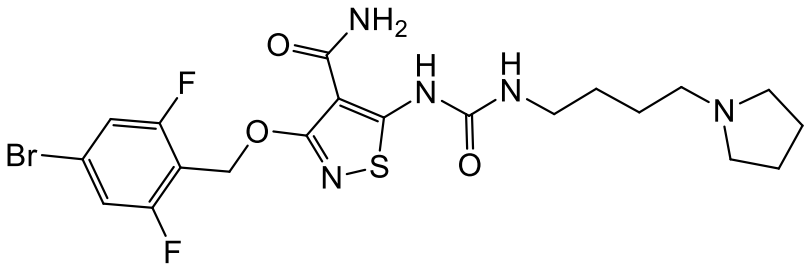
the anterior segment, while providing availability of an effective concentration of the active at the posterior segment.

[0007] The current embodiments provide novel formulations which circumvent the problems encountered in ocular delivery of existing topical therapeutic agents. The current invention accomplishes the combined effects of decreasing corneal and anterior segment drug exposure, while increasing posterior segment bioavailability. By lowering corneal exposure and increasing posterior segment bioavailability, the formulation of the current invention improves ocular tolerability and increases therapeutic index of the active agent.

SUMMARY ~~OF THE INVENTION~~

[0007a] In an aspect of the present disclosure, there is provided a topical, ocular, suspension formulation, comprising:

solid particles of an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof,

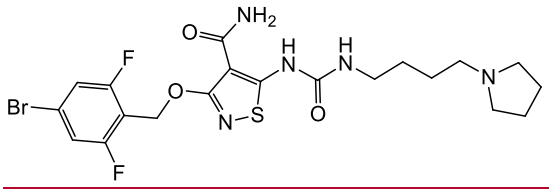
pharmaceutically acceptable excipients selected from hydroxy propyl methyl cellulose (HPMC) and carboxymethyl cellulose and salts thereof, and

a nonionic liquid polymer of the alkyl aryl polyether alcohol type,

wherein the active agent or the pharmaceutically acceptable salt is present in about 0.005% to about 5.0% w/v.

[0007b] In another aspect of the present disclosure, there is provided a topical, ocular, suspension formulation, comprising:

solid particles of an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof,

pharmaceutically acceptable excipients selected from hydroxy propyl methyl cellulose (HPMC) and carboxymethyl cellulose and salts thereof, and

about 0.3% - 1% w/v tromethamine,

about 2% glycerin,

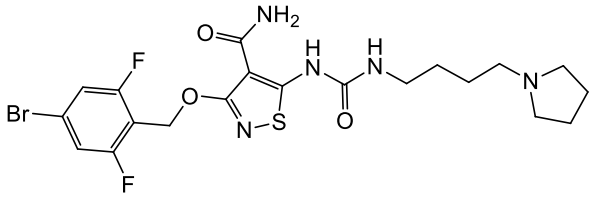
tyloxapol, and

poloxamer,

wherein the active agent or the pharmaceutically acceptable salt is present in about 0.005% to about 5.0% w/v.

[0007c] In a further aspect of the present disclosure, there is provided a topical ocular formulation, the formulation comprising:

(a) an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof;

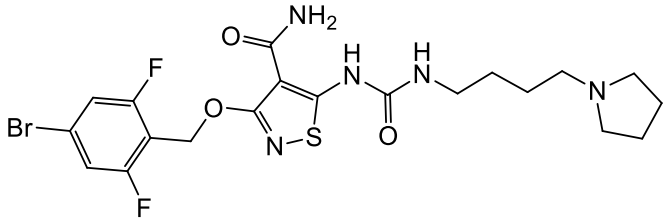
(b) carboxymethylcellulose or a salt thereof; and

(c) pharmaceutically acceptable excipients;

wherein the active agent or the pharmaceutically acceptable salt is present in 0.005% to 5.0% w/v such that the formulation forms a solution or a suspension.

[0007d] In another aspect of the present disclosure, there is provided a topical ocular formulation, comprising:

a. an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof;

b. 0.2% to 1% tromethamine;

c. poloxamer;

d. carboxymethyl cellulose or a salt thereof; and

e. pharmaceutically acceptable excipients;

wherein the active agent or the pharmaceutically acceptable salt is present in 0.1% to 2.0% w/v such that the formulation forms a suspension.

[0007e] In a further aspect of the present disclosure, there is provided a formulation disclosed herein, for use in treating and/or ameliorating a posterior segment disease of the eye, wherein the disease is selected from the group consisting of: diabetic retinopathy, age-related macular degeneration (AMD), pathologic choroidal neovascularization (CNV), pathologic retinal neovascularization, uveitis, retinal vein occlusion, ocular trauma, surgery induced edema, surgery induced neovascularization, cystoid macular edema, ocular ischemia, retinopathy of prematurity, Coat's disease, sickle cell retinopathy, and neovascular glaucoma.

[0007f] In another aspect of the present disclosure, there is provided a use of the formulation disclosed herein, in the manufacture of a medicament for treating and/or ameliorating a posterior segment disease of the eye, wherein the disease is selected from the group consisting of: diabetic retinopathy, age-related macular degeneration (AMD), pathologic choroidal neovascularization (CNV), pathologic retinal neovascularization, uveitis, retinal vein occlusion, ocular trauma, surgery induced edema, surgery induced neovascularization, cystoid macular edema, ocular ischemia, retinopathy of prematurity, Coat's disease, sickle cell retinopathy, and neovascular glaucoma.

[0008] The present ~~invention~~ disclosure relates to pharmaceutical formulations in form of a solution and/or a suspension, which lower exposure to the active agent in the anterior segment of the eye, for example the cornea, while increasing the bioavailability of the agent at the posterior segment of the eye, for example at the central choroid and/or the central retina.

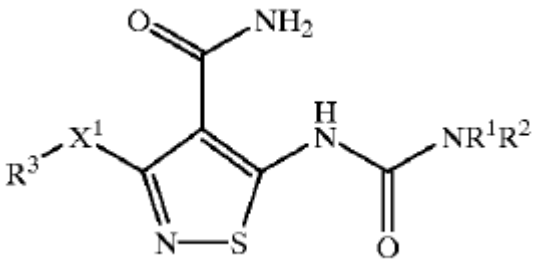
[0009] The ~~embodiment~~examples provide two distinct forms of formulation comprising the active agent, a solution and a suspension, with superior characteristics compared to another composition formed as a gel. The ~~embodiment~~examples provide that the active agent formulated as a solution and/or a suspension are superior compared to when the same active ingredient is formulated as a gel form in delivering the active at the posterior segment of eye, while lowering the exposure in the front of the eye. Increased levels of the active agent in the front of the eye limit ocular tolerability of topical drops containing the active. Therefore, reduced bioavailability of the active agent at the corneal or conjunctival surface, while maintaining adequate concentrations necessary to bind the relevant receptors at the target tissues and confer a therapeutic effect in the posterior segment of the eye, such as the choroid and the retina, are highly desirable and are the outcomes achieved from the specific ~~embodiment~~examples described here.

[0010] The present ~~invention~~ disclosure relates to formulations and methods useful for treating pathological states that arise or are exacerbated by ocular angiogenesis and vascular leakage, for example, in diabetic retinopathy (including background diabetic retinopathy, proliferative diabetic retinopathy and diabetic macular edema); age-related macular degeneration (AMD) (including neovascular (wet/exudative) AMD, dry AMD, and Geographic Atrophy); pathologic choroidal neovascularization (CNV) from any mechanism (*i.e.* high myopia, trauma, sickle cell disease; ocular histoplasmosis, angioid

streaks, traumatic choroidal rupture, drusen of the optic nerve, and some retinal dystrophies); pathologic retinal neovascularization from any mechanism (*i.e.*, sickle cell retinopathy, Eales disease, ocular ischemic syndrome, carotid cavernous fistula, familial exudative vitreoretinopathy, hyperviscosity syndrome, idiopathic occlusive arteriolitis, birdshot retinochoroidopathy, retinal vasculitis, sarcoidosis, or toxoplasmosis); uveitis; retinal vein occlusion (central or branch); ocular trauma; surgery induced edema; surgery induced neovascularization; cystoid macular edema; ocular ischemia; retinopathy of prematurity; Coat's disease; sickle cell retinopathy and/or neovascular glaucoma. The formulation of the current ~~invention~~ disclosure has, at least, one anti-angiogenic agent, anti-inflammatory agent, or anti-vascular permeability agent for use in treating angiogenic ocular disorders.

[0011] According to ~~embodiment~~examples of the ~~invention~~present disclosure, the active agent is a kinase inhibitor. Examples of some kinase inhibitors that can be used to bring about beneficial therapeutic results include inhibitors of receptor tyrosine kinases, for example, without being limiting, VEGFR, FGFR, Tie-2, and Ephrin kinase receptors.

[0012] The ~~embodiment~~examples of the current ~~invention~~ disclosure provide an ophthalmic formulation for treating ocular neovascularization with an active agent of Formula I:



(I)

or a pharmaceutically acceptable salt thereof; and pharmaceutically acceptable excipients; the active agent or the pharmaceutically acceptable salt is present in about 0.02% to about 0.6% w/v such that the formulation forms a solution or suspension, and where the active agent is identified as: X^1 is O or S; R^1 is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, —C(O)(C_1-C_{10} alkyl), —$(CH_2)_t$(C_6-C_{10} aryl), —$(CH_2)_t$(4-10 membered heterocyclic), —C(O)$(CH_2)_t$(C_6-C_{10} aryl), or —C(O)$(CH_2)_t$ (5-10 membered heterocyclic), where t is an integer from 0 to 5; the alkyl group optionally includes 1 or 2 hetero moieties selected from O, S and —N(R^6)— with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; the aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10

membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety or an anion of oxygen; the —$(CH_2)_t$— moieties of the foregoing R^1 groups optionally include a carbon—carbon double or triple bond where t is an integer from 2 to 5; and the foregoing R^1 groups, except H, are optionally substituted by 1 to 3 R^4 groups; R^2 is H; R^3 is —$(CH_2)_t$(C_6-C_{10} aryl), where t is an integer from 0 to 5; optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; the —$(CH_2)_t$— moieties optionally include a carbon—carbon double or triple bond where t is an integer from 2 to 5, and are optionally substituted by 1 to 5 R^4 groups; each R^4 is independently selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, —OR^5, —$C(O)R^5$, —$C(O)OR^5$, —$NR^6C(O)OR^5$, —$OC(O)R^5$, —$NR^6SO_2R^5$, —$SO_2NR^5R^6$, —$NR^6C(O)R^5$, —$C(O)NR^5R^6$, —NR^5R^6, —$S(O)_jR^7$ where j is an integer ranging from 0 to 2, —SO_3H, —$NR^5(CR^6R^7)_tOR^6$, —$(CH_2)_t$(C_6-C_{10} aryl), —$SO_2(CH_2)_t$(C_6-C_{10} aryl), —$S(CH_2)_t$(C_6-C_{10} aryl), —$O(CH_2)_t$(C_6-C_{10} aryl), —$(CH_2)_t$(5-10 membered heterocyclic), and —$(CR^6R^7)_mOR^6$, where m is an integer from 1 to 5 and t is an integer from 0 to 5; the alkyl group optionally contains 1 or 2 hetero moieties selected from O, S and —$N(R^6)$— with the proviso that two O atoms, two S atoms, or an O and S atom are not attached directly to each other; the aryl and heterocyclic R^4 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 5-10 membered heterocyclic group; 1 or 2 carbon atoms in the foregoing heterocyclic moieties are optionally substituted by an oxo (=O) moiety or an anion of oxygen; and the alkyl, aryl and heterocyclic moieties of the foregoing R^4 groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, —$NR^6SO_2R^5$, —$SO_2NR^5R^6$, —$C(O)R^5$, —$C(O)OR^5$, —$OC(O)R^5$, —$NR^6C(O)R^5$, —$C(O)NR^5R^6$, —NR^5R^6, —$(CR^6R^7)_mOR^6$ where m is an integer from 1 to 5, —OR^5 and the substituents listed in the definition of R^5; and each R^5, R^6, and R^7 is independently H or C_1-C_6 alkyl.

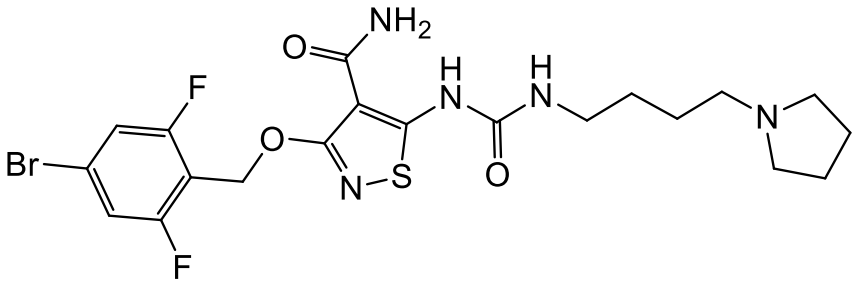
[0013] In a further ~~embodiment~~example of the current ~~invention~~disclosure, R^3 in Formula I is —$(CH_2)_t$(C_6-C_{10} aryl) where t is an integer from 1 to 3 and the R^3 group is optionally substituted by 1 to 4 R^4 groups.

[0014] In another ~~embodiment~~example, R^3 in Formula I of the current ~~invention~~ disclosure is a benzyl, optionally substituted by 1 to 4 substituents independently selected from halo and C_1-C_4 alkyl. R^3 in Formula I of the current ~~invention~~ disclosure is a benzyl substituted by 1 to 4 substituents independently selected from methyl, fluoro, chloro and bromo.

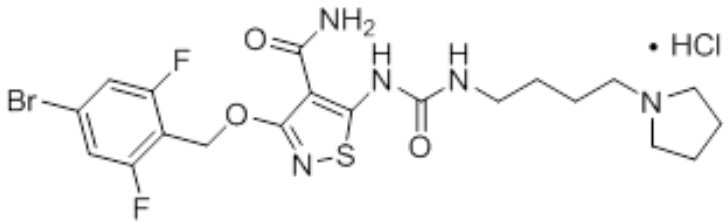
[0015] In some ~~embodiment~~examples, R^1 in Formula I of the current ~~invention~~ disclosure is —$(CH_2)_t$ (5-10 membered heterocyclic), where t is an integer from 0 to 5, optionally substituted by 1 or 2 substituents independently selected from C_1 -C_4 alkyl, hydroxy and hydroxymethyl.

[0016] The present disclosure provides heterocyclic moiety of the R^1 group in Formula I chosen from morpholino, pyrrolidinyl, imidazolyl, piperazinyl, piperidinyl, and 2,5-diaza-bicyclo[2.2.1]hept-2-yl, the t variable of the R^1 group ranges from 2 to 5, and the R^1 group is optionally substituted by one or more hydroxy groups.

[0017] For example, the heterocyclic moiety of the R^1 group in Formula I of the current ~~invention~~ disclosure is pyrrolidine.

[0018] In further ~~embodiment~~examples of the current ~~invention~~disclosure, the active agent is:  (II).

[0019] In some ~~embodiment~~examples of the current ~~invention~~disclosure, the active agent is a hydrochloride salt of compound of formula II, namely Compound-I:



(Compound-I).

[0020] The ~~embodiment~~examples of the current ~~invention~~ disclosure provide formulations of about 0.005% to about 5.0% w/v of the active agent of Formulae (I), (II), or a pharmaceutically acceptable salt thereof for example, Compound-I. In some ~~embodiment~~examples, the concentration of Compound-I or its free base (formula II) in the formulations is about 0.005% - about 0.01%, about 0.01% - about 0.05%, about 0.05% - about 0.1%, about 0.1% - about 0.2%, about 0.2% - about 0.3%, about 0.3% - about 0.4%, about 0.4% - about 0.5%, about 0.5% - about 0.6%, about 0.6% - about 0.7%, about 0.7% - about 0.8%, about 0.8% - about 0.9%, about 0.9% - about 1.0%, about 1.1 - about 2.0%, about 2.1 - about 3.0%, about 3.1 - about 4.0%, or about 4.1- about 5.0% w/v for topical administration. In some ~~embodiment~~examples the formulations include about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about

0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of Compound-I or its free base (formula II).

[0021] The present disclosure provides a solution of the active agent (*e.g.*, Compound-I), which includes one or more solubilizing agents.

[0022] The formulation comprising about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of Formulae (I), (II), or a pharmaceutically acceptable salt thereof, for example, Compound-I, includes a solubilizing agent. The solubilizing agent in the formulation may be cyclodextrin, for example, 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, ethylated-β-cyclodextrin, triacetyl-β-cyclodextrin, peracetylated-β-cyclodextrin, carboxymethyl-β-cyclodextrin, hydroxyethyl -β-cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl-β-cyclodextrin, glucosyl -β-cyclodextrin, maltosyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin, branched-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated-γ-cyclodextrin, trimethyl-γ-cyclodextrin, or combinations thereof.

[0023] In one ~~embodiment~~example, the solubilizing agent in the formulation is 2-hydroxypropyl-β-cyclodextrin or β-cyclodextrin sulfobutyl ether. The formulation comprises one or more of benzalkonium chloride (BAK), sodium chloride, and a pH adjusting agent.

[0024] In additional ~~embodiment~~examples, the formulation comprising about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of the active agent or a pharmaceutically acceptable salt thereof, includes a buffer, for example, tromethamine. In one ~~embodiment~~example, the formulation comprising about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of the active agent or a pharmaceutically acceptable salt thereof, includes about 0.3% - about 1.0% w/v tromethamine, and optionally further includes about 0.005% w/v benzalkonium chloride (BAK).

[0025] The present disclosure provides a formulation having a pH value of about 4.5 to about 7.5 at or under about 40 ^{o}C. In some ~~embodiment~~examples, the pH value of the formulation is between about pH 5.0 to about 7.0. In one ~~embodiment~~example the pH value of the formulation is about 6.0 at or under about 40 ^{o}C.

[0026] The current ~~embodiment~~examples provide use of a formulation of Compound-I or its free base (formula II) for the manufacture of a medicament for accessing posterior segment of the eye and/or for treating and/or ameliorating a posterior segment disease vasculopathic or inflammatory disease of the eye. These include for example, diabetic retinopathy (including background diabetic retinopathy, proliferative diabetic retinopathy and diabetic macular edema); age-related macular degeneration (AMD) (including neovascular (wet/exudative) AMD, dry AMD, and Geographic Atrophy); pathologic choroidal neovascularization (CNV) from any mechanism (*i.e.* high myopia, trauma, sickle cell disease; ocular histoplasmosis, angioid streaks, traumatic choroidal rupture, drusen of the optic nerve, and some retinal dystrophies); pathologic retinal neovascularization from any mechanism (*i.e.*, sickle cell retinopathy, Eales disease, ocular ischemic syndrome, carotid cavernous fistula, familial exudative vitreoretinopathy, hyperviscosity syndrome, idiopathic occlusive arteriolitis; birdshot retinochoroidopathy, retinal vasculitis, sarcoidosis and toxoplasmosis); uveitis; retinal vein occlusion (central or branch); ocular trauma; surgery induced edema; surgery induced neovascularization; cystoid macular edema; ocular ischemia; retinopathy of prematurity; Coat's disease; sickle cell retinopathy and/or neovascular glaucoma.

[0027] In some ~~embodiment~~examples, the exposure time of Compound-I is between 1 and 90 days. In some ~~embodiment~~examples, the dosage regimen involves several courses of topical ocular administration of a formulation comprising Compound-I to a subject for between 1 and 90 days. For example, the dosage regimen involves once daily, twice daily, three times daily or four times daily administration of the formulation for between 1 and 90 days. For example, the dosage regimen involves once, twice, three times, or four times administration of the formulation on alternate days (*i.e.*, on day 1, 3, 5, 7 etc.) for up to 90 days. For example, the dosage regimen involves administering once on day 1, once or twice on day 2 - day 90. For example, the dosage regimen involves administering once, twice, three times, or four times on day 1, followed by once daily for 2-90 days. For example, the dosage regimen involves administering once, twice, three times, four times on day 1, followed by once, twice, three times, or four times on alternate days (*i.e.*, on day 1, 3, 5, 7 etc.) for up to 90 days. For example, one dosage regimen involves once per day or twice per day for 1, 2, 3, 4, or 5 consecutive days. For twice or three daily dosage regimen, subjects receive topical ocular dose of a Compound-I formulation on days 1 and 4 approximately about 4, 6, or 8 hours apart. In another ~~embodiment~~example, subjects receive topical ocular doses of a Compound-I formulation approximately about 4, 6, or 8 hours

apart for four consecutive days. In some ~~embodiment~~examples, subjects receive one or two doses of topical ocular dose of Compound-I formulation per day for 5 consecutive days. In yet other ~~embodiment~~examples, subjects receive one or two doses of topical ocular dose of Compound-I formulation for 5-90 consecutive days. In some ~~embodiment~~examples, subjects receive one or two doses of topical ocular dose of Compound-I formulation for at least 25 consecutive days. In one ~~embodiment~~example, subjects receive one or two topical ocular doses for at least 90 consecutive days or more.

[0028] For example, a formulation comprising about 2 mg/mL BID of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 3 mg/mL BID of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 3 mg/mL QD of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 4 mg/mL BID of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 4 mg/mL QD of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 5 mg/mL BID of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 5 mg/mL QD of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 6 mg/mL BID of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples a formulation comprising about 6 mg/mL QD of Compound-I is administered to one eye or both eyes of a subject for between 1 and 90 days. The dosage regimen for between 1 and 90 days may be any of the regimens involving consecutive or alternate days described in the paragraph above.

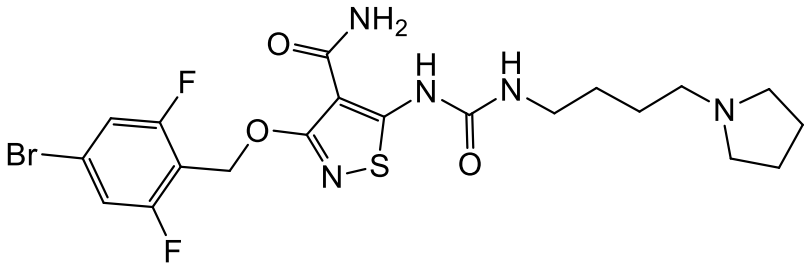
[0029] In some ~~embodiment~~examples, the formulation of Formula (II) or Compound-I is administered to one eye or both eyes of a subject. For example, about 0.2 % - about 0.6% (w/v) of the compound of Formula (II) or about 0.1% – 0.7 % (w/v) of Compound-I comprising formulation of the current disclosure is administered once a day (QD) or twice a day (BID) to one eye or both eyes of a subject for between 1 and 90 days. In some ~~embodiment~~examples, Formula (II) compound or Compound-I is complexed with a complexing agent, *e.g.*, cyclodextrin (*e.g.*, hydroxypropyl-β-cyclodextrin (HP-β-CD, KLEPTOSE® HPB)

CLAIMS

What is claimed is:

1. A topical, ocular, suspension formulation, ~~the formulation~~ comprising:

~~a.~~ solid particles of an active agent of Formula II:



(II),

~~b.~~ or a pharmaceutically acceptable salt thereof, ~~and~~

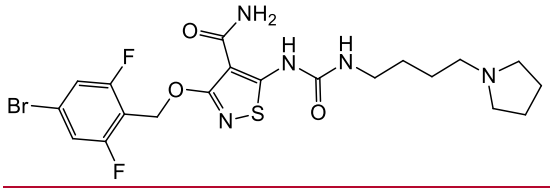
~~c.~~ ~~and~~ pharmaceutically acceptable excipients~~;~~ selected from hydroxy propyl methyl cellulose (HPMC) and carboxymethyl cellulose and salts thereof, and

a nonionic liquid polymer of the alkyl aryl polyether alcohol type,

wherein the active agent or the pharmaceutically acceptable salt is present in about 0.005% to about 5.0% w/v ~~such that the formulation forms a solution or a suspension~~.

2. ~~The formulation of claim 1, comprising a solubilizing agent~~ A topical, ocular, suspension formulation, comprising:

solid particles of an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof,

pharmaceutically acceptable excipients selected from hydroxy propyl methyl cellulose (HPMC) and carboxymethyl cellulose and salts thereof, and

about 0.3% - 1% w/v tromethamine,

about 2% glycerin,

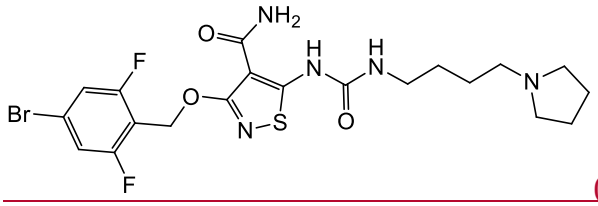
tyloxapol, and

poloxamer,

wherein the active agent or the pharmaceutically acceptable salt is present in about 0.005% to about 5.0% w/v.

3. A topical ocular formulation, the formulation comprising:

(a) an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof;

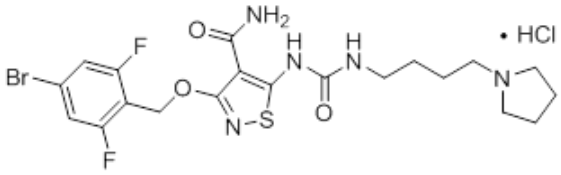
(b) carboxymethylcellulose or a salt thereof; and

(c) pharmaceutically acceptable excipients;

wherein the active agent or the pharmaceutically acceptable salt is present in 0.005% to 5.0% w/v such that the formulation forms a solution or a suspension.

4. The formulation of claim 3, wherein

the active agent is Compound-I



, and

the formulation comprises

a salt of carboxymethylcellulose;

0.2% to 1.0% w/v tromethamine;

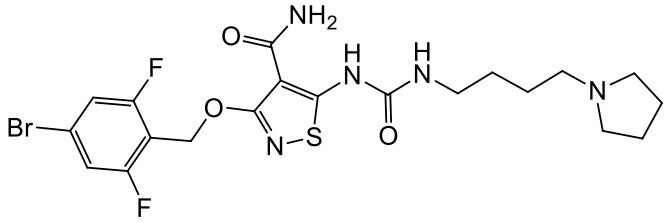
poloxamer; and

1% to 2.0% w/v glycerin; and

the formulation has a pH of about 6.0 at or under 40 °C.

5. A topical ocular formulation, comprising:

a. an active agent of Formula II:



(II),

or a pharmaceutically acceptable salt thereof;

b. 0.2% to 1% tromethamine;

c. poloxamer;

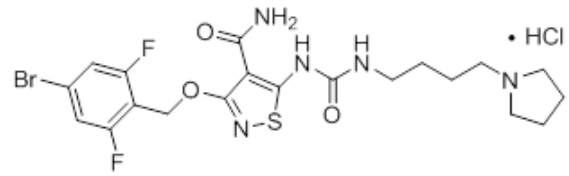
d. carboxymethyl cellulose or a salt thereof; and

e. pharmaceutically acceptable excipients;

wherein the active agent or the pharmaceutically acceptable salt is present in 0.1% to 2.0% w/v such that the formulation forms a suspension.

6. The formulation of claim 5, comprising

a. Compound-I:



;

b. a salt of carboxymethylcellulose;

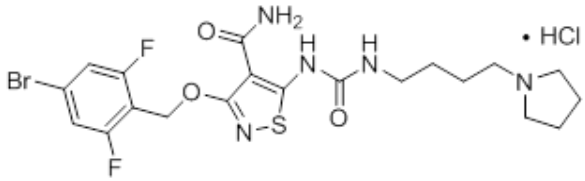
c. 0.2% to 1.0% w/v tromethamine;

d. poloxamer; and

e. 1% to 2% w/v glycerin; and

f. wherein the formulation has a pH of 6.0 at or under 40 °C.

7. The formulation of any one of claims 1-3 and 5, wherein the pharmaceutically acceptable salt is a hydrochloride salt provided by the formula:

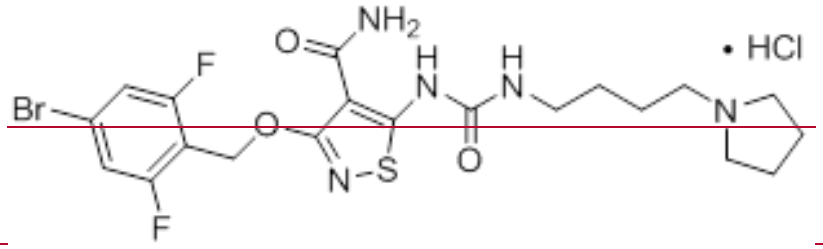


(Compound-I).

8. The formulation of any one of claims 1-7, further comprising a solubilizing agent.

~~3.~~9. The formulation of claim ~~2~~8, wherein the solubilizing agent is cyclodextrin selected from the group consisting of 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, ethylated-β-cyclodextrin, triacetyl-β-cyclodextrin, peracetylated-β-cyclodextrin, carboxymethyl-β-cyclodextrin, hydroxyethyl -β-cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl-β-cyclodextrin, glucosyl -β-cyclodextrin, maltosyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin, branched-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated-γ-cyclodextrin, trimethyl-γ-cyclodextrin, and combinations thereof.

~~4. The formulation of claim 3, wherein the pharmaceutically acceptable salt is a hydrochloride salt provided by the formula:~~



~~(Compound I).~~

~~5.~~10. The formulation of claim ~~3~~8, wherein the solubilizing agent is 2-hydroxypropyl-β-cyclodextrin or β-cyclodextrin sulfobutyl ether.

~~6.~~11. The formulation of any one of claims 1-4 and 7-10~~3~~, comprising about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of the active agent or a pharmaceutically acceptable salt thereof.

~~7.~~12. The formulation of any one of claims 1-11~~3~~, further comprising one or more of benzalkonium chloride (BAK), sodium chloride, and a pH adjusting agent.

~~8.~~13. The formulation of any one of claims 1, 3-4, and 7-12, comprising about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of the active agent or a pharmaceutically acceptable salt thereof, and about 0.3% - about 1% w/v tromethamine.

~~9.~~14. The formulation of any one of claims 1-4 and 7-13, comprising about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of the active agent or a pharmaceutically acceptable salt thereof, about 0.3% - about 1% w/v tromethamine, and about 0.005% w/v benzalkonium chloride (BAK).

~~10.~~15. The formulation of any one of claims 3-14~~1~~, further comprising a nonionic liquid polymer of the alkyl aryl polyether alcohol type~~having a pH value of about 4.5 to about 7.5 at or under about 40 °C~~.

~~11.~~16. The formulation of claim 15, wherein the nonionic liquid polymer of the alkyl aryl polyether alcohol type is tyloxapol~~having a pH value of about 6.0 at or under about 40 °C~~.

~~12.~~17. The formulation of any one of claims 1, 3, and 7-16, further comprising a hydrophilic non-ionic surfactant~~having a pH value of about 5.0 to about 7.0 at or under about 40 °C~~.

~~13.~~18. The formulation of claim 17, wherein the hydrophilic non-ionic surfactant is poloxamer~~formulation is suitable for accessing posterior segment of the eye and/or for treating and/or ameliorating ocular neovascularization~~.

19. The formulation of any one of claims 2, 4-6, and 18, wherein the poloxamer is poloxamer 407.

20. The formulation of any one of claims 1-4 and 5-19, wherein the active agent is present in about 0.1% to about 2.0% w/v.

21. The formulation of any one of claims 1-20 for use in treating and/or ameliorating a posterior segment disease of the eye, wherein the disease is selected from the group consisting of: diabetic retinopathy, age-related macular degeneration (AMD), pathologic choroidal neovascularization (CNV), pathologic retinal neovascularization, uveitis, retinal vein occlusion, ocular trauma, surgery induced edema, surgery induced neovascularization, cystoid macular edema, ocular ischemia, retinopathy of prematurity, Coat's disease, sickle cell retinopathy, and neovascular glaucoma.

~~14.~~22. Use of the formulation of any one of claims 1-20 in the manufacture of a medicament ~~suitable for accessing posterior segment of the eye and/or~~ for treating and/or ameliorating a posterior segment disease of the eye, wherein the disease is selected from the group consisting of: diabetic retinopathy, age-related macular

degeneration (AMD), pathologic choroidal neovascularization (CNV), pathologic retinal neovascularization, uveitis, retinal vein occlusion, ocular trauma, surgery induced edema, surgery induced neovascularization, cystoid macular edema, ocular ischemia, retinopathy of prematurity, Coat's disease, sickle cell retinopathy, and neovascular glaucoma.

~~15. The use according to claim 14, wherein the diabetic retinopathy is background diabetic retinopathy, proliferative diabetic retinopathy, or diabetic macular edema.~~

~~16. The use according to claim 14, wherein the AMD is neovascular AMD, dry AMD, or Geographic Atrophy.~~

~~17. The use according to claim 16, wherein the neovascular AMD is wet or exudative AMD.~~

~~18. The use according to claim 14, wherein the CNV is related to high myopia, trauma, sickle cell disease, ocular histoplasmosis, angioid streaks, traumatic choroidal rupture, drusen of the optic nerve, or some retinal dystrophies.~~

~~19. The use according to claim 14, wherein the pathologic retinal neovascularization is related to sickle cell retinopathy, Eales disease, ocular ischemic syndrome, carotid cavernous fistula, familial exudative vitreoretinopathy, hyperviscosity syndrome, idiopathic occlusive arteriolitis; birdshot retinochoroidopathy, retinal vasculitis, sarcoidosis, or toxoplasmosis.~~

~~20. The use according to claim 14, wherein retinal vein occlusion is central or branch occlusion.~~

~~21. The use according to claim 14, comprising administering the formulation 1, 2, 3, or 4 times daily on consecutive days or on alternate days.~~

~~22. The use according to claim 14, comprising administering the formulation 2 or 3 times daily on consecutive days or on alternate days.~~

~~23. The use according to claim 14, comprising administering twice daily on consecutive days or on alternate days the formulation containing about 0.005%, about 0.05%, about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 2.0%, about 3.0%, about 4.0%, or about 5.0% w/v of the active agent.~~

~~24. The use according to claim 23, wherein the formulation is administered to one eye or both eyes.~~

~~25. The use according to claim 23, wherein the formulation comprises a solubilizing agent.~~

~~26. The use according to claim 25, wherein the solubilizing agent is cyclodextrin selected from the group consisting of selected from the group consisting of 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin, randomly methylated-β-cyclodextrin, ethylated-β-cyclodextrin, triacetyl-β-cyclodextrin, peracetylated-β-cyclodextrin, carboxymethyl-β-cyclodextrin, hydroxyethyl -β-cyclodextrin, 2-hydroxy-3-(trimethylammonio)propyl-β-cyclodextrin, glucosyl -β-cyclodextrin, maltosyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin, branched-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated-γ-cyclodextrin, trimethyl-γ-cyclodextrin, and combinations thereof.~~

~~27. The use according to claim 26, wherein the solubilizing agent is 2-hydroxypropyl-β-cyclodextrin or β-cyclodextrin sulfobutyl ether.~~