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

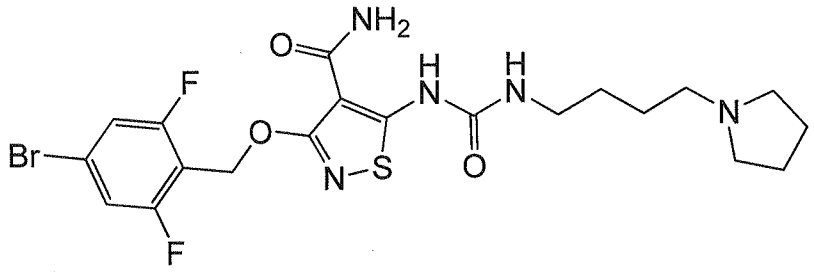
[0007] The current embodiments provide novel formulations which circumvent the problems encountered in ocular delivery of existing topical therapeutic agents. The current invention accomplishes the combined effects of decreasing corneal and anterior segment drug exposure, while increasing posterior segment 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~~

[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.

[0008a] In one aspect of the present disclosure, there is provided a topical ocular formulation, the formulation comprising:

a. an active agent of Formula II:



(II),

b. or a pharmaceutically acceptable salt thereof, and

c. and pharmaceutically acceptable excipients;

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.

[0008b] In another aspect of the present disclosure, there is provided a use of a formulation disclosed herein 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, 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.

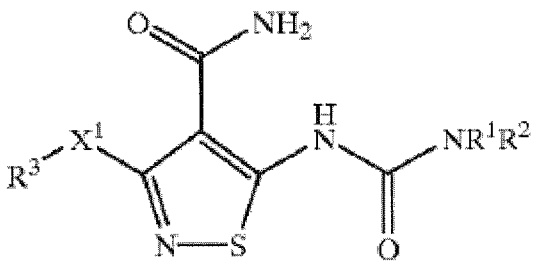
[0009] The embodiments provide two distinct forms of formulation comprising the active agent, a solution and a suspension, with superior characteristics compared to another composition formed as a gel. The embodiments provide that the active agent formulated as a solution and/or a suspension are superior 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 embodiments described here.

[0010] The present invention 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 embodiments of the current ~~invention~~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 embodiments 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 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.

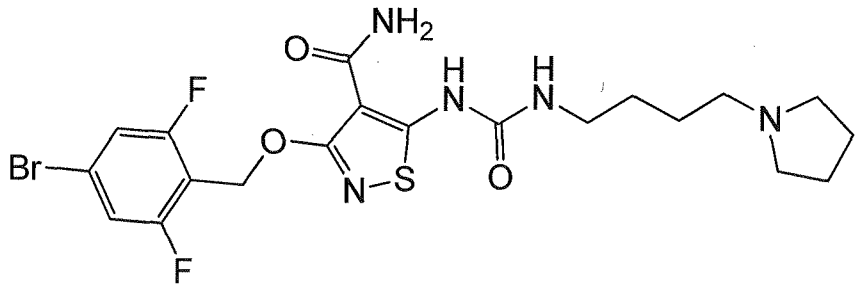
[0014] In another embodiment, R^3 in Formula I of the current ~~invention~~disclosure is a benzyl, optionally substituted by 1 to 4 substituents independently selected from halo and C_1 -C_4 alkyl. R^3 in Formula I of the current ~~invention~~disclosure is a benzyl substituted by 1 to 4 substituents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

[0015] In some embodiments, 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.

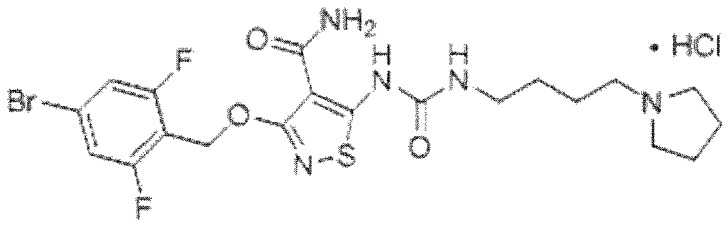
[0017] For example, the heterocyclic moiety of the R^1 group in Formula I of the current ~~invention~~disclosure is pyrrolidine.

[0018] In further embodiments of the current ~~invention~~disclosure, the active agent is:



(II).

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



(Compound-I).

[0020] The embodiments 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 embodiments, 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 embodiments 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