIGURE 7: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF CRYSTALLINE FORM C OF VILAZODONE FREE BASE OBTAINED ACCORDING TO EXAMPLE 11.

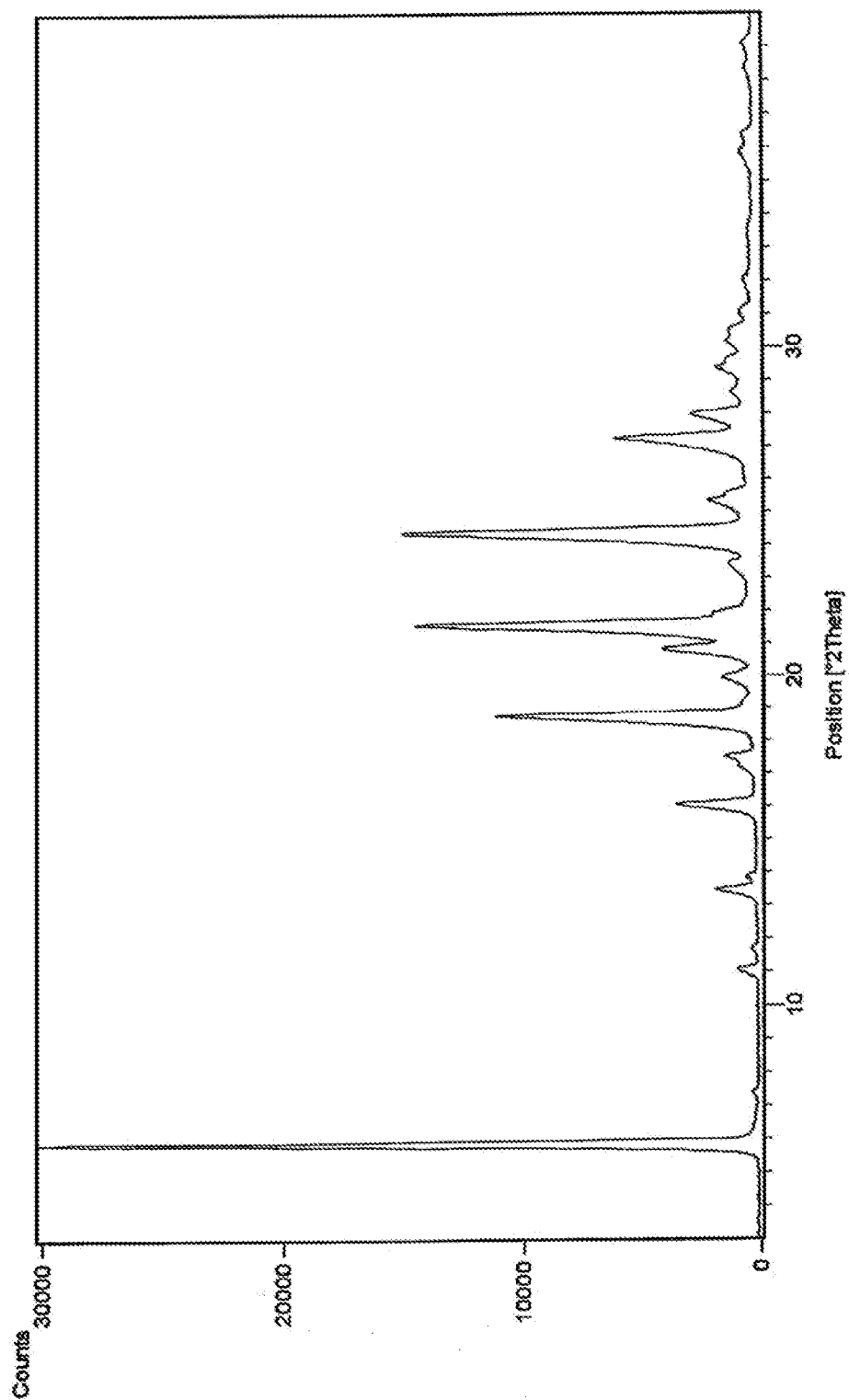


FIGURE 7A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 7.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.91	14.94	100.00
11.10	7.97	3.25
13.53	6.54	5.56
13.87	6.38	1.72
16.08	5.51	13.34
17.19	5.16	2.92
17.56	5.05	4.91
18.82	4.71	39.07
19.95	4.45	5.85
20.75	4.28	14.76
21.60	4.11	50.05
21.96	4.05	6.42
23.43	3.80	4.69
24.42	3.65	52.50
25.35	3.51	7.91
25.57	3.48	4.79
27.26	3.27	21.64
28.00	3.19	10.70
28.59	3.12	4.13
29.37	3.04	6.54
29.65	3.01	4.96
30.15	2.96	4.94
30.56	2.92	4.35
31.13	2.87	2.60
32.08	2.79	2.01
33.73	2.66	1.16
35.84	2.50	2.67
36.41	2.47	2.22
38.32	2.35	1.58
39.12	2.30	1.98

FIGURE 8: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF THE
VILAZODONE HYDROCHLORIDE OBTAINED ACCORDING TO EXAMPLE 12.

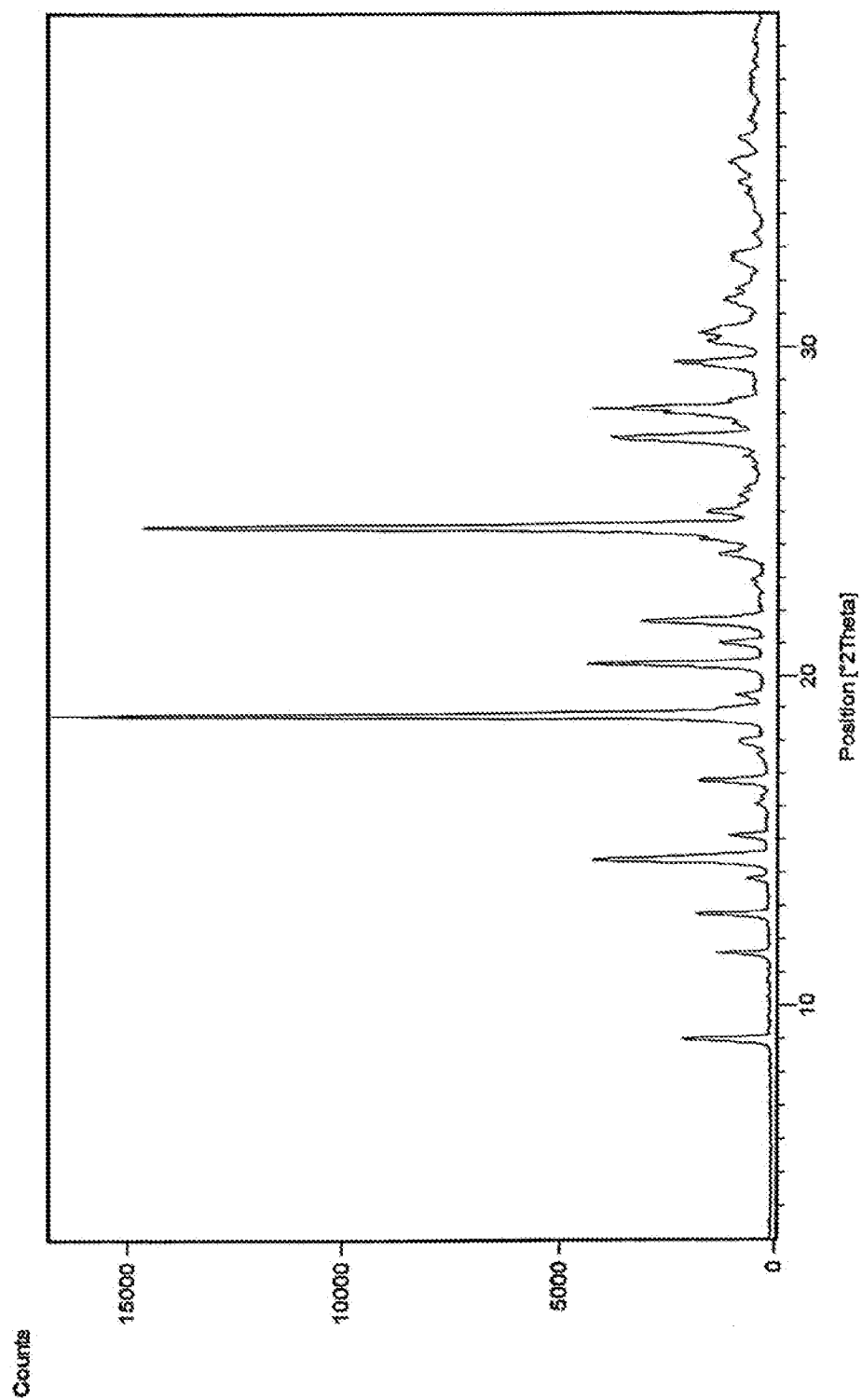


FIGURE 8A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 8.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
9.00	9.82	12.50
11.59	7.63	7.50
12.76	6.94	10.80
13.84	6.40	3.13
14.38	6.16	24.97
14.46	6.13	22.51
15.15	5.85	5.66
16.80	5.28	10.08
18.04	4.92	4.11
18.81	4.72	100.00
19.41	4.57	4.59
20.38	4.36	25.14
21.01	4.23	6.78
21.69	4.10	16.34
22.93	3.88	2.01
23.70	3.75	6.94
24.15	3.68	9.63
24.57	3.62	89.91
24.96	3.56	8.24
25.03	3.56	8.30
25.50	3.49	3.48
25.75	3.46	2.89
26.68	3.34	2.51
27.27	3.27	22.41
27.65	3.23	4.33
27.99	3.18	14.57
28.13	3.17	25.11
28.38	3.14	5.18
29.54	3.02	13.15
30.15	2.96	7.54
30.44	2.94	8.83
30.60	2.92	6.62
31.43	2.85	5.56
31.77	2.82	3.42
32.84	2.73	4.51
34.97	2.57	3.07
35.61	2.52	4.28
36.29	2.48	3.27

FIGURE 9: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF THE VILAZODONE HYDROBROMIDE OBTAINED ACCORDING TO EXAMPLE 14.

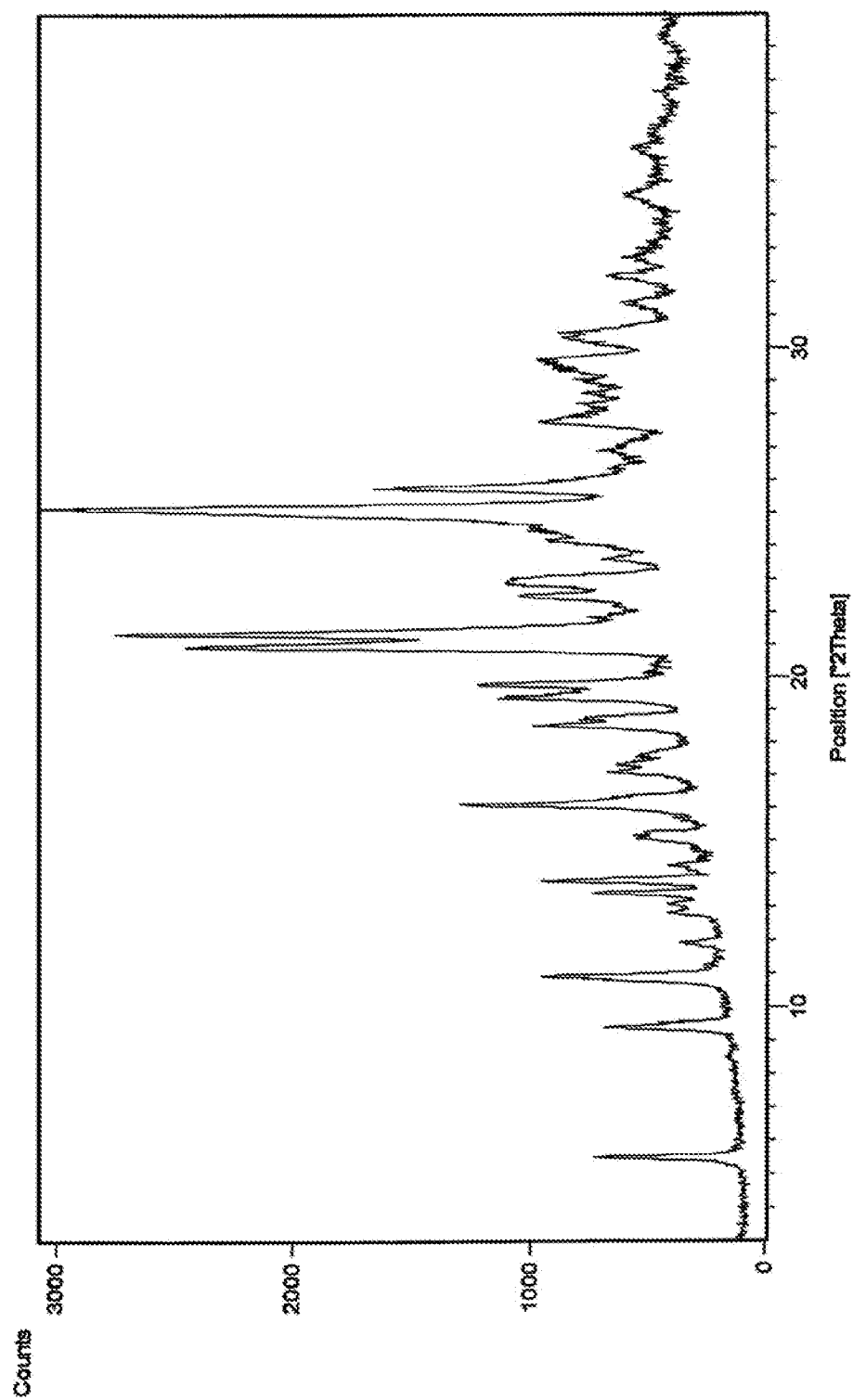


FIGURE 9A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 9.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.50	16.05	22.83
9.38	9.43	19.91
10.92	8.10	28.66
11.93	7.42	6.67
12.80	6.92	8.11
13.43	6.59	20.12
13.78	6.42	28.01
14.28	6.20	6.91
15.05	5.89	11.57
15.25	5.81	11.30
16.12	5.50	40.10
17.09	5.19	15.51
18.53	4.79	26.58
18.76	4.73	19.67
19.35	4.56	32.98
19.80	4.48	34.83
20.90	4.25	74.42
21.29	4.17	87.20
22.49	3.95	28.78
22.84	3.89	29.74
23.06	3.86	26.56
23.58	3.77	14.34
24.12	3.69	21.88
25.14	3.54	100.00
25.73	3.46	49.93
26.89	3.32	13.21
27.75	3.21	23.11
29.65	3.01	22.14
30.39	2.94	17.10
31.36	2.85	8.03
32.18	2.78	10.75
34.60	2.59	7.03
35.95	2.50	5.23

FIGURE 10: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF CRYSTALLINE FORM A OF VILAZODONE FREE BASE OBTAINED ACCORDING TO EXAMPLE 15.

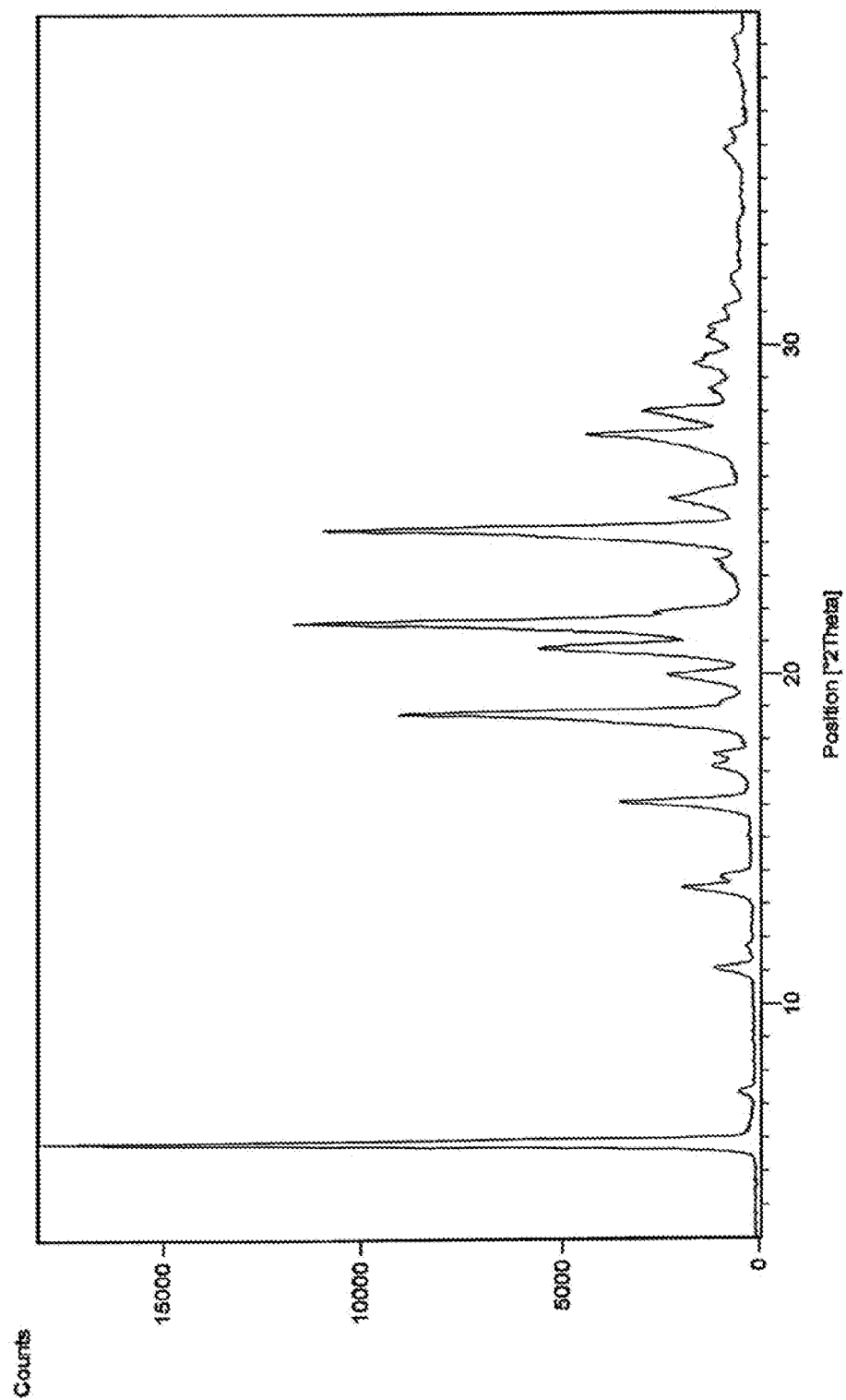


FIGURE 10A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 10.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.91	14.95	100.00
7.40	11.94	2.04
11.11	7.96	5.32
13.54	6.54	9.87
13.92	6.36	3.97
16.13	5.50	19.24
17.21	5.15	5.93
17.58	5.04	5.63
18.86	4.71	47.86
19.99	4.44	11.84
20.87	4.25	28.14
21.63	4.11	63.94
21.94	4.05	13.48
23.47	3.79	5.27
24.44	3.64	61.90
25.35	3.51	11.57
25.63	3.48	6.18
27.32	3.26	24.08
28.07	3.18	14.33
28.70	3.11	6.10
29.44	3.03	8.39
30.23	2.96	6.46
30.62	2.92	5.76
31.18	2.87	3.95
32.13	2.79	3.10
33.53	2.67	1.96
35.87	2.50	3.92
36.49	2.46	2.89
38.41	2.34	2.35
39.21	2.30	2.54

FIGURE 11: X-RAY POWDER DIFFRACTION PATTERN (XRPD) OF THE VILAZODONE HYDROCHLORIDE OBTAINED ACCORDING TO EXAMPLE 16.

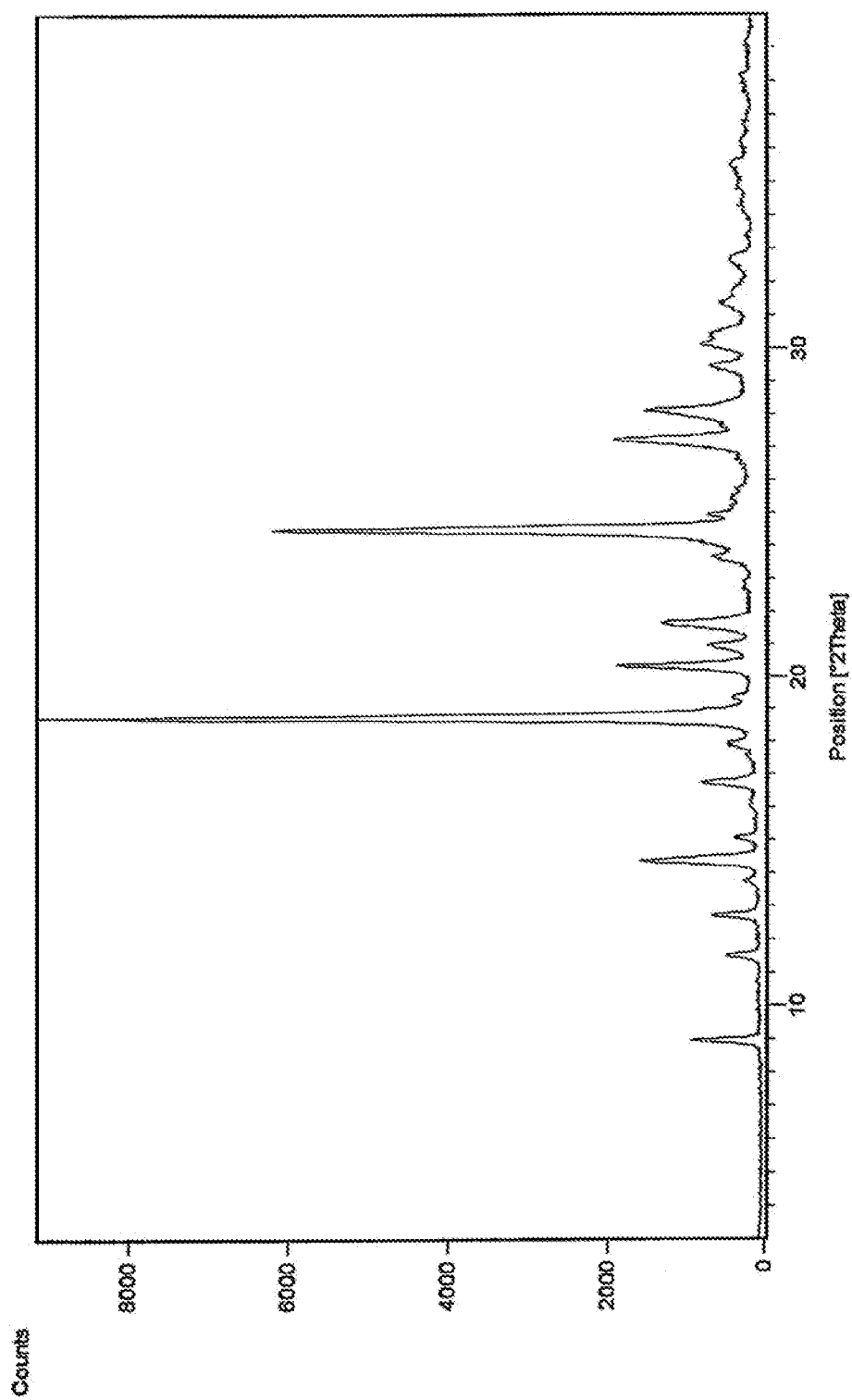


FIGURE 11A: TABLE OF VALUES FOR THE XRPD PATTERN DEPICTED IN FIGURE 11.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
8.96	9.86	10.01
11.52	7.68	4.72
12.72	6.96	6.99
13.77	6.43	2.02
14.37	6.16	17.11
15.10	5.87	3.27
16.09	5.51	1.05
16.78	5.28	7.94
17.96	4.94	4.30
18.76	4.73	100.00
19.36	4.59	3.47
20.32	4.37	20.41
20.97	4.24	6.66
21.66	4.10	13.33
22.81	3.90	1.72
23.68	3.76	6.05
24.51	3.63	67.64
24.92	3.57	6.90
27.27	3.27	19.04
28.11	3.17	15.51
29.45	3.03	6.50
30.13	2.97	7.76
30.42	2.94	5.89
31.36	2.85	4.59
32.80	2.73	2.93
34.22	2.62	1.43
35.60	2.52	2.88
38.14	2.36	1.48