Title: CRYSTALLINE FORMS OF (R)-8-CHLORO-1-METHYL-2,3,4,5-TETRAHYDRO-1H-3-BENZAZEPINE HYDROCHLORIDE

Abstract: The present invention is directed to crystalline forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, compositions containing the same, preparations, and uses thereof.
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
CRystalline Forms of (R)-8-Chloro-1-Methyl-2,3,4,5-Tetrahydro-1H-3-Benzazepine Hydrochloride

FIELD OF THE INVENTION

The present invention relates to crystalline forms of the 5-HT$_{2C}$ agonist, (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, compositions thereof and methods of using the same.

BACKGROUND OF THE INVENTION

Serotonin (5-HT) neurotransmission plays an important role in numerous physiological processes both in health and in psychiatric disorders. As an example, 5-HT has been implicated in the regulation of feeding behavior. It is believed that 5-HT induces a feeling of fullness or satiety so that eating stops earlier and fewer calories are consumed. As the 5-HT$_{2C}$ receptor is expressed in high density in the brain (notably in the limbic structures, extrapyramidal pathways, thalamus and hypothalamus i.e. PVN and DMH, and predominately in the choroid plexus) and is expressed in low density or is absent in peripheral tissues, development of a selective 5-HT$_{2C}$ receptor agonist is desirable, having improved efficacy and safety over other anti-obesity agents and related drugs.

The compound, (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, whose structure is shown below in Formula I, belongs to a class of 5-HT$_{2C}$ agonists that are useful in the treatment of a number of 5-HT$_{2C}$-related diseases and disorders, such as those mentioned above. Preparation and characterization of this compound are described in WO 2003/086306, which is incorporated herein by reference in its entirety. Preparation and characterization of the hydrochloric acid salt of this compound is also described in International Application No. PCT/US04/19279 which is incorporated herein by reference in its entirety. Because drug compounds having, for example, improved stability, solubility, shelf life, and in vivo pharmacology, are consistently sought, there is an ongoing need for new or purer salts, hydrates, solvates, and polymorphic crystalline forms of existing drug molecules. The crystalline forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride described herein help meet this and other needs.

\[ \text{Formula I} \]

\[ \text{Me} \]

\[ \text{Cl} \]

\[ \text{NH} \]
I

(R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a thermogravimetric analysis (TGA) thermogram for crystalline Form I of the invention (TA Instruments TGA Q500 in open cell; 25-350 °C; 10 °C/min).

Figure 2 depicts a differential scanning calorimetry (DSC) thermogram for crystalline Form I of the invention (TA Instruments DSC Q1000; 25-220 °C; 10 °C/min).

Figure 3 depicts a powder X-ray diffraction pattern (XRPD) for a sample containing crystalline Form I (PANalytical X’Pert Plus Powder X-Ray Diffractometer; 5.0°-50.0° 2θ).

Figure 4 depicts a dynamic vapor sorption (DVS) scan for crystalline Form I of the invention (VTI dynamic vapor desorption analyzer).

Figure 5 depicts a thermogravimetric analysis (TGA) thermogram for crystalline Form II of the invention (TA Instruments TGA Q500 in open cell open cell; 25-350 °C; 10 °C/min).

Figure 6 depicts a differential scanning calorimetry (DSC) thermogram for crystalline Form II of the invention (TA Instruments DSC Q1000; 25-220 °C; 10 °C/min).

Figure 7 depicts a powder X-ray diffraction pattern (XRPD) for a sample containing crystalline Form II (PANalytical X’Pert Plus Powder X-Ray Diffractometer; 5.0°-50.0° 2θ).

Figure 8 depicts a dynamic vapor sorption (DVS) scan for crystalline Form II of the invention (VTI dynamic vapor desorption analyzer).

Figure 9 depicts a thermogravimetric analysis (TGA) thermogram for crystalline Form III of the invention (TA Instruments TGA Q500 in open cell open cell; 25-350 °C; 10 °C/min).

Figure 10 depicts a differential scanning calorimetry (DSC) thermogram for crystalline Form III of the invention (TA Instruments DSC Q1000; 25-220 °C; 10 °C/min).

Figure 11 depicts a powder X-ray diffraction pattern (XRPD) for a sample containing crystalline Form III (PANalytical X’Pert Plus Powder X-Ray Diffractometer; 5.0°-50.0° 2θ).

Figure 12 depicts a dynamic vapor sorption (DVS) scan for crystalline Form III of the invention.

SUMMARY OF THE INVENTION

In some embodiments, the present invention provides (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate.

In some embodiments, the present invention provides (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate having crystal Form III.

In some embodiments, the present invention provides (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride Form I.
In some embodiments, the present invention provides (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride Form II.

In some embodiments, the present invention provides compositions comprising the crystalline forms of the invention.

In some embodiments, the present invention provides processes for preparing the crystalline forms of the invention as well as crystalline forms prepared by the processes.

In some embodiments, the present invention provides methods for modulating a 5HT2C receptor comprising contacting said receptor with a crystalline form herein.

In some embodiments, the present invention provides methods of treating disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, or sleep apnea by administering to a patient in need a therapeutically effective amount of a hemihydrate or crystal form described herein.

In some embodiments, the present invention provides methods of decreasing food intake of a mammal comprising administering to said mammal a therapeutically effective amount of a hemihydrate or crystal form described herein.

In some embodiments, the present invention provides methods of inducing satiety in a mammal comprising administering to said mammal a therapeutically effective amount of a hemihydrate or crystal form as described herein.

In some embodiments, the present invention provides methods of controlling weight gain of a mammal comprising administering to said mammal a therapeutically effective amount of a hemihydrate or crystal form as described herein.

In some embodiments, the present invention provides methods of treating obesity comprising administering to a patient a therapeutically effective amount of a hemihydrate or crystal form as described herein.

In some embodiments, the present invention provides use of a compound or crystal form of the invention for use in therapy.

In some embodiments, the present invention provides use of a compound or crystal form of the invention for use in the preparation of a medicament for use in therapy.

**DETAILED DESCRIPTION**

*Crystalline forms*

The present invention provides, *inter alia*, three crystalline forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, individually designated as Form I, Form II, and Form III. Forms I and II are anhydrous, hygroscopic forms, both of which readily convert to Form III, a hemihydrate, upon exposure to moisture.

The various crystalline forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride can be identified by their unique solid state signatures with respect to,
tor example, differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and other solid state methods. Further characterization with respect to water or solvent content of the crystalline forms can be gauged by any of various routine methods such as thermogravimetric analysis (TGA), dynamic vapor sorption (DVS), DSC and other techniques. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary by plus or minus about 4 °C. For XRPD, the relative intensities of the peaks can vary, depending upon the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can often affect the 2-theta values. Therefore, the peak assignments of diffraction patterns can vary by plus or minus about 0.2°. The physical properties distinguishing each of the three crystalline forms of the invention are summarized in Table I below.

<table>
<thead>
<tr>
<th>Form I</th>
<th>Form II</th>
<th>Form III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TGA</strong></td>
<td>Figure 1; negligible weight loss below 150 °C</td>
<td>Figure 5; negligible weight loss below 150 °C</td>
</tr>
<tr>
<td><strong>DSC</strong></td>
<td>Figure 2; 201 °C (melt)</td>
<td>Figure 6; 201 °C (melt)</td>
</tr>
<tr>
<td><strong>XRPD</strong></td>
<td>Figure 3;</td>
<td>Figure 7; 11.4° unique</td>
</tr>
<tr>
<td><strong>DVS</strong></td>
<td>Figure 4; hygroscopic; adsorption transition at about 60% RH; adsorbs about 3.8 wt%; deliquescent above 90% RH; crystalline form changes to Form III after cycle.</td>
<td>Figure 8; hygroscopic; adsorption transition at about 40% RH; adsorbs about 3.8 wt%; deliquescent above 90% RH; crystalline form changes to Form III after cycle</td>
</tr>
<tr>
<td><strong>habit</strong></td>
<td>granular</td>
<td>rods</td>
</tr>
</tbody>
</table>

The absence of weight loss below 150 °C in the TGA data suggests that both Forms I and II are anhydrous, non-solvated crystal forms. This result is in contrast with Form III which displays a dehydration feature calculated as a 3.7% weight loss which is consistent with the theoretical weight loss of 3.7% for a hemihydrate. Analysis by DSC further confirms the TGA results, where only Form III shows a dehydration event at about 95 °C. The individual DSC traces further reveal a melting/decomposition endotherm at about 200-201 °C for each of the three forms.
DVS data for each of the three crystal forms reveals the hygroscopic nature of both Forms I and II, which readily adsorb moisture at RH greater than about 40-60% RH. In addition, both Forms I and II were calculated to adsorb about 3.8 wt% moisture between about 40 and about 80% RH which is consistent with conversion to the hemihydrate (Form III). XRPD carried out on both Forms I and II after the DVS cycle confirmed this conversion. In contrast, the DVS data in connection with Form III shows that it is substantially non-hygroscopic, adsorbing less than 0.5 wt% water at 90% RH and the XRPD pattern showed no change in crystalline form after the DVS cycle.

X-ray powder diffraction data for each of the three forms reveal similar patterns. In fact, the diffraction patterns of Forms I and II share essentially the same peaks, except that Form II has at least one unique peak at about 11.4° (2θ) which is not substantially present in diffraction patterns of Form I. Because both Forms I and II are hygroscopic, diffraction patterns obtained for these forms were often combined with peaks from the hemihydrate, Form III. The diffraction pattern of Form III differs significantly from the diffraction patterns of both Forms I and II, having several unique peaks. Exemplary peaks unique to Form III are set out in Table 1 above.

X-ray powder diffraction peaks for each of the three forms are compared in Table 2 below.

<table>
<thead>
<tr>
<th>Form I</th>
<th>Form II</th>
<th>Form III</th>
</tr>
</thead>
<tbody>
<tr>
<td>degrees (2θ)</td>
<td>degrees (2θ)</td>
<td>degrees (2θ)</td>
</tr>
<tr>
<td>6.5</td>
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<tr>
<td>30.9</td>
<td>30.3</td>
<td>29.0</td>
</tr>
</tbody>
</table>
Hemihydrate

In a first aspect of the invention, the present invention provides a compound which is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate.

In some embodiments, the hemihydrate has an X-ray powder diffraction pattern characteristic of Form III comprising peaks, in terms of 2θ, at about 13.7° and about 14.9°. In further embodiments, the hemihydrate has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.7°, about 14.9°, about 15.4°, about 15.8°, and about 16.7°. In yet further embodiments, the hemihydrate has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.7°, about 14.9°, about 15.4°, about 15.8°, about 16.7°, about 20.1°, or about 21.4°. In yet further embodiments, the hemihydrate has an X-ray powder diffraction pattern substantially as shown in Figure 11, wherein by “substantially” is meant that the reported peaks can vary by about ±0.2°.

In some embodiments, the hemihydrate has a differential scanning calorimetry trace comprising a relatively broad dehydration endotherm at about 90 to about 110 °C (e.g., about 95 °C). In addition, the differential scanning calorimetry trace comprises a further endotherm at about 200 °C. In yet further embodiments, the hemihydrate has a differential scanning calorimetry trace substantially as shown in Figure 10, wherein by “substantially” is meant that the reported DSC feature can vary by about ±4°.

In some embodiments, the hemihydrate has a crystal habit which is rods, thin-plates, blocks, or a mixture thereof.

In some embodiments, the hemihydrate has a dynamic vapor sorption profile substantially as shown in Figure 8, wherein by “substantially” is meant that the reported DVS features can vary by about ±5% RH.

In some embodiments, the hemihydrate has a thermogravimetric analysis profile showing about 3.7% weight loss corresponding to loss of water. In further embodiments, the hemihydrate has a thermogravimetric analysis profile substantially as shown in Figure 9, wherein by “substantially” is meant that the reported TGA features can vary be about ±5 °C.

The hemihydrate can be prepared by any of the suitable procedures known in the art for preparing hydrates of compounds. In some embodiments, the hemihydrate can be prepared by at
least partially dissolving (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride in a crystallizing solvent containing water, and inducing precipitation of the hemihydrate from the crystallizing solvent.

The crystallizing solvent can be any solvent or mixture of solvents that at least partially dissolves (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride and contains water. In some embodiments, the crystallizing solvent contains an alcohol, water, and a hydrocarbon. Suitable alcohols include, for example, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3- pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, or glycerol. In some embodiments, the alcohol is isopropanol (2-propanol). Suitable hydrocarbons include, for example, benzene, cyclohexane, pentane, hexane, toluene, cycloheptane, methylcyclohexane, heptane, ethylbenzene, m-, o-, or p-xylene, octane, indane, nonane, or naphthalene. In some embodiments, the hydrocarbon is cyclohexane.

In some embodiments, the weight ratio of alcohol to water in the crystallizing solvent is about 35:1 to about 25:1, about 32:1 to about 27:1, or about 30:1 to about 28:1. In some embodiments, the weight ratio of alcohol to water is about 29:1. In some embodiments, the weight ratio of alcohol plus water to hydrocarbon in the crystallizing solvent is about 5:1 to about 2:1, about 3:1 to about 2:1, or about 2.5:1. In some embodiments, the weight ratio of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride to crystallizing solvent (e.g., alcohol plus water plus hydrocarbon) is about 1:2 to about 1:15, about 1:6 to about 1:10, or about 1:8.

In some embodiments, the mixture containing the crystallizing solvent and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride is maintained at and/or heated to a temperature of about 40 to about 80, about 50 to about 70, or about 60 °C prior to inducing precipitation.

In some embodiments, the (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride is substantially dissolved in the crystallizing solvent prior to inducing precipitation. Substantial dissolution can be achieved by heating the mixture to a suitable temperature such as between about 40 and about 80 °C (e.g., about 60 °C).

Precipitation of the hemihydrate product can be induced by cooling the mixture containing the crystallizing solvent and (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride. In some embodiments, the mixture is cooled to a temperature of about -15 to about 15 °C. In some embodiments, the mixture is cooled to a temperature of about -5 to about 10 °C. In further embodiments, the mixture is cooled to a temperature of about 0 to about 5 °C.
In some embodiments, the present invention provides a compound which is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride or hydrate thereof, wherein the compound or hydrate thereof gains less than about 1.0 %, less than about 0.5 %, or less than about 0.2 % weight after undergoing a dynamic vapor sorption cycle. The weight gain (if any) can be measured as the difference between the sample weight at the beginning of the cycle and at the end of the cycle. These two points typically occur at or near the same relative humidity (RH) value. For example, a cycle might be started at about 0% RH to about 20% RH, run to about 85% to about 100% RH, and then returned to the starting RH point. In some embodiments, weight gain is measured at a starting/ending point of about 5% RH, 10% RH, or 15% RH. In some embodiments, the cycle is runs through a maximum RH of about 85%, about 90%, about 95%, or about 100%. In some embodiments, the sample shows weight gain of more than about 1%, more than about 2%, or more than about 5% during the cycle at about 80% or greater RH. In some embodiments, the present invention provides a compound which is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride or hydrate thereof having a dynamic vapor sorption profile substantially as shown in Figure 12.

Form I

In a second aspect, the present invention is directed to a crystalline form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Form I) having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, and about 10.2°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, about 12.9, about 17.1°, about 17.5°, and about 17.8°. In further embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, about 12.9, about 17.1°, about 17.5°, about 17.8°, about 18.5°, about 19.5°, and about 19.8°. In yet further embodiments, the crystalline form has an X-ray powder diffraction pattern comprising substantially no peak (e.g., where intensity is less than about 5% of the most intense peak) at about 10.5° to about 11.5°. In yet further embodiments, the crystalline form has an X-ray powder diffraction pattern comprising substantially no peak at about 11.4°. In yet further embodiments, the crystalline form has an X-ray powder diffraction pattern substantially as shown in Figure 3, wherein by “substantially” is meant that the reported peaks can vary by about ±0.2°.

In some embodiments, the crystalline form has a differential scanning calorimetry trace comprising an endotherm at about 201 °C. In further embodiments, the crystalline form has a differential scanning calorimetry trace substantially as shown in Figure 2, wherein by “substantially” is meant that the reported DSC features can vary by about ±4°.

In some embodiments, the crystalline form has a crystal habit which is granular.
In some embodiments, the crystalline form has a dynamic vapor sorption profile substantially as shown in Figure 4, wherein by “substantially” is meant that the reported DVS features can vary by about ±5% RH.

In some embodiments, the crystalline form has a thermogravimetric analysis profile substantially as shown in Figure 1, wherein by “substantially” is meant that the reported TGA features can vary be about ±5 °C.

Form I can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. In some embodiments, Form I can be prepared by heating crystalline (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, where the crystalline (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride contains one or more crystalline forms other than Form I. For example, Form I can be prepared by heating samples containing Forms II or III (hemihydrate), or mixtures thereof. In some embodiments, Forms II or III or mixtures thereof, can be heated to a temperature of at least about 60 °C for time and under conditions suitable for forming Form I. In some embodiments, Forms II or III or mixtures thereof can be heated to at temperature of at least about 60 °C for at least about 2 hours.

Form II

In a third aspect of the invention, the invention provides a crystalline form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Form II) having an X-ray powder diffraction pattern comprising at least one peak, in terms of 2θ, at about 11.4°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, and about 11.4°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, about 11.4°, about 12.9°, about 17.1°, about 17.5°, and about 17.7°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, about 11.4°, about 12.9°, about 17.1°, about 17.5°, about 17.8°, about 18.5°, about 19.5°, and about 19.8°. In some embodiments, the crystalline form has an X-ray powder diffraction pattern substantially as shown in Figure 7, wherein by “substantially” is meant that the reported peaks can vary by about ±0.2°.

In some embodiments, Form II has a differential scanning calorimetry trace comprising an endotherm at about 201 °C. In further embodiments, Form I has a differential scanning calorimetry trace substantially as shown in Figure 6, wherein by “substantially” is meant that the reported DSC feature can vary by about ±4° C.

In some embodiments, Form II has a crystal habit which is rods.

In some embodiments, Form II has a dynamic vapor sorption profile substantially as shown in Figure 8, wherein by “substantially” is meant that the reported DVS features can vary by about ±5% RH.
In some embodiments, Form II has a thermogravimetric analysis profile substantially as shown in Figure 5, wherein by “substantially” is meant that the reported TGA features can vary be about ±5 °C.

Form II can be prepared by any of the suitable procedures known in the art for preparing crystalline polymorphs. For example, Form II can be prepared by dissolving (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride in an anhydrous crystallizing solvent and inducing precipitation such as by cooling or addition of anti-solvent. In some embodiments, Form II can be prepared by combining (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (free base) in a hydrocarbon solvent to form a mixture; optionally removing water from the mixture to form a dehydrated mixture; and adding HCl and alcohol to the dehydrated mixture. Suitable alcohols and hydrocarbon solvents are listed hereinabove. In some embodiments, the hydrocarbon solvent is cyclohexane. In further embodiments, the alcohol is isopropanol. In some embodiments, addition of the alcohol is carried out over the time period of about 15 minutes to about 2 hours. In some embodiments, the weight ratio of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine to cyclohexane is about 1:20 to about 1:10, about 1:17 to about 1:12, or about 1:10 to about 1:5, or about 1:7 to about 1:8. In further embodiments, the weight ratio of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine to alcohol is about 1:1 to about 1:10 about 1:2 to about 1:5, or about 1:3.

Removal of water from the solvent mixture can be carried out by any of routine methods in the art such as by incubation with molecular sieves or by azeotropic distillation. Final water content of the mixture after removing water can be less than about 0.1, preferably less than about 0.05, or more preferably less than about 0.03 wt%. If the water content of the solvent mixture is sufficiently low (e.g., less than about 0.1 wt%), the water removal step can be omitted.

During the formation of the salt, the HCl (e.g., HCl gas) can be added in molar excess relative to (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

Compositions

The present invention further provides compositions containing one or more of the three crystal forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride. In some embodiments, the compositions of the invention include at least about 50, about 60, about 70, about 80, about 90, about 95, about 96, about 97, about 98, or about 99 % by weight of the hemihydrate (e.g., Form III). In some embodiments, the compositions of the invention include at least about 50, about 60, about 70, about 80, about 90, about 95, about 96, about 97, about 98, or about 99 % by weight of Form I. In some embodiments, the compositions of the invention include at least about 50, about 60, about 70, about 80, about 90, about 95, about 96, about 97, about 98, or about 99 % by weight of Form II. In some embodiments, the compositions of the invention contain a mixture of two or more of Forms I, II, and III. In some embodiments,
compositions of the invention include Form I, Form II or the hemihydrate and a pharmaceutically acceptable carrier.

Methods

The crystal forms of the invention have activity as 5-HT\textsubscript{2C} receptor agonists. Accordingly, the crystal forms of the invention can be used in methods of agonizing (e.g., stimulating, increasing activity of, etc.) the 5-HT\textsubscript{2C} receptor by contacting the receptor with any one or more of the crystal forms, or compositions thereof, described herein. In further embodiments, the crystal forms of the invention can be used to agonize 5-HT\textsubscript{2C} receptors in an individual in need of such agonizing by administering a therapeutically effective amount of a crystal form of the invention.

The present invention further provides methods of treating diseases associated with the 5-HT\textsubscript{2C} receptor in an individual (e.g., patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a crystal form of the present invention or a pharmaceutical composition thereof. Example diseases can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the 5-HT\textsubscript{2C} receptor, including under-expression or abnormally low activity of the 5-HT\textsubscript{2C} receptor.

Example diseases include disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea. Example disorders of the central nervous system include depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioral disorders, behavioral disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

The present invention further provides methods of decreasing food intake of a mammal by administering a therapeutically effective amount of a crystal form of the invention.

The present invention further provides methods for inducing satiety in a mammal by administering a therapeutically effective amount of a crystal form of the invention.

The present invention further provides methods for controlling weight gain of a mammal by administering a therapeutically effective amount of a crystal form of the invention.

The present invention further provides methods of treating obesity by administering to a patient a therapeutically effective amount of a crystal form of the invention.

In some embodiments, the above methods further comprise the step of identifying a patient, where the patient is in need of treatment for the particular disease being treated, wherein
the identifying step is performed prior to administration to the patient of the therapeutically effective amount of the crystal form of the invention.

As used herein, the term "treating" refers to, for example, preventing, inhibiting, as well as ameliorating a disease, condition or disorder in an individual.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology) such as stabilizing viral load in the case of a viral infection; and

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as lowering viral load in the case of a viral infection.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the crystal forms of the invention can be administered in the form of pharmaceutical compositions. These compositions can be administered by a variety of routes including oral, rectal, transdermal, topical, subcutaneous, intravenous, intramuscular, and intranasal, and can be prepared in a manner well known in the pharmaceutical art.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the crystal forms of the invention above in combination with one or more pharmaceutically acceptable carriers. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions,
syrups, aerosols (as a soltch or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the crystal form can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the crystal form is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the crystal form is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The crystal form can be effective over a wide dosage range and is generally administered in a therapeutically effective amount. It will be understood, however, that the amount of the crystal form actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual crystal form administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a crystal form of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.
The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the crystal forms and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face mask or tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of crystal form or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of
the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of the crystal forms of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the crystal form, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a crystal form of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, the crystal forms of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the crystal form selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

The crystal forms of the invention can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, antibodies, immune suppressants, anti-inflammatory agents and the like.

In order that the invention disclosed herein may be more efficiently understood, examples are provided below. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting the invention in any manner.

**EXAMPLES**

**Example 1**

**Preparation of Hydrochloric Acid Salt of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine**

To a clean, dry 25 mL round bottom flask were added (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine free amine (220 mg), 3 mL methylene chloride, and 1.74 mL of 1M HCl in ether. The mixture was stirred for 5 minutes at room temperature. The solvent was removed under reduced pressure to give a white solid, the HCl salt. The salt was re-dissolved in methylene chloride (3 mL) and an additional 1.74 mL of 1 M HCl was added and the solution was again stirred at room temperature for 5 minutes. The solvent was removed under reduced pressure to give the desired HCl salt of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (190 mg crude weight, 95 % yield). NMR data was consistent with the desired product.
Example 2

Preparation of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate (Form III)

At 20 to 25°C, 160 g, 689 mM of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride is treated under a nitrogen atmosphere with 359.36 g of isopropanol. The resulting mixture is heated to 60 °C providing a clear solution. After the desired temperature is reached, 12.43 g of water are added followed by 960 g of cyclohexane which are added at 60 to 40 °C. Afterwards the solution is cooled over 2 hours with slow stirring (at 160 rpm) to 20 to 25 °C. After crystallization of the product is observed the resulting suspension is cooled to 0 to 5 °C and stirred afterwards for additional 3 h at 0 to 5°C. The suspension is filtered and the filter cake is washed with 160 g of cyclohexane via the reactor and further 160 g of cyclohexane. From this process 176.81 g of a colorless wet product was obtained, which was dried at 35 to 45 °C, preferentially 40 °C, at 50 mbar, 153.03 g (95.3 weight %) of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate was obtained as a colorless crystalline solid.

Example 3

Preparation of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride crystalline Form II.

Approximately 6.6 g of the free base (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was dissolved in cyclohexane to a volume of about 130 mL. The water content was reduced by azeotropic distillation to a level of less than 0.03%. Further cyclohexane was charged to the flask as required to maintain the same volume. The clear solution was filtered and a mixture of 3.06 g, 83.9 mmol hydrochloric acid gas and 19.38 g isopropanol was added over 60 min at an internal temperature 20°C. The resulting suspension was stirred for at least 2 h, before being filtered. The filter cake was washed with 60 g of acetone cooled to 0 – 10 °C and the product (9.19 g) was dried at 60°C at 30 mbar to provide 5.88 g of Form II.

Example 4

Preparation of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride crystalline Form I.

Form I was prepared by heating a sample of either Form II (e.g., prepared according to Example 2) or Form III (e.g., prepared according to Example 1) to a temperature of about 160 °C.
in a TGA furnace for about 15 min when heated at a rate of about 10 °C/min. Conversion to Form I was detected by XRPD analysis.

Example 5

Stability of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride crystalline Form I.

A sample of Form I was heated to 160 °C in a TGA furnace for about 15 min when heated at a rate of about 10 °C/min. XRPD analysis showed no change in crystal form after heating.

Example 6

Heat stability of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride crystalline Form III.

A sample of Form III was heated to 60 °C for at least 2 hours. XRPD analysis showed substantially no change in crystal form after heating.

A sample of Form III was heated to 60 °C for one day. XRPD analysis showed partial conversion to Form I after heating.

A sample of Form III was heated to 80 °C for 30 minutes. XRPD analysis showed partial conversion to Form I after heating.

A sample of Form III was heated to 80 °C for 1 day. XRPD analysis showed partial conversion to Form I after heating.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patents, patent applications, and journal literature, cited in the present application is incorporated herein by reference in its entirety.
CLAIMS

What is claimed is:

1. A compound which is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate.

2. The hemihydrate of claim 1 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.7° and about 14.9°.

3. The hemihydrate of claim 1 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 13.7°, about 14.9°, about 15.4°, about 15.8°, about 16.7°, about 20.1°, and about 21.4°.

4. The hemihydrate of claim 1 having an X-ray powder diffraction pattern substantially as shown in Figure 11.

5. The hemihydrate of claim 1 having a differential scanning calorimetry trace comprising an endotherm between about 90 and about 110 °C.

6. The hemihydrate of claim 1 having a differential scanning calorimetry trace comprising an endotherm between about 90 and about 110 °C and an endotherm at about 200 °C.

7. The hemihydrate of claim 1 having a differential scanning calorimetry trace substantially as shown in Figure 10.

8. The hemihydrate of claim 1 having a dynamic vapor sorption profile substantially as shown in Figure 12.

9. The hemihydrate of claim 1 having a thermogravimetric analysis profile showing about 3.7% weight loss below about 150 °C.

10. The hemihydrate of claim 1 having a thermogravimetric analysis profile substantially as shown in Figure 9.

11. A composition comprising the hemihydrate of claim 1.

12. The composition of claim 11 wherein said hemihydrate constitutes at least about 50% by weight of said composition.
13. The composition of claim 11 wherein said hemihydrate constitutes at least about 90% by weight of said composition.

14. The composition of claim 11 wherein said hemihydrate constitutes at least about 99% by weight of said composition.

15. A composition comprising the hemihydrate of claim 1 and a pharmaceutically acceptable carrier.

16. A crystal form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Form I) having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, and about 10.2°.

17. The crystal form of claim 16 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, about 12.9°, about 17.1°, about 17.5°, about 17.8°, about 18.5°, about 19.5°, and about 19.8°.

18. The crystal form of claim 16 having an X-ray powder diffraction pattern substantially as shown in Figure 3.

19. A composition comprising the crystal form of claim 16.

20. A composition comprising the crystal form of claim 16 and a pharmaceutically acceptable carrier.

21. A crystal form of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride (Form II) having an X-ray powder diffraction pattern comprising at least one peak, in terms of 2θ, at about 11.4°.

22. The crystal form of claim 21 having an X-ray powder diffraction pattern comprising peaks, in terms of 2θ, at about 6.5°, about 9.6°, about 10.2°, about 11.4°, about 12.9°, about 17.1°, about 17.5°, and about 17.7°.

23. The crystal form of claim 21 having an X-ray powder diffraction pattern substantially as shown in Figure 7.

25. A composition comprising the crystal form of claim 21 and a pharmaceutically acceptable carrier.

26. A compound which is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride or hydrate thereof, wherein said compound or hydrate thereof gains less than about 1.0 % weight after undergoing a dynamic vapor sorption cycle from about 10% RH to about 90% RH.

27. A compound which is (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride or hydrate thereof having a dynamic vapor sorption profile substantially as shown in Figure 12.

28. A method of treating a 5HT\textsubscript{2C}-related disorder comprising administering to a patient in need a therapeutically effective amount of a hemihydrate or crystal form as in any one of claims 1, 2, 16, and 21.

29. The method of claim 28 wherein the 5HT\textsubscript{2C}-related disorder is selected from the group consisting of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

30. The method of claim 28 wherein the 5HT\textsubscript{2C}-related disorder is selected from the group consisting of depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioral disorders, behavioral disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa and premenstrual tension.

31. The method of claim 28 wherein the 5HT\textsubscript{2C}-related disorder is obesity.

32. A compound or crystal form of any one of claims 1, 2, 16, and 21 for use in a method of treatment of the human or animal body by therapy.
33. A compound or crystal form of any one of claims 1, 2, 16, and 21 for use in a method of
treatment of a 5HT\textsubscript{2C}-related disorder of the human or animal body by therapy.

34. A compound or crystal form of any one of claims 1, 2, 16, and 21 for use in a method of
treatment of disorders of the central nervous system; damage to the central nervous
system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, or sleep
apnea of the human or animal body by therapy.

35. A compound or crystal form of any one of claims 1, 2, 16, and 21 for use in a method of
treatment of depression, atypical depression, bipolar disorders, anxiety disorders,
obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual
dysfunction, psychoses, schizophrenia, migraine and conditions associated with cephalic
pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related
behavioral disorders, behavioral disorders associated with dementia, organic mental
disorders, mental disorders in childhood, aggressivity, age-related memory disorders,
chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa
or premenstrual tension of the human or animal body by therapy.

36. A compound or crystal form of any one of claims 1, 2, 16, and 21 for use in a method for
treating obesity of the human or animal body by therapy.

37. Use of a compound or crystal form of any one of claims 1, 2, 16, and 21 for the
manufacture of a medicament for treating a 5HT\textsubscript{2C}-related disorder.

38. Use of a compound or crystal form of any one of claims 1, 2, 16, and 21 for the
manufacture of a medicament for treating disorders of the central nervous system;
damage to the central nervous system; cardiovascular disorders; gastrointestinal
disorders; diabetes insipidus, or sleep apnea.

39. Use of a compound or crystal form of any one of claims 1, 2, 16, and 21 for the
manufacture of a medicament for treating depression, atypical depression, bipolar
disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic
states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and
conditions associated with cephalic pain or other pain, raised intracranial pressure,
epilepsy, personality disorders, age-related behavioral disorders, behavioral disorders
associated with dementia, organic mental disorders, mental disorders in childhood,
aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension.

40. Use of a compound or crystal form of any one of claims 1, 2, 16, and 21 for the manufacture of a medicament for treating obesity.
FIGURE 1

TGA Form I
FIGURE 3

XRPD Form I
FIGURE 5

TGA Form II
FIGURE 6

DSC Form II

Heat Flow (W/g)

Temperature (°C)

180.27°C
77.17% of
201.34°C

Form II
XRPD Form III (hemihydrate)

H: Unique peak to hemihydrate
FIGURE 12

DVS Form III (hemihydrate)

Percent Weight Change

Relative Humidity

Adsorption and Desorption