

FORMULATIONS OF ROCK2 INHIBITORS FOR CNS DISORDERS

FIELD

[0001] The present disclosure provides methods for the treatment of cerebral cavernous malformation and Devic's disease with ROCK2 inhibitors. The present disclosure also provides pharmaceutical formulation for oral administration of Rho-associated protein kinase (ROCK) inhibitors, particularly ROCK2 inhibitors, for the treatment of cerebral cavernous malformation and Devic's disease.

BACKGROUND

[0002] A Rho-associated coiled-coil kinase (ROCK) is a serine/threonine kinase from the AGC (PKA, PKG, and PKC) kinase family and comprises two isoforms, ROCK1 and ROCK2. The two isoforms are expressed and regulated differently in specific tissues. For example, ROCK1 is ubiquitously expressed at a relatively high level, while ROCK2 is preferentially expressed in certain tissues including heart, brain and skeletal muscle. ROCK is a target of the small GTPase Rho and is involved in diverse cellular activities achieved by phosphorylating downstream effector proteins (MLC, LIMK, ERM, MARCKS, CRMP-2, etc.). Studies have shown that various diseases (e.g., pulmonary fibrosis, cardiac-cerebral vascular disease, neurological disease, cancer, etc.) are related to the pathways mediated by ROCK. As such, ROCK2 has been considered as an important target in the development of potential drug therapies.

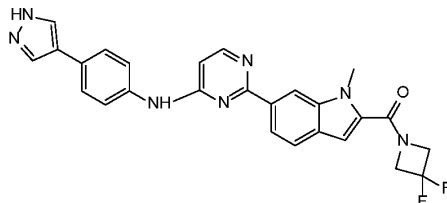
[0003] Many potential drugs suffer from low bioavailability when taken orally. The bioavailability of pharmaceutically active substances when taken orally, depends on the extent to which the pharmaceutically active substance is absorbed from the gastro-intestinal environment across the gastro-intestinal mucosa. Lipophilic pharmaceutical substances may be poorly absorbed from the gastro-intestinal tract, inter alia because of their poor solubility and/or dispersibility in water. There is a demand for oral drug formulations for lipophilic and/or poorly soluble drugs.

SUMMARY

[0004] The disclosure provides methods for the treatment of CNS disorders including cerebral cavernous malformation (CCM) and Devic's disease by administering to a patient in need thereof, a pharmaceutical formulation for oral administration of ROCK2 inhibitors.

[0005] In one aspect, the pharmaceutical formulation for the treatment of CCM or Devic's disease comprises:

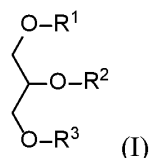
(a) about 1 to about 15 wt % of a compound having a structure:



or a pharmaceutically acceptable salt thereof;

(b) about 15 to 50 wt% of a fatty acid component comprising saturated and/or unsaturated C₈-C₂₄ fatty acids and/or a pharmaceutically acceptable salt thereof;

(c) about 30 to 50 wt% of a first glyceride component comprising one or more glyceride compounds having a structure of Formula (I)

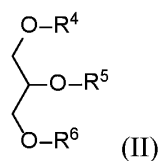


wherein:

each R¹, R², and R³ is independently hydrogen or -C(O)-R^A;

each R^A is independently C₇-C₂₁ alkenyl comprising one or two double bonds, provided that at least one of R¹, R², and R³ is not hydrogen; and

(d) about 10 to 35 wt% of a second glyceride component comprising one or more glyceride compounds having a structure of Formula (II)



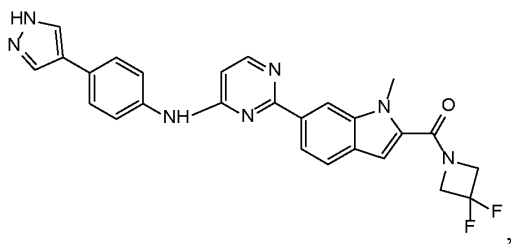
wherein:

each R⁴, R⁵, and R⁶ is independently hydrogen, or -C(O)-R^B,

each R^B is independently C₇-C₂₁ alkyl,

provided that at least one of R^4 , R^5 , and R^6 is not hydrogen.

[0006] The API may include a pharmaceutically acceptable salt of



and particularly an HCl salt thereof.

[0007] In some embodiments, the pharmaceutical formulation may suitably include a saturated or unsaturated C₁₂-C₁₈ fatty acid (e.g., oleic acid) and/or its pharmaceutically acceptable salt (e.g., sodium oleate).

[0008] In some embodiments, the pharmaceutical formulation may suitably include a first glyceride component including one or more of mono-, di-, and/or tri- fatty acid esters of glycerols, which include at least one unsaturated fatty acids (e.g., linear or branched C₇-C₂₁ alkenyl chain).

[0009] In some embodiments, the pharmaceutical formulation may suitably include a second glyceride component including one or more of mono-, di-, and/or tri- fatty acid esters of glycerols, which include saturated fatty acids (e.g., linear or branched C₇-C₂₁ alkyl chain).

[0010] In one aspect, provided is a method of treating Devic's disease by administering the pharmaceutical formulation as described herein to a patient in need thereof.

[0011] In another aspect, provided is a method of treating CCM by administering the pharmaceutical formulation as described herein to a patient in need thereof.

[0012] Other aspects of the disclosure are provided *infra*.

BRIEF DESCRIPTION OF THE FIGURES

[0013] FIG. 1 shows mean oral PK profiles for Compound A-HCl formulation in male and female Beagle dogs at 10 mg/kg (F4 100% solid dispersion vs nanosuspension).

[0014] FIG. 2 shows mean oral PK profiles for Compound A-HCl formulations in SD rats at 50 mg/kg (F4, F5 and F6).

[0015] FIG. 3 shows mean oral PK profiles for Compound A-HCl formulations in beagles at 10 mg/kg (F4, F5 and F6).

[0016] FIG. 4 shows mean oral PK profiles for Compound A-HCl formulations in beagles at 10 mg/kg (F4 and F4a).

[0017] FIGS. 5A and 5B show mean oral PK parameters (C_{max} and AUC) for Compound A-HCl formulations in male and female Beagle dogs at 10 mg/kg (F4, F4 50:50 molecular and solid dispersion and F4 100% solid dispersion).

[0018] FIG. 6A-6P shows the tissue distribution following oral administration of the formulation of Table 7.

[0019] FIG. 7 shows a schematic timeline of the protocol for the in vivo testing of Compound A in a mouse model for cerebral cavernous malformation.

DETAILED DESCRIPTION

[0020] The present disclosure provides methods for the treatment of central nervous system disorders, and particularly cerebral cavernous malformation and Devic's disease, the method comprising orally administering to a patient in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a ROCK2 inhibitor, and particularly of (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone or a pharmaceutically acceptable salt thereof. The oral pharmaceutical formulations disclosed herein may provide enhanced bioavailability of the ROCK2 inhibitor and/or enhanced exposure of the CNS to the ROCK 2 inhibitor.

Definitions

[0021] The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen (N), oxygen (O), and sulfur (S).

[0022] The term "halogen" or "halo" designates -F, -Cl, -Br or -I. Preferred halogens are -F, -Cl and -Br.

[0023] The term "hydroxyl" means -OH.

[0024] The term "oxo" as used herein refers to an oxygen atom that has a double bond to another atom (i.e., the substituent =O), particularly to carbon.

[0025] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which is fully saturated. The alkyl may include a designated number of carbons (e.g., C₁-C₁₀ means one to ten carbons). Alkyl is an uncyclized chain. Examples of alkyl radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0026] A term "alkoxy" is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-).

[0027] The term "alkenyl" refers to a linear or branched hydrocarbon chain having one or more carbon-carbon double bonds. The alkenyl may include a designated number of carbons

(e.g., C₂-C₁₀ means two to ten carbons). Alkenyl is an uncyclized chain. The alkenyl includes vinyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like. When the compound of the present disclosure contains an alkenyl group, the compound may exist as the E-form, the Z-form, or any mixture thereof.

[0028] The term “alkynyl” refers to a linear or branched hydrocarbon chain having a triple bond. The alkynyl includes ethynyl, propynyl, and the like.

[0029] The term “cycloalkyl” refers to saturated, carbocyclic groups having from 3 to 7 carbons in the ring. Cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0030] The term “aryl” as used herein includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as “aryl heterocycles”, “heteroaromatics” or “heteroaryl”. The term “aryl” also includes 7- to 14-membered polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is aromatic (including heteroaryl), e.g., the other cyclic rings can be fused cycloalkyls, cycloalkenyls, aryls, heteroaryl and/or heterocyclic groups. Single-ring heteroaryl groups may have from 1 to 3 ring heteroatoms and fused polycyclic heteroaryl groups may have from 1 to 5 ring heteroatoms, wherein the ring heteroatoms are selected from N, O and S.

[0031] The terms “heterocyclyl”, “heterocyclic” or “heterocycloalkyl” group refer to 3- to 10-membered ring structures, more preferably 5- or 6-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclic groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like.

[0032] The term “alkylaryl,” “aralkyl”, as used herein, refers to a C₁-C₆ alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[0033] As used herein, the definition of each expression, e.g. alkyl, m, n, R, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[0034] It will be understood that "substituted", "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[0035] The term "pharmaceutically-acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds disclosed herein and inorganic and organic basic addition salts of the compounds disclosed herein. It is understood that the reference to a ROCK2 inhibitor includes the neutral compound and any pharmaceutically acceptable salt for of the ROCK2 inhibitor. The pharmaceutically acceptable salt forms which may be selected on the basis of a chosen route of administration and according to standard pharmaceutical practice.

[0036] As set out above, certain embodiments of the ROCK2 inhibitors may contain a basic functional group, such as amino, and are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable acids. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19).

[0037] The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic,

hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0038] In other cases, the compounds provided in this disclosure may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine.

Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., *supra*).

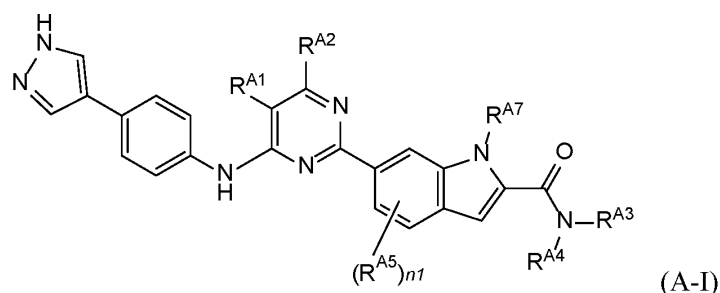
[0039] Certain compounds provided in this disclosure may exist in particular geometric or stereoisomeric forms. The disclosure contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are included in this invention.

[0040] Unless otherwise specified, all amount percents are in percent by weight (wt %). In reference to the amounts of components in the pharmaceutical formulation (e.g., API, fatty acid component(s), first glyceride component, second glyceride component, etc.), the weight percentage of the component does not include the weight of the capsule shell or coating. In other words, the total weight of the pharmaceutical formulation used for calculation of the wt % for each component includes the fill components (e.g., API, fatty acid component(s), first glyceride component, second glyceride component, etc.), but not the capsule shell or coating.

Active Pharmaceutical Ingredients (API)

[0041] The disclosure provides methods for the treatment of central nervous system disorders, and particularly cerebral cavernous malformation and Devic's disease, the method comprising administering to a patient in need thereof pharmaceutical formulations including one or more ROCK2 inhibitors.

[0042] In one aspect, the ROCK2 inhibitor has the structure of Formula (A-I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12};

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, -CN, C_1 - C_3 perfluoro alkyl, $-OR^{A11}$, oxo, $-O-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-NR^{A11}R^{A12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, $-O-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$, $-C(=O)-R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$;

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, halo, -CN, C_1 - C_3 perfluoro alkyl, oxo, $-OR^{A11}$, $-O-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-NR^{A11}R^{A12}$, $-O-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, $-O-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$, $-C(=O)-R^{A11}$, $-C(=O)OR^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)NR^{A11}R^{A12}$, $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, and $-NR^{A11}-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$;

nI is 0 to 3;

R^{A7} is independently selected from the group consisting of H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_7 cycloalkyl, $-(C_1-C_6 \text{ alkyl})-OR^{A11}$, $-(C_1-C_6 \text{ alkyl})-NR^{A11}R^{A12}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)R^{A11}$, $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)OR^{A11}$, and $-(C_1-C_6 \text{ alkyl})_{xI}-C(=O)NR^{A11}R^{A12}$;

each xI is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C_1 - C_6 alkyl;

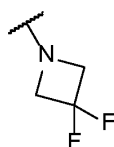
or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group

consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

[0043] In some embodiments, R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide a 4- to 6-membered heterocyclic ring, which is optionally substituted. In some embodiments, -NR^{A3}R^{A4} is



, which may be substituted or unsubstituted. In some embodiments, -NR^{A3}R^{A4} is

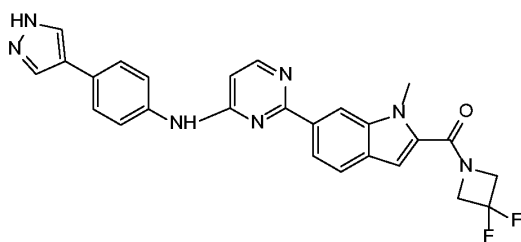


[0044] In some embodiments, R^{A1} and R^{A2} are hydrogen.

[0045] In some embodiments, R^{A7} is unsubstituted C₁-C₃ alkyl. In some embodiments, R^{A7} is unsubstituted methyl.

[0046] In some embodiments, R^{A5} is hydrogen, or n1 is 0.

[0047] In some embodiments, the ROCK2 inhibitor has the structure:

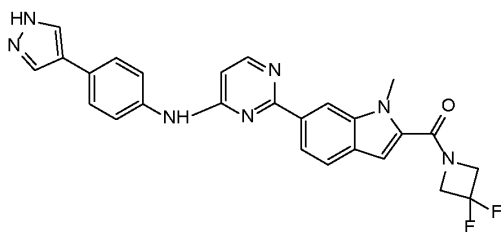


(Compound A), or pharmaceutically

acceptable salt thereof. This compound has the chemical name (6-(4-((4-(1H-pyrazol-4-yl)phenyl)amino)pyrimidin-2-yl)-1-methyl-1H-indol-2-yl)(3,3-difluoroazetidin-1-yl)methanone.

[0048] In some embodiments, the pharmaceutically acceptable salt is HCl.

[0049] In certain embodiments, the API comprises an HCl salt of



[0050] The compounds of Formula (A-I), as well as other disclosed ROCK2 inhibitors, may be synthesized and assayed for ROCK2 inhibition activity *in vitro* as described in, for

example, WO2019/000682, WO 2019/000683, WO2019/001572, WO2020/094111, WO2020/177587, WO2020/259528, WO2022/042711, WO2022/042712 and US Pat. No. 10,323,023, 10,329,282 and 11,390,609, the entire contents of which are each incorporated herein by reference.

[0051] The ROCK2 inhibitor may comprise from about 1-15 wt % of the pharmaceutical formulation, or from about 1-10 wt % of the pharmaceutical formulation, or from about 2-8 wt % of the pharmaceutical formulation, or from about 5-7 wt % of the pharmaceutical formulation.

Pharmaceutical Formulations

[0052] Provided herein, *inter alia*, are pharmaceutical formulations for oral administration to a patient in need thereof, wherein the patient suffers from cerebral cavernous malformation or Devic's disease. In one aspect, the pharmaceutical formulation includes (i) an active pharmaceutical ingredient (API) (e.g., ROCK2 inhibitors, particularly Compound A), and (ii) pharmaceutically acceptable excipients (e.g., lipid formulation including fatty acid components and/or glyceride components).

[0053] The pharmaceutical formulation may suitably include additional excipients such as surfactants, solvents, solubilizing agents, preservatives, anti-oxidants, bulking agents, dissolution enhancers, wetting agents, emulsifiers, suspending agents, antibacterial agents, pH buffering agents, sweeteners, flavoring agents, and combinations thereof.

[0054] The disclosure provides a pharmaceutical formulation that may enhance absorption, controlled release and performance of the API, i.e. compounds of Formula (A-I), and particularly Compound A. In certain embodiments, the pharmaceutical formulation may improve lymphatic uptake channels and avoid drug uptake via the hepatic portal vein thereby improve first-pass metabolism.

[0055] For example, the pharmaceutical formulations provided herein may improve absorption from the gastro-intestinal tract following oral administration of the compound of Formula IA, and particularly Compound A, and exemplary components of the lipid formulations include, but not limited to, triglycerides (e.g., tri-fatty acid (e.g., saturated or unsaturated) esters of glycerol), monoglycerides (e.g., mono-fatty acid (e.g., saturated or unsaturated) esters of glycerol), saturated or unsaturated fatty acids, phospholipids, bile salts and functionalized lipids (e.g., phospholipids). These lipid components may be fully or partially digested upon, e.g., oral in-take, and ultimately release the fatty acids.

[0056] Absorption of fatty acids taken may depend on characteristic of hydrocarbon chains, e.g., chain length, structure, geometry and the like. For example, short chain (e.g., C₂ to C₆) fatty acids and medium chain (e.g., C₈ to C₁₂) fatty acids may be preferably absorbed through the hepatic portal vein when digested, while long chain (e.g., C₁₄ to C₂₂) fatty acids are rather absorbed via the lymphatic system. So, during digestion of lipidic formulations of the API, mixtures of micelles formed of the fatty acids and derivatives are produced allowing the digested components combined with the API, to be taken up by lipid transporter proteins, resulting in the formation of API-containing lipid droplets in mucosal epithelial cells which are packaged up into nascent lipoproteins called chylomicrons. These API-loaded chylomicrons are then secreted into the lacteals of the enteric lymphatic system where they feedback into the central venous return, allowing the distribution of API around the body.

[0057] The disclosure provides methods for the treatment of cerebral cavernous malformation and Devic's disease, the method comprising administering to a patient in need thereof an oral composition for the API including Compound A or its pharmaceutically acceptable salt (e.g., Compound A-HCl), together with the lipidic excipients or components, e.g., a mixture of medium or long chain mono-, di-, or tri- glyceride, long chain fatty acid (C₈ to C₂₂ fatty acids, e.g., oleic acid), medium or long chain triglyceride (e.g., Gelucire 43/01) and long chain surfactant (C₁₄ to C₂₂ fatty acids salt, e.g., sodium oleate). In some embodiments, the API may be formed in a solid dispersion, molecular dispersion, in a solution, or as a combination thereof.

[0058] The term "molecular dispersion" as used herein refers to a solution (liquid phase) including a solute (e.g., API such as Compound A, Compound A-HCl, etc.) dispersed in a solvent. The dispersed phase (solute, e.g., API) may be present homogeneously dispersed in an aqueous solution or water-based solvent phase or in an oil-based solvent phase.

[0059] The term "solid dispersion" as used herein refers to a system containing hydrophobic ingredient (e.g., API) dispersed in a matrix, which may be prepared by the melt (fusion) method, solvent evaporation method, melt extrusion, lyophilization, electrospinning, or the like. The solid dispersion may comprise particles, e.g., having a particle distribution D₉₀ less than about 100 micron, less than about 90 micron, less than about 80 micron, less than about 70 micron, less than about 60 micron, less than about 50 micron, less than about 40 micron, less than about 30 micron, less than about 20 micron, or less than about 10 micron.

[0060] The pharmaceutical formulation may comprise one or more fatty acid components including fatty acids and/or pharmaceutically acceptable salts thereof. The pharmaceutical

formulation may also include a first glyceride component including a mixture of mono-, di-, and/or tri- fatty acid esters of glycerol, which include at least one of unsaturated fatty acids (e.g., linear or branched C₇-C₂₁, C₉-C₂₁, C₁₁-C₂₁, C₁₃-C₁₇ or C₁₅-C₁₇ alkenyl chain). The pharmaceutical formulation may also include a second glyceride component including a mixture of mono-, di- and/or tri- fatty acid esters of glycerol, which are saturated fatty acids (e.g., linear or branched C₇-C₂₁, C₇-C₁₇, or C₇-C₁₇ alkyl chain).

[0061] In certain aspect, the pharmaceutical formulation may comprise:

- (i) one or more fatty acid components including fatty acids and/or pharmaceutically acceptable salts thereof;
- (ii) a first glyceride component including a mixture of mono-, di-, and/or tri- fatty acid esters of glycerol, which include at least one of unsaturated fatty acids (e.g., linear or branched C₇-C₂₁, C₉-C₂₁, C₁₁-C₂₁, C₁₃-C₁₇ or C₁₅-C₁₇ alkenyl chain); and
- (iii) a second glyceride component including a mixture of mono-, di-, and/or tri- fatty acid esters of glycerol, which are saturated fatty acids (e.g., linear or branched C₇-C₂₁, C₇-C₁₉, C₇-C₁₇, C₉-C₂₁, C₉-C₁₉, C₉-C₁₉, C₁₁-C₂₁, C₁₁-C₁₉ or C₁₁-C₁₇ alkyl chain).

[0062] The fatty acid may suitably include saturated or unsaturated hydrocarbon chains, e.g., saturated or unsaturated C₈-C₂₄ fatty acids.

[0063] The “fatty acid” as used herein refers to a compound or moiety having a carboxylic group (-COOH, -COO⁻) attached to a hydrocarbon chain (e.g., saturated or unsaturated, and linear or branched, preferably linear, C₇-C₂₃, C₁₁-C₂₁, C₁₃-C₁₉, or C₁₅-C₁₇ alkyl or alkenyl chain). The fatty acid may be present in a pharmaceutically acceptable salt form (e.g., sodium salt). As would be understood by a person skilled in the art, the number of carbon atoms specified for a particular fatty acid is one more than the number of carbon atoms in its alkyl or alkenyl chain to account for the carbonyl carbon of the fatty acid (i.e., a C₁₈ fatty acid has a C₁₇ alkyl or alkenyl chain). Accordingly, the fatty acid component may comprise one or more of a C₈-C₂₄ fatty acid, or a C₁₂-C₂₂ fatty acid, or a C₁₄-C₂₀ fatty acid, or a C₁₆-C₁₈ fatty acid, which fatty acid may be saturated or unsaturated, preferably unsaturated, and linear or branched, preferably linear.

[0064] In some embodiments, the fatty acid may be present in a pharmaceutically acceptable salt form (e.g., sodium salt). In some embodiments, the fatty acid components may include a fatty acid. In some embodiments, the fatty acid components may be a pharmaceutically acceptable salt form of a fatty acid (e.g., sodium salt). In some

embodiments, the fatty acid components may comprise both a fatty acid and a pharmaceutically acceptable salt form of a fatty acid (e.g., sodium salt).

[0065] Exemplary saturated C₈-C₂₄ fatty acids includes caprylic acid (CH₃(CH₂)₆COOH), capric acid (CH₃(CH₂)₈COOH), lauric acid (CH₃(CH₂)₁₀COOH), myristic acid (CH₃(CH₂)₁₂COOH), palmitic acid (CH₃(CH₂)₁₄COOH), stearic acid (CH₃(CH₂)₁₆COOH), arachidic acid (CH₃(CH₂)₁₈COOH), behenic acid (CH₃(CH₂)₂₀COOH), or lignoceric acid (CH₃(CH₂)₂₂COOH). Exemplary unsaturated C₈-C₂₄ fatty acids includes myristoleic acid (CH₃(CH₂)₃CH=CH(CH₂)₇COOH), palmitoleic acid (CH₃(CH₂)₅CH=CH(CH₂)₇COOH), sapienic acid (CH₃(CH₂)₈CH=CH(CH₂)₄COOH), oleic acid (CH₃(CH₂)₇CH=CH(CH₂)₇COOH), elaidic acid (CH₃(CH₂)₇CH=CH(CH₂)₇COOH), vaccenic acid (CH₃(CH₂)₅CH=CH(CH₂)₉COOH), linoleic acid (CH₃(CH₂)₄CH=CHCH₂CH=CH(CH₂)₇COOH), linoelaidic acid (CH₃(CH₂)₄CH=CHCH₂CH=CH(CH₂)₇COOH), α-linolenic acid (CH₃CH₂CH=CHCH₂CH=CHCH₂CH=CH(CH₂)₇COOH), arachidonic acid (CH₃(CH₂)₄CH=CHCH₂CH=CHCH₂CH=CHCH₂CH=CH(CH₂)₃COOH), eicosapentaenoic acid (CH₃CH₂CH=CHCH₂CH=CHCH₂CH=CHCH₂CH=CHCH₂CH=CH(CH₂)₃COOH), erucic acid (CH₃(CH₂)₇CH=CH(CH₂)₁₁COOH), or docosahexaenoic acid (CH₃CH₂CH=CHCH₂CH=CHCH₂CH=CHCH₂CH=CHCH₂CH=CHCH₂CH=CH(CH₂)₂COOH).

[0066] In certain embodiments, the fatty acid(s) may be unsaturated C₈-C₂₄, C₁₂-C₂₂, C₁₄-C₂₀, or C₁₆-C₁₈ fatty acid(s). In certain embodiments, the fatty acid may be one or more unsaturated C₁₂-C₂₄, C₁₂-C₂₂, C₁₂-C₂₀, or C₁₂-C₁₈ fatty acids. In certain embodiments, the fatty acid may be one or more unsaturated C₁₂-C₂₀ fatty acids. In certain embodiments, the fatty acid may be unsaturated C₁₄-C₂₄, C₁₄-C₂₂, C₁₄-C₂₀, or, C₁₄-C₁₈ fatty acids. Preferred fatty acid includes unsaturated C₁₈ fatty acids, and particularly oleic acid (CH₃(CH₂)₇CH=CH(CH₂)₇COOH).

[0067] In certain embodiments, the fatty acid salt comprises one or more unsaturated C₈-C₂₄, C₁₂-C₂₂, C₁₄-C₂₀, or C₁₆-C₁₈ fatty acid sodium salts. In certain embodiments, the fatty acid salt may be unsaturated C₁₂-C₂₄, C₁₂-C₂₂, C₁₂-C₂₀, or C₁₂-C₁₈ fatty acid sodium salt. In certain embodiments, the fatty acid salt may be unsaturated C₁₄-C₂₄, C₁₄-C₂₂, C₁₄-C₂₀, or, C₁₄-C₁₈ fatty acid sodium salt. Preferred fatty acid salt includes unsaturated C₁₈ fatty acid sodium salt, particularly oleic acid sodium salt (CH₃(CH₂)₇CH=CH(CH₂)₇COONa).

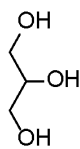
[0068] In embodiments, the fatty acid component comprises a combination of a fatty acid and a fatty acid salt, each for example as provided in the preceding paragraphs.

[0069] In certain aspect, the pharmaceutical formulation comprises the fatty acid component in an amount of about 15 to 50 wt%, about 20 to 45 wt%, about 30 to 45 wt%, about 35 to 45 wt%, or about 35 to 40 wt% based on the weight of the pharmaceutical formulation (i.e., not including the weight of a capsule shell or coating). As used herein, the pharmaceutical formulation refers to the composition comprising the API, the fatty acid and triglyceride components, and any other excipients, but does not include the capsule shell or coating.

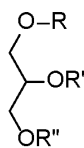
[0070] In embodiments, the fatty acid component comprises a combination of a fatty acid and a fatty acid salt, each for example as provided in the preceding paragraphs. The pharmaceutical formulation may comprise the fatty acid in an amount of about 12 to 48 wt%, about 15 to 45 wt%, of about 25 to 40 wt%, about 30 to 40 wt%, or about 35 to 40 wt% based on the weight of the pharmaceutical formulation. The pharmaceutical formulation may comprise a sodium salt of the fatty acid in an amount of about 1 to 5 wt%, or about 2 to 4 wt%, or about 2 to 3 wt%, based on the weight of the pharmaceutical formulation. The pharmaceutical formulation may comprise oleic acid and sodium oleate.

[0071] The pharmaceutical formulation comprises glyceride components (e.g., a first glyceride component and a second glyceride component), including a mixture of mono-, di-, and/or tri- fatty acid esters of glycerol.

[0072] The term “glycerol” refers to a compound containing triol (three -OH groups) and

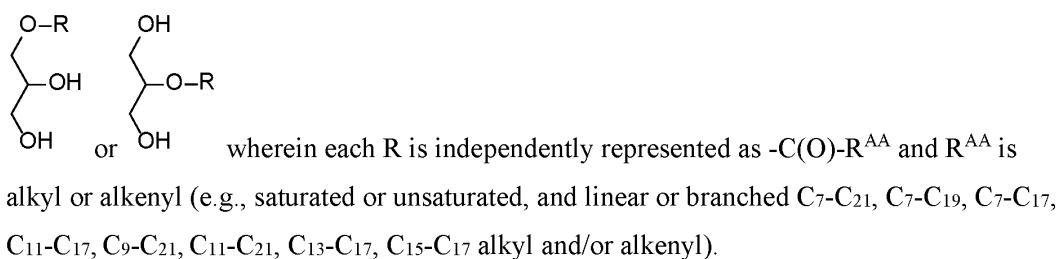


having a structure of . The term “glyceride” as used herein refers to a compound or moiety formed by one to three ester bonds between glycerol and fatty acids (e.g., one, two or

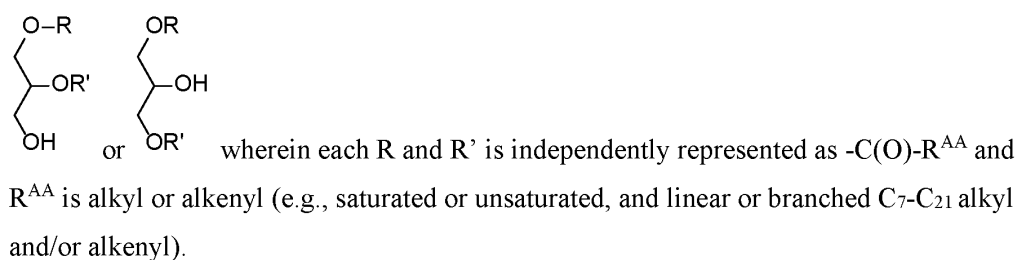
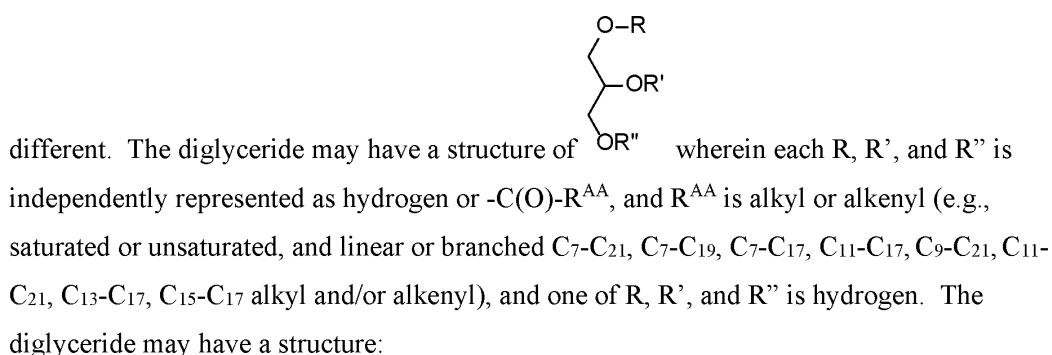


three fatty acids), and having a structure of wherein each R, R', and R'' is hydrogen or -C(O)-R^{AA} and R^{AA} is alkyl or alkenyl (e.g., saturated or unsaturated, and linear or branched C₇-C₂₁, C₇-C₁₉, C₇-C₁₇, C₁₁-C₁₇, C₉-C₂₁, C₁₁-C₂₁, C₁₃-C₁₇, C₁₅-C₁₇ alkyl and/or alkenyl) and at least one of R, R', and R'' is not hydrogen.

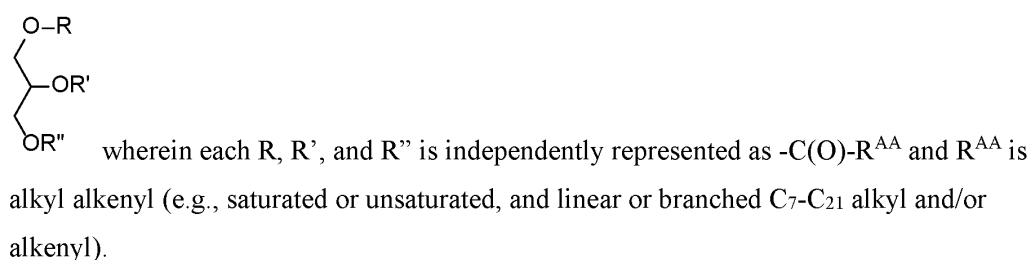
[0073] The term “monoglyceride” or “mono-fatty acid ester of glycerol” as used herein refers to a compound or molecule of glycerol linked to a single fatty acid. The monoglyceride may have a structure of



[0074] The term “diglyceride” or “di-fatty acid esters of glycerol” as used herein refers to a compound or molecule of glycerol linked to two fatty acids, which may be the same or



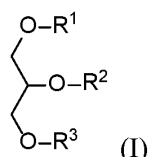
[0075] The term “triglyceride” or “tri-fatty acid esters of glycerol” as used herein refers to a compound or molecule of glycerol linked to three fatty acids, which may be the same or different. The triglyceride may have a structure of



[0076] The pharmaceutical formulation may comprise up to about 75 % of glycerides, or up to about 70 % of glycerides, or up to about 65 % of glycerides, or up to about 60 % of glycerides, or up to about 55 % of glycerides, or up to about 50 % of glycerides. The formulation may comprise at least about 40 % of glycerides, or at least about 45 % of

glycerides, or at least about 50 % of glycerides. The glycerides may comprise the first glyceride component and the second glyceride component.

[0077] The first glyceride component may suitably include one or more of mono-, di-, and/or tri- glycerides that include at least one C₇-C₂₁ alkenyl (including one or two double bonds). The first glyceride component comprises one or more glyceride compounds having a structure of Formula (I)



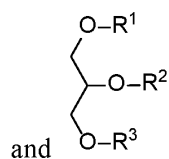
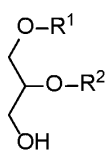
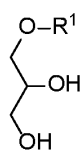
wherein:

each R¹, R², and R³ is independently hydrogen or -C(O)-R^A;

each R^A is independently C₇-C₂₁ alkenyl comprising one or two double bonds, provided that at least one of R¹, R², and R³ is not hydrogen.

[0078] In some embodiments, in Formula (I), each R^A is independently C₇-C₂₁, C₉-C₂₁, C₁₁-C₂₁, C₁₃-C₁₇ or C₁₅-C₁₇ alkenyl (e.g., linear or branched, preferably linear). In some embodiments, in Formula (I), each R^A is independently C₇-C₂₁, C₇-C₁₉, C₁₁-C₁₉, or C₁₁-C₁₇ alkenyl, which includes one or two double bonds. In some embodiments, at least one R^A comprises one or more of C₇ alkenyl, C₉ alkenyl, C₁₁ alkenyl, C₁₃ alkenyl, C₁₅ alkenyl, C₁₇ alkenyl, and combinations thereof. In some embodiments, at least one R^A is C₁₇ alkenyl, which includes one or two double bonds.

[0079] In certain aspect, the first glyceride component includes one or more compounds having one of the following structures:



R¹, R², and R³ are as described above.

[0080] In the first glyceride component, a weight ratio of the compound of mono-, di-, and/or tri- glycerides that include at least one of C₇-C₂₁ alkenyl may be about 32 to 52 : 40 to 55: 5 to 20. In some embodiments, the first glyceride component may include the compound of Formula (I-a), the compound of Formula (I-b), and the compound of Formula (I-c) at a weight ratio of about 32 to 52 : 40 to 55: 5 to 20.

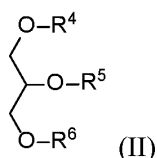
[0081] In the first glyceride component, a weight ratio of mono-, di-, and/or tri- glycerides that include at least one of C₇-C₂₁ alkenyl may be about 32 to 52 : 40 to 55: 5 to 20. In some embodiments, the first glyceride component may alternatively include the compound of Formula (I-a), the compound of Formula (I-b), and the compound of Formula (I-c) at a weight ratio of about 32 to 52 : 40 to 55: 5 to 20.

[0082] Alternatively, the first glyceride component may dominantly (i.e., greater than 50 wt%) include monoglycerides including at least one of C₇-C₂₁ alkenyl. In some embodiments, the first glyceride component may dominantly include diglycerides including at least one of C₇-C₂₁ alkenyl. In some embodiments, the first glyceride component may dominantly include triglycerides including at least one of C₇-C₂₁ alkenyl.

[0083] In embodiments, the first glyceride component comprises mono-, di-, and tri-glycerides of oleic acid and linoleic acid. The relative amounts of mono-, di-, and tri-glycerides may be about 32-52 % mono-glyceride, about 40-55 % di-glycerides, and about 5-20 % triglycerides. The first glyceride component may be Maisine CC.

[0084] In certain aspect, the pharmaceutical formulation comprises the first glyceride component in an amount of about 30 to 50 wt%, or about 30 to 45 wt%, or about 32 to 40 wt%, or about 35 to 40 wt%, based on the weight of the pharmaceutical formulation.

[0085] The second glyceride component may suitably include one or more of mono-, di-, and/or tri- glycerides of C₈ to C₂₂ saturated fatty acids. The second glyceride component includes one or more glyceride compounds having a structure of Formula (II):



wherein:

each R⁴, R⁵, and R⁶ is independently hydrogen, or -C(O)-R^B;

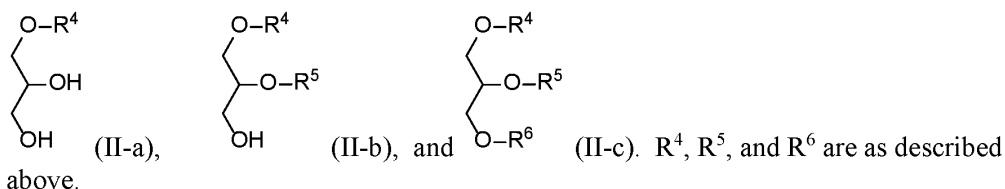
each R^B is independently hydrogen or C₇-C₂₁ alkyl,

provided that at least one of R⁴, R⁵, and R⁶ is not hydrogen.

[0086] In some embodiments, in Formula (II), each R^B is independently C₇-C₂₁, C₇-C₁₉, C₇-C₁₇, C₉-C₂₁, C₉-C₁₉, C₉-C₁₇, C₁₁-C₂₁, C₁₁-C₁₉ or C₁₁-C₁₇ alkyl (e.g., linear or branched). In some embodiments, in Formula (II), each R^B is independently C₇-C₂₁, C₇-C₁₉, C₇-C₁₇, C₇-C₁₅, C₇-C₁₃, C₇-C₁₁, C₉-C₂₁, C₁₁-C₁₇, C₁₁-C₂₁, or C₁₃-C₂₁ alkyl. In some embodiments, one of R^B is C₂₁ alkyl. In some embodiments, one of R^B is C₇ alkyl. In some embodiments, one of R^B is C₉ alkyl. In some embodiments, one of R^B is C₁₁ alkyl. In some embodiments, one of R^B

is C₁₃ alkyl. In some embodiments, one of R^B is C₁₅ alkyl. In some embodiments, one of R^B is C₁₇ alkyl. In some embodiments, one of R^B is C₁₉ alkyl.

[0087] In certain aspect, the second glyceride component includes one or more compounds having one of the following structures:



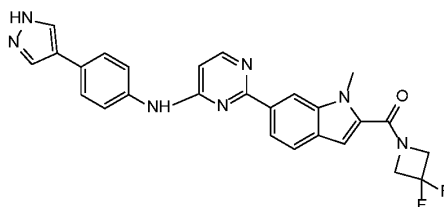
[0088] In some embodiments, the second glyceride component may dominantly (i.e., greater than 50 wt%) include monoglycerides including at least one C₇-C₂₁ alkyl. In some embodiments, the second glyceride component may dominantly include diglycerides including at least one C₇-C₂₁ alkyl. In some embodiments, the second glyceride component may dominantly include triglycerides including at least one C₇-C₂₁ alkyl.

[0089] In embodiments, the second glyceride component comprises triglycerides of C₈ to C₁₈ saturated fatty acids. The second glyceride component may be Gelucire 43/01.

[0090] In certain aspect, the pharmaceutical formulation comprises the second glyceride component in an amount of about 10 to 35 wt%, or about 10 to 30 wt%, or about 10 to 20 wt%, or about 15 to 18 wt%, based on the weight of the pharmaceutical formulation.

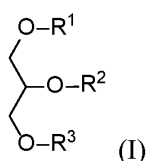
[0091] In certain aspect, the pharmaceutical formulation comprises:

- (i) about 1-15 wt %, or about 1-10 wt %, or about 2-8 wt %, or about 5-7 wt % of the pharmaceutical formulation of a compound having a structure:



or a pharmaceutically acceptable salt thereof, and

- (ii) about 15 to 50 wt%, or about 20 to 45 wt%, or about 30 to 45 wt%, or about 35 to 45 wt%, or about 35 to 40 wt% of the pharmaceutical formulation of a fatty acid component comprising saturated or unsaturated C₈-C₂₄ fatty acids and/or a pharmaceutically acceptable salt thereof;
- (iii) about 30 to 50 wt%, or about 30 to 45 wt%, or about 32 to 40 wt%, or about 35 to 40 wt% of the pharmaceutical formulation of a first glyceride component comprising one or more compounds having a structure of Formula (I)



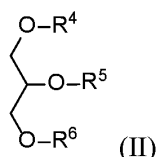
wherein:

each R^1 , R^2 , and R^3 is independently hydrogen or $-C(O)-R^A$;

each R^A is independently C_7 - C_{21} alkenyl comprising one or two double bonds, provided that at least one of R^1 , R^2 , and R^3 is not hydrogen; and

(iv) about 10 to 35 wt%, or about 10 to 30 wt%, or about 10 to 20 wt%, or about 15 to 18 wt% of the pharmaceutical formulation of a second glyceride component comprising:

one or more compounds having a structure of Formula (II)



wherein:

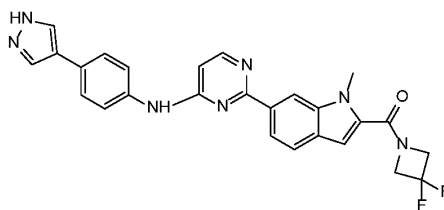
each R^4 , R^5 , and R^6 is independently hydrogen, or $-C(O)-R^B$;

each R^B is independently C_7 - C_{21} alkyl,

provided that at least one of R^4 , R^5 , and R^6 is not hydrogen.

[0092] In certain aspect, the pharmaceutical formulation comprises:

(i) about 1-15 wt %, or about 1-10 wt %, or about 2-8 wt %, or about 5-7 wt % of the pharmaceutical formulation of a compound having a structure:



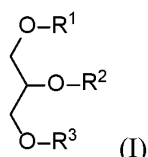
or a pharmaceutically acceptable salt thereof, and

(ii) a fatty acid component comprising:

a saturated or unsaturated C_8 - C_{24} fatty acid in an amount of about 12 to 48 wt%, about 15 to 45 wt%, of about 25 to 40 wt%, about 30 to 40 wt%, or about 35 to 40 wt% of the pharmaceutical formulation; and

a sodium salt of a saturated or unsaturated C₈-C₂₄ fatty acid in an amount of about 1 to 5 wt%, or about 2 to 4 wt%, or about 2 to 3 wt%, of the pharmaceutical formulation;

- (iii) about 30 to 50 wt%, or about 30 to 45 wt%, or about 32 to 40 wt%, or about 35 to 40 wt% of the pharmaceutical formulation of a first glyceride component comprising one or more compounds having a structure of Formula (I)



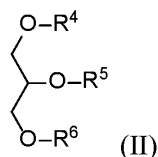
wherein:

each R¹, R², and R³ is independently hydrogen or -C(O)-R^A;

each R^A is independently C₇-C₂₁ alkenyl comprising one or two double bonds, provided that at least one of R¹, R², and R³ is not hydrogen; and

- (iv) about 10 to 35 wt%, or about 10 to 30 wt%, or about 10 to 20 wt%, or about 15 to 18 wt% of the pharmaceutical formulation of a second glyceride component comprising:

one or more compounds having a structure of Formula (II)



wherein:

each R⁴, R⁵, and R⁶ is independently hydrogen, or -C(O)-R^B;

each R^B is independently C₇-C₂₁ alkyl,

provided that at least one of R⁴, R⁵, and R⁶ is not hydrogen.

Dosage Form

[0093] The disclosure also provides a semi-solid or liquid-based formulation when formulated as, including, but not limited to, an emulsion, suspension, solution, elixirs, or syrup in which the ROCK2 inhibitor (e.g., compound A) is dissolved and/or suspended, and for use in the method of treating CCM or Devic's disease.

[0094] The dosage form comprising a compound of the Formula I, and particularly Compound A or its salts, can take the form of solutions, suspensions, emulsion, capsules, soft elastic or hard gelatin capsules, suspensions, and the like preferably in unit dosage forms

suitable for simple administration of precise dosages. The composition may take the forms of liquid- or semi-solid filled capsules for oral administration.

[0095] Capsule dosage forms may include soft capsules and hard capsules. Capsules may be used as an oral dosage form for the administration of a compound of the Formula I, and particularly Compound A or its salts for use in the method of treating CCM or Devic's disease. The capsules may be filled with the active ingredient in the form of a liquid, or a powder suspended in liquid. Hard capsules can be made of unplasticized or low-plasticized gelatin and water to form a stiff capsule that can be filled with either powder or liquid. Soft capsules can be made of highly plasticized soft elastic gelatin and can contain a liquid or semisolid ingredient. These capsules are often referred to as "softgel" or "gelcap" capsules.

[0096] As used herein, the term "capsule" refers to any suitable capsular container or case adapted for oral ingestion, e.g., those adapted for use in conjunction with liquid fill compositions. The term "capsule" may include capsules having a shell composed of soft and/or hard materials, such as gelatin, starches, celluloses, cellulose derivatives (e.g., hydroxypropyl methyl cellulose), hydrocolloids, gums, carrageenans, or any other natural or synthetic material which can be used to encapsulate the liquid composition and be ingested by an animal. Optionally, the shell material can be gelatin and/or hydroxypropyl methyl cellulose. In an embodiment, the shell material is gelatin. The term "capsule" also includes a variety of capsule shapes and sizes. The instant disclosure does not limit the dosage form to a specific type or shape. Any commercially available capsule shells or shell materials can be used.

[0097] In an embodiment, the dosage form of the instant disclosure is a soft capsule. In an embodiment, the dosage form of the instant disclosure is a coated liquid-filled soft capsule. The coated capsule can include a liquid fill encapsulated with a soft capsule shell. The exterior surface of the soft capsule shell can be coated with one or more layers of coating.

[0098] Suitable materials for encapsulating the liquid fill may include heat sealable polymers and gelatin. Examples of heat sealable polymers may include, but are not limited to, modified starches, cellulosic polymers and carrageenans. In an embodiment, the material is gelatin. The gelatin can be natural gelatin, chemically modified gelatin, enzymatically modified gelatin, or combinations thereof.

[0099] The material that forms the capsule shell can further includes water. Water can be present in the original material mass before the capsules are made, in an amount sufficient to allow the processing of the material on the encapsulation machine. After the capsules are formed the majority of the moisture can be removed during the drying process.

[0100] The water can have a plasticizing effect on the material. In addition, a non-volatile plasticizer or blend of plasticizers can be added to the material which forms the capsule shell. The non-volatile plasticizer can be any plasticizer compatible with the material of the capsule shell. For example, the non-volatile plasticizer can be glycerin, maltitol, sorbitan, sorbitol or similar low molecular weight polyhydric alcohols, and mixtures thereof. In embodiments, the ratio of plasticizer to material may determine how hardness or softness the shell.

[0101] The ratio of plasticizer to material in the shell may be sufficient to provide capsules that are not too hard, such that the capsules are brittle and crack if stressed during shipping and handling, and are not too soft, such that the capsules become deformed during shipping and handling. The non-volatile plasticizer can be present in the capsule shell from about 8% to 65% by weight of the capsule shell, from about 10% to 35% by weight of the capsule shell.

[0102] The material which forms the capsule shell can further contain extenders. The extender can be any extender which is compatible with the material. Examples of extenders may include natural or modified natural biopolymers and synthetic polymers. Natural biopolymers may include, for instance, cellulose, starch, starch derivatives, bacterial polysaccharides such as xanthan gum and gellan gum and vegetable gums such as guar gum, locust bean gum, gum tragacanth and gum Arabic and animal derived polymers such as chondroitin sulfate, hyaluronic acid, heparin, collagen and chitosan. An example of a modified natural biopolymer may be modified cellulose. Examples of synthetic polymers may include carbon chain polymers of the vinyl and acrylic types as well as heterochains of the polyoxide and polyamine types.

[0103] A coating can be applied on the exterior surface of the soft capsule shell. The coating can contain one or more layers. Any coating suitable for a soft capsule can be applied to the capsule. The coating can provide, for example, waterproofing and sealing, smoothing, polishing, enteric protection and/or delayed release properties to the liquid-filled capsule. The delayed release can be affected by, for example, temperature or pH. In an embodiment, the coating is an enteric coating.

[0104] The coating can be made by any standard coating ingredient known to those skilled in the art. Coating ingredients may include, but are not limited to, fats, fatty acids, waxes, shellac, ammoniated shellac, cellulose acetate phthalates, celluloses, vinyls, glycols, acrylics and carbohydrate polymers, polymers and co-polymers containing methacrylic acid and methacrylic acid alkyl esters, hydroxypropylmethyl cellulose (HPMC) and combinations thereof.

[0105] The coated capsule can further comprise a finishing coating. In an embodiment, the finishing layer is applied to the coated-capsule. Examples of substance suitable for use in a finishing coating may include, but are not limited to cellulose, vinyls, glycols, acrylics and carbohydrate polymers and/or combinations thereof.

[0106] The liquid fill or semi-solid fill can be encapsulated with a soft capsule shell by any method known in the art. For example, a soft capsule can be made using a standard rotary die soft gelatin capsule machine as described in *The Theory and Practice of Industrial Pharmacy*, ed. Lachman, et al., 2nd Ed., Pt. II, 404-420, Lea & Febiger, 1976. Additional methods include using a plate process (see *The Theory and Practice of Industrial Pharmacy*, ed. Lachman, et al., 2nd Ed., Pt. II, 405, Lea & Febiger, 1976), as well as Globex type seamless capsule machines, which makes large microcapsules (see U.S. Pat. No. 5,254,294), non-standard rotary die machines, which uses extrusion technology to make gel ribbons (see U.S. Pat. Nos. 6,183,845 and 6,340,473), and other methods for making capsules which use high frequency, ultrasonic, or induction welding to seal the capsules (see U.S. Pat. No. 6,352,719). The above-listed U.S. patents and book are hereby incorporated by reference.

[0107] As used herein, the phrase “liquid hard-shell” refers to a hard capsule encapsulating a liquid or semi-solid formulation. Hard capsules can be single unit dosage forms and may comprise a cap and a body, which can be manufactured separately, and which can be supplied empty for filling with the liquid or semi-solid composition. In some embodiments, hard capsules are made from a polymer such as gelatin. An additional component can be water, which acts as a plasticizer. Another hard capsule may be manufactured from hydroxypropylmethyl cellulose (HPMC). Liquid-fill hard capsule can be filled on a filling machine, such as, for example, a high-speed filling machine.

[0108] In one example, disclosed herein is a method of prepare the filled hard capsule. Empty capsules are supplied to the filling machine in a prelocked condition, wherein the capsule body has a cap which is loosely attached thereto. A series of rings or protrusions are provided in the mating surfaces of the cap or body. These rings are configured to enable the cap to be loosely attached to the body so that the cap and body are held together during storage but would enable the cap to be removed prior to filling of the capsule. Once the capsule has been filled, the cap can be replaced and be forced beyond the prelocked position into a fully locked position. Alternatively, other types of capsule filling machines can be used to accept separate supplies of capsule bodies and caps.

[0109] The capsules may be closed at high speed after filling with the formulated composition. During closure of the capsule, the cap is fitted over the body and the body is

pushed up until it locks on the cap. The cap can be close fitting and can be approximately half the length of the body, so the cap can travel for a considerable distance down the capsule body before locking. This may have the effect of a piston in trapping and pressurizing the capsule. The excess gas can escape through the gap between the cap and the body, and vents may be provided in this region so as to facilitate the escape of excess pressure. Alternatively, the capsule may utilize a particularly tight locking mechanism rather than vents

[0110] In an embodiment, the capsule is banded by applying a band of polymer solution around the junction between the cap and body. The polymer solution can be a solution of the same polymer as the capsule cap and/or body in a solvent therefor. Banding can provide a smooth capsule surface for coating, which may prevent movement between the cap and body of the capsule.

[0111] When preparing the filled capsule that is filled with the composition comprising compound A, it is preferred that the composition is in a liquid form at least during the encapsulation process. In an embodiment, the final capsule contains the composition in the liquid form. In an embodiment, the final capsule contains the composition in semi-solid form at room temperature.

[0112] The dosage and frequency (single or multiple doses) of compounds (e.g., Compound A) administered for the treatment of CCM or Devic's disease can vary depending upon a variety of factors, including route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; presence of other diseases or other health-related problems; kind of concurrent treatment; and complications from any disease or treatment regimen. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds disclosed herein.

[0113] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

Method of Administration

[0114] The administration of the pharmaceutical formulation including ROCK2 inhibitors (e.g., compound A) for the treatment of CCM or Devic's disease can be carried out via oral

administration. In certain aspect, the route of administration is oral and the pharmaceutical formulation is provided in the form of capsules, such as soft elastic or hard gelatin capsules.

Method of Treatment

[0115] The present disclosure provides a method for the treatment of CCM, wherein the method comprises orally administering to a subject in need thereof an effective amount of a ROCK2 inhibitor as disclosed herein or a pharmaceutically acceptable salt thereof, in the formulations provided herein.

[0116] Cerebral cavernous malformations (CCMs)—also known as cavernomas and cavernous angiomas—are abnormal clusters of closely packed capillaries that form lesions in the brain, spinal cord, or other parts of the body. The lesions contain slow-moving or clotted blood. The cavernous malformations are characterized by multiple distended “caverns” of blood-filled vasculature through which the blood flows very slowly. Vessels of a cavernous malformation lesion lack the proper junctions between neighboring cells as well as the necessary structural support from smooth muscle and stretchable material (elastin). These properties cause cavernous malformations to leak. Leakage (bleeding) from these vascular lesions is an underlying cause of clinical symptoms associated with the illness. Most often located in the brain, cavernous malformations can also present in the spinal cord, on the skin, and more rarely in the retina.

[0117] Lesions in the brain and spinal cord are particularly fragile and likely to bleed. CCMs in the brain can cause: bleeding in the brain (hemorrhagic stroke), seizures, headaches, back pain, hearing or vision changes and paralysis. CCMs can be fatal, particularly if they cause severe bleeding in the brain.

[0118] CCMs are present in approximately 0.2% of the general population, and account for a large proportion (8-15%) of all brain and spinal vascular malformations. A majority of these people with CCM have only a single lesion, no family history of the disease, and no inherited mutation. These cases are termed ‘sporadic.’ Individuals with the familial (genetic) form of cavernous malformation typically develop multiple lesions and may be more likely to experience symptoms associated with the disorder. People of all ages may be affected by cavernous malformations, with children representing approximately 25% of all diagnosed individuals.

[0119] Cavernous malformations are typically diagnosed by magnetic resonance imaging (MRI). MRI might need to be repeated to check if the cavernous malformation has changed in size or bled recently or if new lesions have formed. Unlike with arteriovenous

malformations (AVMs), angiograms to visualize high blood flow are not performed, because blood in a cavernous malformation flows slowly and cannot be seen with angiography.

[0120] The present disclosure also provides a method for the treatment of Devic's disease, wherein the method comprises orally administering to a subject in need thereof an effective amount of a ROCK2 inhibitor as disclosed herein or a pharmaceutically acceptable salt thereof, in the formulations provided herein.

[0121] Devic's disease, also known as neuromyelitis optica (NMO), is a rare neurologic disorder that affects the eyes and spinal cord. It causes optic neuritis, a condition involving inflammation of the optic nerve that connects the eye with the brain, and that typically leads to vision loss in one or both eyes. Devic's disease also causes an inflammation of the spinal cord, called myelitis. This typically occurs at the same time as optic neuritis, but can occur before or after.

[0122] The hallmark symptom of Devic's disease is a sudden loss of vision in both eyes. Other symptoms may include: balance difficulties, difficulties with bladder or bowel function, muscle weakness in the arms and/or legs, numbness in the arms and legs, and sudden, brief and/or repetitive spasms in the arms and legs.

[0123] Devic's disease is characterized by simultaneous or consecutive attacks of acute optic neuritis (ON) and transverse myelitis (TM). In greater than about 80% of cases, Devic's disease is caused by pathogenetic IgG autoantibodies to aquaporin 4 (AQP4-IgG). Around 10–40% of individuals with Devic's disease who lack AQP4-IgG have IgG autoantibodies to myelin oligodendrocyte glycoprotein (MOG-IgG). AQP4-IgG-positive disease is primarily an autoimmune astrocytopathy, although secondary damage to oligodendrocytes and neurons occurs as a result of astrocyte dysfunction and loss and, probably, bystander inflammation. In contrast, primary demyelination is found in those with MOG-IgG. In a small subgroup of patients, the cause remains unknown (known as idiopathic NMO).

[0124] Devic's disease can occur at any age. The median age at onset was 40 years for patients with AQP4-IgG and 31 years for patients with MOG-IgG in two large European cohorts comprising mainly adults, but may be lower in Asian and Black patients positive for AQP4-IgG. Devic's disease is more common in women than in men, particularly in those with AQP4-IgG (male to female ratio 1:9 to 1:10). The female preponderance is much less pronounced in patients with seronegative NMO and in those with MOG-IgG.

EXAMPLES

Example 1: HCl formulation of Compound A (solid dispersion composition)

[0125] The lipid formulation was developed to enhance the absorption, exposure and performance of compounds of Formula I, and particularly Compound A and its salts, which may have challenging oral bioavailability. The formulation targets lymphatic uptake channels, a largely unsaturable uptake channel, permitting an alternative route for drug absorption. It also minimizes drug uptake via the hepatic portal vein, minimizing first-pass metabolism. Both attributes of the formulation may combine to increase drug exposure.

A. Formulation Excipients

[0126] Maisine® CC: This excipient's chemical name is glycerol mono-linoleate, which may enhance lymphatic absorption of lipophilic, poorly absorbed drugs, such as Compound A, increasing oral absorption whilst minimizing various toxicities (e.g. liver).

[0127] Oleic Acid: The fatty acid component of the formulation may also promote lymphatic drug uptake. The efficiency of fatty acid lymphatic uptake may be dependent on multiple factors, including chain length and saturation state, affecting their ability to form mixed micelles. During the digestion process, oleic acid (C18:1) interacts with lipid transporters, maximizing the efficiency of lipid uptake. Oleic acid signals through the CD36 receptor to enhance the formation of chylomicrons, whilst oleic acid-rich diets produce large chylomicrons, so maximizing drug loading capacity.

[0128] Gelucire® 43/01: Falling within the category of 'hard fat', Gelucire® 43/01 as an excipient may be used to ensure that the lipid formulations solidify at room temperature, ensuring physical stability. Gelucire® 43/01 is a long chain triglyceride, which during digestion releases long chain fatty acids (primarily C₁₂ to C₁₈), which have the right chain length to contribute to lymphatic absorption.

[0129] Sodium Oleate: The use of lipid-based surfactants in the formulation for lymphatic uptake can have variable results and have the potential to negatively affect the absorption. Therefore, is important to select a surfactant in the composition that offers the desired functionality without impacting performance. The performance of sodium oleate is evaluated based on the results of an in-vivo pharmacokinetic study.

B. Lipid solid dispersions

[0130] The use of lipid excipients to enhances the absorption of the API solid dispersions provided herein. We have demonstrated that the lipid composition containing fatty acids and lipid surfactants increased absorption versus an aqueous suspension in Beagle dogs (FIG. 1).

C. *In-vivo* Data Supporting Formulation Development

[0131] Compound A-HCl was formulated into the composition as a fine dispersion. Compound A-HCl API naturally exists as small, low density, non-static, drug particles (typical D90 sub 20 micron). Their dispersion in lipids was initially achieved by adding solid Compound A-HCl to the cooled F4 formulation (ca. 40 °C) and sonicating with a high-powered sonic probe. The composition was evaluated in Beagle dogs in terms of in-vivo pharmacokinetics compared with a Compound A-HCl aqueous nano-suspension formulation.

[0132] Table 1: mean oral PK parameters for Compound A-HCl formulations in male and female beagles at 10 mg/kg

Test formulations	T1/2 Hours	Tmax hours	Cmax ng/ml	AUC last hr*ng/ml
Nanosuspension	0.9	1.8	911.2	3126.5
Lipid solid dispersion	1.5	4	3458.7	13107.6

D. Conclusions

[0133] The sodium oleate-based composition (F4) of Compound A-HCl as 50:50 solid dispersion had superior exposure to the aqueous nanosuspension and that of F4 alone (delivered dose fully solubilized). Therefore, this solid dispersion formulation was selected as the clinical formulation to move into clinical trial supply manufacturing.

[0134] After selection of the F4 50:50 lipid solid dispersion composition (see figure 1), it was found that the unit dose strength needed to be increased as the capsule fill volume needed to be reduced to offer efficiency in large-scale capsule manufacture given that a 00 capsule was selected as appropriate for the Compound A-HCl clinical development pathway with a target dose of 50 mg per capsule. To achieve this dose strength, the amount of Compound A-HCl to be solubilized in the composition needed to be increased by approximately 20%. Initial feasibility investigations increasing the solubilized load of Compound A-HCl were successful, however, on further scale-up a precipitation event occurred, potentially due to pro-longed heating. The F4 100% solid dispersion formulation manufacture does not have a long heating step. Consequently, to achieve the desired 50mg unit dose and avoid potential precipitation problems in the process, the F4 100% solid dispersion formulation was selected as the lead formulation. Feasibility testing for this formulation variant was successfully

conducted by the clinical trial supply CMO (Asymchem), supporting the F4 100% solid dispersion's selection as the lead formulation.

Example 2: HCl formulation of Compound A

A. Formulation Excipients

[0135] Maisine® CC: This excipients chemical comprises glycerol mono-linoleate which may be used to enhance lymphatic absorption of highly lipophilic poorly absorbed drugs, increasing oral absorption whilst minimizing various toxicities (e.g. liver).

[0136] Oleic Acid: Fatty acids have been studied to understand their impact on promoting lymphatic drug uptake. The efficiency of fatty acid lymphatic uptake may depend on multiple factors, including chain length and saturation state, affecting their ability to form mixed micelles. During the digestion process, oleic acid (C18:1) interacts fully with lipid transporters maximizing the efficiency of lipid uptake. Oleic acid signals through the CD36 receptor to enhance the formation of chylomicrons, whilst oleic acid-rich diets produce large chylomicrons, so maximizing drug loading capacity.

[0137] Gelucire® 43/01: Falling within the category of 'hard fat', Gelucire 43/01 is an excipient principally used to ensure that liquid lipid formulations solidify at room temperature, ensuring physical stability of highly saturated formulations. Gelucire 43/01 is a long chain triglyceride, which during digestion releases long chain fatty acids (C14 to C18), which have the right chain length to contribute to lymphatic absorption.

[0138] Sodium Oleate: The use of lipid-based surfactants in the formulation of drugs for lymphatic uptake can have variable results and is known to have the potential to negatively affect the absorption. Therefore, is important to select a surfactant in the composition that offers the desired functionality without impacting performance. Such selections can only be made based on the results of in-vivo pharmacokinetic studies as in section 3.0.

B. Lipid Molecular Dispersions versus Suspensions:

[0139] Compound A-HCl was evaluated for its solubility in a range of excipients and formulations to assess how the API might dissolve and what unit dose strengths may be accessible, with an initial focus on achieving stable molecular dispersions as instructed by the literature.

[0140] Formulations testing determined that oleic acid and Maisine® CC offered minimal solubility as solvents for Compound A-HCl, even on heating. To achieve pre-clinical (10 mg/ml and higher) and clinical (30 mg/ml) dose strengths, Compound A-HCl benefitted from

lipid-based surfactants allowing the compound to be fully solubilized within the composition. The most effective Compound A-HCl solubilizers for oleic acid and Maisine® CC were sodium oleate and sodium stearate (see tables 1 and 2). Cholic acid required the presence of sodium oleate or stearate to be considered for a functional role.

[0141] Subsequently preclinical formulations (10 mg/ml) were manufactured by heating various oleic acid and Maisine® CC compositions to approximately 130 °C with various lipid-compatible surfactants. Compound A-HCl was added with heating and stirring until solubilized. Lastly, Gelucire® 43/01 was added and the composition was allowed to cool and solidify. Initial formulations were evaluated in in-vivo pharmacokinetic models in rats and compared with the alternative Compound A-HCl nano-suspension formulation.

C. Rat Compositions:

[0142] **Table 2.** Composition of preclinical formulations administered to rats in oral pharmacokinetic studies (see also, FIGS. 2 and 3)

Component	F4 HCl salt	F5 HCl salt	F6 HCl salt
Compound A Solid dispersion	0.00%	0.00%	0.00%
Compound A Molecular dispersion	1.19%	1.19%	1.15%
Oleic acid	33.00%	33.00%	32.02%
Cholic acid	0.00%	0.00%	2.97%
Gelucire® 43/01	29.81%	29.81%	28.92%
Sodium Stearate	0.00%	3.00%	0.00%
Sodium Oleate	3.00%	0.00%	2.91%
Maisine® cc	33.00%	33.00%	32.02%
Total	100.00%	100.00%	100.00%
Solubility	Fully soluble	Fully soluble	Fully soluble

[0143] **Table 3:** mean oral PK parameters for Compound A-HCl formulations in SD rats at 50 mg/kg (F4 , F5 and F6).

Test article	T1/2 hours	Tmax hours	Cmax ng/ml	AUC last hr*ng/ml
Nanosuspension	3.56	4.33	1759.18	16929.11
F4	6.23	5.67	2108.35	29445.75
F5	6.47	6.00	2241.74	30990.92
F6	8.55	6.33	1912.34	25502.54

D. Beagle Dog Compositions and Results

Table 4.

Component	F4 HCl salt	F4a HCl salt	F5 HCl salt	F6 HCl salt
Compound A Solid dispersion	0.00%	0.00%	0.00%	0.00%
Compound A Molecular dispersion	1.20%	1.20%	1.17%	1.17%
Oleic acid	32.86%	16.42%	31.90%	31.90%
Cholic acid	0.00%	0.00%	2.92%	2.92%
Gelucire® 43/01	30.10%	30.08%	29.22%	29.22%
Sodium Stearate	0.00%	0.00%	2.89%	0.00%
Sodium Oleate	2.98%	3.04%	0.00%	2.89%
Maisine® cc	32.86%	49.26%	31.90%	31.90%
Total	100.00%	100.00%	100.00%	100.00%
Solubility	Fully soluble	Fully soluble	Fully soluble	Fully soluble

[0144] Table 5: mean oral PK parameters for Compound A-HCl formulations in beagles at 10 mg/kg (F4, F5 and F6)

Test formulation	T1/2 hours	Tmax hours	Cmax ng/ml	AUC last hr*ng/ml
Nanosuspension	0.82	1.33	663.80	2032.14
F4	0.57	2.67	2020.71	6268.92
F5	1.92	2.33	952.35	2821.77
F6	0.71	2.67	904.51	2988.85

[0145] Table 6: mean oral PK parameters for Compound A-HCl formulations in beagles at 10 mg/kg (F4 and F4a)

Test formulation	T1/2 hours	Tmax hours	Cmax ng/ml	AUC last hr*ng/ml
Nanosuspension	1.11	0.92	592.12	1262.94
F4 repeat	0.70	2.50	1342.42	5091.57
F4a	0.70	1.55	467.21	1958.52

E. Molecular/Solid Dispersion Combination Formulations

[0146] The sodium oleate-containing formulation (F4) gave equivalent exposure to a sodium stearate based formulation (F5) in rats (see table 2). However, in a higher mammalian species (Beagle Dog) the highest exposure was clearly achieved by the F4 formulation, suggesting that sodium oleate was not impeding the lymphatic uptake properties of the lipid composition (see FIGS. 3 to 4). Halving the amount of oleic acid (F4a) had no benefit in improving absorption (see FIG. 4).

[0147] As a result, F4 was selected as a lead prototype formulation composition. However, F4 offered limited unit dose strengths in a size 00 capsule (ca. 15-20 mg) when the entire dosage was solubilized. Therefore, to investigate the viability of higher unit dose strengths in clinical compositions for a size 00 capsule, it was decided to assess how the integration of an additional solid dispersion quantity of Compound A-HCl into the F4 formulation would affect pharmacokinetic parameters for Compound A-HCl.

[0148] The F4 composition, which was selected based on its improved PK performance in the rat and dog, was then studied in-vivo such that various percentages of the delivered dose of Compound A-HCl were formulated as a fine dispersion. Compound A-HCl naturally forms small, low density, non-static drug particles (typical D₉₀ less than 20 micron). Their dispersion in lipids was achieved by adding solid Compound A-HCl to the cooled F4 formulation (ca. 40 deg C) and sonicating with a high-powered sonic probe. Both 50:50 and 100% solid dispersion F4-based lipid formulations were produced, and their pharmacokinetic performance was compared to F4.

F. Conclusion

[0149] The sodium oleate-based molecular dispersion formulation of Compound A-HCl (F4) containing an additional equal quantity of solid dispersion of Compound A-HCl (50% of the delivered dose in solution – 50% of the delivered dose in suspension) in the formulation had a superior exposure profile to the F4 formulation, purely containing Compound A-HCl as a molecular dispersion. The results were confirmed in multiple experiments across multiple species and multiple doses.

Example 3

[0150] To further improve the capacity of the formulation for the API (Compound A-HCl salt), a further composition was prepared. The dosage form comprises of a hard gelatin capsule where 50% of the API is in solid dispersion. The strength is 50 mg/capsule. The

capsules size is 00#. The formulation components and amounts are provided in Table 7, below:

Table 7: Composition of Compound A-HCl Capsules

Ingredient	Amount per capsule
Comp. A- HCl	55.6mg ^a (6.95 %)
Gelucire 43/01	129.9mg (16.24%)
Maisine CC	298.9mg (37.36%)
Oleic Acid	298.9mg (37.36%)
Sodium oleate	16.7mg (2.09%)
Total	800mg
00# Empty Hard Gelatin Capsule	1

^a The strength of Compound A capsules, 50mg is calculated based on the freebase.

[0151] The tissue distribution when this formulation is given orally to the test animals is shown in Figure 6.

Example 3. Mouse model for CCM

[0152] An evaluation of a ROCK2 inhibitor, Compound A, is performed according to the scheme presented in Figure 7.

[0153] Animals: C57BL/6J mice are purchased or bred in-house. Gender and sex matched mice are used for AAV infection at P35. Mice are housed under standard pathogen-free conditions with a 12 h light/dark schedule and provided with food and water ad libitum, temperature is between 20 and 24 °C and relative humidity between 45 and 65 rH. All mouse experiments and cares are conducted in accordance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) at the Chinese Institute of Brain Research, Beijing.

[0154] The mice are separated into the following cohorts:

1. Sham control: Total 20 sham-operated mice are kept without any treatment until sacrifice at either P63 or P77.

2. Vehicle: Total 20 mice are orally administered vehicle [0.3% Tween-80 (w/v)] in a volume of 10 mL/kg once daily.
3. Comp. A, 150 mg/Kg: Mice are orally administered vehicle supplemented with Compound A at a dose of 150 mg/kg in a volume of 10 mL/kg once daily.
4. Comp. A, 300 mg/Kg: Mice are orally administered vehicle supplemented with Compound A at a dose of 300 mg/kg in a volume of 10 mL/kg once daily.

[0155] Plasmid construction, adeno-associated virus packaging and injection: The construct pAAV-CAG-MAP3K3^{I441M}-P2A-eGFP and helper vector (pAdDeltaF6) are prepared. The construct leading the endothelial cell-specific infection, pXX2-187-NRGTEWD (BR1), was provided. These constructs are used for generation of AAV-BR1-MAP3K3^{I441M}-P2A-eGFP. Mice are injected with the purified viral particles (3×10^{11} genome copies per mouse) through the superficial temporal vein at P35.

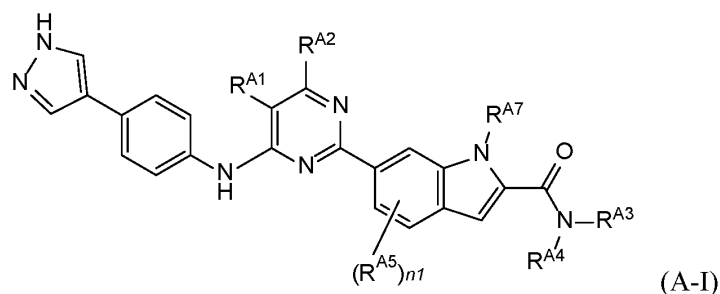
[0156] MRI evaluation: MRI scanning is performed on a Bruker 7.0T MRI Scanner. The mice are under anesthetization using 5% isoflurane/95% oxygen for induction, then 2% isoflurane/98% oxygen for maintenance while undergoing MRI. The parameters for MRI are as follows: repetition time: 350 ms, echo time: 33 ms, RARE factor: 4, field of view: 21x21 mm, acquisition matrix: 256x256, and slice thickness: 0.5 mm. The number of lesions are quantified from T₂-weighted images. As demonstrated by MRI, the mice cohorts receiving Compound A have a marked reduction in lesions compared to the Vehicle cohort, that is dose dependent.

[0157] Measurement of CCM symptom: Before perfusion, 200 μ L of blood are withdrawn through the tail vein and transferred to a EDTA tube containing K₂EDTA, followed by freezing via dry ice. 50 mL of ice-cold 1xPBS is used to perfuse trans-cardiacally a mouse sitting on ice to wash away blood. The brain is removed immediately after perfusion. Half brain is snap frozen using dry ice. The other half brain is immersion-fixed in 10% neutral-buffered formalin for sectioning. Prussian blue staining is performed to determine the percentage of bleeding lesions. To visualize the blood vessel, anti-CD31 antibody with Alexa-594 conjugated antibody is used. The size of the GFP/CD31-positive cells are measured and compared with CD31-positive cells to determine if the treatment reverses the enlarged endothelial cells caused by mutant human MAP3K3. To quantify the pMLC-expressing cells, anti-pMLC antibody with Alexa-594 secondary antibody are used to quantify the percentage of infected cells that express pMLC. The size of the GFP/CD31-positive cells as compared to CD31-positive cells demonstrate that Compound A reverses the enlarged endothelial cells caused by mutant human MAP3K3.

[0158] Isolation of brain endothelial cells: Brain endothelial cells are isolated by enzymatic digestion followed by separation using magnetic-activated cell sorting. Mice are anesthetized with isoflurane and perfused with sterile PBS. Brains are removed and digested by 1 mg/mL of collagenase/dispase and 0.02mg/mL of DNaseI in complete DMEM for 10 minutes at 37 °C with gentle shaking. The digestion is then passed through a 70 µm cell strainer. Cells are then centrifuged, resuspended, and incubated with anti-mouse CD31-conjugated microbeads for 15 minutes at 4 °C. Microbead-bound cells are washed and separated using MACS MS columns according to the protocol from the vendor (Miltenyi Biotec). Cells bound to the magnetic column are eluted and centrifuged for total protein extraction.

WHAT IS CLAIMED:

1. A method for the treatment of cerebral cavernous malformation (CCM), comprising orally administering to a patient in need thereof a pharmaceutical formulation comprising a therapeutically effective amount of a ROCK2 inhibitor.
2. The method of claim 1, wherein the ROCK2 inhibitor has the structure of Formula (A-I):



or a pharmaceutically acceptable salt thereof, wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -

$\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$;

R^{A3} and R^{A4} are each independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, 3- to 10-membered heterocyclyl, $\text{C}_6\text{-C}_{10}$ aryl, 5- to 14-membered heteroaryl, $\text{C}_6\text{-}_{12}$ aralkyl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$;

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, $-\text{OR}^{\text{A11}}$, oxo, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, halo, $-\text{CN}$, $\text{C}_1\text{-C}_3$ perfluoro alkyl, oxo, $-\text{OR}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-\text{O}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-\text{C}(=\text{O})-\text{R}^{\text{A11}}$, $-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, and $-\text{NR}^{\text{A11}}-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$;

n/l is 0 to 3;

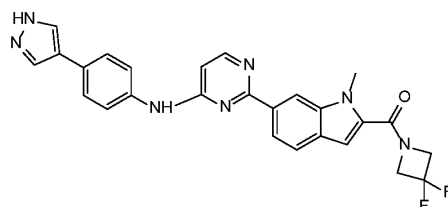
R^{A7} is independently selected from the group consisting of H, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{OR}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})-\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{R}^{\text{A11}}$, $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{OR}^{\text{A11}}$, and $-(\text{C}_1\text{-C}_6 \text{ alkyl})_{x/l}-\text{C}(=\text{O})\text{NR}^{\text{A11}}\text{R}^{\text{A12}}$;

each x/l is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

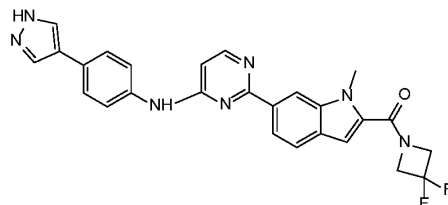
or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

3. The method of claim 2, wherein the ROCK2 inhibitor has the formula:



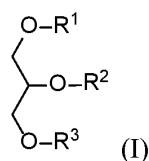
or a pharmaceutically acceptable salt thereof.

4. A method for the treatment of cerebral cavernous malformation (CCM), comprising orally administering to a patient in need thereof a pharmaceutical formulation comprising:
(e) about 1 to about 15 wt % of a compound having a structure:



or a pharmaceutically acceptable salt thereof;

- (a) about 15 to 50 wt% of a fatty acid component comprising saturated and/or unsaturated C₈-C₂₄ fatty acids and/or a pharmaceutically acceptable salt thereof;
(b) about 30 to 50 wt% of a first glyceride component comprising one or more glyceride compounds having a structure of Formula (I)

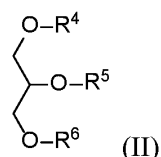


wherein:

each R^1 , R^2 , and R^3 is independently hydrogen or $-C(O)-R^A$;

each R^A is independently C_7 - C_{21} alkenyl comprising one or two double bonds,
provided that at least one of R^1 , R^2 , and R^3 is not hydrogen; and

- (c) about 10 to 35 wt% of a second glyceride component comprising one or more glyceride compounds having a structure of Formula (II)



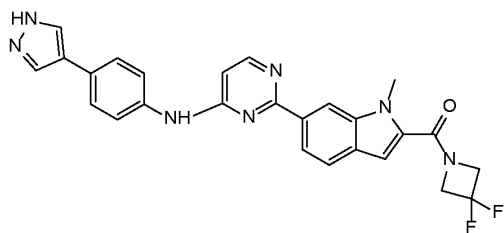
wherein:

each R^4 , R^5 , and R^6 is independently hydrogen, or $-C(O)-R^B$;

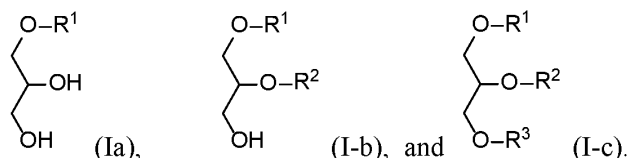
each R^B is independently C_7 - C_{21} alkyl,

provided that at least one of R^4 , R^5 , and R^6 is not hydrogen.

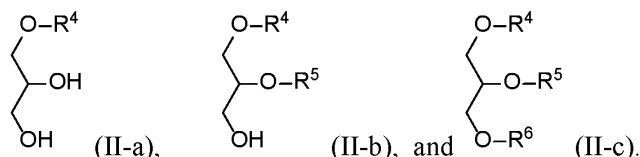
5. The method of claim 4, wherein the API comprises an HCl salt of



6. The method of claim 4 or claim 5, wherein the fatty acid component comprises a saturated or unsaturated C_{12} - C_{18} fatty acid and/or a pharmaceutically acceptable salt thereof.
7. The method of claim 4, wherein the fatty acid component comprises an oleic acid, sodium oleate, or a combination thereof.
8. The method of claim 4, wherein the first glyceride component comprises the one or more glyceride compounds having a structure of Formula (I) and each R^A is independently C_7 - C_{21} alkenyl comprising one or two double bonds.
9. The method of claim 4, wherein the first glyceride component comprises one or more glyceride compounds having the structures:



10. The method of claim 9, wherein a ratio of the compound of Formula (I-a), the compound of Formula (I-b), and the compound of Formula (I-c) is about 32 to 52 : 40 to 55 : 5 to 20.
11. The method of claim 4, wherein the second glyceride component comprises one or more compounds having a structure of Formula (II) and each R^B is independently C₇-C₂₁ alkyl.
12. The method of claim 4, wherein the second glyceride component comprises the one or more glyceride compounds having one of the following structures:



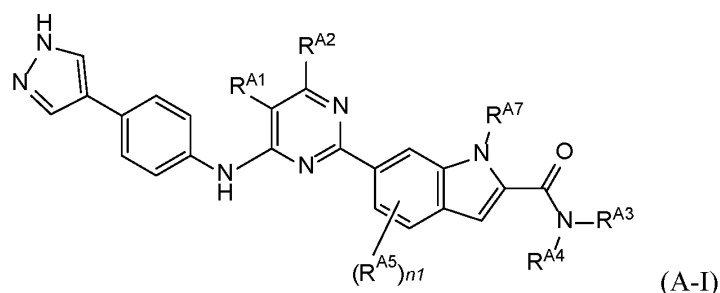
13. The method of claim 4, wherein the API is formulated in a solid dispersion, in a solution, or as combination thereof.
14. The method of claim 4, wherein the pharmaceutical formulation comprises the compound having a structure
-
- or a pharmaceutically acceptable salt thereof in an amount of about 1-10 wt % of the pharmaceutical formulation, or from about 2-8 wt % of the pharmaceutical formulation, or from about 5-7 wt % of the pharmaceutical formulation.

15. The method of claim 4, wherein the pharmaceutical formulation comprises the fatty acid component in an amount of about 20 to 45 wt%, about 30 to 45 wt%, about 35 to 45 wt%, or about 35 to 40 wt%, based on the weight of the pharmaceutical formulation.
16. The method of claim 4, wherein the pharmaceutical formulation comprises:

a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acid in an amount of 12 to 48 wt%, about 15 to 45 wt%, about 25 to 40 wt%, about 30 to 40 wt%, or about 35 to 40 wt%; and

a sodium salt of a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acids in an amount of about 1 to 5 wt%, or about 2 to 4 wt%, or about 2 to 3 wt%,
based on the weight of the pharmaceutical formulation.

17. The method of claim 4, wherein the pharmaceutical formulation comprises the first glyceride component in an amount of about 30 to 45 wt%, or about 32 to 40 wt%, or about 35 to 40 wt% based on the weight of the pharmaceutical formulation.
18. The method of claim 4, wherein the pharmaceutical formulation comprises the second glyceride component in an amount of about 10 to 30 wt%, or about 10 to 20 wt%, or about 15 to 18 wt% based on the weight of the pharmaceutical formulation.
19. The method of claim 4, wherein the pharmaceutical formulation comprises:
Compound A, or a pharmaceutically acceptable salt in an amount of about 1-15 wt %;
a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acid in an amount 12 to 48 wt%;
a sodium salt of a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acids in an amount of about 1 to 5 wt%;
the first glyceride component in an amount of about 30 to 50 wt%; and
the second glyceride component in an amount of about 10 to 35 wt%,
based on the weight of the pharmaceutical formulation.
20. A method for the treatment of Devic's disease, comprising orally administering to a patient in need thereof a pharmaceutical formulation comprising a therapeutically effective amount of a ROCK2 inhibitor.
21. The method of claim 20, wherein the ROCK2 inhibitor has the structure of Formula (A-I):



or a pharmaceutically acceptable salt thereof,

wherein:

R^{A1} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

R^{A2} is selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, -(C₁-C₆ alkyl)_x-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_x-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_x-C(=O)OR^{A11};

alternatively, R^{A1} and R^{A2} are taken together to form a 5- or 6-membered saturated or unsaturated fused ring which may contain from 0 to 2 ring heteroatoms selected from the group consisting of N, O, and S, and which is unsubstituted or substituted with 1 to 3 substituents selected from the group consisting of C₁-C₆ alkyl, halo, -CN, -OH, oxo, -O-(C₁-C₆ alkyl), -O-(C₁-C₆ alkyl)-OH, -O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, C₁-C₃ perfluoro alkyl, -NR^{A11}-(C₁-C₆ alkyl)NR^{A11}R^{A12}, and -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11};

R^{A3} and R^{A4} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, 3- to 10-membered heterocyclyl, C₆-C₁₀ aryl, 5- to 14-membered heteroaryl, C₆₋₁₂ aralkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆

alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12},

alternatively R^{A3} and R^{A4} are taken together with the nitrogen to which they are attached to provide (i) a 4- to 6-membered heterocyclic ring having from 0 to 2 additional ring to heteroatoms selected from N, O and S, or (ii) a 5- to 10-membered hetero bicyclic ring system having from 0 to 3 additional ring heteroatoms selected from N, O and S; wherein the heterocyclic ring or the bicyclic ring system are unsubstituted or are substituted with from 1 to 4 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, -OR^{A11}, oxo, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11},

the dotted lines represent optional double bonds;

each R^{A5} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, halo, -CN, C₁-C₃ perfluoro alkyl, oxo, -OR^{A11}, -O-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-OR^{A11}, -NR^{A11}R^{A12}, -O-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -O-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, -C(=O)-R^{A11}, -C(=O)OR^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12}, -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, and -NR^{A11}-(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11};

nI is 0 to 3;

R^{A7} is independently selected from the group consisting of H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -(C₁-C₆ alkyl)-OR^{A11}, -(C₁-C₆ alkyl)-NR^{A11}R^{A12}, -(C₁-C₆ alkyl)_{x/l}-C(=O)R^{A11}, -(C₁-C₆ alkyl)_{x/l}-C(=O)OR^{A11}, and -(C₁-C₆ alkyl)_{x/l}-C(=O)NR^{A11}R^{A12},

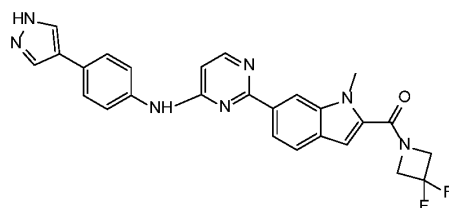
each *xI* is independently selected from 0 and 1; and

each R^{A11} and R^{A12} are independently selected from the group consisting of H and C₁-C₆ alkyl;

or alternatively, R^{A11} and R^{A12} are taken together when both are attached to the same nitrogen to form a 4- to 7- membered heterocyclic ring having from 0 to 2 additional ring heteroatoms selected from the group consisting of N, O and S, and which

heterocyclic ring is unsubstituted or is substituted with 1 to 3 substituents selected from the group consisting of halo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₇ cycloalkyl, -CN, -NH₂, C₁-C₃ perfluoro alkyl, -OH, -O-(C₁-C₆ alkyl), and -(C₁-C₆ alkyl)-OH.

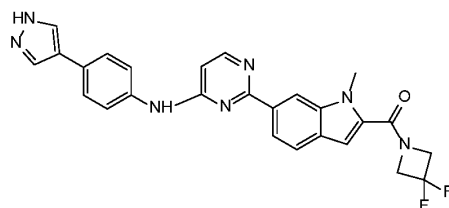
22. The method of claim 21, wherein the ROCK2 inhibitor has the formula:



or a pharmaceutically acceptable salt thereof.

23. A method for the treatment of Devic's disease, comprising orally administering to a patient in need thereof a pharmaceutical formulation comprising:

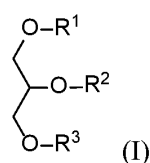
(a) about 1 to about 15 wt % of a compound having a structure:



or a pharmaceutically acceptable salt thereof;

(b) about 15 to 50 wt% of a fatty acid component comprising saturated and/or unsaturated C₈-C₂₄ fatty acids and/or a pharmaceutically acceptable salt thereof;

(c) about 30 to 50 wt% of a first glyceride component comprising one or more glyceride compounds having a structure of Formula (I)

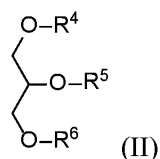


wherein:

each R¹, R², and R³ is independently hydrogen or -C(O)-R^A;

each R^A is independently C₇-C₂₁ alkenyl comprising one or two double bonds, provided that at least one of R¹, R², and R³ is not hydrogen; and

- (d) about 10 to 35 wt% of a second glyceride component comprising one or more glyceride compounds having a structure of Formula (II)



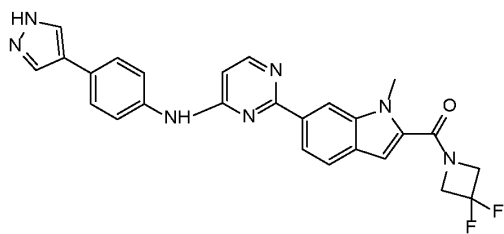
wherein:

each R^4 , R^5 , and R^6 is independently hydrogen, or $-C(O)-R^B$;

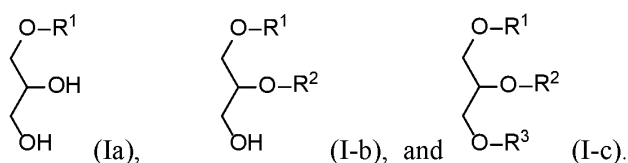
each R^B is independently C_7-C_{21} alkyl,

provided that at least one of R^4 , R^5 , and R^6 is not hydrogen.

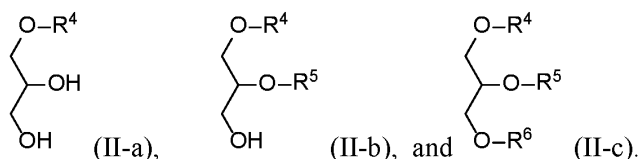
24. The method of claim 23, wherein the API comprises an HCl salt of



25. The method of claim 23 or claim 24, wherein the fatty acid component comprises a saturated or unsaturated $C_{12}-C_{18}$ fatty acid and/or a pharmaceutically acceptable salt thereof.
26. The method of claim 23, wherein the fatty acid component comprises an oleic acid, sodium oleate, or a combination thereof.
27. The method of claim 23, wherein the first glyceride component comprises the one or more glyceride compounds having a structure of Formula (I) and each R^A is independently C_7-C_{21} alkenyl comprising one or two double bonds.
28. The method of claim 23, wherein the first glyceride component comprises one or more glyceride compounds having the structures:



29. The method of claim 28, wherein a ratio of the compound of Formula (I-a), the compound of Formula (I-b), and the compound of Formula (I-c) is about 32 to 52 : 40 to 55 : 5 to 20.
30. The method of claim 23, wherein the second glyceride component comprises one or more compounds having a structure of Formula (II) and each R^B is independently C₇-C₂₁ alkyl.
31. The method of claim 23, wherein the second glyceride component comprises the one or more glyceride compounds having one of the following structures:



32. The method of claim 23, wherein the API is formulated in a solid dispersion, in a solution, or as combination thereof.
33. The method of claim 23, wherein the pharmaceutical formulation comprises the compound having a structure of
-
- or a pharmaceutically acceptable salt thereof in an amount of about 1-15 wt % of the pharmaceutical formulation, or from about 1-10 wt % of the pharmaceutical formulation, or from about 2-8 wt % of the pharmaceutical formulation, or from about 5-7 wt % of the pharmaceutical formulation.

34. The method of claim 23, wherein the pharmaceutical formulation comprises the fatty acid component in an amount of about 20 to 45 wt%, about 30 to 45 wt%, about 35 to 45 wt%, or about 35 to 40 wt%, based on the weight of the pharmaceutical formulation.
35. The method of claim 23, wherein the pharmaceutical formulation comprises:
a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acid in an amount of 12 to 48 wt%, about 15 to 45 wt%, of about 25 to 40 wt%, about 30 to 40 wt%, or about 35 to 40 wt%; and

a sodium salt of a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acids in an amount of about 1 to 5 wt%, or about 2 to 4 wt%, or about 2 to 3 wt%,
based on the weight of the pharmaceutical formulation.

36. The method of claim 23, wherein the pharmaceutical formulation comprises the first glyceride component in an amount of about 30 to 45 wt%, or about 32 to 40 wt%, or about 35 to 40 wt% based on the weight of the pharmaceutical formulation.
37. The method of claim 23, wherein the pharmaceutical formulation comprises the second glyceride component in an amount of about 10 to 30 wt%, or about 10 to 20 wt%, or about 15 to 18 wt% based on the weight of the pharmaceutical formulation.
38. The method of claim 23, wherein the pharmaceutical formulation comprises:
Compound A, or a pharmaceutically acceptable salt in an amount of about 1-15 wt %;
a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acid in an amount 12 to 48 wt%;
a sodium salt of a fatty acid having saturated or unsaturated C₁₂-C₁₈ fatty acids in an amount of about 1 to 5 wt%;
the first glyceride component in an amount of about 30 to 50 wt%; and
the second glyceride component in an amount of about 10 to 35 wt%,
based on the weight of the pharmaceutical formulation.