

CLAIMS

What is claimed is:

- 5 1. A crystalline form of quetiapine hemifumarate having at least one characteristic selected from the group consisting of:
- 1) x-ray reflections at 7.8° , 11.9° , 12.5° , 15.7° , 23.0° , and 23.4° , $\pm 0.2^\circ 2\theta$,
 - 2) absorption bands in FTIR spectroscopy at 639, 1112, 1395, 1616, 1711, and 3423 cm^{-1} , and
 - 10 3) a differential scanning calorimetric thermogram with endothermic peaks at about 130°C and at about 166°C .
2. The crystalline form of quetiapine hemifumarate of claim 1 characterized by x-ray reflections at 7.8° , 11.9° , 12.5° , 15.7° , 23.0° , and 23.4° , $\pm 0.2^\circ 2\theta$.
- 15 3. The crystalline form of quetiapine hemifumarate of claim 2 further characterized by x-ray reflections at 9.0° , 15.6° , 19.7° , 20.0° , 21.6° , and 23.8° , $\pm 0.2^\circ 2\theta$.
4. The crystalline quetiapine hemifumarate of claim 3 having an x-ray diffraction diagram substantially as shown in Figure 1.
- 20 5. The crystalline quetiapine hemifumarate of claim 1 having absorption bands in FTIR spectroscopy at 639, 1112, 1395, 1616, 1711, and 3423 cm^{-1} .
- 25 6. The crystalline quetiapine hemifumarate of claim 5 having an FTIR spectrum substantially as shown in Figure 2.
7. The crystalline quetiapine hemifumarate of claim 1 characterized by a differential scanning calorimetric thermogram with endothermic peaks at about 130°C and at about
- 30 166°C .

8. The crystalline quetiapine hemifumarate of claim 7 having a DSC thermogram substantially as shown in figure 3.
9. The crystalline form of quetiapine hemifumarate of claim 1 that is quetiapine hemifumarate chloroform solvate.
10. The crystalline form of quetiapine hemifumarate of claim 1 that is quetiapine hemifumarate methylene chloride solvate.
11. The crystalline quetiapine hemifumarate of claim 1 wherein the quetiapine hemifumarate is micronized.
12. A method of making crystalline quetiapine hemifumarate having at least one characteristic of form II comprising the steps of:
- combining quetiapine hemifumarate and a treating solvent that is chloroform,
 - refluxing the combination,
 - cooling the combination after reflux, and
 - isolating the crystalline form of quetiapine hemifumarate having at least one characteristic of form II.
13. A method of making crystalline quetiapine hemifumarate having at least one characteristic of form II comprising the steps of:
- combining quetiapine hemifumarate and a treating solvent that is methylene chloride,
 - refluxing the combination,
 - cooling the combination after reflux, and
 - isolating the crystalline form of quetiapine hemifumarate having at least one characteristic of form II.
14. The method of either of claims 12 and 13 wherein the cooling is to a temperature of about room temperature.

15. A method of making crystalline quetiapine hemifumarate having at least one characteristic of form II comprising the steps of:

- 5 a) treating quetiapine hemifumarate with a treating solvent selected from chloroform and methylene chloride, and
- b) isolating the crystalline quetiapine hemifumarate having at least one characteristic of form II.

16. The method of claim 15 wherein the treating is by a reflux method comprising the steps of:

- 10 a) combining quetiapine hemifumarate and treating solvent selected from methylene chloride and chloroform,
- b) refluxing the combination,
- c) cooling the combination after reflux, and
- 15 d) isolating the crystalline quetiapine hemifumarate having at least one characteristic of form II.

17. The method of claim 15 wherein the treating is by a solution method comprising the steps of:

- 20 a) providing a solution of quetiapine hemifumarate in a dipolar aprotic solvent at a dissolution temperature,
- b) combining the solution with a treating solvent selected from chloroform and methylene chloride,
- c) cooling the combination to a temperature of about 20° C or less.

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18. The method of claim 16 wherein the dissolution temperature is about 80° C.

19. Crystalline quetiapine hemifumarate form II dichloromethane solvate characterized by x-ray reflections at 7.8°, 11.9°, 12.5°, 15.7°, 23.0°, and 23.4°, $\pm 0.2^\circ 2\theta$, absorption bands in FTIR at 639, 1112, 1395, 1616, 1711, and 3423 cm^{-1} , and a thermogram in differential scanning calorimetry having endothermic peaks at about 130°C and about 166°C.

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20. Crystalline quetiapine hemifumarate form II chloroform solvate characterized by x-ray reflections at 7.8° , 11.9° , 12.5° , 15.7° , 23.0° , and 23.4° , $\pm 0.2^\circ 2\theta$, absorption bands in FTIR at 639, 1112, 1395, 1616, 1711, and 3423 cm^{-1} , and a thermogram in differential scanning calorimetry having endothermic peaks at about 130°C and about 166°C .

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21 A crystalline form of quetiapine hemifumarate having at least one characteristic selected from the group consisting of:

1) x-ray reflections at about 8.9° , 11.8° , 15.3° , 19.4° , 23.0° , and 23.4° , $\pm 0.2^\circ 2\theta$,

2) absorption bands in FTIR spectroscopy at 748, 758, 1402, 1607, 1715, and

10 2883 cm^{-1} , and

3) a DSC thermogram with endothermic peaks at about 111°C , about 142°C , and about 167°C .

22 The crystalline form of quetiapine hemifumarate of claim 21 characterized by x-ray reflections at about 8.9° , 11.8° , 15.3° , 19.4° , 23.0° , and 23.4° , $\pm 0.2^\circ 2\theta$.

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23. The crystalline form of quetiapine hemifumarate of claim 22 further characterized by x-ray reflections at 16.0° , 17.0° , 17.7° , 18.6° , 20.3° , 20.8° , 21.3° , 21.6° , 26.7° , and 27.4° , $\pm 0.2^\circ 2\theta$.

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24. The crystalline form of quetiapine hemifumarate of claim 23 having an x-ray diffraction diagram substantially as shown in figure 6.

25. The crystalline form of quetiapine hemifumarate of claim 21 having absorption bands in FTIR spectroscopy at 748, 758, 1402, 1607, 1715, and 2883 cm^{-1} .

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26. The crystalline form of quetiapine hemifumarate of claim 25 having an FTIR spectrum substantially as shown in figure 7.

- 27 The quetiapine hemifumarate of claim 21 having a DSC thermogram with endothermic peaks at about 111°C, about 142°C, and about 167°C.
28. The quetiapine hemifumarate of claim 27 wherein the DSC thermogram is substantially as shown in figure 8.
29. The crystalline form of quetiapine hemifumarate of claim 21 that is quetiapine hemifumarate chloroform solvate.
- 10 30. The quetiapine hemifumarate of claim 21 wherein the quetiapine hemifumarate is micronized.
31. A method of making quetiapine hemifumarate having at least one characteristic of form III comprising the steps of:
- 15 a) providing a combination of quetiapine hemifumarate and a dipolar aprotic solvent at a temperature of about 80° C,
- b) mixing the combination with chloroform,
- c) cooling the resulting mixture, and
- d) isolating the quetiapine hemifumarate having at least one characteristic of form
- 20 III from the mixture.
32. The method of claim 31 wherein the mixture is maintained, with agitation, for a holding time.
- 25 33. The method of claim 31 wherein the holding time is at least about 14 hours.
34. Crystalline quetiapine hemifumarate form III chloroform solvate characterized by x-ray reflections at about 8.9°, 11.8°, 15.3°, 19.4°, 23.0°, and 23.4°, $\pm 0.2^\circ 2\theta$, and absorption bands in FTIR at 748, 758, 1402, 1607, 1715, and 2883 cm^{-1} .
- 30 35. A method of making crystalline quetiapine hemifumarate form I comprising the steps of:

- a) providing a solution at about 80° C of quetiapine hemifumarate in a solvent selected from the group consisting of water, alkanol, and dipolar aprotic solvents,
b) combining the solution with an anti-solvent whereby a suspension is obtained,
and
5 c) isolating quetiapine hemifumarate form I from the suspension.

36. The method of claim 35 wherein the solvent is an alkanol and the anti-solvent is selected from the group consisting of ethylacetate, isopropylacetate, acetone, methyl *tert*-butyl ether (MTBE), and acetonitrile.

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37. The method of claim 36 wherein the alkanol is isopropyl alcohol or methanol.

38. The method of claim 35 wherein the solvent is a dipolar aprotic solvent selected from the group consisting of dimethylsulfoxide, dimethylformamide, dimethylacetamide
15 and 1-methyl-2-pyrrolidone and the anti-solvent is selected from the group consisting of water, ethylacetate, dichloromethane, toluene, acetone, acetonitrile, isobutanol, ethylacetate, isopropylacetate and methyl *tert*-butyl ether.

39. A method of making crystalline quetiapine hemifumarate form I comprising the
20 steps of:

- a) providing a solution at about 80° C of quetiapine hemifumarate in a solvent selected from the group consisting of alkanol, and a combination of a dipolar aprotic solvent and water,
b) cooling the solution to a temperature of about 20° C or less, and
25 c) isolating the quetiapine hemifumarate form I from the mixture.

40. The method of claim 39 wherein the alkanol is isopropyl alcohol.

41. The method of claim 39 wherein the dipolar aprotic solvent is
30 dimethylformamide.

42. The method of either of claims 35 or 39 further comprising the steps of post-treating the isolated quetiapine hemifumarate form I by a post-treating method selected from a post-suspension method and a post-recrystallization method.

5 43. The method of claim 42 wherein the post-treatment method is post suspension comprising the steps of:

a) combining the isolated quetiapine hemifumarate form I with a post-suspending solvent selected from dialkyl ketones, aromatic hydrocarbons, cyanoalkanes, dialkyl ethers, and methylene chloride,

10 b) refluxing the combination for a reflux time,

c) cooling the combination to ambient temperature, and

d) isolating quetiapine hemifumarate form I.

15 44. The method of claim 43 further comprising the step of, after cooling of the combination, agitating the cooled combination for an agitating time.

20 45. The method of claim 43 wherein the post-suspending solvent is selected from the group consisting of acetone, toluene, acetonitrile, dichloromethane, and methyl *t*-butyl ether.

46. The method of claim 42 wherein the post-treatment method is post-crystallization comprising the steps of:

25 a) refluxing a solution of the isolated quetiapine hemifumarate form I in a post-crystallization solvent selected from lower alkanols, cyclic ethers, ethyl acetate, and water for a reflux time,

b) cooling the solution to ambient temperature whereby a suspension is formed, and

c) isolating the quetiapine hemifumarate form I.

30 47. The method of claim 46 further comprising the step of agitating the suspension from step b) at ambient temperature for an agitation time.

35 48. The method of claim 46 wherein the post-crystallization solvent is selected from the group consisting of water, ethanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, ethyl acetate, tetrahydrofuran, and 1,4-dioxane.

49. A pharmaceutical composition comprising crystalline quetiapine hemifumarate according to either of claims 1 or 21.

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50. The pharmaceutical composition of claim 49 comprising at least one pharmaceutically acceptable excipient.

51. A method of treatment comprising administering to a mammal the pharmaceutical composition including one or more of quetiapine hemifumarate form II chloroform solvate, quetiapine hemifumarate form II dichloromethane solvate and quetiapine hemifumarate form III chloroform solvate, and at least one pharmaceutically acceptable excipient.

52. A crystalline form of quetiapine hemifumarate characterized by x-ray reflections at 11.9° , 12.5° , 14.6° , 15.7° , and 16.8° , $\pm 0.2^\circ$ 2θ .

53. A crystalline form of quetiapine hemifumarate characterized by x-ray reflections at 8.9° , 11.8° , 15.3° , 19.4° , 23.0° , and 23.4° , $\pm 0.2^\circ$ 2θ .

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