conditions likely to be encountered upon large-scale production, transportation, storage and pre-usage preparation. The ability to control and produce a stable polymorph with a robust manufacturing process can be key for regulatory approval and marketing. Large scale production processes for high purity 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide can be improved by use of particular polymorphic forms. Accordingly, there is a need for various new crystalline forms of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with different chemical and physical stabilities, and formulations and uses of the same.

BRIEF SUMMARY

[0008a] In an aspect of the present disclosure, there is provided a polymorph of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

[0008b] In another aspect of the present disclosure, there is provided a composition comprising a polymorph disclosed herein and a pharmaceutically acceptable carrier.

[0008c] In a further aspect of the present disclosure, there is provided a method of preparing the polymorph disclosed herein, comprising:
(a) mixing 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with a solvent, wherein the solvent is selected from the group consisting of toluene, anisole, heptane, tert-butyl methyl ether (TBME), methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), ethanol, acetonitrile, methanol, butyl acetate (BuOAc), isopropyl acetate (IPAc), 1-butanol, 1-propanol, 2-propanol, methylene dichloride (DCM), water, ethanol/5% water, and isopropyl alcohol (IPA)/5% water; and
(b) subjecting the mixture generated in step (a) to heat/cool cycles.

[0008d] In another aspect of the present disclosure, there is provided a method of preparing the polymorph disclosed herein, comprising:
(a) mixing polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with a solvent, wherein the solvent is THF/5% water (v/v); and
(b) evaporating the mixture of step (a).

[0008e] In a further aspect of the present disclosure, there is provided a method of preparing the polymorph disclosed herein, comprising:
(a) mixing Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with a solvent, wherein the solvent is dioxane/5% water at a temperature of about 50°C; and
(b) evaporating the mixture of step (a).

[0008f] In another aspect of the present disclosure, there is provided a method of preparing the polymorph disclosed herein, comprising:
(a) mixing polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with THF at a temperature of about 40°C, thereby generating a solid; and
(b) heating the solid generated in step (a).

[0008g] In a further aspect of the present disclosure, there is provided a method of preparing the polymorph disclosed herein, comprising:
(a) mixing polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with aqueous 1-propanol, ethanol, denatured ethanol or aqueous denatured ethanol; and
(b) slurring the mixture of step (a).

[0008h] In another aspect of the present disclosure, there is provided a polymorph disclosed herein, or the composition disclosed herein, for use in therapy.

[0008i] In a further aspect of the present disclosure there is provided a use of a polymorph disclosed herein or the composition disclosed herein, in the manufacture of a medicament for treating a disease associated with neuromuscular or non-neuromuscular dysfunction, muscular weakness, and/or muscle fatigue in a subject in need thereof.

[0008j] In another aspect of the present disclosure, there is provided a kit comprising a therapeutically effective amount of the polymorph disclosed herein or the composition disclosed herein.

[0009] In one ~~aspect~~example, provided herein are polymorphs of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

[0010] In another ~~aspect~~example, provided herein are methods of preparing polymorphs of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

[0011] In another ~~aspect~~example, provided herein are compositions containing the polymorphs of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide as described herein.

[0012] In another ~~aspect~~example, provided herein are methods of treating a disease or condition associated with neuromuscular or non-neuromuscular dysfunction, muscular weakness, and/or muscle fatigue.

DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1A shows experimental and simulated X-ray powder diffraction (XRPD) patterns of polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

[0014] FIG. 1B shows differential scanning calorimetry (DSC) and thermographic analysis (TGA) graphs of polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

[0015] FIG. 1C shows a Gravimetric Vapour Sorption (GVS) graph of polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

CLAIMS

1. A polymorph of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide.

2. The polymorph of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 13.0±0.2, 16.3±0.2, 19.7±0.2, 19.9±0.2, and 20.8±0.2 degrees.

3. The polymorph of claim 1 or 2, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 12.3±0.2, 13.0±0.2, 13.8±0.2, 16.3±0.2, 19.7±0.2, 19.9±0.2, 20.8±0.2, 21.7±0.2, 24.5±0.2, and 26.8±0.2 degrees.

4. The polymorph of any one of claims 1-3, characterized by having an XRPD pattern substantially as shown in FIG. 1A or FIG. 12.

5. The polymorph of any one of claims 1-4, characterized by having a DSC graph substantially as shown in FIG. 1B.

6. The polymorph of any one of claims 1-5, characterized by having a melting endotherm onset at about 192 °C as determined by DSC.

7. The polymorph of any one of claims 1-6, characterized by having a TGA graph substantially as shown in FIG. 1B.

8. The polymorph of any one of claims 1-7, characterized by having a GVS graph substantially as shown in FIG. 1C.

9. The polymorph of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 11.6±0.2, 13.0±0.2, 17.4±0.2, 18.9±0.2, and 22.3±0.2 degrees.

10. The polymorph of claim 1 or 9, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 11.6±0.2, 13.0±0.2, 13.2±0.2, 16.6±0.2, 17.4±0.2, 18.9±0.2, 20.7±0.2, 22.3±0.2, 25.5±0.2, and 27.1±0.2 degrees.

11. The polymorph of any one of claims 1, 9, and 10, characterized by having an XRPD pattern substantially as shown in FIG. 2A.

12. The polymorph of any one of claims 1 and 9-11, characterized by having a DSC graph substantially as shown in FIG. 2B.

13. The polymorph of any one of claims 1 and 9-12, characterized by having a melting endotherm onset at about 191 °C as determined by DSC.

14. The polymorph of any one of claims 1 and 9-13, characterized by having a TGA graph substantially as shown in FIG. 2B.

15. The polymorph of any one of claims 1 and 9-14, characterized by having a GVS graph substantially as shown in FIG. 2C.

16. The polymorph of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 7.6±0.2, 15.1±0.2, 18.1±0.2, 21.3±0.2, and 26.8±0.2 degrees.

17. The polymorph of claim 1 or 16, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 7.6±0.2, 15.1±0.2, 18.1±0.2, 18.6±0.2, 19.4±0.2, 20.0±0.2, 21.3±0.2, 23.8±0.2, 25.1±0.2, and 26.8±0.2 degrees.

18. The polymorph of any one of claims 1, 16, and 17, characterized by having an XRPD pattern substantially as shown in FIG. 3A.

19. The polymorph of any one of claims 1 and 16-18, characterized by having a DSC graph substantially as shown in FIG. 3B.

20. The polymorph of any one of claims 1 and 16-19, characterized by having a broad endotherm with onset at about 75°C and/or a melting endotherm onset at about 193 °C as determined by DSC.

21. The polymorph of any one of claims 1 and 16-20, characterized by having a TGA graph substantially as shown in FIG. 3B.

22. The polymorph of any one of claims 1 and 16-21, characterized by having a weight loss of about 23.8% w/w below 120°C as determined by TGA.

23. The polymorph of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 16.4±0.2, 17.0±0.2, 18.1±0.2, 21.8±0.2, and 22.4±0.2 degrees.

24. The polymorph of claim 1 or 23, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 14.4±0.2, 16.4±0.2, 17.0±0.2, 18.1±0.2, 18.6±0.2, 21.8±0.2, 22.4±0.2, 23.8±0.2, 25.8±0.2, and 31.7±0.2 degrees.

25. The polymorph of any one of claims 1, 23, and 24, characterized by having an XRPD pattern substantially as shown in FIG. 4.

26. The polymorph of claim 1, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 17.8±0.2, 23.6±0.2, 23.7±0.2, 24.2±0.2, and 25.2±0.2 degrees.

27. The polymorph of claim 1 or 26, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 5.9±0.2, 13.6±0.2, 16.6±0.2, 17.8±0.2, 18.4±0.2, 23.6±0.2, 23.7±0.2, 24.2±0.2, 25.2±0.2, and 26.5±0.2 degrees.

28. The polymorph of any one of claims 1, 26, and 27, characterized by having an XRPD pattern substantially as shown in FIG. 5A.

29. The polymorph of any one of claims 1 and 26-28, characterized by having a DSC graph substantially as shown in FIG. 5B.

30. The polymorph of any one of claims 1 and 26-29, characterized by having a melting endotherm onset at about 190 °C as determined by DSC.

31. The polymorph of any one of claims 1 and 26-30, characterized by having a TGA graph substantially as shown in FIG. 5B.

32. The polymorph of any one of claims 1 and 26-31, characterized by having a GVS graph substantially as shown in FIG. 5C.

33. A composition comprising a polymorph of any one of claims 1-32 and a pharmaceutically acceptable carrier.

34. A method of preparing the polymorph of any one of claims 2-8, comprising:

(a) mixing 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with a solvent, wherein the solvent is selected from the group consisting of toluene, anisole, heptane, tert-butyl methyl ether (TBME), methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), ethanol, acetonitrile, methanol, butyl acetate (BuOAc), isopropyl acetate (IPAc), 1-butanol, 1-propanol, 2-propanol, methylene dichloride (DCM), water, ethanol/5% water, and isopropyl alcohol (IPA)/5% water; and

(b) subjecting the mixture generated in step (a) to heat/cool cycles.

35. The method of claim 34, wherein the heat/cool cycles comprises cycles between room temperature and about 50°C, wherein the duration of each condition is about four hours.

36. A method of preparing the polymorph of any one of claims 9-15, comprising:

(a) mixing polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with a solvent, wherein the solvent is THF/5% water (v/v); and

(b) evaporating the mixture of step (a).

37. A method of preparing the polymorph of any one of claims 16-22, comprising:

(a) mixing Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with a solvent, wherein the solvent is dioxane/5% water at a temperature of about 50°C; and

(b) evaporating the mixture of step (a).

38. A method of preparing the polymorph of any one of claims 23-25, comprising:

(a) mixing polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with THF at a temperature of about 40°C, thereby generating a solid; and

(b) heating the solid generated in step (a).

39. A method of preparing the polymorph of any one of claims 26-32, comprising:

(a) mixing polymorphic Form I of 1-(2-((((trans)-3-fluoro-1-(3-fluoropyridin-2-yl)cyclobutyl)methyl)amino)pyrimidin-5-yl)-1H-pyrrole-3-carboxamide with aqueous 1-propanol, ethanol, denatured ethanol or aqueous denatured ethanol; and

(b) slurring the mixture of step (a).

40. A polymorph of any one of claims 1-32, or the composition of claim 33, for use in therapy.

~~40~~41. ~~A method of treating a disease associated with neuromuscular or non-neuromuscular dysfunction, muscular weakness, and/or muscle fatigue in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the~~ Use of a polymorph of any one of claims 1-32 or the composition of claim 33, in the manufacture of a medicament for treating a disease associated with neuromuscular or non-neuromuscular dysfunction, muscular weakness, and/or muscle fatigue in a subject in need thereof.

~~41~~42. The use~~method~~ of claim ~~40~~41, wherein the disease is Amyotrophic Lateral Sclerosis (ALS), Spinal Muscular Atrophy (SMA), mobility limitation, Chronic Obstructive Pulmonary Disease (COPD), or myasthenia gravis.

~~42~~43. A kit comprising a therapeutically effective amount of the polymorph of any one of claims 1-32 or the composition of claim 33.