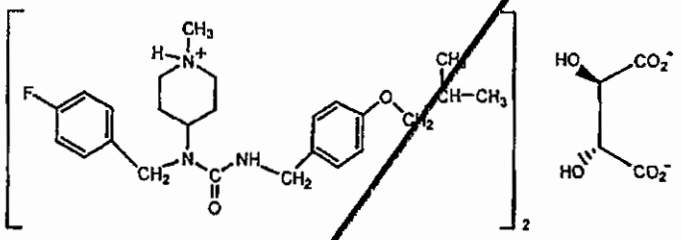
What is claimed is:

1. A crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate that exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 10.7, about 4.84, about 4.57, and about 3.77.

2. The crystalline form of claim 1 that exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 10.7, about 4.84, about 4.57 and about 3.77.

3. A method for the preparation of the crystalline form of claim 1, comprising: suspending of a solid form of a compound of formula IV in an aprotic solvent:



(IV)

stirring the suspension while adding crystal seeds of the crystalline form of claim 1, and isolating the crystalline form of claim 1 from the suspension.

4. The method of claim 3, wherein the temperature of the solvent during the suspending step is from about 30 to about 100 °C.

5. The method of claim 3, wherein the aprotic solvent is selected from the group comprising of one or more of the following: aliphatic or cyclic ethers, carboxylic esters, lactones, alkanes, and aliphatic C_3-C_8 ketones.

6. The method of claim 3, wherein the seeding is carried out at a temperature from about 40 to about 80 °C.

7. The method of claim 3, further comprising cooling the suspension at a rate from about 0.1 to about 1 °C/minute.

8. The method of claim 7, wherein the suspension is cooled to about room temperature.

9. A method for the preparation of the crystalline form of claim 1, comprising:

suspending a crystalline form of N-(4-fluorobenzyl)-N-(l-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate or mixtures of crystalline forms of N-(4-fluorobenzyl)-N-(l-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate in a polar and aprotic solvent at temperatures from about 30 to about 70 ^{0}C;

stirring the suspension while adding crystal seeds of the crystalline form of claim 1; and

isolating of the crystalline solid from the suspension.

10. A method for the preparation of the crystalline form of claim 1, comprising:

dissolving a tartrate salt of N-(4-fluorobenzyl)-N-(l-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide in a solvent at temperatures from about 0 to about 70 ^{0}C;

stirring the resulting solution at a temperature of about 50 to about 70 ^{0}C while adding crystal seeds of the crystalline form of claim 1;

cooling the obtained suspension at a cooling rate of about 5 to about 15 ^{0}C per hour to a temperature of about -20 ^{0}C to about room temperature; and

isolating crystalline solid from the suspension.

11. The method of claim 10, wherein the solvent is tetrahydrofuran.

12. The method of claim 10, wherein the solvent is selected from the group consisting of acetone, dichloromethane, 1,4-dioxane, ethanol, isopropanol, and acetonitrile.

13. A crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate produced by a process comprising:

suspending a crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate or mixtures of crystalline forms of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate in a polar and aprotic solvent at temperatures from about 30 to about 70 °C;

stirring the suspension while adding crystal seeds of the crystalline form of claim 1; and

isolating of the crystalline solid from the suspension.

14. A crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate produced by a process comprising:

dissolving a tartrate salt of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide in tetrahydrofuran or acetone at temperatures from about 0 to about 70 °C;

stirring the resulting solution at a temperature of about 50 to about 70 °C while adding crystal seeds of the crystalline form of claim 1;

cooling the obtained suspension at a cooling rate of about 5 to about 15 °C per hour to a temperature of about -20 °C to about room temperature; and

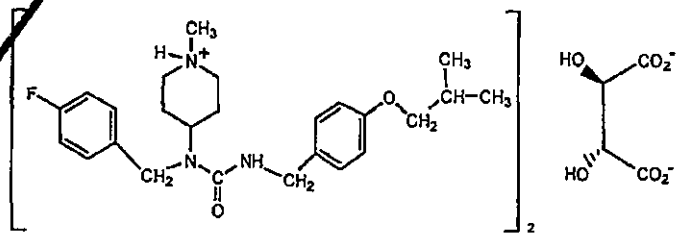
isolating crystalline solid from the suspension.

15. A pharmaceutical composition comprising the crystalline form of claim 15 and a pharmaceutically acceptable carrier or diluent.

16. The crystalline form of claim 2, wherein the crystalline form exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 12.0, about 10.7, about 5.86, about 4.84, about 4.70, about 4.57, and about 3.77.

17. The crystalline form of claim 2, wherein the crystalline form exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 12.0, about 10.7, about 7.4, about 6.9, about 6.6, about 6.2, about 5.86, about 5.53, about 5.28, about 5.16, about 4.84, about 4.70, about 4.57, about 4.38, about 4.09, about 3.94, about 3.77, about 3.71, about 3.49, about 3.46, about 3.25, about 3.08, and about 2.93.

18. A crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide tartrate of formula IV,



(IV)

wherein the crystalline form is at least about 80% pure crystalline form C.

19. The crystalline form of claim 18 wherein the crystalline form is in a 90 % pure crystalline form.

20. The crystalline form of claim 18 wherein the crystalline form is in a 95 % pure crystalline form.

21. The crystalline form of claim 18 wherein the crystalline form is in a 98 % pure crystalline form.

22. The crystalline form of claim 18, which results in a weight loss of about 0.9% below 150 °C as measured by thermogravimetric analysis.

23. The crystalline form of claim 18, which shows an endothermic signal at 177 °C as measured by differential scanning calorimetry.

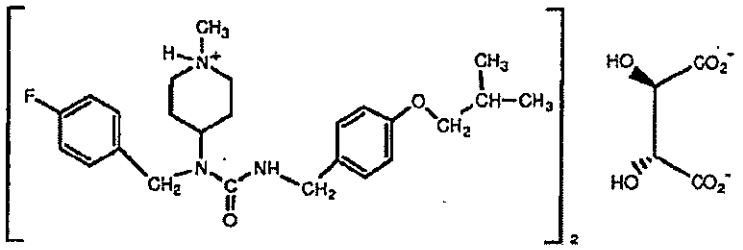
24. The crystalline form of claim 23, wherein the endothermic signal at 177 °C has an enthalpy of fusion of about 129 J/g.

25. The crystalline form of claim 18 that has less than 1000 ppm of residual solvent.

26. The crystalline form of claim 18 that has crystals with a particle size in the range of about 1 μm to about 200 μm.

Claims

1. A method for the preparation of a crystalline form of N-(4-fluorobenayl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methyl-propyloxy)phenylmethyl)carbamide hemi-tartrate of formula IV



(IV)

which

(a) shows an endothermic signal at 177 °C as measured by differential scanning calorimetry with an enthalpy of fusion of about 129 J/g; or
(b) exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 12.0, about 10.7, about 5.86, about 4.84, about 4.70, about 4.57, and about 3.77,

wherein the method comprises:

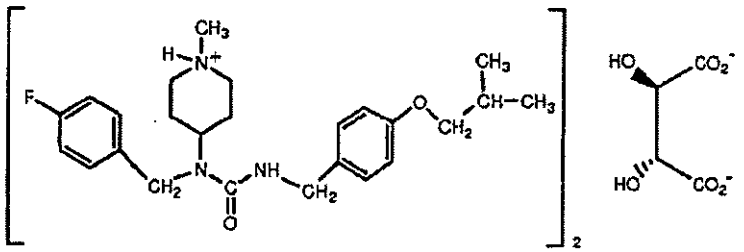
suspending of a solid form of a compound of formula IV in an aprotic solvent, wherein the aprotic solvent is methyl ethyl ketone,
stirring the suspension while adding crystal seeds of the crystalline form having the differential scanning calorimetry signal or the X-ray powder diffraction pattern specified above, and
isolating the crystalline form from the suspension.

2. The method of claim 1, wherein the temperature of the solvent during the suspending step is from about 30 to about 100 °C.

3. The method of claim 1, wherein the seeding is carried out at a temperature from about 40 to about 80 °C.

4. The method of claim 1, wherein the method further comprises cooling the suspension at a rate from about 0.1 to about 1 °C/minute.

5. A method according to claim 1 for the preparation of a crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate of formula IV



(IV)

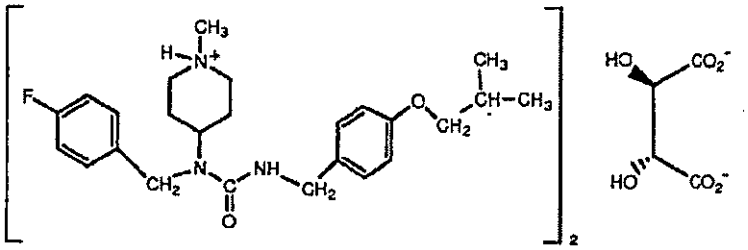
which

(a) shows an endothermic signal at 177 °C as measured by differential scanning calorimetry with an enthalpy of fusion of about 129 J/g; or
(b) exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 12.0, about 10.7, about 5.86, about 4.84, about 4.70, about 4.57, and about 3.77,

wherein the method comprises:

suspending a crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate or mixtures of crystalline forms of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate in a polar and aprotic solvent at temperatures from about 30 to about 70 °C, wherein the polar and aprotic solvent is methyl ethyl ketone;
stirring the suspension while adding crystal seeds of the crystalline form having the differential scanning calorimetry signal or the X-ray powder diffraction pattern specified above; and
isolating of the crystalline solid from the suspension.

6. A method for the preparation of a crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate of formula IV



(IV)

which

(a) shows an endothermic signal at 177 °C as measured by differential scanning calorimetry with an enthalpy of fusion of about 129 J/g; or
(b) exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 12.0, about 10.7, about 5.86, about 4.84, about 4.70, about 4.57, and about 3.77,

wherein the method comprises:

forming a suspension of a solid form of a compound of formula IV in an aprotic solvent at elevated temperature and stirring the suspension, optionally adding crystal seeds of the crystalline form having the differential scanning calorimetry signal or the X-ray powder diffraction pattern specified above, until substantial complete conversion to pure crystalline form having the differential scanning calorimetry signal or the X-ray powder diffraction pattern specified above, wherein the aprotic solvent is methyl ethyl ketone.

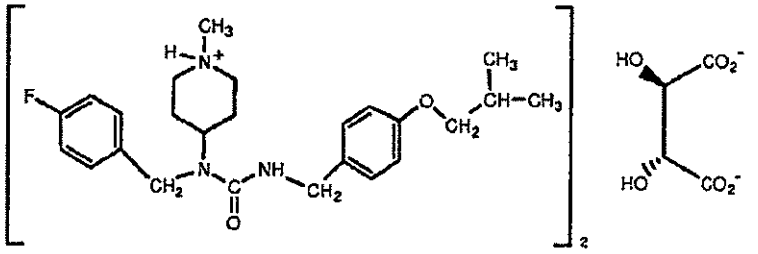
7. The method of claim 6, wherein the elevated temperature is from 20 to 100 °C or from 40 to 80 °C.

8. The method of claim 6 or 7, wherein the adding of the crystal seeds is carried out when the solid compound is in part dissolved, and a saturated solution is formed in which the solid is suspended, and wherein the temperature ranges from 40 to 80 °C or from 55 to 65 °C.

9. The method of any one of claims 6 to 8, wherein the suspension is cooled before isolation of the solid by filtration or centrifugation.

10. The method of claim 9, wherein the cooling is carried out to an end temperature near or below room temperature.

11. A method for the preparation of a crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate of formula IV



(IV)

which

(a) shows an endothermic signal at 177 °C as measured by differential scanning calorimetry with an enthalpy of fusion of about 129 J/g; or
(b) exhibits a X-ray powder diffraction pattern comprising peaks having d-values in angstroms of about 12.0, about 10.7, about 5.86, about 4.84, about 4.70, about 4.57, and about 3.77,

wherein the method comprises:

reacting 4-hydroxybenzaldehyde with isobutylbromide in the presence of potassium iodide and potassium carbonate to produce 4-isobutoxybenzaldehyde;
reacting the 4-isobutoxybenzaldehyde with about 1.5 equivalents of hydroxylamine to produce 4-isobutoxybenzoxime;
reacting the 4-isobutoxybenzoxime with hydrogen in the presence of Raney-Ni and about 13 equivalents of ammonia gas to produce (4-isobutoxyphenyl)methanamine;
adding acetic acid to produce (4-isobutoxyphenyl)methanamine acetate;
treating the (4-isobutoxyphenyl)methanamine acetate with about 30% sodium hydroxide and extracting with toluene to produce (4-isobutoxyphenyl)methanamine;
reacting the (4-isobutoxyphenyl)methanamine with hydrogen chloride gas and phosgene in the presence of toluene to produce 1-isobutoxy-4-(isocyanatomethyl)benzene;
reacting the 1-isobutoxy-4-(isocyanatomethyl)benzene with N-(4-fluorobenzyl)-1-methylpiperidin-4-amine to produce N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide;
dissolving the N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide in 100% ethanol at 40-45 °C, adding a prepared solution of L-(+)-tartaric acid in 100% ethanol, cooling to 35-38 °C, seeding with N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide hemi-tartrate, and cooling to 0-5 °C to produce crystalline N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide hemi-tartrate;
dissolving the N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide hemi-tartrate in 100% ethanol at reflux, filtering the resulting solution, cooling to 48-50 °C, seeding with N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide hemi-tartrate, and cooling to 20-22 °C to produce crystalline N-(1-methylpiperidin-4-yl)-N-(4-fluorophenylmethyl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide hemi-tartrate;
suspending the crystalline N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate in methyl ethyl ketone at 58-63 °C;
cooling the suspension to 12-17 °C, and isolating of the crystalline solid from the suspension.

12. A crystalline form of N-(4-fluorobenzyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide hemi-tartrate obtainable by the method of any one of claims 1 to 11, wherein the crystalline form is in at least 90 % pure crystalline form, with the remainder being other crystalline forms and/or amorphous forms.

13. The crystalline form of claim 12, wherein the crystalline form is in at least 95 % pure crystalline form, with the remainder being other crystalline forms and/or amorphous forms.

14. The crystalline form of claim 12, wherein the crystalline form is in at least 98 % pure crystalline form, with the remainder being other crystalline forms and/or amorphous forms.

15. A pharmaceutical composition comprising the crystalline form of any one of claims 12 to 14, and a pharmaceutically acceptable carrier or diluent.