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(54) Title: PROCESSES FOR PREPARING AMORPHOUS DRUG SUBSTANCE

(57) Abstract: The present disclosure relates to processes for preparing amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

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PROCESSES FOR PREPARING AMORPHOUS DRUG SUBSTANCE

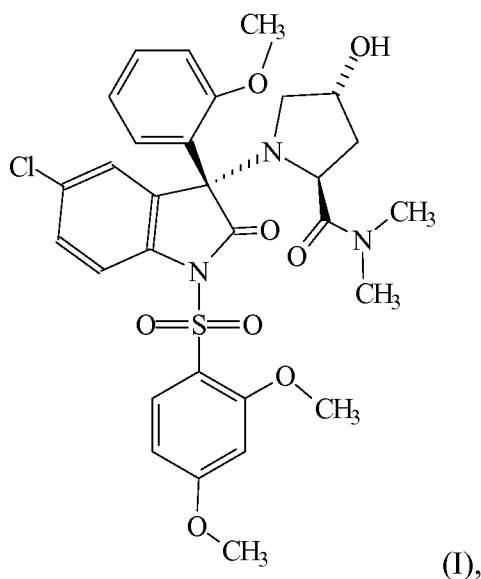
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The present invention relates to processes for preparing amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N,N*-dimethylpyrrolidine-2-carboxamide, a pharmacological agent possessing affinity for the V1b receptors of arginine-vasopressin (AVP).

BACKGROUND OF THE INVENTION

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1-[5-Chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N,N*-dimethylpyrrolidine-2-carboxamide, which has the structure of Formula (I):



is a selective antagonist of V_{1b} receptors. The preparation, physical properties and beneficial pharmacological properties of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide are described in, for example, U.S. Patent No. 6,730,695.

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Amorphous forms of drugs often have greater solubility and dissolution rates, and in some cases different bioavailability patterns, as compared to crystalline or semi-crystalline forms. Despite these advantageous properties, amorphous solid forms are usually less physically stable than crystalline or semi-crystalline forms. This increased instability is caused, at least in part, by a considerable increase in the amount of water that may be taken up by an amorphous form relative to that of a crystalline form of the same chemical entity (*see e.g.* Ahlneck et al., *International Journal of Pharmaceutics*, 62 (1990) 87-95).

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Applicants have discovered that the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide has surprising physical stability. The amorphous form of the present invention is unexpectedly less hygroscopic than semi-crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide. Accordingly, there is a need for amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide and processes for making the same.

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SUMMARY OF THE INVENTION

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The present invention relates to processes for preparing amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide, represented by Formula (I).

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One aspect of the invention is a process of preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising spray drying a solution comprising 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide to form an

amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

In another aspect, the spray drying process comprises:

- a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a feed solution;
- b) pumping the feed solution through an atomizer; and
- c) removing the solvent to form the amorphous form. In one aspect, the suitable solvent comprises one or more solvents selected from the group consisting of dichloromethane, chloroform, ethanol, methanol, 2-propanol, ethyl acetate, acetone, or mixtures thereof, and mixtures thereof with water. In a particular aspect, the suitable solvent comprises a mixture of dichloromethane and ethanol.

Another aspect of the invention is a process of preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising drum drying a solution comprising 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide to form an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide. In one aspect, the solvent is removed in a drying chamber. In a particular aspect, the drying chamber is under vacuum.

In another aspect, the drum drying process comprises:

- a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a feed solution;
- b) pumping the feed solution on heated rotating cylinders; and
- c) removing the solvent to form the amorphous form. In one aspect, the suitable solvent comprises a solvent selected from the group consisting of dichloromethane, methyl acetate, acetone, methyl ethyl ketone, tetrahydrofuran, 2-methyltetrahydrofuran or mixtures thereof, and mixtures thereof with water.

Another aspect of the invention is a process of preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising:

a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a feed solution;

b) mixing the feed solution at a rate between about 0.5 and about 1 ml/minute with a supercritical fluid at a rate between about 20 and about 30 ml/minute, in a vessel at a temperature between about 60 and about 90°C and a pressure between about 80 and about 200 bars;

c) extracting the solvent with supercritical fluid to allow the formation of a powder comprising the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide; and

d) drying the powder by passing supercritical fluid through the powder to obtain the amorphous form. In one aspect, the supercritical fluid is supercritical carbon dioxide. In one aspect, the suitable solvent comprises a solvent selected from the group consisting of dichloromethane, 2-propanol, ethyl acetate, acetone, toluene, and mixtures thereof.

Another aspect of the invention is a process for preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising freeze drying a solution comprising 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide to form an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

In another aspect, the freeze drying process comprises:

a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a solution; and

b) removing the solvent from the solution via freeze-drying. In one aspect, the suitable solvent comprises a solvent selected from the group consisting of ethanol, *tert*-butanol, acetonitrile, acetic acid, dimethyl sulfoxide, isopropanol, or mixtures thereof, and mixtures thereof with water.

In another aspect, the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide prepared according to the processes of the present invention contains less than about 10% by weight, preferably less than 5% by weight, and more preferably is essentially free of crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows X-ray powder diffractograms of amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

FIGURE 2 shows dissolution testing results comparing the solubility/dissolution rates of amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide and semi-crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in aqueous 0.1% sodium lauryl sulfate.

FIGURE 3 shows averaged hygroscopicity testing results for samples of amorphous 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide and semi-crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

FIGURES 4A and 4B show photomicrographs of amorphous solid 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide under unstressed (Figure 4A) and stressed (Figure 4B) conditions.

FIGURE 5 shows an X-ray powder diffractogram of semi-crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and Abbreviations

As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

Å	Angstrom
DS	Drug substance
g	gram
HPLC	high performance liquid chromatography
kg	kilogram
L	liter
mg	milligram
ml	milliliter
NMP	N-methyl-2-pyrrolidinone
rpm	revolutions per minute

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated shall be understood to have the following meanings.

The term “drug substance,” as used herein, refers to 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

“Amorphous” means a solid that it is in a non-crystalline state. Amorphous solids generally possess crystal-like short range molecular arrangement, but no long range order of molecular packing as are found in crystalline solids. The solid state form of a solid, such as the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide, may be determined by Polarized Light Microscopy, X-Ray Powder Diffraction (XPRD), Differential Scanning Calorimetry (DSC), or other standard techniques known to those of skill in the art.

The amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide prepared in accordance with the present invention preferably contains less than about 10% by weight of crystalline forms of the drug substance, and more preferably is essentially free of crystalline forms of the drug substance. By “essentially free of crystalline forms of the drug substance,” it is meant that no crystalline forms of the drug substance can be detected within the limits of a conventional powder X-ray diffractometer, such as described herein.

In a preferred aspect of the invention, the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide prepared according to the processes of the invention is substantially free of impurities.

By “substantially free,” it is meant that the amorphous form of the drug substance contains less than 10% by weight, preferably less than 5% by weight, and more preferably less than 2% by weight, of impurity or impurities.

The term “semi-crystalline,” as used herein, refers to a mixture of crystalline drug substance with amorphous drug substance and/or crystalline material that is a solvate or hydrate, wherein at least about 10% to less than 100% by weight of the drug substance is in crystalline form.

In one aspect of the invention, the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is prepared by dissolving the drug substance in a suitable solvent to form a feed solution and then spray drying the feed solution to form an amorphous form of the drug substance. A “suitable solvent,” as used herein, is a solvent or mixture of solvents in which the drug substance has adequate solubility, e.g. solubility that is greater than about 1 mg/ml. Examples of suitable solvents for spray drying include dichloromethane, chloroform, ethanol, methanol, 2-propanol, ethyl acetate, acetone, or mixtures thereof, which includes mixtures with water. A particular solvent is a mixture of dichloromethane and ethanol.

Spray drying is a process well known to those skilled in the art. In a preferred spray drying process of the present invention, the amorphous solid of the drug substance is formed by dispersing or dissolving the drug substance in a suitable solvent to form a feed solution,

pumping the feed solution through an atomizer into a drying chamber, and removing the solvent to form the amorphous solid in the drying chamber. A drying chamber uses hot gases, such as forced air, nitrogen, nitrogen-enriched air, or argon to dry particles. The feed solution can be atomized by conventional means well known in the art, such as a two-fluid sonicating
5 nozzle, a two-fluid non-sonicating nozzle, and the like.

To form the feed solution for spray drying, the drug is dissolved or dispersed in the suitable solvent at a concentration between about 0.1% w/v to about 25% w/v.

In a second aspect of the invention, the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is prepared using conventional drum drying
10 techniques. In a preferred drum drying process of the present invention, the amorphous solid of the drug substance is formed by dispersing or dissolving the drug substance in a suitable solvent or a mixture of solvents to form a feed solution, pumping the feed solution on heated rotating cylinders, and removing the solvent to form the amorphous solid, such as in a drying
15 chamber. The drying chamber is generally placed under vacuum. Examples of suitable solvents for drum drying include dichloromethane, methyl acetate, acetone, methyl ethyl ketone, tetrahydrofuran, 2-methyltetrahydrofuran or mixtures thereof, which includes mixtures with water. Preferred solvent mixtures include acetone and water and methyl ethyl ketone with a small amount of water, e.g. less than about 10% water in methyl ethyl ketone (v/v).

In a third aspect of the invention, the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is prepared by crystallization using
20 supercritical fluids. In a preferred supercritical fluid method, the 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is prepared by dissolving the drug
25 substance in a suitable solvent to form a feed solution and then mixing the feed solution with a supercritical fluid, for example supercritical carbon dioxide (CO₂) in a vessel at a temperature between about 60 and about 90°C and a pressure between about 80 and about 200 bars. The feeding rate of the supercritical CO₂ is between about 20 and about 30 ml/minute, whereas the
30 feeding rate of the solution is between about 0.5 and about 1 ml/minute.

The solvent is extracted with supercritical CO₂ to allow the formation of the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide. At the

end of the process, the powder obtained is dried by passing supercritical CO₂ through the powder.

Examples of preferred suitable solvents for the supercritical fluid process include dichloromethane, 2-propanol, ethyl acetate, acetone, toluene, and the like. A more preferred
5 suitable solvent is dichloromethane.

In a fourth aspect of the invention, the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is prepared by conventional freeze drying methods. A preferred freeze-drying process of the present invention involves dissolving the
10 drug substance in a suitable solvent and then removing the solvent via freeze-drying.

Examples of preferred suitable solvents for the freeze-drying process include ethanol, *tert*-butanol, acetonitrile, acetic acid, dimethyl sulfoxide, isopropanol, or mixtures thereof, which includes mixtures with water.

The following examples will further illustrate the invention, without, however, limiting
15 it thereto. Suitable 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide starting material for the herein described procedures includes, but is not limited to, 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-
20 hydroxy-N,N-dimethylpyrrolidine-2-carboxamide prepared by the procedures described in U.S. Patent No. 6,730,695. Any form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide may be used as starting material for the preparation of the amorphous form of the drug substance according to the procedures described herein.

EXAMPLE 1

Spray drying preparation of amorphous drug substance

1.8 Grams of drug substance were added to a mixture of 30 ml dichloromethane and 30 ml ethanol. The resulting clear feed solution was pumped through an ultrasonic atomizer
30 (commercially available from Sonotek, operated at a frequency of 60Hz in top spray mode with an inlet gas temperature of 20°C and an outlet gas temperature of 18°C) into a drying chamber using a Harvard syringe pump at a feed rate of 2.2 ml/minute. The solvent was removed to provide an amorphous solid.

EXAMPLE 2

Spray drying preparation of amorphous drug substance

The amorphous drug substance was prepared according to the procedure described in Example 1, above. However, dichloromethane was used as the solvent instead of a mixture of
5 dichloromethane and ethanol.

EXAMPLE 3

Drum drying preparation of amorphous drug substance

10 13.5 Kilograms of the drug substance were dissolved in 13.5 kg of 80/20 (volume/volume) acetone:water mix at room temperature. The resulting clear feed solution was pumped over 2 contrarotating cylinders (rotation speed 5 rpm) of a vacuum bicylinder drum dryer at a mean rate of 7.8 kg of solution/hour. The cylinder temperature was approximately 85°C and the pressure was approximately 25 mbar. 13.9 kg of product
15 containing about 3% of solvent were obtained. The residual solvent was further removed by vacuum drying to provide the desired amorphous solid.

EXAMPLE 4

Drum drying preparation of amorphous drug substance

20 4.5 kg of the drug substance were dissolved in 4.5 kg of methyl acetate at room temperature. The resulting clear feed solution was pumped over 2 contrarotating cylinders (rotation speed 5 rpm) of a vacuum bicylinder drum dryer at a mean feed rate of 16.8 kg of solution/hour. The cylinder temperature was approximately 80°C and the pressure was approximately 60 mbar. 4.6 kg of product containing about 5% of methyl acetate were
25 obtained. The residual solvent was further removed by vacuum drying to provide the desired amorphous solid.

EXAMPLE 5

Drum drying preparation of amorphous drug substance

30 50 g of the drug substance were dissolved in 50 g of methylene chloride at room temperature. The resulting clear feed solution was pumped over 2 contrarotating cylinders (rotation speed 5 rpm) of a vacuum bicylinder drum dryer at a mean feed rate of 2.4 kg of solution/hour. The cylinder temperature was approximately 82°C and the pressure was

approximately 85 mbar. 40.5 g of product containing about 1% of solvent were obtained. The residual solvent was further removed by vacuum drying to provide the desired amorphous solid.

EXAMPLE 6

Freeze Drying preparation of amorphous drug substance

Solutions of 4% of drug substance (weight/weight) were mixed with organic co-solvent (either 80%, 90%, or 100% tertbutylalcohol/water) and placed in 3 ml, glass-tubing vials. The batch for freeze-drying runs contained 20 vials, each of them filled with 2 ml of solution corresponding to an initial product thickness of about 10 mm. The vials were semi-stoppered and carefully deposited in rows on an aluminum tray in a freeze dryer.

The solutions were lyophilized using the following lyophilisation cycles: During the freezing step, the solutions were cooled to -50°C at a cooling rate of 1°C/min and were maintained at this temperature for 2 hours. The primary drying was performed at a shelf temperature of -45°C for 18 hours at 6 Pa. The secondary drying was performed at a shelf temperature of 25°C for 6 hours at 5 Pa. The condenser temperature was kept constant during the experiments at around -70°C.

The freeze-dryer used was a model SMH45 manufactured by Usifroid (France). The freeze-drying chamber contained 3 shelves providing a total shelf area of 0.45m². The freeze-dryer-chamber had a volume equal to 120 L and the total pressure values were measured with a capacitance manometer MKS Baratron 622 (MKS instruments, USA). This sensor was connected to an acquisition system 2700 (Keithley instruments, USA) in order to record all necessary data. A rapid closing pneumatic butterfly valve (response time inferior at 0.5 seconds) was used to isolate the condenser from the sublimation chamber.

The products obtained appeared to be 100% amorphous by X-Ray Power Diffractometry.

EXAMPLE 7

Supercritical fluid preparation of amorphous drug substance

1 g of the drug substance was dissolved in 50 ml of isopropanol at room temperature. The resulting clear feed solution was pumped into a crystallization vessel at a flow rate of 0.2 ml/min. Simultaneously, a liquid solution of CO₂ was pumped in the crystallization vessel at a flow rate of 10 ml/min. The vessel was placed in temperature and pressure conditions so

that the mixture of the two solutions was supercritical. The pressure was fixed at 120 bars, and the temperature of the vessel was fixed at 60°C. At the end of the process, the powder obtained was dried by passing supercritical CO₂ through the powder. 0.31 g of the desired product was obtained. The product appeared to be 100% amorphous by X-Ray Power
5 Diffractometry.

EXAMPLE 8

Supercritical fluid preparation of amorphous drug substance

5 g of the drug substance was dissolved in 50 ml of dichloromethane at room
10 temperature. The resulting clear feed solution was pumped into a crystallization vessel at a flow rate of 0.6 ml/min. Simultaneously, a liquid solution of CO₂ was pumped in the crystallization vessel at a flow rate of 20 ml/min. The vessel was placed in temperature and pressure conditions so that the mixture of the two solutions was supercritical. The pressure was fixed at 120 bars, and the temperature of the vessel is fixed at 60°C. At the end of the
15 process, the powder obtained was dried by passing supercritical CO₂ through the powder. The residual solvent was further removed by vacuum drying at 60°C to provide the desired amorphous solid. 3.12 g of the product was obtained. The product appeared to be 100% amorphous by X-Ray Power Diffractometry.

20 EXPERIMENTALS

X-Ray Power Diffractometry (XRPD) (Figures 1 and 5)

XRPD patterns for Examples 1 and 2 and semi-crystalline drug substance are obtained with a Bruker D8[®] ADVANCE X-ray powder diffractometer using copper K-alpha radiation. The instrument is equipped with parallel beam optics, and the tube voltage and amperage are
25 set to 40 kV and 40 mA, respectively. Samples are scanned at a rate of 1.0 degree/minute from 2 to 40 degrees in angle 2-theta.

The lack of peaks in the X-ray powder diffraction pattern (Figure 1) of Example 1 (upper curve) and Example 2 (lower curve) demonstrates the amorphous nature of the material.

30 An X-ray powder diffraction pattern for semi-crystalline drug substance is shown in Figure 5.

Dissolution Testing (Figure 2)

Dissolution tests of Example 1 and semi-crystalline drug substance were conducted with a paddle-type drug dissolution testing bath (available from Distek Inc.) at 75 rpm and a HP 8453 UV brand spectrophotometer at a wavelength of 280 nm. The following parameters were used: the drug substance concentration was 100 mg/L media, the dissolution media was 0.1% sodium lauryl sulfate in water, and the temperature was 37°C. The percent dissolved was determined by UV absorbance from 0 to 60 minutes at 10 minute intervals.

The results of dissolution testing, which are shown in Figure 2, indicate that the amorphous form of the drug substance has greater solubility/dissolution in aqueous 0.1% sodium lauryl sulfate than semi-crystalline drug substance.

Hygroscopicity Testing (Figure 3)

Hygroscopicity tests were conducted on samples of amorphous drug substance and semi-crystalline drug substance. Hygroscopicity of these samples was measured with a VTI moisture sorption system. The samples were predried at 60°C and run from 5 to 95% relative humidity at 25°C. Equilibrium criteria was 0.01 wt % in 5 minutes.

Figure 3 shows the resulting averaged hygroscopicity for two samples of amorphous drug substance versus three samples of semi-crystalline drug substance. The data illustrate the lower moisture uptake for the amorphous material versus the higher moisture uptake for the semi-crystalline material.

Stability Testing (Figure 4)

Samples of the amorphous form of the drug substance were stored at 40°C/75% relative humidity in open glass vials to determine if polymorphic changes would be observed. The chamber humidity was controlled via a saturated sodium chloride aqueous solution. Samples were analyzed at 2 months.

The stressed and unstressed samples were examined with an Olympus BX-60 microscope under polarized light at a magnification of 100X to determine if birefringence was observed, indicative of crystallinity. Both the unstressed (Figure 4A) and the stressed (Figure 4B) samples are essentially amorphous.

These results indicate that no significant differences are present between the stressed and unstressed (initial) samples.

CLAIMS

What is claimed is:

1. A process of preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising spray drying a solution comprising 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide to form an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.
5
2. The process according to claim 1, wherein spray drying is comprised of:
 - a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a feed solution;
15
 - b) pumping the feed solution through an atomizer; and
 - c) removing the solvent to form the amorphous form.
3. The process according to claim 2, wherein the suitable solvent comprises one or more solvents selected from the group consisting of dichloromethane, chloroform, ethanol, methanol, 2-propanol, ethyl acetate, and acetone, and mixtures in any combination thereof, and mixtures thereof with water.
20
4. The process according to claim 3, wherein the suitable solvent comprises a mixture of dichloromethane and ethanol.
25
5. The process according to claim 1, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 10% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.
30

6. The process according to claim 1, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 5% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

7. The process according to claim 1, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is essentially free of crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

8. A process of preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising drum drying a solution comprising 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide to form an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

9. The process according to claim 8, wherein drum drying is comprised of:

- a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a feed solution;
- b) pumping the feed solution on heated rotating cylinders; and
- c) removing the solvent to form the amorphous form.

10. The process according to claim 9, wherein the solvent is removed in a drying chamber.

11. The process according to claim 10, wherein the drying chamber is under vacuum.

12. The process according to claim 9, wherein the suitable solvent comprises a solvent selected from the group consisting of dichloromethane, methyl acetate, acetone, methyl ethyl

ketone, tetrahydrofuran, and 2-methyltetrahydrofuran, and mixtures in any combination thereof, and mixtures thereof with water.

13. The process according to claim 8, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 10% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

14. The process according to claim 8, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 5% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

15. The process according to claim 8, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is essentially free of crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

16. A process of preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide,

said process comprising:

a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a feed solution;

b) mixing the feed solution at a rate between about 0.5 and about 1 ml/minute with a

supercritical fluid at a rate between about 20 and about 30 ml/minute, in a vessel at a temperature between about 60 and about 90°C and a pressure between about 80 and about 200 bars;

c) extracting the solvent with supercritical fluid to allow the formation of a powder comprising the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide; and

5 d) drying the powder by passing supercritical fluid through the powder to obtain the amorphous form.

17. The process according to claim 16, wherein the supercritical fluid is supercritical carbon dioxide.

10

18. The process according to claim 16, wherein the suitable solvent comprises a solvent selected from the group consisting of dichloromethane, 2-propanol, ethyl acetate, acetone, toluene, and mixtures thereof.

15

19. The process according to claim 16, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 10% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

20

20. The process according to claim 16, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 5% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

25

21. The process according to claim 16, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is essentially free of crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

30

22. A process for preparing an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide comprising freeze drying a solution comprising 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide to form an amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

23. The process according to claim 22, wherein freeze drying is comprised of:

- a) dissolving 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide in a suitable solvent to form a solution; and
- b) removing the solvent from the solution via freeze-drying.

24. The process according to claim 23, wherein the suitable solvent comprises a solvent selected from the group consisting of ethanol, *tert*-butanol, acetonitrile, acetic acid, dimethyl sulfoxide, and isopropanol, and mixtures in any combination thereof, and mixtures thereof with water.

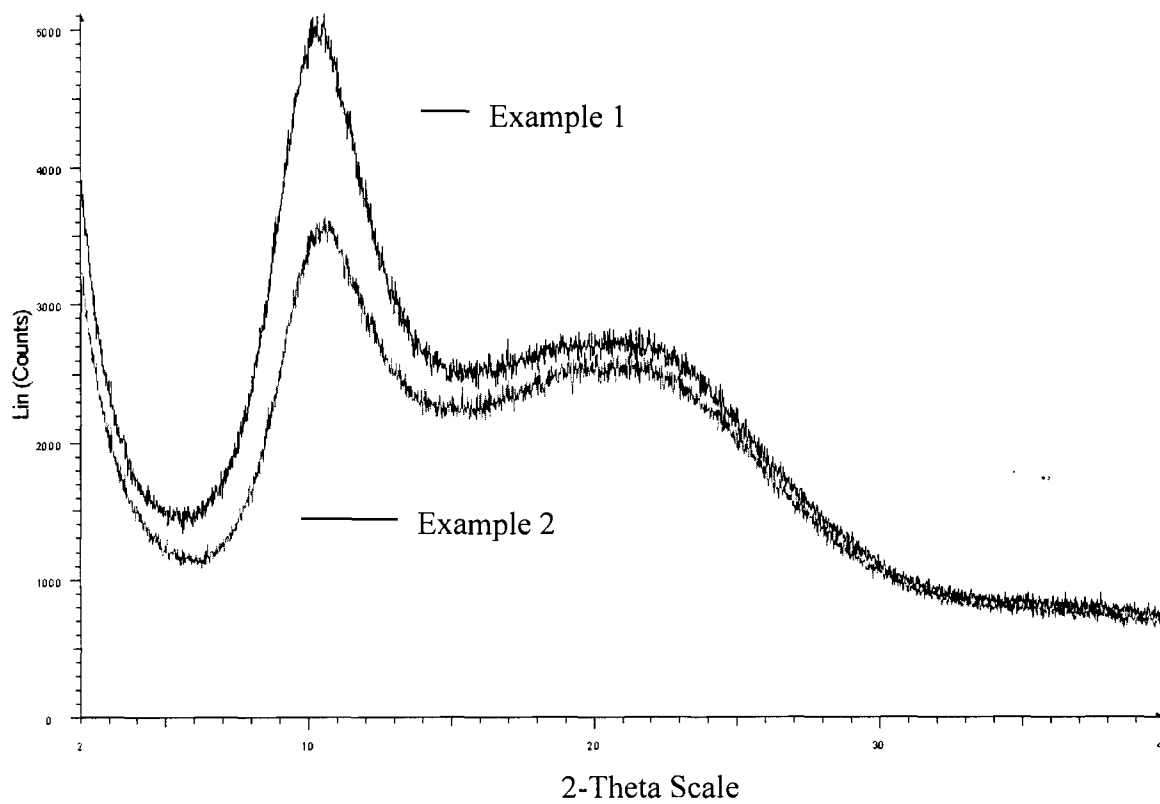
25. The process according to claim 22, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 10% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

26. The process according to claim 22, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide contains less than about 5% by weight crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.

27. The process according to claim 22, wherein the amorphous form of 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide is essentially free of crystalline 1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-N,N-dimethylpyrrolidine-2-carboxamide.
- 5

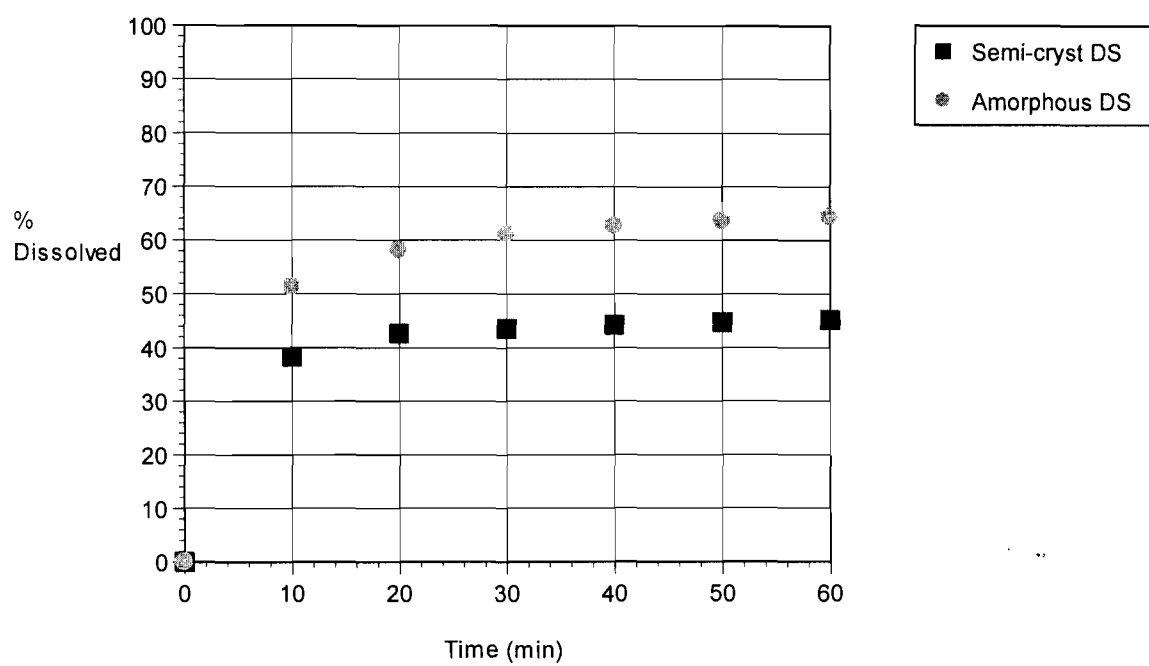
Sheet 1/5

FIGURE 1



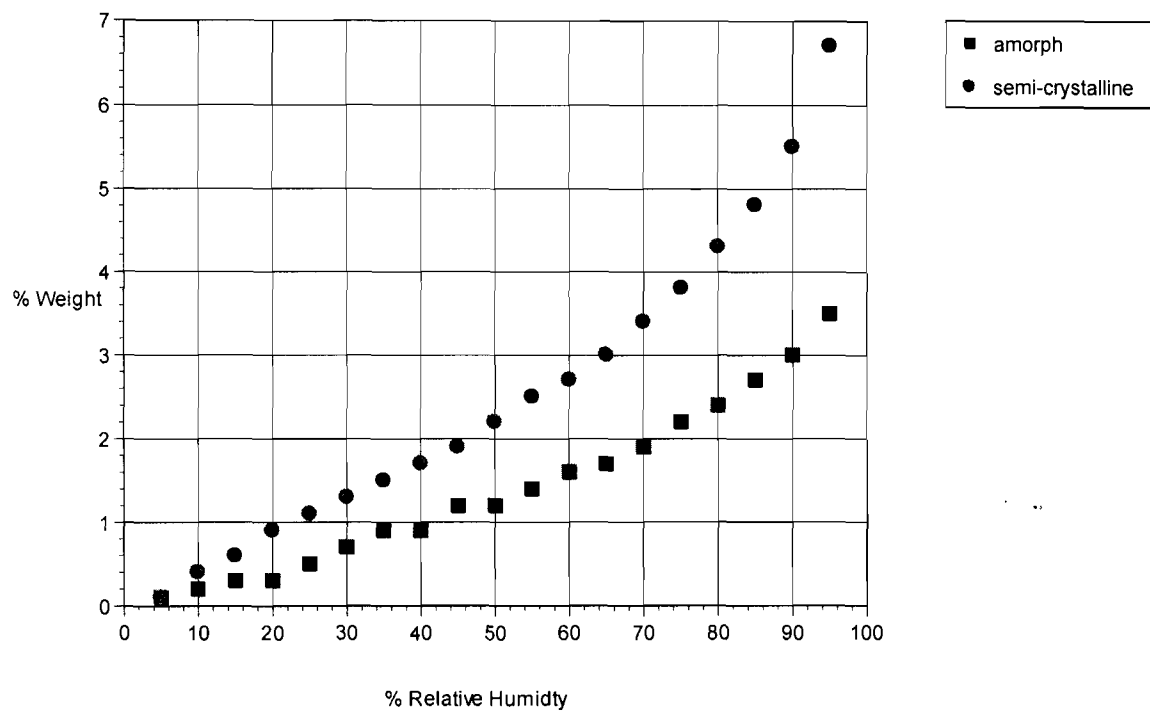
Sheet 2/5

FIGURE 2



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FIGURE 3



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FIGURE 4A
Unstressed

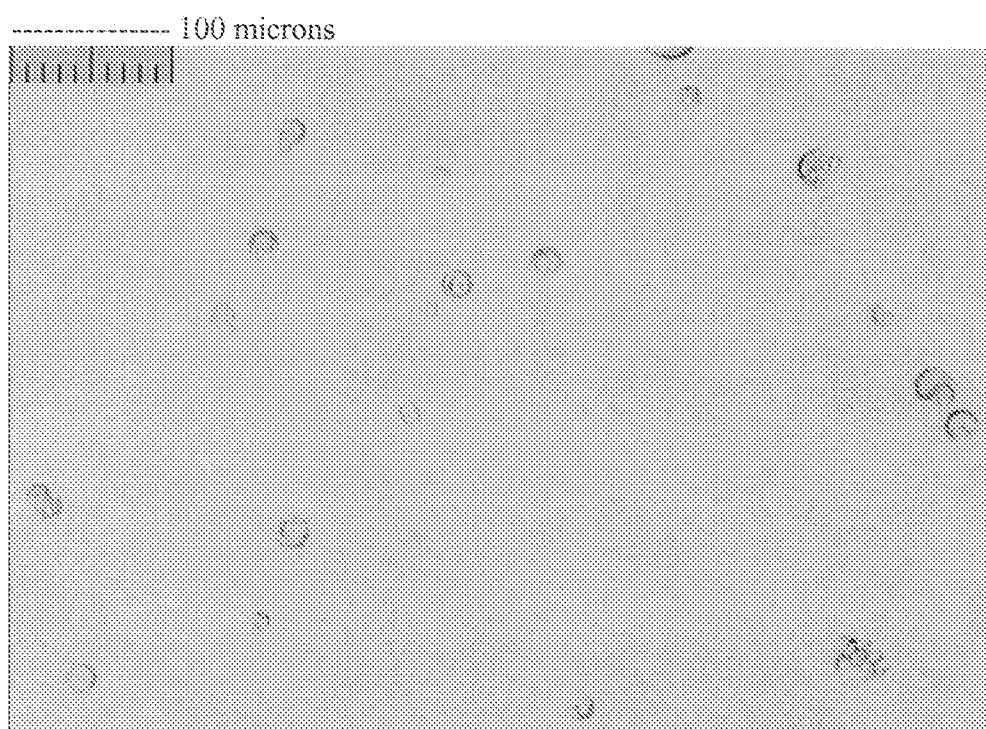
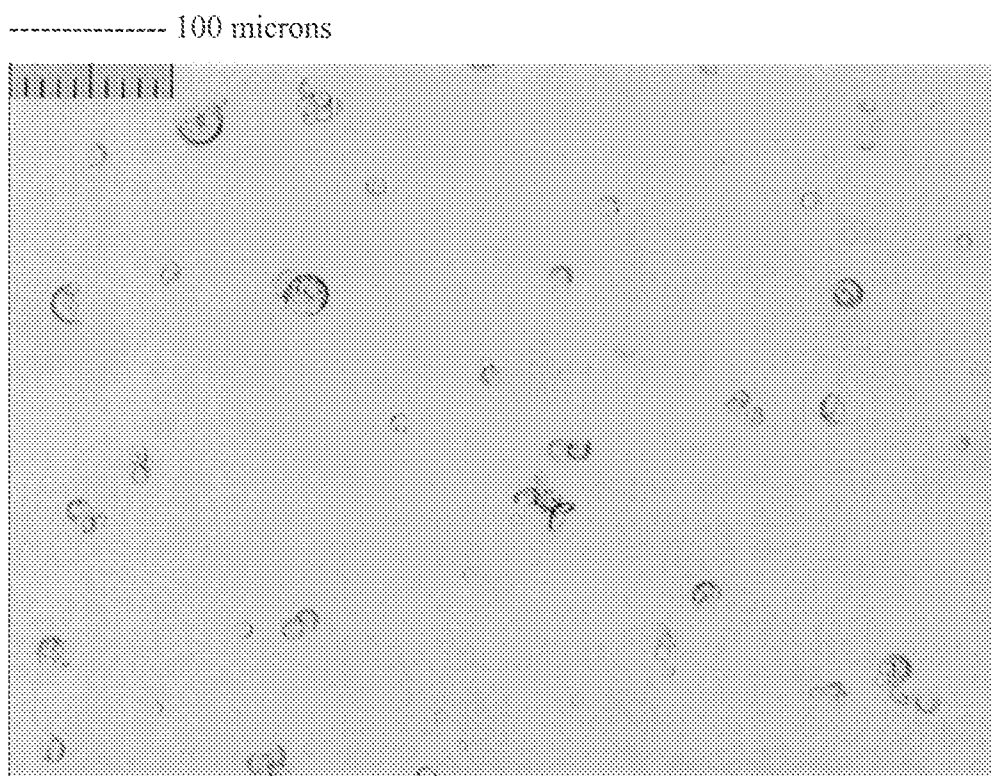
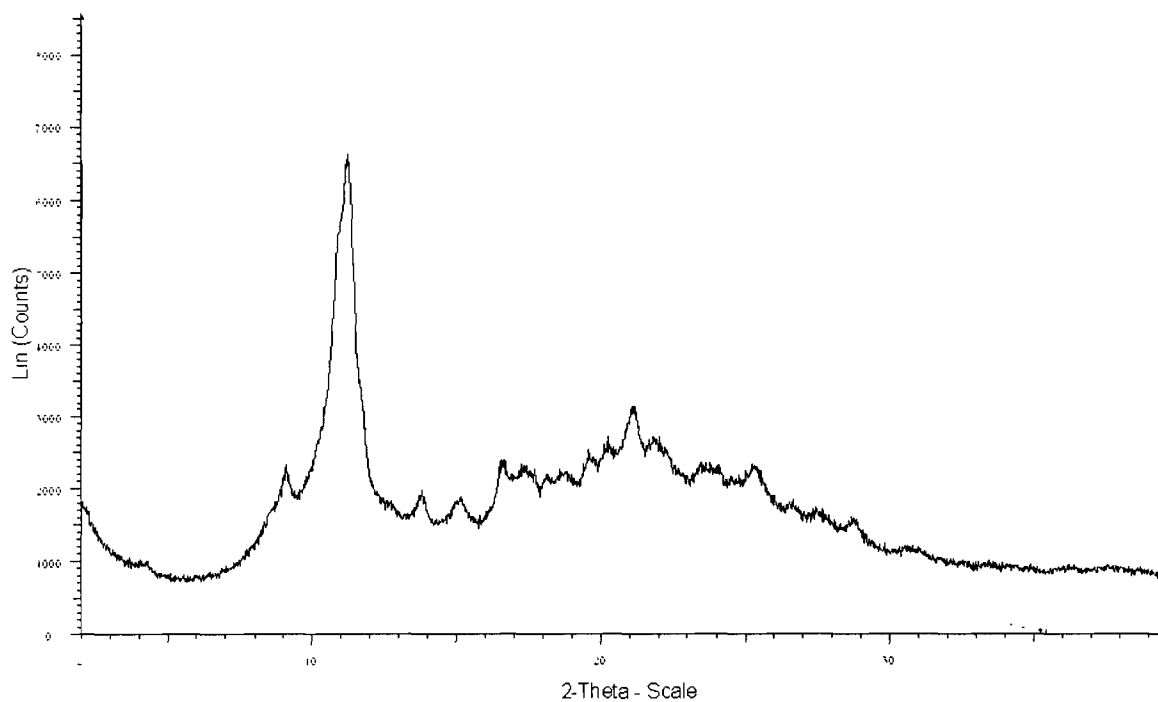


FIGURE 4B
Stressed



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FIGURE 5



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/043936

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/14 A61K9/16 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, FSTA, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 730 695 B2 (ROUX RICHARD [FR] ET AL) 4 May 2004 (2004-05-04) cited in the application column 3, line 1 - line 14 column 20, line 15 - line 43 column 21, line 33 - line 44 examples 7,8 claims 1-13	1-27
A	YU L: "AMORPHOUS PHARMACEUTICAL SOLIDS: PREPARATION, CHARACTERIZATION AND STABILIZATION" ADVANCED DRUG DELIVERY REVIEWS, ELSEVIER BV, AMSTERDAM, NL, vol. 48, no. 1, 16 May 2001 (2001-05-16), pages 27-42, XP009065056 ISSN: 0169-409X the whole document	1-27

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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

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

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

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

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

* & * document member of the same patent family

Date of the actual completion of the international search

1 September 2009

Date of mailing of the international search report

10/09/2009

Name and mailing address of the ISA/

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Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/043936

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No

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