METHODS OF TREATMENT OF TRIGEMINAL NEURALGIA

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application claims priority to U.S.S.N. 63/058,630 filed on July 30, 2020, the contents of which is incorporated herein by reference in its entirety.

FIELD

[002] The present disclosure relates to the field of medicine and the treatment of trigeminal neuralgia. More specifically, the present disclosure relates to use of compositions comprising 2-chloro-4-[1-(4-fluorophenyl)-2,5-dimethyl-1*H*-imidazol-4-ylethynyl]pyridine, or a pharmaceutically acceptable salt thereof, in the treatment or amelioration of trigeminal neuralgia.

BACKGROUND

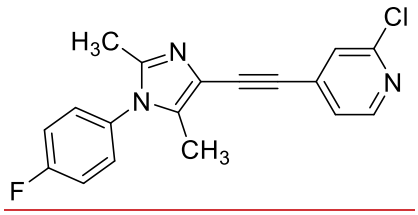
[001] Trigeminal neuralgia (TGN or TN) is a chronic pain condition that affects the trigeminal nerve, which carries sensation from the face to brain. TGN includes typical and atypical trigeminal neuralgia, as well as classical, secondary and idiopathic TGN. The typical form results in episodes of severe, sudden, shock-like pain in one side of the face that lasts for seconds to a few minutes, while the atypical form results in a constant burning pain that is less severe. The pain resulted from TGN has a significant impact on activities of daily living, which can lead to severe depression and anxiety.

[002] While medications such as anticonvulsants (e.g., carbamazepine) or antidepressants (e.g., amitriptyline) can help alleviate the pain caused by TGN, some of these medications have significant side effects, thereby limiting their medical use.

[003] Therefore, there is an unmet medical need to develop new methods for treating TGN without significant side effects.

SUMMARY

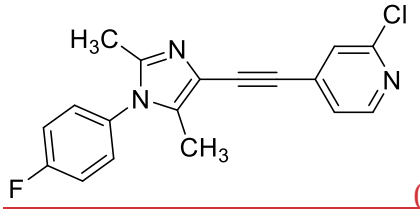
[003a] In a first aspect of the present disclosure, there is provided a use of a composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating trigeminal neuralgia (TGN), wherein the compound is of Formula I:



(I).

[003b] In another aspect of the present disclosure, there is provided a use of a solid pharmaceutical composition in the manufacture of a medicament for treating trigeminal neuralgia,

wherein the solid pharmaceutical composition comprises a pharmaceutical excipient and a solid form of a compound of Formula I:

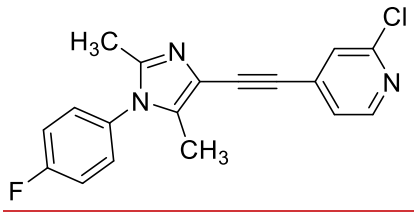


(I),

wherein the solid form is a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, characterized by at least three peaks selected from the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°); and has a particle size (Dv50) of less than or equal to about 100 µm; and

wherein the solid pharmaceutical composition is the form of a matrix pellet.

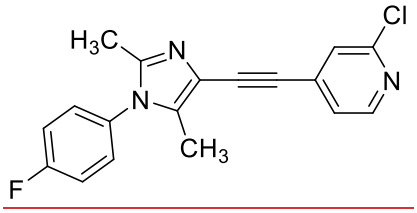
[003c] In yet another aspect of the present disclosure, there is provided a use of a composition comprising a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating trigeminal neuralgia, wherein the mGlu5 NAM is a compound of Formula I:



(I).

[003d] In a further aspect of the present disclosure, there is provided a use of a composition comprising a therapeutically effective amount of an mGlu5 negative allosteric modulator

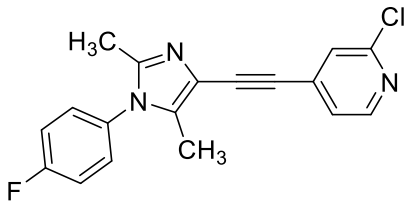
(NAM), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating trigeminal neuralgia, wherein the mGlu5 NAM is a compound of Formula I:



(I),

wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 1.5 mg to about 3.5 mg once daily.

[004] In one ~~aspect~~example, provided herein are methods of treating trigeminal neuralgia (TGN), comprising administering to a subject in need thereof a composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, wherein the compound is of Formula I:



(I).

[005] In some ~~embodiment~~example**s**, treating uses a composition comprising a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, wherein Form A has an X-ray powder diffraction (XRPD) pattern as substantially shown in FIG. 1. Specifically, Form A is characterized by the following X-ray powder diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°). The crystalline Form A typically has a T_m of about 180-190 °C by differential scanning calorimetry (DSC) analysis.

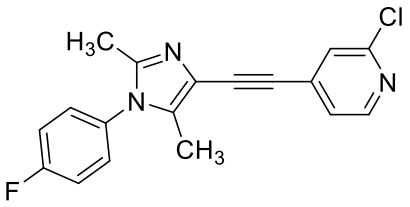
[006] In some ~~embodiment~~example**s**, treating uses a composition comprising a crystalline monohydrate form (Form B) of a monosulfate salt of the compound of Formula I, wherein Form B has an XRPD pattern as substantially shown in FIG. 2. The crystalline Form B typically has a T_m of about 60-70 °C by DSC analysis.

[007] In some ~~embodiment~~example**s**, treating uses a composition comprising a crystalline hemihydrate form (Form C) of a hemisulfate salt of the compound of Formula I, wherein Form C has an XRPD pattern as substantially shown in FIG. 3. The crystalline Form C typically has a T_m of about 90-100 °C by DSC analysis.

[008] In some ~~embodiment~~example**s**, the composition used is a tablet formulation such as a modified release tablet formulation, or a matrix pellet formulation such as a modified release matrix pellet formulation, which can be encapsulated in a capsule, as defined herein.

[009] In some ~~embodiment~~example**s**, treating uses a composition comprising a pharmaceutically acceptable salt of the compound of Formula I, wherein said salt is 90% by weight or more (e.g., 95% by weight or more, or 99% by weight or more) in crystalline Form A based on the total weight of the salt present in the composition.

[0010] The present disclosure also includes a solid pharmaceutical composition comprising a solid form of a compound of Formula I:



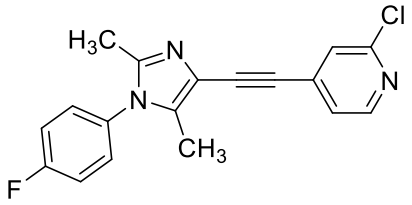
(I),

wherein the solid form is a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, characterized by at least three peaks selected from the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°); and has a median particle size (Dv50) of less than or equal to about 100 µm, wherein the solid pharmaceutical composition is the form of a matrix pellet. In some ~~embodiment~~examples, the solid form has a particle size of less than 47 µm (e.g., about 25 µm or less, or about 10 µm or less).

[0011] In some ~~embodiment~~examples, the pharmaceutical composition comprises the Form A monosulfate salt characterized by the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°).

[0012] In some ~~embodiment~~examples, the pharmaceutical composition comprises the Form A monosulfate salt characterized by an XRPD pattern as substantially shown in FIG. 1.

[0013] The present disclosure also includes a method of preparing a matrix pellet comprising a crystalline anhydrate form (Form A) of a monosulfate salt of a compound of Formula I:



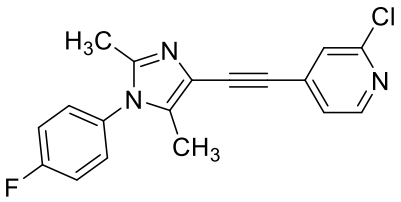
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wherein the method comprises: granulating the Form A monosulfate salt and one or more polymers with purified water to form a mixture; extruding, spheronizing, drying, and sieving the mixture to afford a solid material; and blending the solid material with another pharmaceutical excipient to afford a matrix pellet.

[0014] In some ~~embodiment~~examples, the method of preparation further comprises filling the matrix pellet into a capsule to form a matrix pellet capsule. In some ~~embodiment~~examples, the one or more polymers are selected from the group consisting of a cellulose such as microcrystalline

cellulose, methacrylic acid copolymer, and hypromellose. In some ~~embodiment~~example, the other pharmaceutical excipient is talc.

[0015] In another ~~aspect~~example, provided herein are methods of treating TGN, comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM) or a pharmaceutically acceptable salt thereof, wherein the mGlu5 NAM is a compound of Formula I:



(I).

[0016] The details of one or more ~~embodiment~~examples of the present disclosure are set forth in the description below. Other features, objects, and advantages of the present disclosure will be apparent from the below drawings, description and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 depicts an exemplary XRPD pattern of a crystalline anhydrate form (Form A) of a monosulfate of the compound of Formula I.

[0018] FIG. 2 depicts an exemplary XRPD pattern of a crystalline monohydrate form (Form B) of a monosulfate of the compound of Formula I.

[0019] FIG. 3 depicts an exemplary XRPD pattern of a crystalline hemihydrate form (Form C) of a hemisulfate of the compound of Formula I.

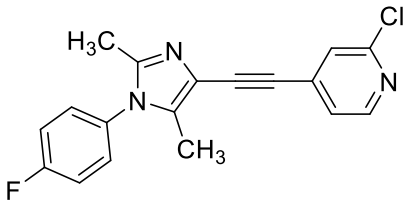
DETAILED DESCRIPTION

[0020] As generally described herein, the present disclosure provides methods of treating trigeminal neuralgia (TGN) in a subject in need thereof. The present disclosure also describes treating TGN by using certain crystalline forms of pharmaceutically acceptable salts of the compound of Formula I. In addition, the present disclosure provides a solid form of a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, wherein the solid form has a particle size (Dv50) of less than or equal to about 100 μm (e.g., less than 47 μm, or 10 μm or less).

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating trigeminal neuralgia (TGN), ~~comprising administering to a subject in need thereof a composition comprising a therapeutically effective amount of a compound or a pharmaceutically acceptable salt thereof,~~ wherein the compound is of Formula I:



(I).

2. The ~~method~~ use of claim 1, wherein ~~administering comprises administering~~ the compound of Formula I is to be administered in its free base form.

3. The ~~method~~ use of claim 1, wherein ~~administering comprises administering~~ the compound of Formula I is to be administered in the form of a pharmaceutically acceptable salt thereof.

4. The ~~method~~ use of claim 3, wherein the pharmaceutically acceptable salt is a monosulfate salt or a hemisulfate salt.

5. The ~~method~~ use of claim 4, wherein the pharmaceutically acceptable salt is in a crystalline form or an amorphous form.

6. The ~~method~~ use of claim 5, wherein the pharmaceutically acceptable salt comprises a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, wherein Form A is characterized by at least three peaks selected from the following

X-ray powder diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°).

7. The ~~method~~ use of claim 6, wherein Form A is characterized by the following X-ray powder diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°).

8. The ~~method~~ use of claim 6 or 7, wherein Form A has an X-ray powder diffraction (XRPD) pattern as substantially shown in Figure 1.

9. The ~~method~~ use of claim 5, wherein the pharmaceutically acceptable salt comprises a crystalline monohydrate form (Form B) of a monosulfate salt of the compound of Formula I, wherein Form B has an XRPD pattern as substantially shown in Figure 2.

10. The ~~method~~ use of claim 5, wherein the pharmaceutically acceptable salt comprises an amorphous form of a monosulfate salt of the compound of Formula I, characterized by an infrared spectrum having bands at 2730, 2592, 2219, 1633, 1586, 1570, 1513, 1375, 1343, 1293, 1226, 1157, 1130, 1084, 1040, 986, 903, 848, 788, 712 and 670 cm^{-1} (±3 cm^{-1}).

11. The ~~method~~ use of claim 5, wherein the pharmaceutically acceptable salt comprises a crystalline hemihydrate form (Form C) of a hemisulfate salt of the compound of Formula I, wherein Form C has an XRPD pattern as substantially shown in Figure 3.

12. The ~~method~~use of any one of claims 1-11, wherein the composition is an immediate release formulation encapsulated in a capsule, a modified release tablet formulation, or a modified release pellet formulation encapsulated in a capsule.

13. The ~~method~~use of claim 12, wherein the composition is a modified release pellet formulation encapsulated in a capsule, and the compound of Formula I, or a pharmaceutically acceptable salt thereof, is present in an amount from about 0.05 mg to about 20 mg.

14. The ~~method~~use of any one of claims 1-13, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is present in the composition in an amount from about 0.01% to about 20% by weight, based on the total weight of the composition.

15. The ~~method~~use of claim 14, wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is present in the composition in an amount from about 0.05% to about 15% by weight, based on the total weight of the composition.

16. The ~~method~~use of claim 6, wherein the composition is a modified release pellet formulation encapsulated in a capsule, and a Form A monosulfate salt of the compound of Formula I is present in the composition in an amount from about 0.05 mg to about 20 mg.

17. The ~~method~~use of claim 16, wherein the Form A monosulfate salt is present in the composition in an amount from about 0.01% to about 20% by weight, based on the total weight of the composition.

18. The ~~method~~use of claim 17, wherein the Form A monosulfate salt is present in the composition in an amount from about 0.05% to about 15% by weight, based on the total weight of the composition.

19. The ~~method~~use of claim 6, wherein the composition is an immediate release formulation encapsulated in a capsule, comprising the following formulation:

	mg/capsule
Form A of monosulfate salt	0.065
Lactose Monohydrate	108.934
Starch Maize Partially Pregelatinized (type 1500)	60.00
Croscarmellose Sodium	8.00
Povidone 30	15.00
Sodium lauryl sulfate	1.00
Talc	6.00
Magnesium Stearate	1.00
Total	200.00

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20. The ~~method~~use of claim 6, wherein the composition is an immediate release formulation encapsulated in a capsule, comprising the following formulation:

	mg/capsule
Form A of monosulfate salt	0.650
Lactose Monohydrate	109.349
Starch Maize Partially Pregelatinized (type 1500)	60.00
Croscarmellose Sodium	8.00
Povidone 30	15.00
Sodium lauryl sulfate	—
Talc	6.00
Magnesium Stearate	1.00
Total	200.00

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21. The ~~method~~use of claim 6, wherein the composition is an immediate release formulation encapsulated in a capsule, comprising the following formulation:

	mg/capsule
Form A of monosulfate salt	2.602
Lactose Monohydrate	107.398
Starch Maize Partially Pregelatinized (type 1500)	60.00
Croscarmellose Sodium	8.00
Povidone 30	15.00
Sodium lauryl sulfate	—
Talc	6.00
Magnesium Stearate	1.00
Total	200.00

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22. The ~~method~~use of claim 6, wherein the composition is an immediate release formulation encapsulated in a capsule, comprising the following formulation:

	mg/capsule
Form A of monosulfate salt	26.02
Lactose Monohydrate	83.98
Starch Maize Partially Pregelatinized (type 1500)	60.00
Croscarmellose Sodium	8.00
Povidone 30	15.00
Sodium lauryl sulfate	—
Talc	6.00
Magnesium Stearate	1.00
Total	200.00

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23. The ~~method~~use of claim 6, wherein the composition is a modified release pellet formulation encapsulated in a capsule, and the composition comprises a formulation selected from the group consisting of Formulation 1, Formulation 2, Formulation 3, and Formulation 4, as shown in the table below.

Group	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Ingredient	Quantity (mg/capsule)			
Form A monosulfate	0.13	0.26	0.65	1.30
Microcrystalline cellulose	64.62	129.24	64.10	128.20
Methacrylic acid copolymer	30.00	60.00	30.00	60.00
Hypromellose	5.00	10.00	5.00	10.00
Talc	0.25	0.50	0.25	0.50
Total	100.00	200.00	100.00	200.00

24. The ~~method~~use of claim 6, wherein the pharmaceutically acceptable salt is 90% by weight or more of the crystalline Form A based on the total weight of the salt present in the composition.

25. The ~~method~~use of claim 24, wherein the pharmaceutically acceptable salt is 95% by weight or more of the crystalline Form A based on the total weight of the salt present in the composition.

26. The ~~method~~use of claim 25, wherein the pharmaceutically acceptable salt is 99% by weight or more of the crystalline Form A based on the total weight of the salt present in the composition.

27. The ~~method~~use of any one of claims 1-26, wherein ~~administering comprises administering once daily~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof is to be administered once daily.

28. The ~~method~~use of any one of claims 1-27, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 0.1 mg to about 4.0 mg once daily.

29. The ~~method~~use of any one of claims 1-28, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 0.1 mg to about 3.5 mg once daily.

30. The ~~method~~use of any one of claims 1-29, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 0.1 mg to about 3.0 mg once daily.

31. The ~~method~~use of any one of claims 1-30, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 1.0 mg to about 4.0 mg once daily.

32. The ~~method~~use of any one of claims 1-30, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 1.5 mg to about 3.5 mg once daily.

33. The ~~method~~use of any one of claims 1-32, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 4.0 mg, about 3.5 mg, about 3.0 mg, about 2.5 mg, about 2.0 mg, about 1.5 mg, or about 1.0 mg once daily.

34. The ~~method~~use of any one of claims 1-33, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 3.5 mg once daily.

35. The ~~method~~use of any one of claims 1-33, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 1.5 mg once daily.

36. The ~~method~~use of any one of claims 1-35, wherein ~~administering comprises administering orally~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered orally.

37. The ~~method~~use of any one of claims 1-36, wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered as a unit dose.

38. The ~~method~~use of any one of claims 1-37, wherein the TGN is classical TGN.

39. The ~~method~~use of any one of claims 1-38, wherein the TGN is idiopathic TGN.

40. The ~~method~~use of any one of claims 1-39, wherein the therapeutic effect of the treatment is determined by:

a. reduction of the activity of high-voltage activated calcium channels;

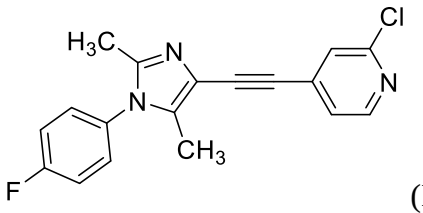
b. reduction of the activity of voltage-gated sodium channels;

c. suppression of the propagation of an ion channel action potential; or

d. suppression of the rapid firing of neurons.

41. Use of a solid pharmaceutical composition in the manufacture of a medicament for ~~A method of~~ treating trigeminal neuralgia, ~~comprising administering to a subject in need thereof a solid pharmaceutical composition,~~

wherein the solid pharmaceutical composition comprises a pharmaceutical excipient and a solid form of a compound of Formula I:



(I),

wherein the solid form is a crystalline anhydrate form (Form A) of a monosulfate salt of the compound of Formula I, characterized by at least three peaks selected from the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°); and has a particle size (Dv50) of less than or equal to about 100 µm; and

wherein the solid pharmaceutical composition is the form of a matrix pellet.

42. The ~~method~~use of claim 41, wherein the solid form has a particle size of less than 47 µm.

43. The ~~method~~use of claim 41, wherein the solid form has a particle size of less than or equal to about 25 µm.

44. The ~~method~~use of claim 41, wherein the solid form has a particle size of less than or equal to about 10 µm.

45. The ~~method~~use of any one of claims 41-44, wherein the Form A monosulfate salt is present in the composition in an amount of 1% by weight or less, based on the total weight of the composition.

46. The ~~method~~use of claim 45, wherein the Form A monosulfate salt is present in the composition in an amount of 0.5% by weight or less, based on the total weight of the composition.

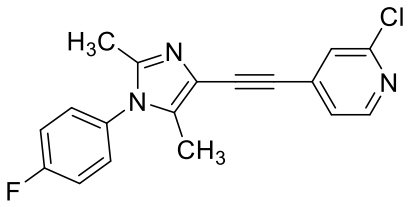
47. The ~~method~~use of any one of claims 41-46, wherein the pharmaceutical excipient comprises one or more of a polymer, a binder, a disintegrant, a lubricant, and a glidant.

48. The ~~method~~use of claim 47, the polymer is one or more polymers selected from the group consisting of a cellulose, methacrylic acid copolymer, and hypromellose.

49. The ~~method~~use of any one of claims 41-48, wherein the Form A monosulfate salt is characterized by the following XRPD peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2 Theta): 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1, and 29.9 (±0.2°).

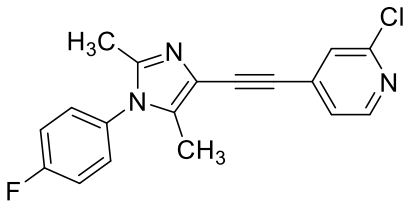
50. The ~~method~~use of any one of claims 41-49, wherein the Form A monosulfate salt has an XRPD pattern as substantially shown in Figure 1.

51. Use of a composition comprising a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating trigeminal neuralgia, ~~comprising administering to a subject in need thereof a composition comprising a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM), or a pharmaceutically acceptable salt thereof,~~ wherein the mGlu5 NAM is a compound of Formula I:



(I).

52. Use of a composition comprising a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~A method of~~ treating trigeminal neuralgia, ~~comprising administering to a subject in need thereof a composition comprising a therapeutically effective amount of an mGlu5 negative allosteric modulator (NAM), or a pharmaceutically acceptable salt thereof,~~ wherein the mGlu5 NAM is a compound of Formula I:



(I),

wherein ~~administering comprises administering~~ the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered in an amount of about 1.5 mg to about 3.5 mg once daily.