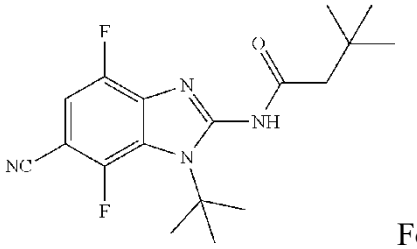
Claims

1. A solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprising

i) an intragranular portion comprising the Kv7.2/7.3 potassium channel activator, a hydrophilic matrix polymer, a filler, and a binder; and

ii) an extragranular portion comprising an extended-release polymer, optionally a hydrophilic matrix polymer, and a lubricant;

wherein the Kv7.2/7.3 potassium channel activator is of Formula I or a pharmaceutically acceptable salt thereof



Formula I.

2. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 1, wherein the hydrophilic matrix polymer of i) comprises a hydroxypropyl methylcellulose having a viscosity of 50–200 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12.0%.

3. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein the hydrophilic matrix polymer of i) comprises a hydroxypropyl methylcellulose having a viscosity of 80-120 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 7.0-12.0%.

4. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein the filler of i) is microcrystalline cellulose and the binder of i) is hydroxypropylcellulose.

5. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein in i) the Kv7.2/7.3 potassium channel activator comprises 5-60 wt%, the hydrophilic matrix polymer comprises 4 to 10 wt%, the filler

comprises 40 to 90 wt%, and the binder comprises 0.5 to 4 wt%, all based on the total weight of the intragranular portion, excluding water.

6. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein in ii) the extended-release polymer comprises a hydroxypropyl methylcellulose having a viscosity of 50,000–200,000 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12.0%.

7. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein in ii) the extended-release polymer comprises a hydroxypropyl methylcellulose having a viscosity of 75,000–140,000 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 7.0-12.0%.

8. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein in ii) the extended-release polymer comprises 20 to 40 wt%, more specifically 25-28 wt% of the total weight of the intragranular and extragranular portions.

9. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein in ii) the lubricant comprises sodium stearyl fumarate and the hydrophilic matrix polymer is present and comprises a hydroxypropyl methylcellulose having a viscosity of 50–200 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12%.

10. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein in ii) the extended-release polymer comprises 20 to 40 wt%, the lubricant comprises 0.05 to 2 wt%, and the hydrophilic matrix polymer is present and comprises 1 to 5 wt%, all based on the total weight of the intragranular and extragranular portions.

11. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein the formulation has a dissolution such that at 2 hours less than 25%, preferably less than 20% of the Kv7.2/7.3 potassium channel activator is

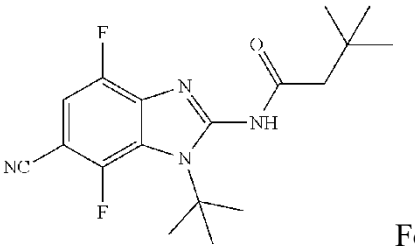
released, wherein dissolution is measured in 900 mL of pH 6.8 phosphate buffer with 3% sodium lauryl sulfate (SLS) in a USP Dissolution Apparatus 2 with stationary basket at 50 rpm.

12. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 11, wherein at 4 hours 35-65%, preferably about 50% of the Kv7.2/7.3 potassium channel activator is released.

13. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 12, wherein at 8 hours, greater than 80%, preferably greater than 85% of the Kv7.2/7.3 potassium channel activator is released.

14. A solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprising a hydrophilic matrix polymer and an extended-release polymer, wherein the formulation has a dissolution such that at 2 hours less than 25%, preferably less than 20% of the Kv7.2/7.3 potassium channel activator is released, wherein dissolution is measured in 900 mL of pH 6.8 phosphate buffer with 3% SLS in a USP Dissolution Apparatus 2 with stationary basket at 50 rpm,

wherein the Kv7.2/7.3 potassium channel activator is of formula I or a pharmaceutically acceptable salt thereof



Formula I.

15. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 14, wherein at 4 hours 35-65%, preferably about 50% of the Kv7.2/7.3 potassium channel activator is released.

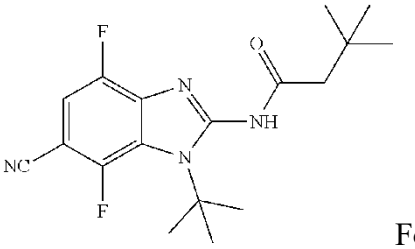
16. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 15, wherein at 8 hours greater than 80%, preferably greater than 85% of the Kv7.2/7.3 potassium channel activator is released.

17. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of claims 14-16, wherein the hydrophilic matrix polymer is in an intragranular portion and the extended-release polymer is in an extragranular portion.

18. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 17, wherein the hydrophilic matrix polymer comprises a hydroxypropyl methylcellulose having a viscosity of 50–200 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12%, and the extended-release polymer comprises a hydroxypropyl methylcellulose having a viscosity of 50,000–200,000 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12%.

19. A solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation, wherein a 24-hour peak-to-trough ratio of Kv7.2/7.3 potassium channel activator plasma level is about 1 to about 3 when a single dose of the Kv7.2/7.3 potassium channel activator formulation is orally administered to a human subject,

wherein the Kv7.2/7.3 potassium channel activator is of formula I or a pharmaceutically acceptable salt thereof



Formula I.

20. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 19, wherein the extended-release Kv7.2/7.3 potassium channel activator formulation comprises a hydrophilic matrix polymer and an extended-release polymer.

21. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 20, wherein the hydrophilic matrix polymer comprises a hydroxypropyl methylcellulose having a viscosity of 50–200 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12%, and the extended-release polymer comprises hydroxypropyl methylcellulose having a viscosity of 75,000–140,000 cPs at 2% in water at 20°C and a hydroxypropyl substitution of 5.0-12%.

22. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, in the form of a tablet comprising 10 to 100 mg of the Kv7.2/7.3 potassium channel activator.

23. A solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims for use in the treatment of a Kv7 associated disorder.

24. The use of claim 23, wherein the Kv7 associated disorder is epilepsy.

25. The use of claim 23, wherein the subject is suffering from focal seizures.