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.

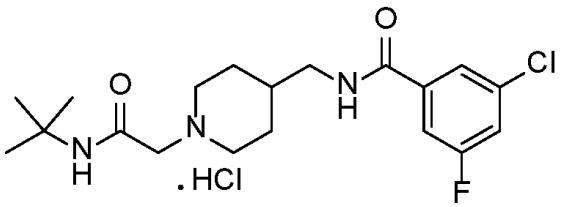
BACKGROUND

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 an aspect of the present disclosure, there is provided a crystalline form of the compound of formula (II)



formula (II)

wherein the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern comprising the following peaks at the diffraction angle 2θ: 26.6±0.2, 16.2±0.2 and 17.4±0.2.

In another aspect of the present disclosure, there is provided an oral dosage form comprising the crystalline form as disclosed herein and a modified-release polymer.

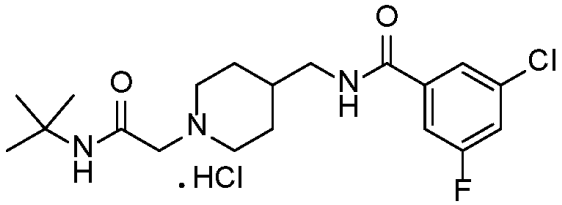
In a further aspect of the present disclosure, there is provided a use of the crystalline form as disclosed herein or the oral dosage form as disclosed herein in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein the neurological disorder is selected from the group consisting of epilepsy, seizure, pain, ataxia, tinnitus and a disorder of wakefulness.

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

CLAIMS

1. A crystalline form of the compound of formula (II)



formula (II)

wherein the crystalline form is characterized by an X-ray powder diffraction (XRPD) pattern comprising the following peaks at the diffraction angle 2θ:

16.2±0.2, 17.4±0.2, and 26.6±0.2.

2. The crystalline form of claim 1, wherein the XRPD pattern comprises one or more of the following peaks at the diffraction angle 2θ: 16.2±0.2, 17.4±0.2, 22.6±0.2, 26.6±0.2 and 11.5±0.2.

3. The crystalline form of claim 1, wherein the XRPD pattern comprises the following peaks at the diffraction angle 2θ: 26.6±0.2, 16.2±0.2, 17.4±0.2, 22.6±0.2, 11.5±0.2, 23.9±0.2, 18.3±0.2, 19.2±0.2, 18.5±0.2, and 20.0±0.2.

4. The crystalline form of claim 1, wherein the crystalline form is characterized by an XRPD pattern substantially as shown in FIG. 1.

5. The crystalline form of claim 1, wherein the crystalline form has a melting point onset at 226.6 °C as determined by differential scanning calorimetry (DSC).

6. The crystalline form of claim 1, wherein the crystalline form has a DSC profile substantially as shown in FIG. 2.

7. An oral dosage form comprising the crystalline form of any one of claims 1-6 and a modified-release polymer.

8. The oral dosage form of claim 7, wherein the modified-release polymer is selected from the group consisting of a hydrophilic matrix polymer, a hydrophobic matrix polymer and a polyacrylate polymer.

9. The oral dosage form of claim 8, wherein the modified-release polymer is a hydrophilic matrix polymer.

10. The oral dosage form of claim 9, wherein the hydrophilic matrix polymer is hypromellose.

11. The oral dosage form of claim 7, wherein the oral dosage form further comprises a diluent.

12. The oral dosage form of claim 11, wherein the diluent is selected from the group consisting of a cellulose derivative, a starch, anhydrous lactose, lactose monohydrate, di-calcium phosphate (DCP), and a sugar alcohol.

13. The oral dosage form of claim 12, wherein the diluent is a cellulose derivative.

14. The oral dosage form of claim 13, wherein the cellulose derivative is microcrystalline cellulose.

15. The oral dosage form of claim 11, wherein the diluent is a sugar alcohol.

16. The oral dosage form of claim 15, wherein the sugar alcohol is selected from the group consisting of sorbitol, xylitol and mannitol.

17. The oral dosage form of claim 16, wherein the diluent is mannitol.

18. The oral dosage form of claim 7, wherein the oral dosage form further comprises a glidant.

19. The oral dosage form of claim 18, wherein the glidant is selected from the group consisting of fumed silica, talc, and magnesium carbonate.

20. The oral dosage form of claim 19, wherein the glidant is colloidal silicon dioxide.

21. The oral dosage form of claim 7, wherein the oral dosage form further comprises a lubricant.

22. The oral dosage form of claim 21, wherein the lubricant is selected from the group consisting of magnesium stearate, calcium stearate, stearic acid, talc, silica and fats.

23. The oral dosage form of claim 22, wherein the lubricant is magnesium stearate.

24. Use of the crystalline form of any one of claims 1-6 or the oral dosage form of any one of claims 7-23 in the manufacture of a medicament for treating a neurological disorder in a subject in need thereof, wherein the neurological disorder is selected from the group consisting of epilepsy, seizure, pain, ataxia, tinnitus and a disorder of wakefulness.

25. The use of claim 24, wherein the neurological disorder is epilepsy.