

EXTENDED-RELEASE FORMULATIONS OF Kv7.2/7.3 POTASSIUM CHANNEL
ACTIVATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application 63/518,859 filed on August 10, 2023, which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0001] The present disclosure is related to extended-release formulations of a Kv7.2/7.3 potassium channel activator, particularly formulations having specified in vitro dissolution profiles, and which provide specified pharmacokinetic parameters upon administration.

BACKGROUND

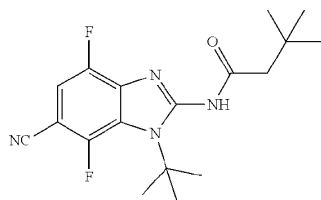
[0002] Potassium (K^+) channels, present on the plasma membranes of most cell types, are the most diverse class of all ion channels and are associated with a wide range of physiological functions including the regulation of the electrical properties of excitable cells. The Kv7 genes (originally termed KCNQ, a name assigned by the HUGO Gene Nomenclature Committee (HGNC)) were assigned to a subfamily of voltage-gated K^+ channels by the International Union of Pharmacology (IUPHAR). The Kv7 subfamily consists of five homologous pore-forming α subunits, Kv7.1-7.5, that have a structure typical of voltage-gated K^+ channels with 6TM-spanning regions (S1-S6) flanked by intracellular N-terminal and C-terminal domains, a typical voltage-sensor domain located in S4 comprised of alternating positively-charged residues and a single P region between S5 and S6 of each subunit. The channels are formed as tetramers of the primary α subunits, either as homotetramers or heterotetramers. Neurons are known to express Kv7 channels comprised of Kv7.2-7.5 α subunits. Some of these gene products may be exclusively neuronal while others, such as Kv7.4 and Kv7.5, can be found in other tissues such as smooth and skeletal muscle. Of note, reduction or removal of the influence of Kv7.2 and Kv7.3 channels can dramatically alter neuronal excitability.

[0003] As described in U.S. Patent No. 10,851,067, Kv7.2/7.3 potassium channel activators were predicted to be useful to treat various forms of epilepsy. What is needed are novel formulations of Kv7.2/7.3 potassium channel activators, particularly those suitable for

the treatment of epilepsy and other conditions responsive to Kv7.2/7.3 potassium channel activators.

BRIEF SUMMARY

[0004] In an aspect, a solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprises 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.

[0005] In another aspect, a solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprises 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.

[0006] In another aspect, a solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation provides a 24-hour peak-to-trough ratio of Kv7.2/7.3 potassium channel activator plasma level of 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] Fig. 1 shows dissolution profiles for BHV-7000 10 mg extended-release tablets.

[0008] Fig. 2 shows mean plasma concentration (ng/mL) vs. time for BHV-7000 extended-release tablets administered as a single dose to human subjects.

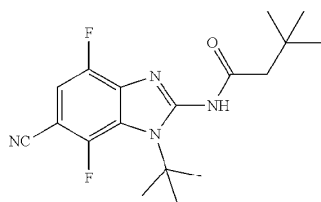
[0009] Fig. 3 shows dissolution profiles for BHV-7000 10 mg, 25 mg, 50 mg, and 75 mg extended-release tablets.

[0010] The above-described and other features will be appreciated and understood by those skilled in the art from the following detailed description, drawings, and appended claims.

DETAILED DESCRIPTION

[0011] Described herein are extended-release formulations of Kv7.2/7.3 potassium channel activators, including oral, extended-release formulations for once daily dosing. In the treatment of epilepsy, for example, extended-release formulations are desirable to improve patient compliance, to improve quality of life, to maintain therapeutic systemic drug levels, and to minimize side effects. In patients with poor adherence to their anti-seizure medications, breakthrough seizures as well as increased side effects such as dizziness, sleepiness, double/blurred vision, poor coordination, unsteadiness, headache and gastrointestinal intolerance can be observed. During development of an extended-release formulation of BHV-7000, it was found that certain formulations provided a spike in mean plasma concentration within 4-8 hours after release. It was unexpectedly found that an extended-release formulation with a slow-release profile could avoid this initial spike in mean plasma concentration and provide a more consistent release profile. Specifically, it is preferred that the extended-release formulations have a 24-hour peak-to-trough Kv7.2/7.3 potassium channel activator plasma level of about 1 to about 3.

[0012] In an aspect the Kv7.2/7.3 potassium channel activator is formula I or a pharmaceutically acceptable salt thereof



Formula I.

[0013] “Pharmaceutically acceptable salt” is meant to indicate those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a patient without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al. (1977) J. Pharm. Sciences, Vol. 6, 1-19, describes

pharmaceutically acceptable salts in detail. A pharmaceutically acceptable “salt” is any acid addition salt, preferably a pharmaceutically acceptable acid addition salt, including, but not limited to, halogenic acid salts such as hydrobromic, hydrochloric, hydrofluoric and hydroiodic acid salt; an inorganic acid salt such as, for example, nitric, perchloric, sulfuric and phosphoric acid salt; an organic acid salt such as, for example, sulfonic acid salts (methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, benzenesulfonic or p-toluenesulfonic, acetic, malic, fumaric, succinic, citric, benzoic, gluconic, lactic, mandelic, mucic, pantoic, pantothenic, oxalic and maleic acid salts; and an amino acid salt such as aspartic or glutamic acid salt. The acid addition salt may be a mono- or di-acid addition salt, such as a di-hydrohalogenic, di-sulfuric, di-phosphoric or di-organic acid salt. In all cases, the acid addition salt is used as an achiral reagent which is not selected on the basis of any expected or known preference for the interaction with or precipitation of a specific optical isomer of the products of this disclosure.

[0014] If stereochemistry is not indicated, a name or structural representation includes any stereoisomer, or any mixture of stereoisomers and Applicant reserves the right to specifically identify and claim a compound as a single stereoisomer or any particular mixture of stereoisomers.

[0015] Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to embodiments herein possess two or more asymmetric centers, they may additionally exist as diastereomers. Embodiments herein include all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. In some embodiments, the formulas are shown without a definitive stereochemistry at certain positions. Embodiments herein include all stereoisomers of such formulas and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general formula may be obtained by stereospecific or stereoselective synthesis using optically pure or enantioenriched starting materials or reagents of known configuration. The scope of embodiments herein as described and claimed encompasses the racemic forms of the compounds as well as the individual enantiomers, diastereomers, and stereoisomer-enriched mixtures and Applicant reserves the right to specifically identify and claim a compound in any such form.

[0016] The compounds disclosed herein can exist as and therefore include all stereoisomers, conformational isomers and mixtures thereof in all proportions as well as isotopic forms such as deuterated compounds and Applicant reserves the right to specifically identify and claim a compound in any such form.

[0017] In an aspect, a solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation includes i) an intragranular portion and ii) an extragranular portion. In an aspect, the i) intragranular portion comprises, consists essentially of, or consists of the Kv7.2/7.3 potassium channel activator, a hydrophilic matrix polymer, a filler, and a binder. The ii) extragranular portion comprises, consists essentially of, or consists of an extended-release polymer, a lubricant, and optionally a hydrophilic matrix polymer. The Kv7.2/7.3 potassium channel activator is of formula I or a pharmaceutically acceptable salt thereof.

[0018] In an aspect the Kv7.2/7.3 potassium channel activator is embedded or dispersed in the hydrophilic matrix polymer and the filler in the intragranular portion. In another aspect, the Kv7.2/7.3 potassium channel activator comprises 5-60 wt%, specifically 10 to 45 wt%, and more specifically 15 to 45 wt% of the total weight of the intragranular portion, excluding water. In specific aspect, the Kv7.2/7.3 potassium channel activator comprises about 15 wt%, about 30 wt% or about 45 wt% of the total weight of the intragranular portion, excluding water.

[0019] In an aspect, the Kv7.2/7.3 potassium channel activator comprises 5-60 wt%, specifically 10 to 40 wt%, and more specifically 10 to 30 wt% of the total weight of the intragranular portion plus the extragranular portion. In specific aspect, the Kv7.2/7.3 potassium channel activator comprises about 10 wt%, about 20 wt% or about 30 wt% of the total weight of the intragranular portion plus the extragranular portion.

[0020] Exemplary hydrophilic matrix polymers include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), poly(ethylene oxide), poly(vinyl alcohol), xanthan gum, carbomers, carrageenan, and mixtures thereof. Other similar hydrophilic polymers may also be employed. Hydrophilic matrix polymer swell and eventually dissolve in water. Without being held to theory, it is believed that the Kv7.2/7.3 potassium channel activator is released by both diffusion from the matrix polymer and erosion of the matrix polymer. The release of the Kv7.2/7.3 potassium channel activator may be controlled by the amount and viscosity/molecular weight of the hydrophilic matrix polymer. In general, using a greater amount of the hydrophilic matrix polymer decreases the dissolution rate, as does using a higher molecular weight polymer. Using a lower molecular weight hydrophilic matrix polymer increases the dissolution rate. Thus, in an aspect, the

hydrophilic matrix polymer in the intragranular portion is a release controlling polymer in the formulations.

[0021] In an aspect, the hydrophilic matrix polymer is a low-viscosity HPMC (50–200 cPs at 2% in water at 20°C) with moderate hydroxypropyl substitution (5.0–12.0%). The viscosity of an HPMC is determined by testing under standard conditions, including the concentration of HPMC in the solution and the temperature of the solution. As used herein, such conditions are 2% polymer in water at 20°C. The degree of substitution may be expressed as a weight percentage of the substituent or as a molar ratio of substituent to glucose unit. For a cellulose derivative that has two different substituents, such as HPMC, the polymeric form may be described by the degree of substitution for each substituent.

[0022] An exemplary low-viscosity HPMC (80–120 cPs at 2% in water at 20°C) with moderate hydroxypropyl substitution (7.0–12.0%) for inclusion in the intragranular portion is commercially available as METHOCEL™ K100LV, more specifically METHOCEL™ K100LVCR. METHOCEL™ K100LV has a methoxyl content of 22–24%.

[0023] In an aspect, the hydrophilic matrix polymer comprises 4 to 10 wt%, specifically 5–9 wt%, and more specifically 5.5 to 8 wt% of the total weight of the intragranular portion, excluding water. In an aspect, the hydrophilic matrix polymer comprises about 6 wt% of the intragranular portion, excluding water.

[0024] Fillers, also called diluents, increase the bulk or volume of the final product, ensure a consistent dosage form size, provide uniform mixing, and/or aid in manufacturing of a dosage form. Exemplary fillers include lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tabletolose®, various grades of Pharmatose®, Microtose®, Fast-FloC®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Solka-Floc®), other cellulose derivatives, sucrose, sorbitol, mannitol, dextrans, maltodextrins, dextrose, fructose, kaolin, mannitol, sorbitol, sucrose, sugar, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g., basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulphate, calcium carbonate, sodium alginate, and mixtures thereof. In some embodiments the filler is microcrystalline cellulose, such as Avicel® PH-101.

[0025] In an aspect, the filler comprises 40 to 90 wt%, specifically 45 to 85 wt%, and more specifically 45 to 80 wt% of the total weight of the intragranular portion, excluding water.

[0026] Binders improve the processability of tablets and granulates and help ensure dosage form integrity during processing. Exemplary binders include polyvinylpyrrolidone

(povidone), crosslinked polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, silicified microcrystalline cellulose, polyvinyl alcohol, starch, acacia, alginic acid, sodium alginate, and the like, and mixtures thereof. In an aspect, the binder is a hydroxypropylcellulose with 53.4 to 80.5% hydroxypropoxy groups. In an aspect, the binder is KLUCELTM EXF, an ultra-fine hydroxypropylcellulose binder.

[0027] In an aspect, the binder comprises 0.5 to 4 wt%, specifically 1.5 to 3 wt% of the total weight of the intragranular portion, excluding water.

[0028] In an aspect, 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%, the filler is microcrystalline cellulose, and the binder is hydroxypropylcellulose.

[0029] In an aspect, the intragranular portion comprises 5-60 wt%, preferably 10 to 45 wt%, and more preferably 15 to 45 wt% of the Kv7.2/7.3 potassium channel activator of Formula I or a pharmaceutically acceptable salt thereof; 4 to 10 wt%, specifically 5-9 wt%, and more specifically 5.5 to 8 wt% of 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%; 40 to 90 wt%, specifically 40 to 85 wt%, and more specifically 45 to 80 wt% of microcrystalline cellulose; and 0.5 to 4 wt%, specifically 1.5 to 3 wt% of hydroxypropylcellulose, all based on the total weight of the intragranular portion, excluding water.

[0030] The intragranular portion can be prepared, for example, by wet granulation. In an exemplary wet granulation process, the Kv7.2/7.3 potassium channel activator, the hydrophilic matrix polymer, and the filler are mixed in a mixer to form a blend. The blend is then added to a binder solution (binder dissolved in water) form a wet blend. The wet blend is then granulated to produce wet granules. Wet granulation processes include fluidized bed granulation, top spray granulation, high shear granulation, and low shear granulation. The wet granules can be screened to provide granules of a specified size and optionally dried, for example, to produce dried granules. If desired, the dried granules can be milled and/or sized.

[0031] The intragranular portion (e.g., the granules produced by wet granulation and drying) are then mixed with the extended-release polymer of the extragranular portion, optionally a hydrophilic matrix polymer, and lubricated with a lubricant..

[0032] The extended-release polymer of the extragranular portion provides release of active agent over a controlled or extended period of time. Exemplary extended-release polymers include homopolymers or copolymers, such as random copolymers, block copolymers, and graft copolymers, such as cellulosic polymers, such as methylcellulose,

hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose, microcrystalline cellulose, and polysaccharides and their derivatives; polyalkylene oxides, particularly poly(ethylene oxide), polyethylene glycol and poly(ethylene oxide)-polypropylene oxide copolymers; acrylic acid and methacrylic acid polymers, copolymers and esters thereof, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl methacrylate, and copolymers thereof, with each other or with additional acrylate species such as aminoethyl acrylate; maleic anhydride copolymers; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropyl-acrylamide); polyalkylene oxides; poly(olefinic alcohol)s such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyols such as glycerol, polyglycerol (particularly highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more polyalkylene oxides, e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol and polyoxyethylated glucose; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); polyvinylamines; polyvinylacetates, including polyvinylacetate per se as well as ethylene-vinyl acetate copolymers, polyvinyl acetate phthalate, and the like, polyimines, such as polyethyleneimine; starch and starch-based polymers; polyurethane hydrogels; chitosan; polysaccharide gums; xanthan gum; zein; and shellac, ammoniated shellac, shellac-acetyl alcohol, shellac n-butyl stearate, and mixtures thereof.

[0033] In an embodiment, the extended-release polymer comprises a cellulosic polymer, such as an alkyl substituted cellulose derivative, specifically HPMC. In an aspect, the extended-release polymer comprises a high-viscosity HPMC (50,000–200,000 cPs at 2% in water at 20°C) with moderate hydroxypropyl substitution (5.0–12.0%).

[0034] An exemplary high-viscosity HPMC (75,000–140,000 cPs at 2% in water at 20°C) with moderate hydroxypropyl substitution (7.0–12.0%) is commercially available as METHOCEL™ K100M Premium. METHOCEL™ K100M has a methoxyl content of 22–24%.

[0035] In an aspect, the extended-release polymer comprises 20 to 40 wt%, specifically 25 to 35 wt%, and more specifically 25–28 wt% of the total weight of the intragranular and extragranular portions.

[0036] The lubricant reduces friction during mixing of the intragranular and extragranular portions as well as during tableting. Exemplary lubricants include talc, magnesium stearate, sodium stearyl fumarate, stearic acid, zinc stearate, calcium stearate, magnesium trisilicate, polyethylene glycol, and mixtures thereof. An exemplary lubricant is PRUV® sodium stearyl fumarate.

[0037] In an aspect, the lubricant comprises 0.05 to 2 wt%, specifically 0.05 to 0.15 wt% of the total weight of the intragranular and extragranular portions.

[0038] In an aspect, the extragranular portion optionally comprises a hydrophilic matrix polymer, such as METHOCEL™ K100LV.

[0039] In an aspect, 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%.

[0040] In an aspect, the hydrophilic matrix polymer comprises 0 to 8 wt%, specifically 1 to 5 wt% of the total weight of the intragranular and extragranular portions.

[0041] In an aspect, the solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprises, consists essentially of, or consists of

- i) an intragranular portion comprising the Kv7.2/7.3 potassium channel activator, 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%, microcrystalline cellulose, and hydroxypropylcellulose, and
- ii) an extragranular portion comprising 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%, sodium stearyl fumarate, and optionally a hydrophilic matrix polymer,

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

[0042] In an aspect, the solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprises, consists essentially of, or consists of

- i) an intragranular portion comprising 5–60 wt% of the Kv7.2/7.3 potassium channel activator, 4 to 10 wt% of 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%, 50 to 90 wt% of microcrystalline cellulose and 0.5

to 4 wt% of hydroxypropylcellulose, based on the weight of the intragranular portion, and

- ii) an extragranular portion comprising 20 to 40 wt% of 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%, 0.05 to 2 wt% of sodium stearyl fumarate, and optionally a hydrophilic matrix polymer,

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

[0043] In addition to the foregoing components, the intragranular and extragranular portions may include additional components so long as the additional components provide the desired dissolution profile and/or pharmacokinetic parameters. Exemplary additional components include diluents, binders, surfactants, solubilizers, co-solvents, absorbents, colorants, dyes, permeation enhancers, stabilizers, osmotic agents, disintegrants, wetting agents, plasticizers, tableting aids, glidants, lubricants, antistatic agents, dispersants, and mixtures thereof.

[0044] Once the intragranular portion and the extragranular portion are mixed, the mixture can be filled into a capsule (e.g., a hard, soft, or gel capsule) or compressed into a tablet, for example, by direct compression. Exemplary compression forces are 5 kN to 100 kN, 5 kN to 75 kN, and most commonly from 10 kN to 30 kN.

[0045] The tablet or capsule can further comprise a protective top coat layer comprising, for example, a coating polymer and optionally one or more excipients such as, for example, a plasticizer, an anti-adherent or glidant, one or more pigments/opacifying agents, and mixtures thereof.

[0046] In an aspect, the coating may be a water-soluble film coating that has no influence on the release of the Kv7.2/7.3 potassium channel activator. The thickness of a soluble film coating may be from about 20 μm to about 100 μm , for example.

[0047] Exemplary film coating materials include, for example, cellulose derivatives, such as cellulose ethers, for example methylcellulose, hydroxypropylcellulose or hydroxypropylmethylcellulose; mixtures of polyvinyl pyrrolidone or of a copolymer of polyvinyl pyrrolidone and polyvinyl acetate with hydroxypropylmethylcellulose; mixtures of shellac with hydroxypropylmethylcellulose, polyvinyl acetate or copolymers thereof with polyvinyl pyrrolidone; or mixtures of water-soluble cellulose derivatives, such as hydroxypropylmethylcellulose, water-insoluble ethylcellulose, and mixtures thereof. These coating agents may, if desired, be used in admixture with other adjuncts, such as talc, wetting

agents, for example polysorbates (for example for facilitating application), or pigments (for example, for marking purposes). Depending on the solubility of the constituents, these coatings can be applied in aqueous solution or in organic solution (for example, solutions of shellac or ethylcellulose in organic solvents). Mixtures of acrylates that are water-insoluble per se may also be used. For example, the copolymer of ethyl acrylate and methyl methacrylate may be used in an aqueous dispersion, with one or more water-soluble adjuncts, such as lactose, polyvinyl pyrrolidine, polyethylene glycol or hydroxypropylmethylcellulose.

[0048] Exemplary plasticizers for the protective top coat include, for example, triacetin, diethyl phthalate, dibutyl sebacate, tributyl sebacate polyethylene glycol, and mixtures thereof.

[0049] Exemplary anti-adherent or glidants for the protective top coat include, for example, talc, fumed silica, magnesium stearate, and mixtures thereof.

[0050] In an aspect, the solid, oral extended-release Kv7.2/7.3 potassium channel activator formulations include a hydrophilic matrix polymer and an extended-release polymer, wherein the Kv7.2/7.3 potassium channel activator is of formula I or a pharmaceutically acceptable salt thereof. In an aspect, the hydrophilic matrix polymer is in an intragranular portion and the extended-release polymer is in an extragranular portion.

[0051] In an aspect, the oral, extended-release dosage form releases the active agent over a period of about 24 hours. In another aspect, the oral, extended-release dosage form releases the active agent over a period of about 12 hours. In another aspect, the oral, extended-release dosage form releases the active agent over a period of about 8 hours. In yet another aspect, the oral, extended-release dosage form releases the active agent over a period of about 6 hours.

[0052] In an aspect, the oral, extended-release dosage form is for once per day dosing, that is, about once every 24 hours. In another aspect, the oral, extended-release dosage form is for twice per day dosing, that is, about once every 12 hours. In another aspect, the oral, extended-release dosage form is for dosing 3 times per day, about once every 8 hours. In another aspect, the oral, extended-release dosage form is for dosing 4 times per day, about once every 6 hours.

[0053] In any of the forgoing embodiments, the solid, oral extended-release Kv7.2/7.3 potassium channel activator formulations have a specified *in vitro* dissolution profile. In an aspect, dissolution is measured in an appropriate dissolution media maintaining sink conditions in a USP Dissolution Apparatus. In an aspect, dissolution is measured in vitro in

900 mL of pH 6.8 phosphate buffer with 3% (w/v) sodium lauryl sulfate (SLS), in a USP Dissolution Apparatus 2 with stationary basket at 50 rpm.

[0054] In an aspect, a Kv7.2/7.3 potassium channel activator formulation of the present disclosure 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 an appropriate dissolution media maintaining sink conditions in a USP Dissolution Apparatus or in 900 mL of pH 6.8 phosphate buffer with 3% SLS in a USP Dissolution Apparatus 2 with stationary basket at 50 rpm. In another aspect, at 4 hours 35-65%, preferably about 50% of the Kv7.2/7.3 potassium channel activator is released. In another aspect, at 8 hours greater than 80%, preferably greater than 85% of the Kv7.2/7.3 potassium channel activator is released. In another aspect, a Kv7.2/7.3 potassium channel activator formulation of the present disclosure releases greater than 95% of the Kv7.2/7.3 potassium channel activator after 14-24 hours.

[0055] In an aspect, a Kv7.2/7.3 potassium channel activator formulation of the present disclosure releases less than 25%, preferably less than 20% of the Kv7.2/7.3 potassium channel activator after 2 hours; and less than 50%, preferably less than 40% of the Kv7.2/7.3 potassium channel activator after 4 hours.

[0056] In another aspect, a Kv7.2/7.3 potassium channel activator formulation of the present disclosure releases less than 25%, preferably less than 20% of the Kv7.2/7.3 potassium channel activator after 2 hours; 35-65%, preferably about 50% of the Kv7.2/7.3 potassium channel activator after 4 hours; and greater than 80%, preferably greater than 85% of the Kv7.2/7.3 potassium channel activator after 8 hours.

[0057] In an aspect, the formulations described herein have favorable pharmacokinetics, particularly when administered to human subjects in single doses and in multiple doses. Pharmacokinetic profiles are the time course of active agent absorption, distribution, metabolism and excretion. Pharmacokinetic profiles can be determined after a single dose or after multiple doses.

[0058] As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, the term "patient" refers to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human. In some embodiments, the subject is a non-human animal such as a farm animal (e.g., a horse, pig, or cow) or a pet (e.g., a dog or cat). In a specific embodiment, the subject is a human.

[0059] The term “peak-to-trough ratio” refers to a comparison of the values for a peak (e.g., a high point in a line graph) plasma level of active agent and a trough (e.g., a low point in a line graph) level over a set amount of time. For example, a line graph with plasma concentration values ranging from 400 ng/ml (peak) compared to 200 ng/ml (trough) over a 24 hour period, gives a peak-to-trough ratio of 2 for that time.

[0060] “ $C_{\max}$ ” is the maximum observed plasma concentration. An oral drug administration results in one $C_{\max}$, but may result in greater than one “peak plasma concentration” or “plasma concentration peak” (for example, following the administration of a pulsed dose formulation).

[0061] The term “mean maximum plasma concentration” (mean $C_{\max}$) is the maximum mean plasma drug concentration found in multiple plasma samples.

[0062] “Mean plasma concentration” is the geometric mean blood plasma concentration found in multiple plasma samples.

[0063] The term “ $T_{\max}$ ” is the time at which the peak (maximum) observed blood plasma drug concentration for each individual participating in the bioavailability study.

[0064] AUC is a measurement of the area under the plasma concentration-time curve, and is representative of the amount of drug absorbed following administration of a single dose of a drug.

[0065] The term “ $AUC_{0-\infty}$ ” or “ AUC_{inf} ” is the mean area under the plasma concentration-time curve extrapolated to infinity. It is calculated as the arithmetic mean of the area under the plasma concentration-time curve from time 0 extrapolated to infinity, calculated for each individual participating in the bioavailability study.

[0066] In an aspect, described herein is an extended-release Kv7.2/7.3 potassium channel activator (e.g., of formula I or a pharmaceutically acceptable salt thereof) formulation, wherein the 24-hour peak-to-trough ratio of the 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. In an aspect, the human subject is an adult human subject. In another aspect, the 24-hour peak-to-trough ratio of the Kv7.2/7.3 potassium channel activator plasma level is about 1 to about 2.

[0067] The terms “therapeutically effective amount” or “therapeutic dose” as used herein are interchangeable and may refer to the amount of an active agent or pharmaceutical compound or composition that elicits a clinical, biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinical professional. A clinical, biological or medical response may

include, for example, one or more of the following: (1) preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display pathology or symptoms of the disease, condition or disorder, (2) inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptoms of the disease, condition or disorder or arresting further development of the pathology and/or symptoms of the disease, condition or disorder, and (3) ameliorating a disease, condition or disorder in an individual that is experiencing or exhibiting the pathology or symptoms of the disease, condition or disorder or reversing the pathology and/or symptoms experience or exhibited by the individual.

[0068] In any of the foregoing aspect, the solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation is in the form of a tablet comprising 10 to 100 mg of the Kv7.2/7.3 potassium channel activator, such as 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 mg.

[0069] The term “treat,” “treated,” or “treating” may be taken to mean prophylaxis of a specific disorder, disease or condition, alleviation of the symptoms associated with a specific disorder, disease or condition and/or prevention of the symptoms associated with a specific disorder, disease or condition. In some embodiments, the term refers to slowing the progression of the disorder, disease or condition or alleviating the symptoms associated with the specific disorder, disease or condition. In some embodiments, the term refers to alleviating the symptoms associated with the specific disorder, disease or condition. In some embodiments, the term refers to restoring function which was impaired or lost due to a specific disorder, disease or condition.

[0070] In an aspect, included is a method of treating a Kv7 associated disorder comprising administering a therapeutically effective amount of a compound of Formula 1, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. The Kv7 associated disorder may be selected from the group consisting of epilepsy, neonatal spasms, pain, migraine, a disorder of neurotransmitter release, a smooth muscle contractility disorder, a dyskinesia, dystonia, mania, a hearing disorder, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, anxiety, substance abuse, schizophrenia, a bladder disorder, a vasculature disorder, tinnitus, benign familial neonatal seizures, epilepsy, neurological disease via reduced basal M-current (and subsequent neuronal hyperexcitability), sensorineural hearing impairment, intellectual disability, epileptic encephalopathy, treatment-resistant epilepsy, cortical atrophy, neurological impairment,

infantile spasms with hypsarrhythmia, myoclonic-tonic seizures, myoclonic seizures, tonic seizures, absence and focal-onset seizures with impaired awareness, congenital neurological disorder with intellectual disability or epileptic encephalopathy, benign familial neonatal convulsions, severe epileptic encephalopathies, congenital neurodevelopmental disorder with phenotypes of nonsyndromic intellectual disability or epileptic encephalopathy, neonatal spasms, neonatal seizures, epileptic encephalopathy, benign familial neonatal convulsions type 1, benign familial neonatal seizures 1, neonatal seizures associated with hypoxic-ischemic injury, epileptic spasms, epileptic encephalopathy, early infantile epileptic encephalopathy 7, early infantile epileptic encephalopathy with delayed psychomotor development, generalized tonic seizures, abnormal globus pallidus morphology, apnea, cerebral edema, dystonia, facial erythema, muscular hypotonia, febrile seizures, hypoplasia of the corpus callosum, hypsarrhythmia, focal clonic seizure, generalized tonic-clonic seizures, myokymia, spastic tetraparesis, gynecological system disorders, and combinations thereof. In some embodiments, the wherein the Kv7 associated disorder is selected from epilepsy, neonatal spasms, pain, migraine, a disorder of neurotransmitter release, a smooth muscle contractility disorder, a dyskinesia, dystonia, mania, a hearing disorder, neuropathic pain, inflammatory pain, persistent pain, cancer pain, postoperative pain, anxiety, substance abuse, schizophrenia, a bladder disorder, a vasculature disorder, tinnitus, frontotemporal dementia (FTD), familial FTD, or amyotrophic lateral sclerosis. In embodiments, such compound may be administered in a pharmaceutical composition as described herein.

[0071] In some embodiments, the gynecological system disorders are selected from the group consisting of pre-term labor, post-partum hemorrhage, uterine atony, uterine perforation, uterine hyper-stimulation, menorrhagia, metrorrhagia, menometrorrhagia, dysmenorrhea and endometriosis.

[0072] KCNQ genes encode five Kv7 potassium channel subunits (1-5). A functional Kv7 potassium channel can be assembled using a combination of these five subunits arranged as homotetramers or heterotetramers. KCNQ2, KCNQ3, KCNQ4, and KCNQ5 are expressed in the nervous system and have been associated with a range of disorders involving neuronal excitability.

[0073] Embodiments herein are directed to methods of treating a disorder associated with a KCNQ subunit comprising administering a therapeutically effective amount of a compound of Formula 1, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0074] Compounds described herein have been shown to activate the Kv7 potassium channel. Mutations in the gene, KCNQ2, which encodes the Kv7 potassium channel result in a wide range of disorders. Embodiments herein are directed to methods of treating a disorder associated with a KCNQ2 mutation comprising administering a therapeutically effective amount of a compound of Formula 1, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. The disorder associated with a KCNQ2 mutation is selected from the group consisting of neonatal spasms, neonatal seizures, epilepsy, benign familial neonatal epilepsy (KCNQ2-BFNE), epileptic encephalopathy (KCNQ2-NEE), benign familial neonatal convulsions type 1 (BFNC), benign familial neonatal seizures 1 (BFNS1), neonatal seizures associated with hypoxic-ischemic injury, epileptic spasms, epileptic encephalopathy, early infantile epileptic encephalopathy 7 (EIEE7), early infantile epileptic encephalopathy with delayed psychomotor development, generalized tonic seizures, abnormal globus pallidus morphology, apnea, cerebral edema, dystonia, facial erythema, muscular hypotonia, febrile seizures, hypoplasia of the corpus callosum, hypsarrhythmia, focal clonic seizure, generalized tonic-clonic seizures, myokymia, spastic tetraparesis, and combinations thereof. In embodiments, such compound may be administered in a pharmaceutical composition as described herein.

[0075] The extended-release formulations described herein are particularly useful to treat epilepsy. The main symptom of epilepsy is repeated seizures. In order to determine the type of epilepsy or the epileptic syndrome that a patient is suffering from, an investigation into the type of seizures that the patient is experiencing is undertaken. Focal (partial) seizures where the seizure originates within networks limited to only one hemisphere, are also split into sub-categories. Here the seizure is characterized according to one or more features of the seizure, including aura, motor, autonomic and awareness / responsiveness. Where a seizure begins as a localized seizure and rapidly evolves to be distributed within bilateral networks this seizure is known as a Bilateral convulsive seizure, which is the proposed terminology to replace Secondary Generalized Seizures (generalized seizures that have evolved from focal seizures and are no longer remain localized).

[0076] Focal seizures where the subjects awareness / responsiveness is altered are referred to as focal seizures with impairment and focal seizures where the awareness or responsiveness of the subject is not impaired are referred to as focal seizures without impairment.

[0077] Focal seizures may occur in epilepsy syndromes including: Lennox-Gastaut Syndrome; Tuberous Sclerosis Complex; Dravet Syndrome; CDKL5; Neuronal ceroid

lipofuscinoses (NCL); febrile infection related epilepsy syndrome (FIRES); Aicardi syndrome and brain abnormalities.

[0078] The invention is further illustrated by the following non-limiting examples.

Examples

Development of BHV-7000 dosage form

[0079] The initial formulation for BHV-7000 used in early Phase 1 clinical trials was a spray-dried dispersion suspension that required twice daily dosing to achieve the anticipated therapeutic concentrations for assessment of safety prior to initiation of Phase 2/3 trials. An extended release tablet was developed to reduce the peak-to-trough ratio observed with the suspension and enable once daily dosing of BHV-7000. In healthy adults administered a single 10 mg dose, relative to the original spray-dried dispersion suspension formulation, the extended release tablet reduced BHV-7000 C_{max} approximately 4-fold with minimal impact on the overall absorption, as measured by AUC. During development of a BHV-7000 a Kv7.2/7.3 potassium channel activator formulation, it was observed that the BHV-7000 spray-dried dispersion suspension resulted in high peak-to-trough ratio requiring twice daily dosing to achieve anticipated therapeutic concentrations. In order to have a once daily dosing option with reduced peak-to-trough ration without impacting the overall absorption, extended release tablet formulations were developed. The extended-release formulations were found to have different release profiles depending upon the composition- referred to as ER(fast) and ER(slow):

ER (fast): As used herein, an ER (fast) formulation releases at least >85% of the active agent by 8 hrs as determined by *in vitro* dissolution testing as described herein.

ER (slow): As used herein, an ER (slow) formulation releases at least >85% of the active agent by 12 – 14 hrs as determined by *in vitro* dissolution testing as described herein.

[0080] The composition of an exemplary ER (slow formulation) is provided in Table 1.

Table 1: 10 mg ER (slow) tablet formulation

	Ingredient	Amount/ 10 mg tablet
Intra-Granular	BHV-7000	10 mg
	Microcrystalline cellulose (MCC) Avicel® PH 101	100 mg
	HPMC (low viscosity) METHOCEL™ K 100 PREMIUM LVCR	10 mg
Binder	HPC KLUCEL™ EXF	3 mg
	Purified water	q.s.
Extra-granular	HPMC METHOCEL™ K100M PREMIUM DC2	67.75
Lubricant	Sodium stearyl fumarate (PRUV®-JRS)	2.25 mg
	Total	193 mg

[0081] The ER (slow) tablet was prepared as follows: The intragranular portion of the formulation was prepared by mixing the BHV-7000, MCC and low-viscosity HPMC with granulating fluid (HPC binder in water). The resulting granules were dried and mixed with high viscosity HPMC, lubricated with sodium stearyl fumarate and compressed into tablets.

[0082] The ER (fast) tablet had a similar composition to ER (slow), the METHOCEL™ K100M PREMIUM DC2 was replaced with METHOCEL™ K 100 PREMIUM LVCR from the extragranular portion.

[0083] Dissolution profiles for exemplary ER (slow) and ER (fast) formulations are shown in FIG. 1. Dissolution was performed in pH 6.8 phosphate buffer with 3% SLS in a USP Dissolution Apparatus 2 with stationary basket at 50 rpm.

[0084] Single dose pharmacokinetic studies in humans were also performed and the results are shown in Figure 2. A single 10 mg dose of an exemplary ER (slow) and ER (fast) tablet were administered to (number, description) human subjects and the plasma concentration vs. time was determined. As shown in FIG. 2, the ER (fast) dosage form exhibits a spike in mean plasma concentration at about 8 hours in this study, while the ER (slow) dosage form has a smaller peak to trough ratio.

[0085] Based on release characteristics, nonparametric simulation, and preliminary pharmacokinetic studies, the ER (slow) formulation was selected for further development.

[0086] Dosage forms with 25 mg, 50 mg and 75 mg of BHV-7000 were prepared as shown in Table 2.

Table 2: 25, 50 and 75 mg ER (slow) tablet formulation

	Ingredient	Amount/ 25 mg tablet	Amount/ 50 mg tablet	Amount/ 75 mg tablet
Intra-Granular	BHV-7000	25 mg	50 mg	75 mg
	MCC Avicel® PH 101	130 mg	105 mg	80 mg
	HPMC METHOCEL™ K 100 PREMIUM LVCR	10 mg	10 mg	10 mg
Binder	HPC KLUCEL™ EXF	3 mg	3 mg	3 mg
	Purified water	q.s.	q.s.	q.s.
Extra-granular	HPMC METHOCEL™ K 100 PREMIUM LVCR	12 mg	12 mg	12 mg
	HPMC METHOCEL™ K100M PREMIUM DC2	67.75 mg	67.75 mg	67.75 mg
Lubricant	Sodium stearyl fumarate (PRUV®-JRS)	2.25 mg	2.25 mg	2.25 mg
	Total	250	250	250

[0087] As shown in FIG. 3, the three Tablet formulations of Tables 1 and 2 exhibit similar dissolution characteristics. Dissolution was performed in pH 6.8 phosphate buffer with 3% SLS in a USP Dissolution Apparatus 2 with stationary basket at 50 rpm.

Table 3: Dissolution data and similarity values

Time, hr	% Dissolved			
	Table 1, 10 mg,	Table 2, 25 mg	Table 2, 50 mg	Table 3, 75 mg
0	0	0	0	0
1	6	7	6	7
2	14	15	16	15
3	23	24	25	24
4	32	32	34	32
5	40	41	43	40
6	48	48	51	48
7	55	56	59	55

8	62	63	66	62
10	75	75	79	73
12	88	87	91	84
14	95	96	99	93
16	98	100	101	98
18	98	101	102	100
20	98	101	102	100
24	98	101	102	100
	f₁ Value	1	6	2
	f₂ value	94	75	87

[0088] The f_1 factor is the percent difference between the two dissolution profiles at each time point and is a measurement of the relative error between the two profiles. The f_2 factor is a measurement of the similarity in the percent dissolution between the two profiles.

[0089] In determining similarity of dosage forms, f_1 values (difference factor) up to 15 (0–15) and f_2 values (similarity factor) greater than 50 (50–100) ensure the “sameness” or “equivalence” of the two profiles. The 25, 50, and 75 mg tablets have high equivalence to the 10 mg tablet, illustrating high similarity.

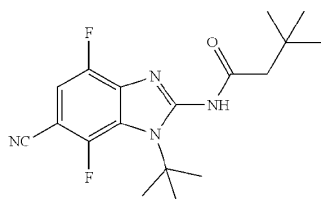
[0090] The use of the terms “a” and “an” and “the” and similar referents (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms first, second etc. as used herein are not meant to denote any particular ordering, but simply for convenience to denote a plurality of, for example, layers. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”) unless otherwise noted. Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The endpoints of all ranges are included within the range and independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the

specification should be construed as indicating any non-claimed element as essential to the practice of the invention as used herein.

[0091] While the invention has been described with reference to an exemplary embodiment, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from the essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed as the best mode contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the appended claims. Any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

Claims

1. A solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation comprising
- iii) an intragranular portion comprising the Kv7.2/7.3 potassium channel activator, a hydrophilic matrix polymer, a filler, and a binder; and
 - iv) 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.

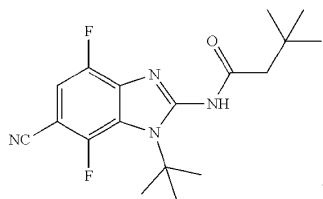
11. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims, wherein the formulation has a dissolution such that at 2 hours less than 25%, preferably less than 20% of the Kv7.2/7.3 potassium channel activator is released, wherein dissolution is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

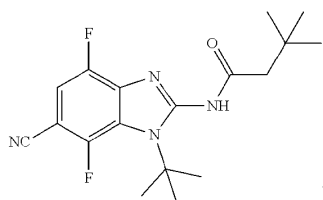
16. The solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of claim 15, wherein at 8 hours greater than 80%, preferably greater than 85% of the Kv7.2/7.3 potassium channel activator is released.

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 method of treating a Kv7 associated disorder in a subject in need of treatment for a Kv7 associated disorder comprises administering to the subject the solid, oral extended-release Kv7.2/7.3 potassium channel activator formulation of any of the foregoing claims.

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

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