[0004] Direct injection into the eye, using conventional needles and syringes has been reported to be effective, but requires professional training and raises concerns about safety (Maurice, *J. Ocul. Pharmacol. Ther.* 17:393-401 (2001)). It also would be desirable to be able to minimize the number and/or frequency of eye injection treatments needed to deliver therapeutically effective amounts of drug to the ocular tissue sites that need it.

[0005] The suprachoroidal space (SCS) of the eye has been studied, and its cannulation described as a possible route for drug delivery. *See, e.g.*, Olsen, et al., *American J. Ophthalmology* 142(5): 777-87 (Nov. 2006).; PCT Patent Application Publication No. WO 2007/100745.

[0006] It therefore would be desirable to provide better, safer, more effective techniques for the direct delivery of therapeutic agents to posterior segment eye tissues, for example, to treat a posterior ocular disorder. It further would be desirable to provide better, safer, more effective techniques for the direct delivery of therapeutic agents to the SCS for the treatment of choroidal maladies, for example, choroidal maladies associated with vascular abnormalities. The present invention addresses these and other needs.

SUMMARY OF THE INVENTION

[0007] Disclosed are to non-surgical ophthalmic therapies in human patients in need of such treatment, and more particularly to the infusion of a drug formulation into the suprachoroidal space of the eye for targeted, local drug delivery, for the treatment of posterior ocular disorders, choroidal maladies and other diseases associated with vascular abnormalities.

[0007a] In one aspect, there is provided use of a drug formulation comprising triamcinolone in the manufacture of a medicament for treating a posterior ocular disorder in a human subject in need thereof, characterized in that the drug formulation is to be administered non-surgically in an effective amount to the suprachoroidal space (SCS) of the eye of the human subject in need of treatment of the disorder.

[0008] In one example, a method is provided for treating a posterior ocular disorder in a human subject in need of treatment. In one example, the method comprises non-surgically administering an effective amount of a drug formulation to the suprachoroidal space (SCS) of the eye of the subject in need of treatment of the posterior ocular disorder or choroidal malady. In a further example, upon administration, the drug formulation flows away from the insertion site and is substantially localized to the posterior segment of the eye. In one example, the posterior ocular disorder is an ocular inflammatory condition such as

uveitis, scleritis, glaucoma, ocular sarcoidosis, optic neuritis, macular edema, diabetic retinopathy, macular degeneration, a corneal ulcer, an autoimmune disorder, ophthalmic manifestations of AIDS, optic nerve degeneration, geographic atrophy, choroidal disease or retinitis. The condition in one embodiment is acute. In anotherexample, the condition is chronic.

[0009] In another embodiment, the a method is provided for the treatment of a choroidal malady, e.g., ocular neovascularization, polypoidal choroidal vasculopathy, choroidal sclerosis, central sirrus choroidopathy, a multi-focal choroidopathy or a choroidal dystrophy (e.g., central gyrate choroidal dystrophy, serpiginous choroidal dystrophy, total central choroidal atrophy). In one example, the method comprises non-surgically administering a drug formulation comprising an effective amount of an anti-inflammatory drug, a vascular endothelial growth factor (VEGF) modulator, a platelet derived growth factor (PDGF) modulator, an angiogenesis inhibitor, an immunosuppressive agent, a vascular permeability inhibitor, or a combination thereof, to the SCS of the patient in need of treatment. In a further example, the effective amount of the drug administered to the SCS provides higher efficacy or a greater therapeutic effect of the drug, compared to the identical drug dose administered intravitreally, intracamerally, topically, parenterally or orally. In even a further example, the patient undergoing treatment via SCS drug therapy was not previously responsive to a different type of therapy for the same condition.

[0010] In yet another example, a method for decreasing subretinal exudation and bleeding in a subject is provided. In a further example, the method comprises non-surgically administering a drug formulation comprising an effective amount of an effective amount of an anti-inflammatory drug, a vascular endothelial growth factor (VEGF) modulator, a vlatelet derived growth factor (PDGF) modulator, an angiogenesis inhibitor, an immunosuppressive agent, a vascular permeability inhibitor, or a combination thereof, to the SCS of the patient in need of treatment, wherein administration of the drug formulation reduces subretinal exudation and bleeding experienced by the patient, as compared to the identical dosage of the drug administered intravitreally to the patient.

[0011] In one example, a method for treating a posterior ocular disorder or a choroidal malady in a human patient is provided. In a furtherexample, the method comprises non-

surgically administering an effective amount of a drug formulation to the suprachoroidal space (SCS) of the eye of the subject in need of treatment of the posterior ocular disorder or choroidal malady. In a further example, the intraocular elimination half life ($t_{1/2}$) of the drug administered to the SCS is greater than the intraocular $t_{1/2}$ of the drug, when administered intravitreally, intracamerally, topically, parenterally or orally. In another example, the mean intraocular maximum concentration (C_{max}) of the drug, when administered to the SCS via the methods described herein, is greater than the intraocular C_{max} of the drug, when administered intravitreally, intracamerally, topically, parenterally or orally. In another example, the mean intraocular area under the curve (AUC_{0-t}) of the drug, when administered to the SCS via the methods described herein, is greater than the intraocular AUC_{0-t} of the drug, when administered intravitreally, intracamerally, topically, parenterally or orally. In yet another example, the intraocular time to peak concentration (t_{max}) of the drug, when administered to the SCS via the methods described herein, is greater than the intraocular t_{max} of the drug, when the same drug dose is administered intravitreally, intracamerally, topically, parenterally or orally. In a further example, the drug formulation comprises an effective amount of an anti-inflammatory drug (e.g., a steroid or NSAID), a VEGF modulator (e.g., VEGF antagonist), a platelet derived growth factor (PDGF) modulator, an angiogenesis inhibitor, an immunosuppressive agent, a vascular permeability inhibitor, or a combination thereof.

[0012] In one example, the method for treating a posterior ocular disorder or choroidal malady in a human subject comprises delivering a drug formulation via a hollow microneedle to the SCS of the eye of the human subject in need of treatment. In a further example, delivering the drug formulation comprises inserting a hollow microneedle into the eye of the human subject at an insertion site, the microneedle having a tip end with an opening; and infusing over a period of time a drug formulation through the inserted microneedle and into the SCS space away from the insertion site. The drug formulation administered to the SCS, in one embodiment, flows away from the insertion site and is substantially localized to the posterior segment of the eye, thereby increasing the therapeutic efficacy of the dose of the drug compared to the therapeutic efficacy of the same drug dose administered by another means (e.g. intravitreally, intracamerally, topically, parenterally, and/or orally). In another example, the dose of the drug sufficient to elicit a therapeutic response when administered to the SCS is less

than the dosage of the drug sufficient to elicit a therapeutic response when administered intravitreally, topically, parenterally or orally. In anotherexample, the drug formulation is delivered to the SCS by a hollow microneedle inserted into the sclera at the equator of the eye or between the equator and the limbus of the eye. In a further embodiment, the hollow microneedle is inserted in the insertion site at a 90 degree angle (perpendicular).

[0013] The drug formulation delivered by the methods described herein, in one example, comprises an effective amount of an anti-inflammatory drug, for example a steroid or a non-steroidal anti-inflammatory drug (NSAID). In another example, the drug delivered to the SCS via the methods described herein is a steroid, immunosuppressive, antimetabolite, T-cell inhibitor, alkylating agent, biologic, TNFα antagonist, interleukin antagonist, neuroprotectant, vascular endothelial growth factor (VEGF) antagonist, platelet derived growth factor (PDGF) antagonist, or a combination thereof. In another example, the drug affects inflammation, neuroprotection, complement inhibition, drusen formation, scar formation, reduction in choriocapillaris or choroidal neocasvularization. In another example, the drug formulation comprises microparticles and/or nanoparticles of the drug. In one example, the drug formulation comprises microparticles having a D_{50} of 1 μm or less and/or a D_{99} of 10 μm or less.

[0014] Also disclosed is a method for treating a posterior ocular disorder in a human subject in need thereof comprising non-surgically administering a drug formulation to the SCS of the eye of the human subject, wherein upon administration, the drug formulation flows away from the insertion site and is substantially localized to the posterior segment. In one example of the method, the intraocular pressure of the eye remains substantially constant during administration of the drug formulation to the SCS. In another example, administration of the drug formulation to the SCS of the eye results in a decreased number of side effects, or a reduced severity of one or more side effects, compared to administration of the same drug dose intravitreally, intracamerally, topically, orally or parenterally.

[0015] Also disclosed is a method for treating a choroidal malady in a human patient in need of treatment. In one example, the method comprises non-surgically administering a drug formulation comprising an effective amount of an

anti-inflammatory drug, a vascular endothelial growth factor (VEGF) modulator, a platelet derived growth factor (PDGF) modulator, an angiogenesis inhibitor, an immunosuppressive agent or a vascular permeability inhibitor, to the suprachoroidal space (SCS) of the eye of the patient. In a further example, the human patient, prior to administration of the drug formulation, was previously treated for the choroidal malady and was not properly responsive to the treatment.

[0016] Also disclosed is a method for treating ocular neovascularization in a human patient in need of treatment. In oneexample, the method comprises non-surgically administering a drug formulation comprising an effective amount of an anti-inflammatory drug, a vascular endothelial growth factor (VEGF) modulator (e.g., a VEGF antagonist), a platelet derived growth factor (PDGF) modulator (e.g., a PDGF antagonist), an angiogenesis inhibitor, an immunosuppressive agent or a vascular permeability inhibitor, to the suprachoroidal space (SCS) of the eye of the patient. In a furtherexample, the ocular neovascularization is a choroidal neovascularization. In oneexample, the human patient being treated for the ocular neovascularization, prior to administration of the drug formulation, was previously treated for the ocular neovascularization and was not properly responsive to the treatment.

[0017] The drug formulation delivered by the methods described herein, in oneexample, comprises an effective amount of an anti-inflammatory drug, for example a steroidal compound or a non-steroidal anti-inflammatory drug (NSAID). In anotherexample, the drug delivered to the SCS via the methods described herein is a vascular permeability inhibitor, an angiogenesis inhibitor or a VEGF modulator, *e.g.*, a VEGF antagonist. In oneexample, the VEGF antagonist is a VEGF receptor antagonist or a soluble VEGF receptor. In one example, the drug formulation comprises drug microparticles having a D_{50} of 1 μm or less and/or a D_{99} of 10 μm or less. In a further example, the drug formulation comprises triamcinolone.

[0018] Also disclosed is a method for treating a choroidal malady or a posterior ocular disorder in a human subject in need thereof is provided comprising non-surgically administering a drug formulation to the SCS of the eye of the human subject, wherien, the intraocular pressure of the eye remains substantially constant during administration of the

drug formulation to the SCS. In another example, administration of the drug formulation to the SCS of the eye of the patient in need of treatment of the posterior ocular disorder or choroidal malady results in a decreased number of side effects, or a reduced severity of one or more side effects, compared to administration of the same drug dose intravitreally, intracamerally, topically, orally or parenterally. In one example, the side effect reduced by the methods described herein is subretinal exudation and/or bleeding.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] FIGS. 1A, 1B, 1C, and **1D** are cross-sectional illustrations of the tissue structures of a human eye. The eye as a whole (A), a close-up of the cornea (**1B**), and a close-up of the sclera and associated tissue in an eye without fluid in the suprachoroidal space (**1C**) or with fluid in the suprachoroidal space (**1D**).

[0020] FIG. 2 is a cross-sectional view of a microneedle device comprising a hollow microneedle disposed in an elongated body according to one embodiment.

[0021] FIG. 3 is a cross-sectional view of the elongated body of the microneedle devices shown in **FIG. 2**.

[0022] FIG. 4 is an illustration of a microneedle device according to one embodiment.

[0023] FIG. 5 is an illustration of a microneedle device according to one embodiment.

[0024] FIGS. 6A and **6B** illustrate an embodiment of a process for using a hollow microneedle to deliver drug into the suprachoroidal space of an eye, where the process includes inserting the hollow microneedle into the sclera and infusion of a fluid drug formulation into the suprachoroidal space.

[0025] FIG. 7A shows a comparison of a hollow microneedle according to one embodiment as compared to the tip of a conventional 30 gauge hypodermic needle. **FIG. 7B** shows a schematic illustration of a custom acrylic mold shaped to fit a whole eye.

[0026] FIGS. 8A and **8B** are brightfield microscopic images of saggital cross sections of a pig eye before and after infusion of sulforhadamine, respectively.

CLAIMS

1. Use of a drug formulation comprising triamcinolone in the manufacture of a medicament for treating a posterior ocular disorder in a human subject in need thereof, characterized in that the drug formulation is to be

administered non-surgically in an effective amount to the suprachoroidal space (SCS) of the eye of the human subject in need of treatment of the disorder.

2. The use of claim 1, wherein the posterior ocular disorder is ocular inflammation, uveitis, retinal vein occlusion, wet age-related macular degeneration, or diabetic macular edema.

3. The use of claim 2, wherein the uveitis is acute posterior uveitis.

4. The use of claim 1, wherein the effective amount of the drug formulation sufficient to elicit a therapeutic response when administered to the SCS is less than the effective amount of the drug formulation sufficient to elicit a therapeutic response when administered intravitreally, intracamerally, topically, parenterally or orally.

5. The use of claim 1, wherein the retention of the drug formulation in the posterior segment of the eye is greater than the retention of the drug formulation in the posterior segment of the eye when the drug formulation is administered intravitreally, intracamerally, topically, parenterally or orally.

6. The use of claim 1, wherein an intraocular C_{max} of the drug formulation is greater than an intraocular C_{max} of the drug formulation, when the drug formulation is administered intravitreally, intracamerally, topically, parenterally or orally.

7. The use of claim 1, wherein the systemic exposure of the drug formulation is less than the systemic exposure of the drug formulation when the drug formulation is administered intravitreally, intracamerally, topically, parenterally or orally.

8. The use of claim 1, wherein the non-surgically administering includes conveying the effective amount of the drug formulation to the SCS via a microneedle having a length of from about 500 μm to about 1500 μm.

9. The use of claim 1, wherein the drug formulation comprises a suspension of microparticles or nanoparticles.

10. The use of claim 1, wherein the drug formulation is triamcinolone acetonide.

11. The use of claim 1, wherein the intraocular pressure of the eye of the subject varies by no more than about 10% during the administration of the drug formulation.

12. The use of claim 4, wherein a dosage of the drug sufficient to elicit a therapeutic response when administered to the SCS is 50% or less of a dosage of the drug sufficient to elicit a therapeutic response when administered intravitreally, intracamerally, topically, parenterally or orally.

13. The use of claim 9, wherein the microparticles have a D_{50} of 2 μm or less.

14. The use of claim 1, further comprising a second drug to be non-surgically administered to the eye of the subject, wherein the second drug comprises a VEGF modulator.

15. The use of claim 14, wherein the VEGF modulator is a VEGF antagonist.

16. The use of claim 15, wherein the VEGF antagonist is selected from a VEGF-receptor kinase antagonist, an anti-VEGF antibody or fragment thereof, an anti-VEGF receptor antibody, an anti-VEGF aptamer, a small molecule VEGF antagonist, a thiazolidinedione, a quinoline or a designed ankyrin repeat protein (DARPin).

17. The use of claim 15, wherein the VEGF antagonist is aflibercept.

18. The use of claim 14, wherein the second drug further comprises a PDGF antagonist.

19. The use of claim 14, wherein the posterior ocular disorder is diabetic macular edema.