PHARMACEUTICAL FORMULATIONS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Application No. 62/423,124, filed on November 16, 2016, and U.S. Provisional Application No. 62/545,857, filed on August 15, 2017, which are herein incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Monoacylglycerol lipase (MAGL) is an enzyme responsible for hydrolyzing endocannabinoids such as 2-AG (2-arachidonoylglycerol), an arachidonate based lipid, in the nervous system. 1,1,1,3,3,3-Hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a MAGL inhibitor.

SUMMARY

[0003] Provided herein are pharmaceutical formulations in solid dosage form comprising 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof. In one example, described herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 1 mg to about 60 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof;

(b) about 5 mg to about 425 mg of a polymeric carrier;

(c) about 0.2 mg to about 10 mg of a surfactant; and

(d) 0.2 mg to about 10 mg of a glidant.

[0003a] In one aspect, provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) 1 mg to 60 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof;

(b) 50 mg to 175 mg of microcrystalline cellulose;

(c) 6 mg to 15 mg of croscarmellose sodium; and

(d) 0.5 mg to 2.5 mg of magnesium stearate

[0004] In some examples, the pharmaceutical formulation comprises about 10 mg to about 150 mg of the polymeric carrier. In some examples, the pharmaceutical formulation comprises about 14 mg to about 85 mg of the polymeric carrier. In some

examples, the polymeric carrier is selected from polyvinyl pyrrolidone K30 (PVP K30), polyvinyl pyrrolidone K17 (PVP K17), polyvinyl pyrrolidone K12 (PVP K12), polyvinyl pyrrolidone vinyl acetate (PVPVA 64), hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose acetylsuccinate (HPMC AS), and methylmethacrylate polymers (Eudragit polymers). In some examples, the polymeric carrier is polyvinyl pyrrolidone K30 (PVP K30). In some examples, the polymeric carrier is polyvinyl pyrrolidone vinyl acetate (PVPVA 64). In some examples, the pharmaceutical formulation comprises about 0.2 mg to about 4 mg of a surfactant. In some examples, the pharmaceutical formulation comprises about 0.4 mg to about 2 mg of a surfactant. In some

examples, the surfactant is selected from polysorbates, polaxomers, bile salts, glyceryl monostearate, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, copolymers of ethylene oxide and propylene oxide, and d-α-tocopheryl polyethylene glycol succinate (Vitamin E TPGS). In some examples, the surfactant is Polysorbate 80 (Tween 80). In some examples, the pharmaceutical formulation comprises about 0.2 mg to about 4 mg of a glidant. In some examples, the pharmaceutical formulation comprises about 0.4 mg to about 2 mg of a glidant. In some examples, the glidant is silicon dioxide or talc. In some examples, the glidant is silicon dioxide. In some examples, the pharmaceutical formulation further comprises a buffer selected from potassium dihydrogen phosphate, sodium bicarbonate, magnesium carbonate, sodium citrate, sodium dihydrogen phosphate, dipotassium monohydrogen phosphate, and disodium monohydrogen phosphate. In some examples, the pharmaceutical formulation comprises about 0.1 mg to about 5 mg of potassium dihydrogen phosphate. In some examples, the pharmaceutical formulation comprises about 0.2 mg to about 2 mg of potassium dihydrogen phosphate. In some examples, the pharmaceutical formulation further comprises about 1 mg to about 65 mg of a plasticizer. In some examples, the pharmaceutical formulation further comprises about 1 mg to about 30 mg of a plasticizer. In some examples, the pharmaceutical formulation further comprises about 2 mg to about 15 mg of a plasticizer. In some examples, the plasticizer is selected from PEG 400, triethyl citrate, triacetin, acetyl tributyl citrate, acetyl triethyl citrate, stearic acid, glycerin, polyethylene glycols, polyethylene glycol monomethyl ether, propylene glycol, sorbitol sorbitan solution, castor oil, diacetylated monoglycerides, dibutyl sebacates, and diethyl phthalate. In some examples, the plasticizer is PEG 400. In some examples, the pharmaceutical formulation further comprises about 15 mg to about 850 mg of a filler. In some examples, the pharmaceutical formulation further comprises about 20 mg to about 400 mg of a filler. In some examples, the pharmaceutical formulation further comprises about 30 mg to about 200 mg of a filler. In some examples, the filler is selected from lactose, mannitol, dicalcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, starch, and pregelatinized starch (Starch 1500). In some examples, the filler is lactose, mannitol, or microcrystalline cellulose. In some examples, the filler is microcrystalline cellulose. In some examples, the pharmaceutical formulation further comprises about 3 mg to about 150 mg of a disintegrant. In some examples, the pharmaceutical formulation further comprises about 5 mg to about 50 mg of a disintegrant. In some examples, the pharmaceutical formulation further comprises about 6 mg to about 30 mg of a disintegrant. In some examples, the disintegrant is selected from povidone, crospovidone, hypromellose, croscarmellose sodium, hydroxypropyl cellulose, and polyvinyl alcohol. In some examples, the

disintegrant is crospovidone. In some examples, the disintegrant is croscarmellose sodium. In some examples, the pharmaceutical formulation further comprises about 0.1 mg to about 10 mg of a lubricant. In some examples, the pharmaceutical formulation further comprises about 0.2 mg to about 4 mg of a lubricant. In some examples, the pharmaceutical formulation further comprises about 0.3 mg to about 1.5 mg of a lubricant. In some examples, the lubricant is selected from magnesium stearate, stearic acid, and sodium stearyl fumarate. In some examples, the lubricant is sodium stearyl fumarate. In some examples, the lubricant is magnesium stearate.

[0005] In some examples, described herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 1 mg to about 60 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof;

(b) about 20 mg to about 400 mg of a filler;

(c) about 3 mg to about 150 mg of a disintegrant; and

(d) about 0.1 mg to about 10 mg of a lubricant.

In some examples, the pharmaceutical formulation further comprises about 30 mg to about 200 mg of a filler. In some examples, the pharmaceutical formulation further comprises about 50 mg to about 175 mg of a filler. In some examples, the filler is selected from lactose, mannitol, dicalcium phosphate, microcrystalline cellulose, silicified microcrystalline cellulose, starch, and pregelatinized starch (Starch 1500). In some examples, the filler is lactose, mannitol, or microcrystalline cellulose. In some examples, the filler is microcrystalline cellulose. In some examples, the pharmaceutical formulation further comprises about 5 mg to about 50 mg of a disintegrant. In some examples, the pharmaceutical formulation further comprises about 5 mg to about 25 mg of a disintegrant. In some examples, the pharmaceutical formulation further comprises about 6 mg to about 15 mg of a disintegrant. In some examples, the disintegrant is selected from povidone, crospovidone, hypromellose, croscarmellose sodium, hydroxypropyl cellulose, and polyvinyl alcohol. In some examples, the disintegrant is crospovidone. In some examples, the disintegrant is croscarmellose sodium. In some examples, the pharmaceutical formulation further comprises about 0.2 mg to about 4 mg of a lubricant. In some examples, the pharmaceutical formulation further comprises about 0.5 mg to about 2.5 mg of a lubricant. In some examples, the lubricant is selected from magnesium stearate, stearic acid, and sodium stearyl fumarate. In some examples, the lubricant is sodium stearyl fumarate. In some examples, the lubricant is magnesium stearate.

[0006] In some examples, the pharmaceutical formulation comprises about 1 mg to about 30 mg of the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof. In some examples, the pharmaceutical formulation comprises about 2 mg to about 15 mg of the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof. In some examples, the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a free base. In some examples, the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a hydrochloride salt. In some examples, the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a fumarate salt.

[0007] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 2 mg to about 12 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;
(b) about 14 mg to about 72.5 mg of polyvinyl pyrrolidone K30 (PVP K30);
(c) about 2 mg to about 13 mg of PEG 400;
(d) about 0.4 mg to about 2 mg of Polysorbate 80 (Tween 80);
(e) about 0.4 mg to about 2 mg of silicon dioxide;
(f) about 0.2 mg to about 1 mg of potassium dihydrogen phosphate;
(g) about 33 mg to about 170 mg of microcrystalline cellulose;
(h) about 6 mg to about 30 mg of crospovidone; and
(i) about 0.3 mg to about 1.5 mg of sodium stearyl fumarate.

[0008] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 2 mg to about 12 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;
(b) about 17 mg to about 85 mg of polyvinyl pyrrolidone vinyl acetate (PVPVA 64);
(c) about 0.4 mg to about 2 mg of Polysorbate 80 (Tween 80);
(d) about 0.4 mg to about 2 mg of silicon dioxide;
(e) about 0.2 mg to about 1 mg of potassium dihydrogen phosphate;
(f) about 33 mg to about 170 mg of microcrystalline cellulose;
(g) about 6 mg to about 30 mg of crospovidone; and
(h) about 0.3 mg to about 1.5 mg of sodium stearyl fumarate.

[0009] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 2 mg to about 12 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 14 mg to about 72.5 mg of polyvinyl pyrrolidone K30 (PVP K30);

(c) about 1 mg to about 13 mg of PEG 400;

(d) about 0.4 mg to about 2 mg of Polysorbate 80 (Tween 80);

(e) about 0.4 mg to about 2 mg of silicon dioxide;

(f) about 0.2 mg to about 1 mg of potassium dihydrogen phosphate;

(g) about 33 mg to about 170 mg of microcrystalline cellulose;

(h) about 6 mg to about 30 mg of croscarmellose sodium; and

(i) about 0.3 mg to about 1.5 mg of sodium stearyl fumarate; and

(j) about 2 mg to about 10 mg of Opadry AMB II Beige.

[0010] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 10 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 72.1 mg of polyvinyl pyrrolidone K30 (PVP K30);

(c) about 12.9 mg of PEG 400;

(d) about 2 mg of Polysorbate 80 (Tween 80);

(e) about 2 mg of silicon dioxide;

(f) about 1 mg of potassium dihydrogen phosphate;

(g) about 168.5 mg of microcrystalline cellulose;

(h) about 30 mg of crospovidone; and

(i) about 1.5 mg of sodium stearyl fumarate.

[0011] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 10.7 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 72.1 mg of polyvinyl pyrrolidone K30 (PVP K30);

(c) about 12.9 mg of PEG 400;

(d) about 2 mg of Polysorbate 80 (Tween 80);

(e) about 2 mg of silicon dioxide;

(f) about 1 mg of potassium dihydrogen phosphate;

(g) about 168.5 mg of microcrystalline cellulose;

(h) about 30 mg of crospovidone; and

(i) about 1.5 mg of sodium stearyl fumarate.

[0012] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 10 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 85 mg of polyvinyl pyrrolidone vinyl acetate (PVPVA 64);

(c) about 2 mg of Polysorbate 80 (Tween 80);

(d) about 2 mg of silicon dioxide;

(e) about 1 mg of potassium dihydrogen phosphate;

(f) about 168.5 mg of microcrystalline cellulose;

(g) about 30 mg of crospovidone; and

(h) about 1.5 mg of sodium stearyl fumarate.

[0013] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 2.1 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 156 mg of microcrystalline cellulose;

(c) about 10 mg of croscarmellose sodium; and

(d) about 1.7 mg of magnesium stearate.

[0014] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 10.7 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 147 mg of microcrystalline cellulose;

(c) about 10.2 mg of croscarmellose sodium; and

(d) about 1.7 mg of magnesium stearate.

[0015] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 53.6 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 104 mg of microcrystalline cellulose;

(c) about 10 mg of croscarmellose sodium; and

(d) about 1.7 mg of magnesium stearate.

[0016] Further provided herein is a pharmaceutical formulation in a solid dosage form comprising:

(a) about 2.1 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;

(b) about 15.1 mg of polyvinyl pyrrolidone K30 (PVP K30);

(c) about 1.6 mg of PEG 400;

(d) about 0.4 mg of Polysorbate 80 (Tween 80);

(e) about 0.4 mg of silicon dioxide;

(f) about 0.4 mg of potassium dihydrogen phosphate;

(g) about 121.7 mg of microcrystalline cellulose;

(h) about 7.5 mg of croscarmellose sodium;

(i) about 0.8 mg of sodium stearyl fumarate; and

(j) about 6.0 mg of Opadry AMB II Beige.

[0017] In some examples, the solid dosage form is selected from a powder, a tablet, a bite-disintegration tablet, a chewable tablet, a caplet, a capsule, a gelcap, an effervescent powder, a rapid-disintegration tablet, an abuse-deterrent tablet, a modified release tablet, a modified release caplet, a modified release capsule, and an aqueous suspension produced from a powder. In some examples, the solid dosage form is a tablet. In some examples, the pharmaceutical formulation further comprises about 2 mg to about 10 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 4 mg to about 8 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 2 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 3 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 4 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 5 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 6 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 7 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 8 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 9 mg of a film coating. In some examples, the pharmaceutical formulation further comprises about 10 mg of a film coating. In some examples, the film coating is Opadry AMB II Beige. In some examples, the solid dosage form is a caplet. In some examples, the solid dosage form is a capsule. In some examples, the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof, is crystalline. In some examples, the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof, is amorphous. In some examples, the pharmaceutical formulation is manufactured by a hot melt extrusion process. In some examples, the pharmaceutical formulation is manufactured by a sprayed-dried dispersion (SDD) process. In some examples, the pharmaceutical formulation comprises a self-emulsifying drug delivery system, a self-microemulsifying drug delivery system, or a self-nanoemulsifying drug delivery system.

[0018] In another example, provided herein is a method of treating pain in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical formulation described herein. In some examples the pain is neuropathic pain. In some examples, the pain is inflammatory pain.

[0019] In another example, provided herein is a method of treating epilepsy/seizure disorder, multiple sclerosis, neuromyelitis optica (NMO), Tourette syndrome, Alzheimer disease, or abdominal pain associated with irritable bowel syndrome in a patient in need thereof, comprising administering to the patient in need thereof a therapeutically effective amount of a pharmaceutical formulation described herein.

DETAILED DESCRIPTION OF THE INVENTION

Certain Terminology

[0020] The singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a drug” includes reference to one or more of such drugs, and reference to “an excipient” includes reference to one or more of such excipients. When ranges are used herein, all combinations and sub-combinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range varies between 1% and 15% of the stated number or numerical range.

[0021] The terms “formulation” and “composition,” as used herein, are used interchangeably and refer to a mixture of two or more compounds, elements, or molecules. In some aspects the terms “formulation” and “composition” may be used to refer to a mixture of one or more active agents with a carrier or other excipients.

[0022] The terms “active agent,” “active pharmaceutical agent,” “drug,” “active ingredient,” and variants thereof are used interchangeably to refer to an agent or substance that has measurable

specified or selected physiologic activity when administered to a subject in a significant or effective amount.

[0023] The compound described herein, 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof, is a MAGL inhibitor compound. 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate or a pharmaceutically acceptable salt thereof, refers to a compound with the following structure:

CLAIMS

What is claimed is:

1. A pharmaceutical formulation in a solid dosage form comprising:
   (a) 1 mg to 60 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate, or a pharmaceutically acceptable salt thereof;
   (b) 50 mg to 175 mg of microcrystalline cellulose;
   (c) 6 mg to 15 mg of croscarmellose sodium; and
   (d) 0.5 mg to 2.5 mg of magnesium stearate.

2. The pharmaceutical formulation according to claim 1, wherein the 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate is a hydrochloride salt.

3. The pharmaceutical formulation in a solid dosage form according to claim 1 comprising:
   (a) 2.1 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;
   (b) 156 mg of microcrystalline cellulose;
   (c) 10 mg of croscarmellose sodium; and
   (d) 1.7 mg of magnesium stearate.

4. The pharmaceutical formulation in a solid dosage form according to claim 1 comprising:
   (a) 10.7 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;
   (b) 147 mg of microcrystalline cellulose;
   (c) 10.2 mg of croscarmellose sodium; and
   (d) 1.7 mg of magnesium stearate.

5. The pharmaceutical formulation in a solid dosage form according to claim 1 comprising:
   (a) 53.6 mg of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(2-(pyrrolidin-1-yl)-4-(trifluoromethyl)benzyl)piperazine-1-carboxylate hydrochloride salt;
   (b) 104 mg of microcrystalline cellulose;
   (c) 10 mg of croscarmellose sodium; and

(d) 1.7 mg of magnesium stearate.

6. The pharmaceutical formulation of any one of claims 1-5, wherein the solid dosage form is a tablet.

7. The pharmaceutical formulation of any one of claims 1-5, wherein the solid dosage form is a capsule.