FORMULATIONS OF T-TYPE CALCIUM CHANNEL MODULATORS AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to and the benefit of U.S. Provisional Patent Application Numbers 62/873,022, filed July 11, 2019, 62/934,820, filed November 13, 2019, and 62/958,923, filed January 9, 2020, each of which is incorporated herein by reference in its entirety.

BACKGROUND

T-type calcium channels are low-voltage activated ion channels that mediate the influx of calcium into cells. Aberrant function of these ion channels is associated with several diseases or conditions, including psychiatric disorder (e.g., mood disorder (e.g., major depressive disorder)), pain, tremor (e.g., essential tremor), epilepsy, or an epilepsy syndrome (e.g., absence seizures and juvenile myoclonic epilepsy). Accordingly, compounds that selectively modulate T-type calcium channel in mammals may be useful in treatment of such disease states.

SUMMARY

Described herein are compositions and dosage forms useful for preventing and/or treating a disease or condition relating to aberrant function of a T-type calcium channel, such as epilepsy and epilepsy syndromes (e.g., absence seizures, juvenile myoclonic epilepsy, or a genetic epilepsy) and mood disorders (e.g., major depressive disorder). The present disclosure further comprises methods for modulating the function of a T-type calcium channel.

In one aspect of the present disclosure, there is provided an oral dosage form comprising:

the compound of formula (I) or a pharmaceutically acceptable salt thereof; and

a modified-release polymer.

In another aspect of the present disclosure, there is provided a crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 16.2±0.2, 17.4±0.2, and 26.6±0.2; or

(ii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2; or

(iii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.

In a further aspect of the present disclosure, there is provided a crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 21.9±0.2, 18.5±0.2, and 17.8±0.2; or

(ii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, and 20.5±0.2; or

(iii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, 20.5±0.2, 25.2±0.2, 16.9±0.2, 24.2±0.2, 28.6±0.2, and 21.2±0.2.

In another aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein, or the crystalline form disclosed herein, in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof.

In a further aspect of the present disclosure, there is provided a use of the oral dosage form disclosed herein, or the crystalline form disclosed herein, in the manufacture of a medicament for treating a psychiatric disorder in a subject in need thereof.

In another aspect of the present disclosure, there is provided a use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form disclosed herein, or the crystalline form disclosed herein, in the manufacture of a medicament that results in reduction of the essential tremor as assessed by The Essential Tremor Rating Assessment Scale (TETRAS) score; or as assessed by accelerometer-based upper limb score; or that results in reduction of sigma frequency band.

In a further aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form disclosed herein, or the crystalline form disclosed herein, for use in therapy.

In one example, the present disclosure provides a pharmaceutical composition comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof, and an excipient that functions to modify the release rate of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

In one example, the present disclosure provides an oral dosage form comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof; and a modified-release polymer (e.g., a controlled-release polymer, hydrophilic matrix polymers, e.g., an HPMC polymer as a hydrophilic matrix polymer, hydrophobic matrix polymers (e.g., ethyl cellulose, ethocel), or polyacrylate polymers (e.g., Eudragit RL100, Eudragit RS100)). In some examples, the dosage form comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)). In other examples, the dosage form comprises from about 1 mg to about 40

mg (e.g., about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).

The dosage form disclosed herein may comprise from about 10% by weight to about 70% by weight of the modified-release polymer. The dosage form disclosed herein may comprise a diluent (e.g., microcrystalline cellulose).

In another example, the present disclosure discloses an oral dosage form comprising: from about 15 mg to 25 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg of an HPMC polymer.

In another example, the present disclosure provides an oral dosage form comprising: from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% by weight to about 64% by weight of an HPMC polymer.

Also provided herein is an oral dosage form comprising: from about 3 mg to 8 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg of an HPMC polymer.

In one example, provided herein is an oral dosage form comprising: from about 3% by weight to about 8% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% to about 64% by weight of an HPMC polymer.

The present disclosure provides, in part, an oral (e.g., particulate) composition comprising: the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and a modified-release polymer (e.g., a controlled-release polymer, hydrophilic matrix polymers, e.g., an HPMC polymer , hydrophobic matrix polymers (e.g., ethyl cellulose, ethocel), or polyacrylate polymers (e.g., Eudragit RL100, Eudragit RS100)).

In some examples, the composition comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)). In certain examples, the composition comprises from about 1 mg to about 40 mg (e.g., about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)).

Also provided herein is an oral (e.g., particulate) composition comprising: from about 15 mg to 25 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg HPMC.

In another example, the present disclosure provides an oral (e.g., particulate) composition comprising: from about 14% by weight to about 25% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% to about 64% by weight of an HPMC polymer.

Provided herein, in part, is an oral (e.g., particulate) composition comprising: from about 3 mg to 8 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 55 mg to 65 mg HPMC.

The present disclosure discloses, in part, an oral (e.g., particulate, swellable core) composition comprising: from about 3% by weight to about 8% by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)); and from about 53% to about 64% by weight of an HPMC polymer.

In one example, the present disclosure provides a crystalline form of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 16.2±0.2, 17.4±0.2, and 26.6±0.2.

In another example, the present disclosure provides a crystalline form of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ): 21.9±0.2, 18.5±0.2, and 17.8±0.2.

The present disclosure provides, in part, a method of treating a neurological disorder in a subject in need thereof, wherein the method comprises administering to the subject the oral dosage, the composition, or the crystalline form disclosed herein. In some examples, the neurological disorder is epilepsy. In other examples, the epilepsy is juvenile epilepsy. In certain examples, the epilepsy is genetic epilepsy (e.g., CACNA1G related genetic generalized epilepsy). In some examples, the neurological disorder is absence seizure. In other examples, the neurological disorder is absence epilepsy (e.g., CACNA1H related absence epilepsy). In certain examples, the neurological disorder is epilepsy related to CACNA1G, H or I. In some examples, the epilepsy is childhood absence epilepsy (CAE). In other examples, the epilepsy is juvenile absence epilepsy (JAE). In certain examples, the epilepsy is Lenox-Gastaut Syndrome. In some examples, the neurological disorder is

pain (e.g., acute pain, chronic pain, neuropathic pain, inflammatory pain, nociceptive pain, central pain; e.g., thalamic pain; or migraine). In other examples, the neurological disorder is tremor (e.g., essential tremor, Parkinson's tremor, or cerebellar tremor, CACNA1G related tremor). In certain examples, the neurological disorder is ataxia (e.g., spinocerebellar ataxia, or spinocerebellar ataxia with CACNA1G mutations). In other examples, the neurological disorder is tinnitus. In some examples, the neurological disorder is a disorder of wakefulness.

In another example, provided herein is a method of treating a psychiatric disorder in a subject in need thereof, wherein the method comprises administering to the subject the oral dosage, the composition, or the crystalline form disclosed herein. In some examples, the psychiatric disorder is a mood disorder. In other examples, the mood disorder is major depressive disorder.

In certain examples of the methods described herein, the dosage form is administered to the subject once a day. The dosage form may be administered to the subject twice a day. The dosage form may be administered to the subject every other day.

In some examples of the methods described herein, about 15 mg to 25 mg (e.g., about 20 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) may be administered to the subject daily or about 30 mg to 50 mg (e.g., about 40 mg) of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) is administered to the subject daily.

In certain examples of the methods described herein, the dosage form, upon administration to the subject, may have a reduced C_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified-release polymer, e.g., an HPMC polymer). In other examples of the methods disclosed herein, the dosage form, upon administration to the subject, may have a greater t_{max} value than a reference oral dosage form (e.g., a dosage form with any intended release rate profile e.g., modified release rate profile, a dosage form that does not have a modified release rate profile, a dosage form that does not have a modified-release polymer, e.g., an HPMC polymer).

Also provided herein is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the

compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the number of seizures.

In one example, provided herein is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the seizure density as measured by Electroencephalogram (EEG).

Provided herein, in part, is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the mean seizure duration as measured by EEG.

In another example, disclosed herein is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the cumulative seizure duration as measured by EEG.

Provided herein, in part, is a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage, the composition, or the crystalline described herein) that results in reduction of the total time with 2.5-4Hz spike wave discharges after hyperventilation and photic stimulation challenges as measured by EEG.

In another example, a method of treating a generalized epileptic syndrome with absence seizures in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form) that results in reduction of global severity as measured by Clinical Global Impression-Severity (CGI-S) or Clinical Global Impression-Improvement (CGI-I) scores is provided herein.

Also provided herein is a method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula

(I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of the essential tremor as assessed by The Essential Tremor Rating Assessment Scale (TETRAS) score. In some examples, the reduction of the essential tremor is assessed by The Essential Tremor Rating Assessment Scale (TETRAS) upper limb score. In other examples, the reduction of the essential tremor is assessed by TETRAS-ADL (activities of daily living). the reduction of the essential tremor is assessed by TETRAS performance subscale score or TETRAS performance individual items.

Also provided herein is a method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage, the composition, or the crystalline form disclosed herein) that results in reduction of the essential tremor as assessed by accelerometer-based upper limb score.

In another example, provided herein is a method of treating an essential tremor in a patient in need thereof, comprising administering to the patient a sufficient amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof (e.g., the compound of formula (II)) (e.g., the oral dosage form, the composition, or the crystalline form disclosed herein) that results in reduction of sigma frequency band. In some examples, the essential tremor is upper limb tremor.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing **Brief Description of the Figures**, **Detailed Description**, **Examples**, and **Claims**.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a powder X-ray diffractogram of form C of the compound of formula (II).

FIG. 2 is a differential scanning calorimetry (DSC) thermogram of form C of the compound of formula (II).

FIG. 3 is a thermogravimetric analysis (TGA) thermogram of form C of the compound of formula (II).

FIG. 4 is a hot stage microscopy (HSM) photomicrographs of form C of the compound of formula (II).

CLAIMS

1. An oral dosage form comprising:

the compound of formula (I) or a pharmaceutically acceptable salt thereof; and

a modified-release polymer.

2. The dosage form of claim 1, wherein the dosage form comprises from about 0.9 % by weight to about 40 % by weight of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

3. The dosage form of claim 1, wherein the dosage form comprises from about 1 mg to about 40 mg of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

4. The dosage form of claim 1 or 3, wherein the compound of formula (I) or a pharmaceutically acceptable salt thereof is in a crystalline form.

5. The dosage form of claim 4, wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 16.2±0.2, 17.4±0.2, and 26.6±0.2; or

(ii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2; or

(iii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.

6. The dosage form of claim 4 or 5, wherein the crystalline form has a X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern depicted in FIG. 1.

7. The dosage form of any one of claims 4-6, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about 226.6 °C.

8. The dosage form of any one of claims 1 and 3-6, wherein the dosage form comprises from about 55 mg to 65 mg of the modified-release polymer.

9. The dosage form of any one of claims 1 and 3-6, wherein the dosage form comprises from about 10% by weight to about 70% by weight of the modified-release polymer.

10. The dosage form of any one of claims 1 and 3-9, wherein the dosage form further comprises a diluent.

11. The dosage form of claim 10, wherein the diluent comprises microcrystalline cellulose.

12. The dosage form of claim 11, wherein the dosage form comprises from about 15 mg to 40 mg microcrystalline cellulose; or

wherein the dosage form comprises from about 15% by weight to about 35% by weight microcrystalline cellulose.

13. The dosage form of any one of claims 1 and 3-12, wherein the dosage form further comprises a glidant.

14. The dosage form of claim 13, wherein the glidant comprises colloidal silicon dioxide.

15. The dosage form of any one of claims 1 and 3-14, wherein the dosage form further comprises a lubricant.

16. The dosage form of claim 15, wherein the lubricant comprises magnesium stearate.

17. The dosage form of any one of claims 1 and 3-16, wherein the dosage form further comprises a coating.

18. The dosage form of any one of claims 1 and 3-17, wherein the dosage form is administered to a patient once daily or twice daily.

19. The dosage form of any one of claims 1 and 3-18, wherein the dosage form is a tablet, a capsule or a suspension.

20. A crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 16.2±0.2, 17.4±0.2, and 26.6±0.2; or

(ii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, and 26.6±0.2; or

(iii) 11.5±0.2, 16.2±0.2, 17.4±0.2, 18.3±0.2, 18.5±0.2, 19.2±0.2, 20.0±0.2, 22.6±0.2, 23.9±0.2, and 26.6±0.2.

21. The crystalline form of claim 20, wherein the crystalline form has a X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern depicted in FIG. 1.

22. The crystalline form of claim 20 or 21, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about 226.6 °C.

23. A crystalline form of the compound of formula (II), wherein the crystalline form exhibits an X-ray powder diffraction pattern comprising peaks at the following diffraction angles (2θ):

(i) 21.9±0.2, 18.5±0.2, and 17.8±0.2; or

(ii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, and 20.5±0.2; or

(iii) 21.9±0.2, 18.5±0.2, 17.8±0.2, 10.2±0.2, 20.5±0.2, 25.2±0.2, 16.9±0.2, 24.2±0.2, 28.6±0.2, and 21.2±0.2.

24. The crystalline form of claim 23, wherein the crystalline form has a X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern depicted in FIG. 7.

25. The crystalline form of claim 23 or 24, wherein the crystalline form has a melting point onset as determined by differential scanning calorimetry at about 97.9, 131.6, 223.7, 83.8, 128.9, 168.9, or 224.4 °C.

26. Use of the oral dosage form of any one of claims 1, and 3-19, or the crystalline form of any one of claims 23-25, in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof.

27. The use of claim 26, wherein the neurological disorder is selected from the group consisting of epilepsy, seizure, pain, tremor, ataxia, tinnitus, and a disorder of wakefulness.

28. The use of claim 26, wherein the tremor is an essential tremor, Parkinson's tremor, or cerebellar tremor, or a CACNA1G related tremor.

29. Use of the oral dosage form of any one of claims 1, 3-19, or the crystalline form of any one of claims 23-25, in the manufacture of a medicament for treating a psychiatric disorder in a subject in need thereof.

30. The use of claim 29, wherein the psychiatric disorder is a mood disorder.

31. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form of any one of claims 1, 3-19, or the crystalline form of any one of claims 23-25, in the manufacture of a medicament that results in reduction of the essential tremor as assessed by The Essential Tremor Rating Assessment Scale (TETRAS) score; or as assessed by accelerometer-based upper limb score; or that results in reduction of sigma frequency band.

32. The use of claim 131, wherein the reduction of the essential tremor is assessed by The Essential Tremor Rating Assessment Scale (TETRAS) upper limb score; or TETRAS-ADL (activities of daily living); or TETRAS performance subscale score or TETRAS performance individual items.

33. The use of claim 31 or 32, wherein the essential tremor is upper limb tremor.

34. A compound of formula (I) or a pharmaceutically acceptable salt thereof, or the oral dosage form of any one of claims 1, 3-19, or the crystalline form of any one of claims 23-25, for use in therapy.