CRYSTALLINE FORMS OF A RYANODINE RECEPTOR MODULATOR AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/135,083, filed January 8, 2021, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The sarcoplasmic reticulum (SR) is a structure in cells that functions, among other things, as a specialized intracellular calcium (Ca^{2+}) store. Ryanodine receptors (RyRs) are channels in the SR that open and close to regulate the release of Ca^{2+} from the SR into the intracellular cytoplasm of the cell. Release of Ca^{2+} into the cytoplasm from the SR increases cytoplasmic Ca^{2+} concentration. Open probability of RyRs refers to the likelihood that a RyR is open at any given moment, and therefore capable of releasing Ca^{2+} into the cytoplasm from the SR. Three RyR isoforms are known. RyR1 is the predominant isoform expressed in mammalian skeletal muscle, and is predominantly found in cardiac muscle, whereas RyR3 expression is low in skeletal muscle.

[0003] Ca^{2+} release from the SR is modulated by several RyR binding proteins. Calstabin1 (FKBP12) and calstabin2 (FKBP12.6) stabilize the closed state of the RyR1 and RyR2, respectively. Mutations in *RYR1 or RYR2* are characterized by reduced binding of Calstabin 1 or Calstabin2, respectively, and inappropriate channel opening not related to contraction signals. This channel opening is further exacerbated by post-translational modifications such as PKA-phosphorylation, oxidation, or nitrosylation of the RyR channel. The resulting dissociation of Calstabin can lead to leaky channels, which exhibit a pathologic increase in the open probability under resting conditions. The SR Ca^{2+} leak leads to a reduction in SR Ca^{2+} content, with less Ca^{2+} available for release and consequently weaker muscle contractions.

SUMMARY

[0003a] In an aspect, there is provided a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, wherein if an X-ray diffraction pattern of the crystalline form is obtained using measurement conditions, the measurement conditions comprising:

Start Position [°2θ]	3.00
End Position [°2θ]	54.99
Step Size [°2θ]	0.018
Scan Step Time [s]	34.92

Measurement Temperature [°C]	25.00
K-Alpha1 [Å]	1.54
K-Alpha2 [Å]	1.54
K-Beta [Å]	1.39
Spinning	Yes

then at least four X-ray diffraction peaks selected from 7.3 ± 0.1, 13.2 ± 0.1, 14.6 ± 0.1, 17.1 ± 0.1, 18.0 ± 0.1, 18.3 ± 0.1, 23.2 ± 0.1, 23.9 ± 0.1, 24.4 ± 0.1, and 28.6 ± 0.1 degrees two theta (°θ) are observed.

[0003b] In another aspect, there is provided a pharmaceutical composition comprising in unit dosage form the crystalline form as defined above, and at least one pharmaceutically-acceptable excipient.

[0003c] In another aspect, there is provided a use of the crystalline form as defined above, or pharmaceutical composition as defined above, in the manufacture of a medicament for treating a condition in a subject associated with a ryanodine receptor.

[0003d] In another aspect, there is provided a crystalline form as defined above, or pharmaceutical composition as defined above, for use in therapy.

[0003e] In another aspect, there is provided a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, , wherein if an X-ray diffraction pattern of the crystalline form is obtained using measurement conditions, the measurement conditions comprising:

Start Position [°2θ]	3.00
End Position [°2θ]	54.99
Step Size [°2θ]	0.018
Scan Step Time [s]	34.92
Measurement Temperature [°C]	25.00
K-Alpha1 [Å]	1.54
K-Alpha2 [Å]	1.54
K-Beta [Å]	1.39
Spinning	Yes

then at least four X-ray diffraction peaks selected from 9.8 ± 0.1, 11.8 ± 0.1, 13.5 ± 0.1, 14.0 ± 0.1, 14.3 ± 0.1, 17.4 ± 0.1, 18.9 ± 0.1, 19.6 ± 0.1, 22.1 ± 0.1, 26.6 ± 0.1, and 27.2 ± 0.1 degrees two theta (°θ) are observed, wherein the crystalline form comprises a population of particles, wherein at least about 90% by mass of the particles comprise a diameter of no greater than about 20 microns.

[0003f] In another aspect, there is provided a pharmaceutical composition comprising in unit dosage form the crystalline form as defined above, and at least one pharmaceutically-acceptable excipient.

[0003g] In another aspect, there is provided a use of the crystalline form as defined above, or pharmaceutical composition as defined above, in the manufacture of a medicament for treating of a condition in a subject associated with a ryanodine receptor.

[0003h] In another aspect, there is provided a crystalline form as defined above, or pharmaceutical composition as defined above, for use in therapy.

[0003i] In another aspect, there is provided a pharmaceutical composition comprising in unit dosage form a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, wherein if a melting point of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and

(b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument,

then a melting point of 201-203 °C (T_{onset}) is obtained, wherein the unit dosage form is a gastro-resistant tablet.

[0003j] In another aspect, there is provided a use of a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate in the manufacture of a medicament for treating RYR1-related myopathy in a subject, wherein if a melting point of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and

(b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument,

then a melting point of 201-203 °C (T_{onset}) is obtained.

[0004] In some examples, the present disclosure provides a composition comprising a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, wherein if a melting point of the crystalline form is obtained by: (a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and (b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument, then a melting point of

208-210 °C (T_{onset}) is obtained.

[0005] In some examples, the present disclosure provides a composition comprising a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate for use in a method of treating a condition, wherein if a melting point of the crystalline form is obtained by: (a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and (b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument, then a melting point of 208-210 °C (T_{onset}) is obtained.

[0006] In some examples, the present disclosure provides a composition comprising a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, wherein if a melting point of the crystalline form is obtained by: (a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and (b) increasing the temperature of the temperature-controlled chamber at a scan rate of about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument, then a melting point of 201-203 °C (T_{onset}) is obtained.

[0007] In some examples, the present disclosure provides a composition comprising a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, for use in a method of treating a condition, wherein if a melting point of the crystalline form is obtained by (a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and (b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument, then a melting point of 201-203 °C (T_{onset}) is obtained.

[0008] In some examples, the present disclosure provides a method of treating a condition, comprising administering to a subject in need thereof a therapeutically-effective amount of a composition, the composition comprising a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate.

DESCRIPTION OF THE DRAWINGS

[0009] **FIG. 1** depicts a characteristic X-ray diffraction (XRD) pattern of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate Form 1.

[0010] **FIG. 2** depicts a characteristic Differential Scanning Calorimetry (DSC) profile of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate Form 1.

CLAIMS

WHAT IS CLAIMED IS:

1. A crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, wherein if an X-ray diffraction pattern of the crystalline form is obtained using measurement conditions, the measurement conditions comprising:

Start Position [°2θ]	3.00
End Position [°2θ]	54.99
Step Size [°2θ]	0.018
Scan Step Time [s]	34.92
Measurement Temperature [˚C]	25.00
K-Alpha1 [Å]	1.54
K-Alpha2 [Å]	1.54
K-Beta [Å]	1.39
Spinning	Yes

then at least four X-ray diffraction peaks selected from 7.3 ± 0.1, 13.2 ± 0.1, 14.6 ± 0.1, 17.1 ± 0.1, 18.0 ± 0.1, 18.3 ± 0.1, 23.2 ± 0.1, 23.9 ± 0.1, 24.4 ± 0.1, and 28.6 ± 0.1 degrees two theta (˚θ) are observed.

2. The crystalline form of claim 1, wherein X-ray diffraction peaks at 7.3 ± 0.1, 14.6 ± 0.1, 18.0 ± 0.1, 22.4 ± 0.1, and 24.4 ± 0.1 degrees two theta (˚θ) are observed.

3. The crystalline form of claim 1 or 2, wherein X-ray diffraction peaks at 7.3 ± 0.1, 11.1 ± 0.1, 14.6 ± 0.1, 18.0 ± 0.1, 19.2 ± 0.1, 22.4 ± 0.1, 23.2 ± 0.1, and 24.4 ± 0.1 degrees two theta (˚θ) are observed.

4. The crystalline form of any one of claims 1-3, wherein X-ray diffraction peaks at 7.3 ± 0.1, 11.0 ± 0.1, 11.1 ± 0.1, 11.5 ± 0.1, 13.2 ± 0.1, 14.6 ± 0.1, 15.2 ± 0.1, 17.1 ± 0.1, 18.0 ± 0.1, 18.3 ± 0.1, 19.2 ± 0.1, 20.2 ± 0.1, 21.4 ± 0.1, 22.4 ± 0.1, 23.2 ± 0.1, 23.9 ± 0.1, 24.4 ± 0.1 and 28.6 ± 0.1 degrees two theta (˚θ) are observed.

5. The crystalline form of any one of claims 1-4, wherein X-ray diffraction peaks substantially as shown in **FIG. 6** are observed.

6. The crystalline form of any one of claims 1-5, wherein if a thermogravimetric analysis of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at 25 ˚C in a temperature-controlled chamber; and

(b) increasing the temperature at a scan rate of about 10 ˚C/minute to 250 ˚C using a

thermogravimetric analysis instrument,

then a thermogravimetric analysis profile substantially as shown in **FIG. 8** is obtained.

7. The crystalline form of any one of claims 1-6, wherein if a dynamic vapor sorption profile of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at 25 °C and 50% relative humidity in a temperature-controlled and humidity-controlled chamber until mass variation is less than 0.002% per minute for 6 hours;

(b) increasing the relative humidity from 50% to 90% at a rate of 10% per hour;

(c) equilibrating the sample at 90% relative humidity until mass variation of less than 0.002% per minute for 6 hours is observed;

(d) decreasing the relative humidity from 90% to 0% at a rate of 10% per hour;

(e) equilibrating the sample at 0% relative humidity until mass variation of less than 0.002% per minute for 6 hours is observed; and

(f) increasing the relative humidity from 0% to 50% at a rate of 10% per hour,

then a dynamic vapor sorption profile substantially as shown in **FIG. 9** is obtained.

8. The crystalline form of any one of claims 1-7, wherein if a melting point of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and

(b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument,

then a melting point of 208-210 °C (T_{onset}) is obtained

9. The crystalline form of any one of claims 1-8, wherein the crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate is characterized by a differential scanning calorimetry profile substantially as shown in **FIG. 7**.

10. The crystalline form of any one of claims 1-9, wherein the crystalline form comprises a population of particles, wherein at least about 90% by mass of the particles comprise a diameter of no greater than about 90 microns.

11. The crystalline form of any one of claims 1-9, wherein the crystalline form comprises a population of particles, wherein at least about 50% by mass of the particles comprise a diameter of no greater than about 30 microns.

12. The crystalline form of any one of claims 1-9, wherein the crystalline form comprises a population of particles, wherein at least about 50% by mass of the particles comprise a diameter of between about 10 microns and about 30 microns.

13. A pharmaceutical composition comprising in unit dosage form the crystalline form of any one of claims 1-12, and at least one pharmaceutically-acceptable excipient.

14. The pharmaceutical composition of claim 13, wherein the unit dosage form is a gastro-resistant tablet.

15. The pharmaceutical composition of claim 13 or 14, comprising an amount of the crystalline form equivalent to about 20 mg to about 200 mg of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid.

16. Use of the crystalline form of any one of claims 1-12 or pharmaceutical composition of any one of claims 13-15 in the manufacture of a medicament for treating a condition in a subject associated with a ryanodine receptor.

17. The use of claim 16, wherein the condition is a cardiac condition.

18. The use of claim 17, wherein the cardiac condition is characterized by an irregular heartbeat.

19. The use of claim 17, wherein the cardiac condition is catecholaminergic polymorphic ventricular tachycardia.

20. The use of claim 17, wherein the cardiac condition is catecholaminergic polymorphic ventricular tachycardia type 1.

21. The use of claim 17, wherein the cardiac condition is heart failure.

22. The use of claim 16, wherein the condition is RYR1-related myopathy.

23. The use of claim 16, wherein the condition is Duchenne Muscular Dystrophy.

24. The use of claim 16, wherein the condition is sarcopenia.

25. The use of any one of claims 16-24, wherein the crystalline form is to be administered in a therapeutically effective amount, wherein the therapeutically-effective amount is about 200 mg per day.

26. The use of any one of claims 16-24, wherein the crystalline form is to be administered in a therapeutically-effective amount, wherein the therapeutically-effective amount is about 300 mg per day.

27. The use of any one of claims 16-24, wherein the crystalline form to be administered in a therapeutically-effective amount, wherein the therapeutically-effective amount is about 400 mg per day.

28. A crystalline form of any one of claims 1-12 or pharmaceutical composition of any one of claims 13-15, for use in therapy.

29. A crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, , wherein if an X-ray diffraction pattern of the crystalline form is obtained using measurement conditions, the measurement conditions comprising:

Start Position [°2θ]	3.00
End Position [°2θ]	54.99
Step Size [°2θ]	0.018
Scan Step Time [s]	34.92
Measurement Temperature [˚C]	25.00
K-Alpha1 [Å]	1.54
K-Alpha2 [Å]	1.54
K-Beta [Å]	1.39
Spinning	Yes

then at least four X-ray diffraction peaks selected from 9.8 ± 0.1, 11.8 ± 0.1, 13.5 ± 0.1, 14.0 ± 0.1, 14.3 ± 0.1, 17.4 ± 0.1, 18.9 ± 0.1, 19.6 ± 0.1, 22.1 ± 0.1, 26.6 ± 0.1, and 27.2 ± 0.1 degrees two theta (˚θ) are observed, wherein the crystalline form comprises a population of particles, wherein at least about 90% by mass of the particles comprise a diameter of no greater than about 20 microns.

30. The crystalline form of claim 29, wherein X-ray diffraction peaks at 9.8 ± 0.1, 11.0 ± 0.1, 17.4 ± 0.1, 21.6 ± 0.1 and 22.6 ± 0.1 degrees two theta (˚θ) are observed.

31. The crystalline form of claim 29 or 30, wherein X-ray diffraction peaks at 9.8 ± 0.1, 11.0 ± 0.1, 11.8 ± 0.1, 15.0 ± 0.1, 17.4 ± 0.1, 21.6 ± 0.1, 22.1 ± 0.1, and 22.6 ± 0.1 degrees two theta (˚θ) are observed.

32. The crystalline form of any one of claims 29-31, wherein X-ray diffraction peaks at 9.8 ± 0.1, 11.0 ± 0.1, 11.4 ± 0.1, 11.8 ± 0.1, 13.5 ± 0.1, 14.0 ± 0.1, 14.3 ± 0.1, 15.0 ± 0.1, 17.4 ± 0.1, 18.9 ± 0.1, 19.3 ± 0.1, 19.6 ± 0.1, 20.3 ± 0.1, 21.6 ± 0.1, 22.1 ± 0.1, 22.6 ± 0.1, 26.6 ± 0.1, and 27.2 ± 0.1 degrees two theta (˚θ) are observed.

33. The crystalline form of any one of claims 29-32, wherein X-ray diffraction peaks substantially as shown in **FIG. 1** are observed.

34. The crystalline form of any one of claims 29-33 wherein if a thermogravimetric analysis of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at 25 ˚C in a temperature-controlled chamber; and

(b) increasing the temperature at a scan rate of about 10 ˚C/minute to 250 ˚C using a

thermogravimetric analysis instrument,

then a thermogravimetric analysis profile substantially as shown in **FIG. 3** is obtained.

35. The crystalline form of any one of claims 29-34, wherein if a dynamic vapor sorption profile of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at 25 °C and 50% relative humidity in a temperature-controlled and humidity-controlled chamber until mass variation of less than 0.002% per minute for 6 hours is obtained;

(b) increasing the relative humidity from 50% to 90% at a rate of 10% per hour;

(c) equilibrating the sample at 90% relative humidity until mass variation of less than 0.002% per minute for 6 hours is obtained;

(d) decreasing the relative humidity from 90% to 0% at a rate of 10% per hour;

(e) equilibrating the sample at 0% relative humidity until mass variation of less than 0.002% per minute for 6 hours is observed; and

(f) increasing the relative humidity from 0% to 50% at a rate of 10% per hour,

then a dynamic vapor sorption profile substantially as shown in **FIG. 4** is obtained.

36. The crystalline form of any one of claims 29-35, wherein if a melting point of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and

b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument,

then a melting point of 201-203 °C (T_{onset}) is obtained, wherein the crystalline form comprises a population of particles, wherein at least about 90% by mass of the particles comprise a diameter of no greater than about 20 microns.

37. The crystalline form of any one of claims 29-36, wherein the crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate is characterized by a differential scanning calorimetry profile substantially as shown in **FIG. 2**.

38. The crystalline form of any one of claims 29-37, wherein the crystalline form comprises a population of particles, wherein at least about 50% by mass of the particles comprise a diameter of no greater than 10 microns.

39. The crystalline form of any one of claims 29-38, wherein the crystalline form comprises a population of particles, wherein at least about 50% by mass of the particles comprise a diameter of between about 6.9 microns and about 9.75 microns.

40. A pharmaceutical composition comprising in unit dosage form the crystalline form of any

one of claims 29-39, and at least one pharmaceutically-acceptable excipient,

41. The pharmaceutical composition of claim 40, wherein the unit dosage form is a gastro-resistant tablet.

42. Use of the crystalline form of any one of claims 29-39 or pharmaceutical composition of claim 40 or claim 41 in the manufacture of a medicament for treating of a condition in a subject associated with a ryanodine receptor.

43. The use of claim 42, wherein the condition is a cardiac condition.

44. The use of claim 43, wherein the cardiac condition is characterized by an irregular heartbeat.

45. The use of claim 43, wherein the cardiac condition is catecholaminergic polymorphic ventricular tachycardia.

46. The use of claim 43, wherein the cardiac condition is catecholaminergic polymorphic ventricular tachycardia type 1.

47. The use of claim 43, wherein the cardiac condition is heart failure.

48. The use of claim 42, wherein the condition is RYR1-related myopathy.

49. The use of claim 42, wherein the condition is Duchenne Muscular Dystrophy.

50. The use of claim 42, wherein the condition is sarcopenia.

51. The use of any one of claims 42-50, wherein the crystalline form is to be administered in a therapeutically effective amount, wherein the therapeutically-effective amount is about 200 mg per day.

52. The use of any one of claims 42-50, wherein the crystalline form is to be administered in a therapeutically effective amount, wherein the therapeutically-effective amount is about 300 mg per day.

53. The use of any one of claims 42-50, wherein the crystalline form is to be administered in a therapeutically effective amount, wherein the therapeutically-effective amount is about 400 mg per day.

54. A crystalline form of any one of claims 29-39 or pharmaceutical composition of claim 40 or claim 41, for use in therapy.

55. A pharmaceutical composition comprising in unit dosage form a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate, wherein if a melting point of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at a temperature of about 20 ˚C in a temperature-controlled chamber; and

(b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument,

then a melting point of 201-203 °C (T_{onset}) is obtained, wherein the unit dosage form is a gastro-resistant tablet.

56. Use of a crystalline form of 4-[(7-methoxy-2,3-dihydro-1,4-benzothiazepin-4(5H)yl)methyl]benzoic acid hemifumarate in the manufacture of a medicament for treating RYR1-related myopathy in a subject, wherein if a melting point of the crystalline form is obtained by:

(a) equilibrating a sample of said crystalline form at a temperature of about 20 °C in a temperature-controlled chamber; and

(b) increasing the temperature of the temperature-controlled chamber at about 10 °C/minute to 250 °C using a differential scanning calorimetry instrument,

then a melting point of 201-203 °C (T_{onset}) is obtained.