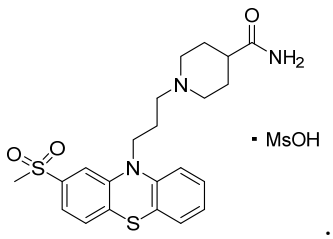
Claims

1. A crystalline form of metopimazine mesylate, 

.

2. The crystalline form of claim 1, wherein the crystalline form comprises less than 10 wt. % of amorphous forms.

3. The crystalline form of claim 1 or 2, wherein the crystalline form is in non-solvate form.

4. The crystalline form of claim 3, wherein the crystalline form comprises less than 10 wt. % of solvate forms.

5. The crystalline form of any preceding claim, wherein the crystalline form comprises metopimazine mesylate Crystal Form A.

6. A crystalline form of metopimazine mesylate characterized by an X-ray powder diffraction (XRPD) pattern comprising two or more of the following 2θ values: 9.37°, 9.87°, 14.33°, 15.26°, 15.91°, 16.55°, 17.52°, 17.75°, 18.75°, 19.09°, 19.72°, 20.80°, 21.22°, 21.77°, 23.29°, 23.91°, 24.44°, 25.37°, 26.39°, 26.92°, 27.96°, 28.23°, 28.78°, 29.27°, 29.64°, 30.67°, 31.29°, 31.84°, 32.09°, 32.99°, 33.40°, 33.99°, 35.91°, 36.80°, 37.41°, 37.92°, and 39.27° ± 0.2°.

7. The crystalline form of claim 6, characterized by an XRPD pattern comprising two or more of the following 2θ values: 9.37°, 9.87°, 14.33°, 15.26°, 15.91°, 16.55°, 17.52°, 17.75°, 18.75°, 19.09°, 19.72°, 20.80°, 21.22°, 21.77°, 23.29°, 23.91°, 24.44°, and 25.37° ± 0.2°.

8. The crystalline form of claim 6, characterized by an XRPD pattern comprising three or more of the following 2θ values: 9.37°, 9.87°, 14.33°, 15.26°, 15.91°, 16.55°, 17.52°,

17.75°, 18.75°, 19.09°, 19.72°, 20.80°, 21.22°, 21.77°, 23.29°, 23.91°, 24.44°, and 25.37° ± 0.2°.

9. The crystalline form of claim 6, characterized by an XRPD pattern comprising four or more of the following 2θ values: 9.37°, 9.87°, 14.33°, 15.26°, 15.91°, 16.55°, 17.52°, 17.75°, 18.75°, 19.09°, 19.72°, 20.80°, 21.22°, 21.77°, 23.29°, 23.91°, 24.44°, and 25.37° ± 0.2°.

10. The crystalline form of claim 6, characterized by an XRPD pattern comprising peaks at the following 2θ values: 15.91° and 18.75° ± 0.2°.

11. The crystalline form of claim 6, characterized by an XRPD pattern comprising peaks at the following 2θ values: 15.91°, 18.75°, and 24.44° ± 0.2°.

12. A crystalline form of metopimazine mesylate characterized by an XRPD pattern comprising one or more of the following 2θ values: 9.37°, 15.26°, 15.91°, 18.75°, 19.09°, 20.80°, 21.22°, 21.77°, and 24.44° ± 0.2°.

13. The crystalline form of claim 12, characterized by an XRPD pattern comprising two or more of the following 2θ values: 9.37°, 15.26°, 15.91°, 18.75°, 19.09°, 20.80°, 21.22°, 21.77°, and 24.44° ± 0.2°.

14. The crystalline form of claim 12, characterized by an XRPD pattern comprising three or more of the following 2θ values: 9.37°, 15.26°, 15.91°, 18.75°, 19.09°, 20.80°, 21.22°, 21.77°, and 24.44° ± 0.2°.

15. A crystalline form of metopimazine mesylate characterized by a ^{13}C solid state Nuclear Magnetic Resonance (ssNMR) spectrum comprising at least one peak, expressed as chemical shift in ppm, selected from the following: 176.8, 176.4, 142.2, 141.7, 140.9, 140.0, 128.3, 127.0, 126.2, 125.1, 121.1, 119.9, 114.7, 110.9, 57.0, 55.7, 50.6, 47.1, 45.6, 42.1, 40.2, 27.4, and 21.3 ± 0.20 ppm.

16. The crystalline form of claim 15, characterized by a ^{13}C ssNMR spectrum comprising at least three peaks, expressed as chemical shift in ppm, selected from the following: 176.8,

176.4, 142.2, 141.7, 140.9, 140.0, 128.3, 127.0, 126.2, 125.1, 121.1, 119.9, 114.7, 110.9, 57.0, 55.7, 50.6, 47.1, 45.6, 42.1, 40.2, 27.4, and 21.3 ± 0.20 ppm.

17. The crystalline form of claim 15, characterized by a ^{13}C ssNMR spectrum comprising at least four peaks, expressed as chemical shift in ppm, selected from the following: 176.8, 176.4, 142.2, 141.7, 140.9, 140.0, 128.3, 127.0, 126.2, 125.1, 121.1, 119.9, 114.7, 110.9, 57.0, 55.7, 50.6, 47.1, 45.6, 42.1, 40.2, 27.4, and 21.3 ± 0.20 ppm.

18. The crystalline form of claim 15, characterized by a ^{13}C ssNMR spectrum comprising at least six peaks, expressed as chemical shift in ppm, selected from the following: 176.8, 176.4, 142.2, 141.7, 140.9, 140.0, 128.3, 127.0, 126.2, 125.1, 121.1, 119.9, 114.7, 110.9, 57.0, 55.7, 50.6, 47.1, 45.6, 42.1, 40.2, 27.4, and 21.3 ± 0.20 ppm.

19. The crystalline form of claim 15, characterized by a ^{13}C ssNMR spectrum comprising at least one peak, expressed as chemical shifts in ppm, selected from the following: 21.3, 27.4, 42.1, 50.6, 57.0, 114.7, 119.9, 121.1, 176.4 and 176.8 ± 0.20 ppm.

20. The crystalline form of claim 15, characterized by a ^{13}C ssNMR spectrum comprising at least three peaks, expressed as chemical shifts in ppm, selected from the following: 21.3, 27.4, 42.1, 50.6, 57.0, 114.7, 119.9, 121.1, 176.4 and 176.8 ± 0.20 ppm.

21. The crystalline form of claim 15, characterized by a ^{13}C ssNMR spectrum comprising at least six peaks, expressed as chemical shifts in ppm, selected from the following: 21.3, 27.4, 42.1, 50.6, 57.0, 114.7, 119.9, 121.1, 176.4 and 176.8 ± 0.20 ppm.

22. A crystalline form of metopimazine mesylate characterized by a differential scanning calorimetry pattern comprising a single endotherm comprising an onset temperature range of 208 °C to 212 °C.

23. The crystalline form of claim 22, wherein the single endotherm comprises an onset temperature range of 208 °C to 211 °C.

24. The crystalline form of claim 22, wherein the single endotherm comprises an onset temperature range of 209 °C to 210 °C.

25. The crystalline form of any one of claims 22-24, wherein the single endotherm comprises a peak temperature range of 213 °C to 214 °C.

26. The crystalline form of any one of claims 22-25, wherein the single endotherm comprises an enthalpy of transition of 95-100 J/g.

27. The crystalline form of claim 26, wherein the single endotherm comprises an enthalpy of transition of 96-98 J/g.

28. The crystalline form of claim 26, wherein the single endotherm comprises an enthalpy of transition of 97-98 J/g.

29. A crystalline form of metopimazine mesylate characterized by a thermogravimetric analysis profile comprising a total weight loss of 0.4% up to 150.0 °C.

30. A composition comprising the crystalline form of any one of claims 6-29, wherein the composition comprises less than 10 wt. % of other crystalline forms of metopimazine mesylate.

31. The composition of claim 30, wherein the composition comprises less than 1 wt. % of other crystalline forms of metopimazine mesylate.

32. The composition of claim 30 or 31, wherein the composition comprises less than 10 wt. % of amorphous forms of metopimazine mesylate.

33. The composition of claim 32, wherein the composition comprises less than 1 wt. % of amorphous forms of metopimazine mesylate.

34. A pharmaceutical composition comprising the crystalline form of any one of claims 1-33 and a pharmaceutically acceptable excipient.

35. The pharmaceutical composition of claim 34, wherein the pharmaceutical composition is suitable for administering administering orally, intraduodenally, intracolonically,

enterally, topically, intranasally, non-orally, buccally, sublingually, by inhalation, or rectally.

36. The pharmaceutical composition of claim 35, wherein the composition is suitable for administering orally.

37. The pharmaceutical composition of claim 35, wherein the composition is suitable for administering sublingually.

38. The pharmaceutical composition of any one of claims 34-37, wherein the pharmaceutical composition is formulated as a tablet, a capsule, a paste, a powder, a suspension, a suppository, an extended-release formulation, or a modified-release formulation.

39. The pharmaceutical composition of claim 38, wherein the composition is formulated as an extended release formulation.

40. The pharmaceutical formulation of claim 38, wherein the composition is formulated as a capsule.

41. The pharmaceutical composition of any one of claims 34-40, wherein the composition comprises 5 mg of the crystalline form of metopimazine mesylate.

42. The pharmaceutical composition of any one of claims 34-40, wherein the composition comprises 10 mg of the crystalline form of metopimazine mesylate.

43. The pharmaceutical composition of any one of claims 34-40, wherein the composition comprises 20 mg of the crystalline form of metopimazine mesylate.

44. The pharmaceutical composition of any one of claims 34-43, wherein the composition is suitable for administration one time per day.

45. The pharmaceutical composition of any one of claims 34-43, wherein the composition is suitable for administration two times per day.

46. The pharmaceutical composition of any one of claims 34-43, wherein the composition is suitable for administration three times per day.

47. The pharmaceutical composition of any one of claims 34-43, wherein the composition is suitable for administration four times per day.

48. The pharmaceutical composition of any one of claims 34-47, wherein between about 5 mg and about 160 mg of the crystalline form of metopimazine mesylate is administered per day.

49. The pharmaceutical composition of any one of claims 34-47, wherein the composition is suitable for administration of more than 20 mg of the crystalline form of metopimazine mesylate per day.

50. Use of a pharmaceutical composition of any one of claims 34-49 in the manufacture of a medicament for the treatment of an enteric nervous system disorder in a human subject in need thereof.

51. The use of claim 50, wherein the enteric nervous system disorder is a chronic disorder.

52. The use of claim 50, wherein the enteric nervous system disorder is an acute disorder.

53. The use of claim 50, wherein the enteric nervous system disorder is selected from the group consisting of gastroparesis, Irritable Bowel Syndrome, lysosomal storage disorders, intestinal dysmotility, ganglioneuroma, multiple endocrine neoplasia type 2B (MEN2B), gastrointestinal neuropathy, functional dyspepsia, gastroesophageal reflux disease (GERD), and intestinal neuronal dysplasia.

54. The use of any of claims 50-53, wherein the enteric nervous system disorder comprises a symptom selected from the group consisting of early satiety, post-prandial fullness, abdominal fullness, nausea, vomiting, delayed gastric emptying, diarrhea, abdominal pain, gas, bloating, gastroesophageal reflux, reduced appetite, and constipation.

55. The use of claim 54, wherein the enteric nervous system disorder symptom comprises nausea.

56. The use of claim 54, wherein the enteric nervous system disorder symptom comprises vomiting.

57. Use of a pharmaceutical composition of any one of claims 34-49 in the manufacture of a medicament for the treatment of gastroparesis in a human subject in need thereof.

58. The use of claim 57, wherein gastroparesis is diabetic gastroparesis.

59. The use of claim 57, wherein the gastroparesis is idiopathic gastroparesis.

60. The use of any of claims 57-59, wherein the gastroparesis comprises a symptom selected from the group consisting of early satiety, post-prandial fullness, abdominal fullness, nausea, vomiting, delayed gastric emptying, diarrhea, abdominal pain, gas, bloating, gastroesophageal reflux, reduced appetite, and constipation.

61. The use of claim 60, wherein the gastroparesis symptom comprises nausea.

62. The use of claim 60, wherein the gastroparesis symptom comprises vomiting.

63. Use of a pharmaceutical composition of any one of claims 34-49 in the manufacture of a medicament for the treatment of nausea associated with gastroparesis in a human subject in need thereof.

64. Use of a pharmaceutical composition of any one of claims 34-49 in the manufacture of a medicament for the treatment of vomiting associated with gastroparesis in a human subject in need thereof.

65. Use of a pharmaceutical composition of any one of claims 34-49 in the manufacture of a medicament for treating or improving gastric emptying in a human subject in need thereof.

66. Use of a pharmaceutical composition of any one of claims 34-49 in the manufacture of a medicament for the treatment of functional and motility disorders of a GI tract in a human subject in need thereof.

67. The use of any one of claims 50-66, wherein the pharmaceutical composition is to be administered to the subject chronically.

68. The use of any one of claims 50-66, wherein the pharmaceutical composition is to be administered to the subject acutely.

69. The use of any one of claims 50-66, wherein the pharmaceutical composition is to be administered to the subject for at least 6 days.

70. The use of claim 69, wherein the pharmaceutical composition is to be administered to the subject for at least 7 days.

71. The use of claim 69, wherein the pharmaceutical composition is to be administered to the subject for at least four weeks.

72. The use of claim 69, wherein the pharmaceutical composition is to be administered to the subject for at least 12 weeks.

73. The use of any one of claims 50-72, wherein the pharmaceutical composition is to be administered to the subject one time per day.

74. The use of any one of claims 50-72, wherein the pharmaceutical composition is to be administered to the subject two times per day.

75. The use of any one of claims 50-72, wherein the pharmaceutical composition is to be administered to the subject three times per day.

76. The use of any one of claims 50-72, wherein the pharmaceutical composition is to be administered to the subject four times per day.

77. The use of any one of claims 50-76, wherein the medicament comprises between about 5 mg and about 160 mg of the metopimazine mesylate, and the medicament is to be administered to the subject daily.

78. The use of any one of claims 50-76, wherein the medicament comprises more than 20 mg of metopimazine mesylate, and the medicament is to be administered to the subject daily.

79. The pharmaceutical composition of any one of claims 34-49 for use in therapy.