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(54) Title: FORMULATIONS FOR OCULAR TREATMENT

(57) Abstract: Diseases and conditions associated with tissues of the body, including tissues in the eye, can be effectively treated by administering therapeutic agents to those tissues. Described herein are self-emulsifying formulations and methods for delivering therapeutic agents to such tissues. A self-emulsifying formulation may be delivered to an aqueous medium of a subject, including but not limited to the vitreous. A method may, for instance, be used to administer rapamycin or related compounds to treat or prevent choroidal neovascularization associated with age-related macular degeneration, or to treat dry AMD. A self-emulsifying formulation may also be administered systemically, such as orally, to treat transplant rejection in a subject. A self-emulsifying formulation may comprise rapamycin, related compounds, or other therapeutic agents.

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FORMULATIONS FOR OCULAR TREATMENT

David WEBER

FIELD

[0001] Described herein are methods and self-emulsifying formulations for the treatment of ocular diseases and conditions by delivery of therapeutic agents, particularly the treatment of age-related macular degeneration (“AMD”) by delivery of a self-emulsifying formulation comprising rapamycin to a subject or to the eye of a subject.

CROSS-REFERENCES TO RELATED APPLICATIONS

[0002] The present application is related to and claims priority from U.S. Provisional Patent Application Serial No. 60/664,040 titled “Liquid Formulations For Treatment Of Diseases Or Conditions,” filed Mar. 21, 2005, U.S. Provisional Patent Application Serial No. 60/664,306 titled “In Situ Gelling Formulations And Liquid Formulations For Treatment of Diseases Or Conditions,” filed Mar. 21, 2005, and U.S. Provisional Patent Application Serial No. 60/651,790, titled “Formulations For Ocular Treatment,” filed Feb. 9, 2005, each of which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND

[0003] The retina of the eye contains the cones and rods that detect light. In the center of the retina is the macula lutea, which is about 1/3 to 1/2 cm in diameter. The macula provides detailed vision, particularly in the center (the fovea), because the cones are higher in density. Blood vessels, ganglion cells, inner nuclear layer and cells, and the plexiform layers are all displaced to one side (rather than resting above the cones), thereby allowing light a more direct path to the cones.

[0004] Under the retina are the choroid, comprising a collection of blood vessels embedded within a fibrous tissue, and the deeply pigmented epithelium, which overlays the choroid layer. The choroidal blood vessels provide nutrition to the retina (particularly its visual cells).

[0005] There are a variety of retinal disorders for which there is currently no treatment or for which the current treatment is not optimal. Retinal disorders such as uveitis (an inflammation of the uveal tract: iris, ciliary body, and choroid), macular degeneration, macular edema, proliferative diabetic retinopathy, and retinal detachment generally are all retinal disorders that are difficult to treat with conventional therapies.

[0006] Age-related macular degeneration (AMD) is the major cause of severe visual loss in the United States for individuals over the age of 60. AMD occurs in either an atrophic or less commonly an exudative form. The atrophic form of AMD is also called "dry AMD," and the exudative form of AMD is also called "wet AMD."

[0007] In exudative AMD, blood vessels grow from the choriocapillaris through defects in Bruch's membrane, and in some cases the underlying retinal pigment epithelium. Organization of serous or hemorrhagic exudates escaping from these vessels results in fibrovascular scarring of the macular region with attendant degeneration of the neuroretina, detachment and tears of the retinal pigment epithelium, vitreous hemorrhage and permanent loss of central vision. This process is responsible for more than 80% of cases of significant visual loss in subjects with AMD. Current or forthcoming treatments include laser photocoagulation, photodynamic therapy, treatment with VEGF antibody fragments, treatment with pegylated aptamers, and treatment with certain small molecule agents.

[0008] Several studies have recently described the use of laser photocoagulation in the treatment of initial or recurrent neovascular lesions associated with AMD (Macular Photocoagulation Study Groups (1991) in *Arch. Ophthalmol.* 109:1220; *Arch. Ophthalmol.* 109:1232; *Arch. Ophthalmol.* 109:1242). Unfortunately, AMD subjects with subfoveal lesions subjected to laser treatment experienced a rather precipitous reduction in visual acuity (mean 3 lines) at 3 months follow-up. Moreover, at two years post-treatment treated eyes had only marginally better visual acuity than their untreated counterparts (means of 20/320 and 20/400, respectively). Another drawback of the procedure is that vision after surgery is immediately worse.

[0009] Photodynamic therapy (PDT) is a form of phototherapy, a term encompassing all treatments that use light to produce a beneficial reaction in a subject. Optimally, PDT destroys unwanted tissue while sparing normal tissue. Typically, a compound called a photosensitizer is administered to the subject. Usually, the photosensitizer alone has little or no effect on the subject. When light, often from a laser, is directed onto a tissue

containing the photosensitizer, the photosensitizer is activated and begins destroying targeted tissue. Because the light provided to the subject is confined to a particularly targeted area, PDT can be used to selectively target abnormal tissue, thus sparing surrounding healthy tissue. PDT is currently used to treat retinal diseases such as AMD. PDT is currently the mainstay of treatment for subfoveal choroidal neovascularization in subjects with AMD (Photodynamic Therapy for Subfoveal Choroidal Neovascularization in Age Related Macular Degeneration with Verteporfin (TAP Study Group) *Arch Ophthalmol.* 1999 117:1329-1345.

[0010] Choroidal neovascularization (CNV) has proven recalcitrant to treatment in most cases. Conventional laser treatment can ablate CNV and help to preserve vision in selected cases not involving the center of the retina, but this is limited to only about 10% of the cases. Unfortunately, even with successful conventional laser photocoagulation, the neovascularization recurs in about 50-70% of eyes (50% over 3 years and >60% at 5 years). (Macular Photocoagulation Study Group, *Arch. Ophthalmol.* 204:694-701 (1986)). In addition, many subjects who develop CNV are not good candidates for laser therapy because the CNV is too large for laser treatment, or the location cannot be determined so that the physician cannot accurately aim the laser. Photodynamic therapy, although utilized in up to 50% of new cases of subfoveal CNV has only marginal benefits over natural history, and generally delays progression of visual loss rather than improving vision which is already decreased secondary to the subfoveal lesion. PDT is neither preventive or definitive. Several PDT treatments are usually required per subject and additionally, certain subtypes of CNV fare less well than others.

[0011] Thus, there remains a long-felt need for methods and formulations that may be used to optimally prevent or significantly inhibit choroidal neovascularization and to prevent and treat wet AMD, and to treat or prevent dry AMD.

[0012] In addition to AMD, choroidal neovascularization is associated with such retinal disorders as presumed ocular histoplasmosis syndrome, myopic degeneration, angioid streaks, idiopathic central serous chorioretinopathy, inflammatory conditions of the retina and or choroid, and ocular trauma. Angiogenic damage associated with neovascularization occurs in a wide range of disorders including diabetic retinopathy, venous occlusions, sickle cell retinopathy, retinopathy of prematurity, retinal detachment, ocular ischemia and trauma.

[0013] Uveitis is another retinal disorder that has proven difficult to treat using existing therapies. Uveitis is a general term that indicates an inflammation of any component of the uveal tract. The uveal tract of the eye consists of the iris, ciliary body, and choroid. Inflammation of the overlying retina, called retinitis, or of the optic nerve, called optic neuritis, may occur with or without accompanying uveitis.

[0014] Uveitis is most commonly classified anatomically as anterior, intermediate, posterior, or diffuse. Posterior uveitis signifies any of a number of forms of retinitis, choroiditis, or optic neuritis. Diffuse uveitis implies inflammation involving all parts of the eye, including anterior, intermediate, and posterior structures.

[0015] The symptoms and signs of uveitis may be subtle, and vary considerably depending on the site and severity of the inflammation. Regarding posterior uveitis, the most common symptoms include the presence of floaters and decreased vision. Cells in the vitreous humor, white or yellow-white lesions in the retina and/or underlying choroid, exudative retinal detachments, retinal vasculitis, and optic nerve edema may also be present in a subject suffering from posterior uveitis.

[0016] Ocular complications of uveitis may produce profound and irreversible loss of vision, especially when unrecognized or treated improperly. The most frequent complications of posterior uveitis include retinal detachment; neovascularization of the retina, optic nerve, or iris; and cystoid macular edema.

[0017] Macular edema (ME) can occur if the swelling, leaking, and hard exudates noted in background diabetic retinopathy (BDR) occur within the macula, the central 5% of the retina most critical to vision. Background diabetic retinopathy (BDR) typically consists of retinal microaneurisms that result from changes in the retinal microcirculation. These microaneurisms are usually the earliest visible change in retinopathy seen on exam with an ophthalmoscope as scattered red spots in the retina where tiny, weakened blood vessels have ballooned out. The ocular findings in background diabetic retinopathy progress to cotton wool spots, intraretinal hemorrhages, leakage of fluid from the retinal capillaries, and retinal exudates. The increased vascular permeability is also related to elevated levels of local growth factors such as vascular endothelial growth factor. The macula is rich in cones, the nerve endings that detect color and upon which daytime vision depends. When increased retinal capillary permeability effects the macula, blurring occurs in the middle or just to the side of the central visual field, rather like looking through cellophane. Visual

loss may progress over a period of months, and can be very annoying because of the inability to focus clearly. ME is a common cause of severe visual impairment.

[0018] There have been many attempts to treat CNV and its related diseases and conditions, as well as other conditions such as macular edema and chronic inflammation, with pharmaceuticals. For example, use of rapamycin to inhibit CNV and wet AMD has been described in U.S. Application No. 10/665,203, which is incorporated herein by reference in its entirety. The use of rapamycin to treat inflammatory diseases of the eye has been described in US patent number 5,387,589, titled Method of Treating Ocular Inflammation, with inventor Prasad Kulkarni, assigned to University of Louisville Research Foundation, the contents of which is incorporated herein in its entirety.

[0019] Particularly for chronic diseases, including those described herein, there is a great need for long acting methods for delivering active compounds to the posterior segment to treat CNV in such diseases as AMD, macular edema, proliferative retinopathies, and chronic inflammation.

[0020] Rapamycin is poorly soluble in aqueous environments. Hence, formulations are needed to increase the solubility of rapamycin in order to more effectively deliver it to aqueous environments, such as the vitreous, aqueous humor of the eye, sclera, conjunctiva, the area between the sclera and the conjunctiva, the gastrointestinal tract, and other aqueous environments.

[0021] Direct delivery of therapeutic agents to the eye as opposed to systemic administration may be advantageous because the therapeutic agent concentration at the site of action is increased relative to the therapeutic agent concentration in a subject's circulatory system. Additionally, therapeutic agents may have undesirable side effects when delivered systemically to treat posterior segment disease. Thus, localized drug delivery promotes efficacy while decreasing side effects and systemic toxicity.

SUMMARY

[0022] The methods and self-emulsifying formulations described herein allow delivery of a therapeutic agent to a subject or to the eye of a subject, and address one or more of the difficulties described above. Unless the context indicates otherwise, it is intended that the subjects on whom all of the methods of treatment may be performed include human subjects. As such, the methods and self-emulsifying formulations described herein can be

used to deliver a variety of therapeutic agents for extended periods of time and can be used for the prevention and treatment of a number of diseases of the eye.

[0023] Described herein are methods and self-emulsifying formulations for administering to a human subject an amount of rapamycin effective to treat or prevent wet AMD.

Described herein are methods and self-emulsifying formulations for administering to a human subject an amount of rapamycin effective to treat or prevent dry AMD. Described herein are methods and self-emulsifying formulations for administering to a human subject an amount of rapamycin effective to treat or prevent transition of dry AMD to wet AMD.

[0024] As described in further detail in the *Detailed Description* section, the methods and self-emulsifying formulations may also be used for delivery to a subject or to the eye of a subject of therapeutically effective amounts of rapamycin for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of wet AMD. In some variations, the methods and self-emulsifying formulations are used to treat wet AMD. In some variations, the methods and self-emulsifying formulations are used to prevent wet AMD. In some variations, the methods and self-emulsifying formulations are used to treat or prevent dry AMD. In some variations, the methods and self-emulsifying formulations are used to prevent transition from dry AMD to wet AMD. The methods and self-emulsifying formulations may also be used for delivery to a subject or to the eye of a subject of therapeutically effective amounts of rapamycin for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of CNV. The methods and self-emulsifying formulations may also be used for delivery to a subject or to the eye of a subject of therapeutically effective amounts of rapamycin for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of angiogenesis in the eye. Other diseases and conditions that may be treated, prevented, inhibited, have onset delayed, or caused to regress using rapamycin are described in the *Diseases and Conditions* section of the *Detailed Description*.

[0025] As described in further detail in the *Detailed Description*, the methods and self-emulsifying formulations may also be used for delivery to a subject or to the eye of a subject of therapeutically effective amounts of therapeutic agents other than rapamycin for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of wet AMD or dry AMD. Therapeutic agents that may be used are described in detail in the *Therapeutic Agents* section. Such therapeutic agents include but are not limited to

immunophilin binding compounds. Immunophilin binding compound that may be used include but are not limited to the limus family of compounds described further in the Therapeutic Agents section herein, including rapamycin, SDZ-RAD, tacrolimus, everolimus, pimecrolimus, CCI-779, AP23841, ABT-578, and analogs, salts and esters thereof. The methods and self-emulsifying formulations may also be used for delivery to a subject or to the eye of a subject of therapeutically effective amounts of therapeutic agents for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of CNV. The methods and self-emulsifying formulations may also be used for delivery to a subject or to the eye of a subject of therapeutically effective amounts of therapeutic agents for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of angiogenesis in the eye. Other diseases and conditions that may be treated, prevented, inhibited, have onset delayed, or caused to regress using therapeutic agents other than rapamycin are described in the *Diseases and Conditions* section of the *Detailed Description*.

[0026] Described in the *Detailed Description* are various formulations, routes of administration, and self-emulsifying formulations that may be used for delivering a therapeutically effective amount of rapamycin or other therapeutic agents for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of wet AMD, dry AMD, CNV, angiogenesis or other diseases or conditions of the eye.

[0027] In some variations the self-emulsifying formulations described herein form a milky or whitish colored semi-contiguous or semi-solid non-dispersed mass relative to the medium in which it is placed, when placed in the vitreous.

[0028] Routes of administration that may be used to administer a self-emulsifying formulation include but are not limited to (1) placement of the self-emulsifying formulation by injection into an aqueous medium in the body, including but not limited to injection into the vitreous, aqueous humor, sclera, conjunctiva, and the area in between the sclera and conjunctiva; or (2) oral administration of the self-emulsifying formulation. The self-emulsifying formulation may be administered systemically, including but not limited to the following delivery routes: rectal, vaginal, infusion, intramuscular, intraperitoneal, intraarterial, intrathecal, intrabronchial, intracisternal, cutaneous, subcutaneous, intradermal, transdermal, intravenous, intracervical, intraabdominal, intracranial, intraocular, intrapulmonary, intrathoracic, intratracheal, nasal, buccal, sublingual, oral,

parenteral, or nebulised or aerosolized using aerosol propellants. In some variations, the self-emulsifying formulation is administered subconjunctivally. In some variations, the self-emulsifying formulation is administered intravitreally.

[0029] The self-emulsifying formulations described herein may be used in any aqueous medium in which they form an emulsion.

[0030] Described are various self-emulsifying formulations and methods for the treatment, prevention, inhibition, delaying of the onset of, or causing the regression of wet AMD, dry AMD, CNV, angiogenesis or other diseases or conditions of the eye.

[0031] One self-emulsifying formulation described herein comprises a self-emulsifying formulation of rapamycin or other therapeutic agent. The self-emulsifying formulation may self-emulsify upon introduction to an aqueous environment. The droplets in the emulsion may generally be of any size, including but not limited to those up to 5,000 nm.

[0032] In some variations, the self-emulsifying formulation comprises rapamycin, a solvent, and a surfactant. As non-limiting examples, the surfactant may be nonionic, such as cremophor EL, and the solvent may be a fatty acid, such as oleic acid, Imwitor 742, Softigen 767, or Capmuls PG8. The self-emulsifying formulation may further comprise ethanol.

[0033] As a non-limiting example, the self-emulsifying formulation comprises rapamycin, Cremophor EL, Capmuls PG8, and ethanol.

[0034] In some variations, the self-emulsifying formulation comprises rapamycin or another therapeutic agent. Such self-emulsifying formulation may generally contain any concentration of rapamycin or other therapeutic agent as limited by the solubility of the rapamycin or other therapeutic agent in the solvent. Various solvents and concentrations that may be used are described in the *Detailed Description*.

[0035] The self-emulsifying formulations described herein may deliver rapamycin or other therapeutic agents for an extended period of time. One nonlimiting example of such an extended release delivery system is a self-emulsifying formulation that delivers rapamycin to a subject or to the eye of a subject in an amount sufficient to maintain an amount effective to treat, prevent, inhibit, delay onset of, or cause regression of wet age-related macular degeneration for an extended period of time. In some variations, the self-emulsifying formulation is used to treat wet age-related macular degeneration for an extended period of time. In some variations, the self-emulsifying formulation is used to

prevent wet age-related macular degeneration for an extended period of time. In some variations, the self-emulsifying formulation is used to prevent transition of dry AMD to wet AMD for an extended period of time. In one nonlimiting example, the self-emulsifying formulation delivers the rapamycin to the vitreous, sclera, retina, choroid, macula, or other tissues of a subject in an amount sufficient to treat, prevent, inhibit, delay onset of, or cause regression of wet age-related macular degeneration for at least about three, about six, about nine, or about twelve months. In some variations, the level of rapamycin is sufficient to treat AMD. In some variations, the level of rapamycin is sufficient to prevent onset of wet AMD.

[0036] Other extended periods of release are described in the *Detailed Description*.

[0037] Concentrations and doses are described in the *Detailed Description*.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] FIGURE 1 shows the concentration of rapamycin in the vitreous of rabbit eyes after intravitreal injection.

DETAILED DESCRIPTION

[0039] Described herein are self-emulsifying formulations and methods relating to delivery of therapeutic agents to a subject or to the eye of a subject. These self-emulsifying formulations and methods may be used for the treatment, prevention, inhibition, delaying onset of, and causing regression of diseases and unwanted conditions of the posterior segment, including but not limited to choroidal neovascularization; macular degeneration; age-related macular degeneration, including wet AMD and dry AMD; retinal angiogenesis; chronic uveitis; and other retinoproliferative conditions.

[0040] Herein are described (1) self-emulsifying formulations, (2) the therapeutic agents that may be delivered to a subject or an eye of a subject using the self-emulsifying formulations and methods described herein, (3) the diseases and conditions that may be treated by delivery of the therapeutic agents, (4) routes of administration for delivery of the self-emulsifying formulations and methods, and (5) treatment of CNV and wet or dry AMD by delivery of rapamycin to a subject or to the eye of a subject using the described self-emulsifying formulations.

[0041] The term “about,” as used herein, refers to the level of accuracy that is obtained when the methods described herein, such as the methods in the examples, are used.

Self-emulsifying formulations

[0042] As used herein, a self-emulsifying formulation refers to a formulation that forms an emulsion upon contact with an aqueous medium. The droplets in the emulsion may generally be of any size. Emulsions formed by the self-emulsifying formulation may be of any type, including but not limited to micro- and nano-emulsions. One nonlimiting example of a self-emulsifying formulation is one that forms an oil-in-water-type dispersion upon contact with an aqueous medium, wherein the dispersion is stabilized by surfactant molecules.

[0043] One self-emulsifying formulation described herein comprises a therapeutic agent, a solvent, and a surfactant. The surfactant component may comprise a single surfactant or a combination of surfactants. The solvent component may comprise a single solvent or a combination of solvents. The therapeutic agent component may comprise a single therapeutic agent or a combination of therapeutic agents.

[0044] Note that there is some overlap between components that may be solvents and that may be surfactants, and therefore the same component may in some systems be used as either a solvent or a surfactant.

[0045] Self-emulsifying formulations may optionally further comprise stabilizers, excipients, gelling agents, adjuvants, antioxidants, and/or other components as described herein. In one described formulation, the surfactant is nonionic.

[0046] Herein are described self-emulsifying formulations for delivery of the therapeutic agents described in the *Therapeutic Agents* section. Delivery of therapeutic agents using the self-emulsifying formulations described herein may be used to treat, prevent, inhibit, delay the onset of, or cause the regression of the diseases and conditions described in the *Diseases and Conditions* section. The self-emulsifying formulations described herein may comprise any of the therapeutic agents described in the *Therapeutic Agents* section, including but not limited to rapamycin. The self-emulsifying formulations described herein may comprise one or more than one therapeutic agent. Other self-emulsifying formulations in addition to those explicitly described herein may be used.

[0047] The self-emulsifying formulations described may enhance the solubility of therapeutic agents, including but not limited to rapamycin, for improved delivery to aqueous environments such as the gastrointestinal tract, the vitreous, aqueous humor, sclera, conjunctiva, and the area in between the sclera and conjunctiva, or other aqueous environments. Such enhanced solubility may result in greater bioavailability of the therapeutic agent. Additionally, such enhanced solubility may further allow for increased concentrations of therapeutic agents, including but not limited to rapamycin, for delivery via the self-emulsifying formulations described.

[0048] In some variations the therapeutic agent is between about 0.1 to about 25% of the total weight of the formulation; between about 0.5 to about 20%; between about 1 to about 15%; between about 1.5 to about 10%; or between about 2 to about 8%; between about 3 to about 6%; or between about 5 to about 10% of the total weight of the formulation.

[0049] By "about" a certain amount of a component of a formulation is meant 90-110% of the amount stated.

[0050] In some variations the solvent is between about 2 to about 70 % of the total weight of the formulation; between about 10 to about 60%; between about 25 to about 55%; between about 30 to about 50%; or between about 35 to about 45%; between about 2 to about 10%; between about 10 to about 20%; between about 20 to about 30%; between about 30 to about 40%; between about 40 to about 45%; between about 40 to about 45%; between about 45 to about 50%; between about 50 to about 60%; or between about 50 to about 70%.

[0051] In some variations the surfactant is between about 2 to about 70 % of the total weight of the formulation; between about 10 to about 60%; between about 25 to about 55%; between about 30 to about 50%; or between about 35 to about 45%; between about 2 to about 10%; between about 10 to about 20%; between about 20 to about 30%; between about 30 to about 40%; between about 40 to about 45%; between about 40 to about 45%; between about 45 to about 50%; between about 50 to about 60%; or between about 50 to about 70% of the total weight of the formulation.

[0052] Nonlimiting examples of self-emulsifying formulations are those with an active therapeutic agent or agents such as rapamycin between about 0.1 and about 40% by weight of the total; a solvent between about 20% and about 80% by weight of the total; and a surfactant between about 20% and about 80% by weight of the total. The formulations may

optionally further comprise co-surfactants, stabilizing agents, excipients, adjuvants, antioxidants, etc., between about 0 and about 40% by weight of the total.

[0053] In some variations, the liquid formulations described herein have a viscosity of between 40% and 120% centipoise. In some variations the liquid formulations described herein have a viscosity of between 60% and 80% centipoise.

Therapeutic Agents

[0054] Most generally, any compounds currently known or yet to be discovered that are useful in treating, preventing, inhibiting, delaying the onset of, or causing the regression of the diseases and conditions described herein may be therapeutic agents for use in the self-emulsifying formulations, and methods described herein.

[0055] Therapeutic agents that may be used include compounds that act by binding members of the immunophilin family of cellular proteins. Such compounds are known as "immunophilin binding compounds." Immunophilin binding compounds include but are not limited to the "limus" family of compounds. Examples of limus compounds that may be used include but are not limited to cyclophilins and FK506-binding proteins (FKBPs), including sirolimus (rapamycin) and its water soluble analog SDZ-RAD (Novartis), TAF-93 (Isotechnika), tacrolimus, everolimus, RAD-001 (Novartis), pimecrolimus, temsirolimus, CCI-779 (Wyeth), AP23841 (Ariad), AP23573 (Ariad), and ABT-578 (Abbott Laboratories). Limus compound analogs and derivatives that may be used include but are not limited to the compounds described in U.S. Patents 5,527,907; 6,376,517; and 6,329,386 and U.S. Patent Application No. 09/950,307, each of which is incorporated herein by reference in their entirety. Therapeutic agents also include analogs, prodrugs, salts and esters of limus compounds.

[0056] The term rapamycin is used interchangeably herein with the terms sirolimus and rapa.

[0057] Other rapamycin derivatives that may be used include, without limitation, 7-epi-rapamycin, 7-thiomethyl-rapamycin, 7-epi-trimethoxyphenyl-rapamycin, 7-epi-thiomethyl-rapamycin, 7-demethoxy-rapamycin, 32-demethoxy-rapamycin, 2-desmethyl-rapamycin, mono- and di-ester derivatives of rapamycin, 27-oximes of rapamycin; 42-oxo analog of rapamycin; bicyclic rapamycins; rapamycin dimers; silyl ethers of rapamycin; rapamycin arylsulfonates and sulfamates, mono-esters and di-esters at positions 31 and 42, 30-

demethoxy rapamycin, and other derivatives described in Vezina et al., "Rapamycin (AY-22,989), A New Antifungal Antibiotic. I. Taxonomy Of The Producing Streptomycete And Isolation Of The Active Principle" J. Antibiot. (Tokyo) 28:721-726 (1975); Sehgal et al., "Rapamycin (AY-22,989), A New Antifungal Antibiotic. II. Fermentation, Isolation And Characterization" J. Antibiot. (Tokyo) 28:727-732 (1975); Sehgal et al., "Demethoxyrapamycin (AY-24,668), A New Antifungal Antibiotic" J. Antibiot. (Tokyo) 36:351-354 (1983); and Paiva et al., "Incorporation Of Acetate, Propionate, And Methionine Into Rapamycin By Streptomyces hygroscopicus" J Nat Prod 54:167-177 (1991), WO 92/05179, EP 467606, Caufield et al., "Hydrogenated Rapamycin Derivatives" U.S. Pat. No. 5,023,262; Kao et al., "Bicyclic Rapamycins" U.S. Pat. No. 5,120,725; Kao et al., "Rapamycin Dimers" U.S. Pat. No. 5,120,727; Failli et al., "Silyl Ethers Of Rapamycin" U.S. Pat. No. 5,120,842; Failli et al., "Rapamycin 42-Sulfonates And 42-(N-carboalkoxy) Sulfamates Useful As Immunosuppressive Agents" U.S. Pat. No. 5,177,203; Nicolaou et al., "Total Synthesis Of Rapamycin" J. Am. Chem. Soc. 115: 4419-4420 (1993); Romo et al, "Total Synthesis Of (-) Rapamycin Using An Evans-Tishchenko Fragment Coupling" J. Am. Chem. Soc. 115:7906-7907 (1993); and Hayward et al, "Total Synthesis Of Rapamycin Via A Novel Titanium-Mediated Aldol Macrocyclization Reaction" J. Am. Chem. Soc., 115:9345-9346 (1993) , each of which is incorporated herein by reference in its entirety.

[0058] The limus family of compounds may be used in the self-emulsifying formulations and methods for the treatment, prevention, inhibition, delaying the onset of, or causing the regression of angiogenesis-mediated diseases and conditions of the eye, including choroidal neovascularization. The limus family of compounds may be used to prevent, treat, inhibit, delay the onset of, or cause regression of AMD, including wet or dry AMD. Rapamycin may be used to prevent, treat, inhibit, delay the onset of, or cause regression of angiogenesis-mediated diseases and conditions of the eye, including choroidal neovascularization. Rapamycin and rapamycin derivatives and analogs may be used to prevent, treat, inhibit, delay the onset of, or cause regression of AMD, including wet or dry AMD.

[0059] Other therapeutic agents that may be used include those disclosed in the following patents and publications, the contents of each of which is incorporated herein in its entirety: PCT publication WO 2004/027027, published April 1, 2004, titled Method of inhibiting

choroidal neovascularization, assigned to Trustees of the University of Pennsylvania; US patent number 5,387,589, issued February 7, 1995, titled Method of Treating Ocular Inflammation, with inventor Prasad Kulkarni, assigned to University of Louisville Research Foundation; US patent number 6,376,517, issued April 23, 2003, titled Pipecolic acid derivatives for vision and memory disorders, assigned to GPI NIL Holdings, Inc; PCT publication WO 2004/028477, published April 8, 2004, titled Method subretinal administration of therapeutics including steroids: method for localizing pharmacodynamic action at the choroid and retina; and related methods for treatment and or prevention of retinal diseases, assigned to Innorx, Inc; US patent number 6,416,777, issued July 9, 2002, titled Ophthalmic drug delivery device, assigned to Alcon Universal Ltd; US patent number 6,713,081, issued March 30, 2004, titled Ocular therapeutic agent delivery device and methods for making and using such devices, assigned to Department of Health and Human Services; US patent number 5,100,899, issued Mar. 31, 1992, titled Methods of inhibiting transplant rejection in mammals using rapamycin and derivatives and prodrugs thereof .

[0060] Other therapeutic agents that may be used include pyrrolidine, dithiocarbamate (NF κ B inhibitor); squalamine; TPN 470 analogue and fumagillin; PKC (protein kinase C) inhibitors; Tie-1 and Tie-2 kinase inhibitors; inhibitors of VEGF receptor kinase; proteasome inhibitors such as Velcade™ (bortezomib, for injection; ranibuzumab (Lucentis™) and other antibodies directed to the same target; pegaptanib (Macugen™); vitronectin receptor antagonists, such as cyclic peptide antagonists of vitronectin receptor-type integrins; α -v/ β -3 integrin antagonists; α -v/ β -1 integrin antagonists; thiazolidinediones such as rosiglitazone or troglitazone; interferon, including γ -interferon or interferon targeted to CNV by use of dextran and metal coordination; pigment epithelium derived factor (PEDF); endostatin; angiostatin; tumistatin; canstatin; anecortave acetate; acetamide; triamcinolone; tetrathiomolybdate; RNA silencing or RNA interference (RNAi) of angiogenic factors, including ribozymes that target VEGF expression; Accutane™ (13-*cis* retinoic acid); ACE inhibitors, including but not limited to quinopril, captopril, and perindozril; inhibitors of mTOR (mammalian target of rapamycin); 3-aminothalidomide; pentoxifylline; 2-methoxyestradiol; colchicines; AMG-1470; cyclooxygenase inhibitors such as nepafenac, rofecoxib, diclofenac, rofecoxib, NS398, celecoxib, vioxx, and (E)-2-alkyl-2(4-methanesulfonylphenyl)-1-phenylethene; t-RNA synthase modulator; metalloprotease 13 inhibitor; acetylcholinesterase inhibitor; potassium channel blockers;

endorepellin; purine analog of 6-thioguanine; cyclic peroxide ANO-2; (recombinant) arginine deiminase; epigallocatechin-3-gallate; cerivastatin; analogues of suramin; VEGF trap molecules; apoptosis inhibiting agents; Visudyne™, snET2 and other photo sensitizers, which may be used with photodynamic therapy (PDT); inhibitors of hepatocyte growth factor (antibodies to the growth factor or its receptors, small molecular inhibitors of the c-met tyrosine kinase, truncated versions of HGF e.g. NK4).

[0061] Other therapeutic agents that may be used include anti-inflammatory agents, including, but not limited to nonsteroidal anti-inflammatory agents and steroidal anti-inflammatory agents. In some variations, active agents that may be used in the self-emulsifying formulations are ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, antibacterials, antihypertensives, pressors, antiprotozoal agents, antiviral agents, antifungal agents, anti-infective agents, antitumor agents, antimetabolites, and antiangiogenic agents.

[0062] Steroidal therapeutic agents that may be used include but are not limited to 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucoronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, triamcinolone hexacetonide, and any of their derivatives.

[0063] In some variations, cortisone, dexamethasone, fluocinolone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone, or their derivatives, may

be used. The self-emulsifying formulation may include a combination of two or more steroidal therapeutic agents.

[0064] In some variations, the steroidal therapeutic agent constitutes from about 0.05% to about 50% by weight of the self-emulsifying formulation. In some variations, the steroid constitutes from about 0.05% to about 10%, between about 10% to about 20%; between about 30% to about 40%; or between about 40% to about 50% by weight of the self-emulsifying formulation.

[0065] Other nonlimiting examples of therapeutic agents that may be used include but are not limited to anaesthetics, analgesics, cell transport/mobility impeding agents such as colchicines, vincristine, cytochalasin B and related compounds; carbonic anhydrase inhibitors such as acetazolamide, methazolamide, dichlorphenamide, diamox and neuroprotectants such as nimodipine and related compounds; antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, cephalixin, oxytetracycline, chloramphenicol, rifampicin, ciprofloxacin, aminosides, gentamycin, erythromycin and penicillin, quinolone, ceftazidime, vancomycin imipeneme; antifungals such as amphotericin B, fluconazole, ketoconazole and miconazole; antibacterials such as sulfonamides, sulfadiazine, sulfacetamide, sulfamethizole and sulfisoxazole, nitrofurazone and sodium propionate; antivirals, such as idoxuridine, trifluorothymidine, trifluorouridine, acyclovir, ganciclovir, cidofovir, interferon, DDI, AZT, foscarnet, vidarabine, irbavirin, protease inhibitors and anti-cytomegalovirus agents; antiallergenics such as sodium cromoglycate, antazoline, methapyrilone, chlorpheniramine, cetirizine, pyrilamine and propenpyridamine; synthetic glucocorticoids and mineralocorticoids and more generally hormones forms derivating from the cholesterol metabolism (DHEA, progesterone, estrogens); non-steroidal anti-inflammatories such as salicylate, indomethacin, ibuprofen, diclofenac, flurbiprofen, piroxicam and COX2 inhibitors; antineoplastics such as carmustine, cisplatin, fluorouracil; adriamycin, asparaginase, azacitidine, azathioprine, bleomycin, busulfan, carboplatin, carmustine, chlorambucil, cyclophosphamide, cyclosporine, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin, estramustine, etoposide, etretinate, filgrastin, floxuridine, fludarabine, fluorouracil, florymesterone, flutamide, goserelin, hydroxyurea, ifosfamide, leuprolide, levamisole, limustine, nitrogen mustard, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, pentostatin, pipobroman, plicamycin, procarbazine, sargramostin, streptozocin,

tamoxifen, taxol, teniposide, thioguanine, uracil mustard, vinblastine, vincristine and vindesine; immunological drugs such as vaccines and immune stimulants; insulin, calcitonin, parathyroid hormone and peptide and vasopressin hypothalamus releasing factor; beta adrenergic blockers such as timolol, levobunolol and betaxolol; cytokines, interleukines and growth factors epidermal growth factor, fibroblast growth factor, platelet derived growth factor, transforming growth factor beta, ciliary neurotrophic growth factor, glial derived neurotrophic factor, NGF, EPO, PLGF, brain nerve growth factor (BNGF), vascular endothelial growth factor (VEGF) and monoclonal antibodies or fragments thereof directed against such growth factors; anti-inflammatories such as hydrocortisone, dexamethasone, fluocinolone, prednisone, prednisolone, methylprednisolone, fluorometholone, betamethasone and triamcinolone; decongestants such as phenylephrine, naphazoline and tetrahydrazoline; miotics and anti-cholinesterases such as pilocarpine, carbachol, di-isopropyl fluorophosphate, phospholine iodine and demecarium bromide; mydriatics such as atropine sulphate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine; sympathomimetics such as epinephrine and vasoconstrictors and vasodilators, anticlotting agents such as heparin, antifibrinogen, fibrinolysin, anticlotting activase, antidiabetic agents include acetohexamide, chlorpropamide, glipizide, glyburide, tolazamide, tolbutamide, insulin and aldose reductase inhibitors, hormones, peptides, nucleic acids, saccharides, lipids, glycolipids, glycoproteins and other macromolecules include endocrine hormones such as pituitary, insulin, insulin-related growth factor, thyroid, growth hormones; heat shock proteins; immunological response modifiers such as muramyl dipeptide, cyclosporins, interferons (including alpha-, beta- and gamma-interferons), interleukin-2, cytokines, FK506 (an epoxy-pyrido-oxaazacyclotricosine-tetrone, also known as Tacrolimus), tumor necrosis factor, pentostatin, thymopentin, transforming factor beta2, erythropoetin; antineogenesis proteins (e.g. anti VEGF, interferons), antibodies (monoclonal, polyclonal, humanized, etc.) or antibodies fragments, oligoaptamers, aptamers and gene fragments (oligonucleotides, plasmids, ribozymes, small interference RNA (SiRNA), nucleic acid fragments, peptides), immunomodulators such as endoxan, thalidomide, tamoxifene; antithrombolytic and vasodilator agents such as rtPA, urokinase, plasmin; nitric oxide donors, nucleic acids, dexamethasone, cyclosporin A, azathioprine, brequinar, gusperimus, 6-mercaptopurine, mizoribine, rapamycin, tacrolimus (FK-506), folic acid analogs (e.g., denopterin, edatrexate, methotrexate, piritrexim,

pteropterin, Tomudex®, trimetrexate), purine analogs (e.g., cladribine, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine), pyrimidine analogs (e.g., ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, doxifluridine, emitefur, enocitabine, floxuridine, fluorouracil, gemcitabine, tegafur) fluocinolone, triaminolone, anecortave acetate, fluorometholone, medrysone, and prednisolone. In some variations the immunosuppressive agent is dexamethasone. In other variations the immunosuppressive agent is cyclosporin A.

[0066] In other variations the formulation comprises a combination of one or more therapeutic agents.

[0067] Other nonlimiting examples of therapeutic agents that may be used in the formulations described herein include antibacterial antibiotics, aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambarmycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micromomicin, neomycin, neomycin undecylenate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamfenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), P-lactams (e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefinenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, ceftazidime, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteteram, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephacetrile sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cephapirin sodium, cephradine, pivcefalexin), cephamycins (e.g., cefbuperazone, cefinetazole, cefminox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems, flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin g benethamine, penicillin g benzathine, penicillin g benzhydrylamine, penicillin g calcium,

penicillin g hydrabamine, penicillin g potassium, penicillin g procaine, penicillin n, penicillin o, penicillin v, penicillin v benzathine, penicillin v hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin), other (e.g., ritipenem), lincosamides (e.g., clindamycin, lincomycin), macrolides (e.g., azithromycin, carbomycin, clarithromycin, dirithromycin, erythromycin, erythromycin acistrate, erythromycin estolate, erythromycin glucoheptonate, erythromycin lactobionate, erythromycin propionate, erythromycin stearate, josamycin, leucomycins, midecamycins, miokamycin, oleandomycin, primycin, rokitamycin, rosaramicin, roxithromycin, spiramycin, troleandomycin), polypeptides (e.g., amphomycin, bacitracin, capreomycin, colistin, enduracidin, enviomycin, fusafungine, gramicidin s, gramicidin(s), mikamycin, polymyxin, pristinamycin, ristocetin, teicoplanin, thiostrepton, tuberactinomycin, tyrocidine, tyrothricin, vancomycin, viomycin, virginiamycin, zinc bacitracin), tetracyclines (e.g., apicycline, chlortetracycline, clomocycline, demeclocycline, doxycycline, guamecyclyline, lymecyclyline, meclocyclyline, methacycline, minocyclyline, oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancyclyline, tetracycline), and others (e.g., cycloserine, mupirocin, tuberin); synthetic antibacterials, 2,4-Diaminopyrimidines (e.g., brodimoprim, tetroxoprim, trimethoprim), nitrofurans (e.g., furaltadone, furazolum chloride, nifuradene, nifuratel, nifurfoline, nifurpirinol, nifurprazine, nifurtoinol, nitrofurantoin), quinolones and analogs (e.g., cinoxacin, ciprofloxacin, clinafloxacin, difloxacin, enoxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, miloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, rosoxacin, rufloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin), sulfonamides (e.g., acetyl sulfamethoxypyrazine, benzylsulfamide, chloramine-b, chloramine-t, dichloramine t, n2-formylsulfisomidine, n4- β -d-glucosylsulfanilamide, mafenide, 4'-(methylsulfamoyl)sulfanilamide, nopyrylsulfamide, phthalylsulfacetamide, phthalylsulfathiazole, salazosulfadimidine, succinylsulfathiazole, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanol, sulfalene, sulfaloxic acid, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 4-sulfanilamidosalicylic

acid, n4-sulfanilylsulfanilamide, sulfanilylurea, n-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfatolamide, sulfisomidine, sulfisoxazole) sulfones (e.g., acedapsone, acediasulfone, acetosulfone sodium, dapsone, diathymosulfone, glucosulfone sodium, solasulfone, succisulfone, sulfanilic acid, p-sulfanilylbenzylamine, sulfoxone sodium, thiazolsulfone), and others (e.g., clofoctol, hexedine, methenamine, methenamine anhydromethylene-citrate, methenamine hippurate, methenamine mandelate, methenamine sulfosalicylate, nitroxoline, taurolidine, xibomol), antifungal antibiotics, polyenes (e.g., amphotericin b, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin), others (e.g., azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrrolnitrin, siccanin, tubercidin, viridin), synthetic antifungals, allylamines (e.g., butenafine, naftifine, terbinafine), imidazoles (e.g., bifonazole, butoconazole, chlordantoin, chlormidazole, cloconazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanconazole, miconazole, omoconazole, oxiconazole nitrate, sertaconazole, sulconazole, tioconazole), thiocarbamates (e.g., tolciolate, tolindate, tolnaftate), triazoles (e.g., fluconazole, itraconazole, saperconazole, terconazole) others (e.g., acrisorcin, amorolfine, biphenamine, bromosalicylchloranilide, buclosamide, calcium propionate, chlorphenesin, ciclopirox, cloxyquin, coparaffinate, diamthazole dihydrochloride, exalarnide, flucytosine, halethazole, hexetidine, loflucarban, nifuratel, potassium iodide, propionic acid, pyrithione, salicylanilide, sodium propionate, sulbentine, tenonitroazole, triacetin, ujothion, undecylenic acid, zinc propionate), antineoplastics, antibiotics and analogs (e.g., aclacinomycins, actinomycin fl, anthramycin, azaserine, bleomycins, cactinomycin, carubicin, carzinophilin, chromomycins, dactinomycin, daunorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, idarubicin, menogaril, mitomycins, mycophenolic acid, nogalamycin, olivomycines, peplomycin, pirarubicin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, zinostatin, zorubicin), antimetabolites (e.g. folic acid analogs (e.g., denopterin, edatrexate, methotrexate, piritrexim, pteropterin, Tomudex®, trimetrexate), purine analogs (e.g., cladribine, fludarabine, 6-mercaptapurine, thiamiprine, thioguanine), pyrimidine analogs (e.g., ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, doxifluridine, emitefur, enocitabine, floxuridine, fluorouracil, gemcitabine, tagafur), antiinflammatory agents,

steroidal antiinflammatory agents, acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortal, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylamino-acetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, and triamcinolone hexacetonide, non-steroidal antiinflammatory agents, aminoarylcarboxylic acid derivatives (e.g., enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, tolfenamic acid), arylacetic acid derivatives (e.g., aceclofenac, acemetacin, alclofenac, amfenac, amtolmetin guacil, bromfenac, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac, isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, zomepirac), arylbutyric acid derivatives (e.g., bumadizon, butibufen, fenbufen, xenbucin), arylcarboxylic acids (e.g., clidanac, ketorolac, tinoridine), arylpropionic acid derivatives (e.g., alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprolen, piroprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, zaltoprofen), pyrazoles (e.g., difenamizole, epirizole), pyrazolones (e.g., apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebuzone, propyphenazone, ramifenazone, suxibuzone, thiazolinobutazone), salicylic acid derivatives (e.g., acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalmide, phenyl acetylsalicylate,

phenyl salicylate, salacetamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine), thiazinecarboxamides (e.g., ampiroxicam, droxicam, isoxicam, lomoxicam, piroxicam, tenoxicam), ϵ -acetamidocaproic acid, s-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, α -bisabolol, bucolome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, superoxide dismutase, tenidap, and zileuton.

[0068] The therapeutic agents may also be used in combination with other therapeutic agents and therapies, including but not limited to agents and therapies useful for the treatment, prevention, inhibition, delaying onset of, or causing regression of angiogenesis or neovascularization, particularly choroidal neovascularization. In some variations, the additional agent or therapy is used to treat angiogenesis or neovascularization, particularly CNV. Non-limiting examples of such additional agents and therapies include pyrrolidine, dithiocarbamate (NF κ B inhibitor); squalamine; TPN 470 analogue and fumagillin; PKC (protein kinase C) inhibitors; Tie-1 and Tie-2 kinase inhibitors; inhibitors of VEGF receptor kinase; proteasome inhibitors such as Velcade™ (bortezomib, for injection; ranibuzumab (Lucentis™) and other antibodies directed to the same target; pegaptanib (Macugen™); vitronectin receptor antagonists, such as cyclic peptide antagonists of vitronectin receptor-type integrins; α -v/ β -3 integrin antagonists; α -v/ β -1 integrin antagonists; thiazolidinediones such as rosiglitazone or troglitazone; interferon, including γ -interferon or interferon targeted to CNV by use of dextran and metal coordination; pigment epithelium derived factor (PEDF); endostatin; angiostatin; tumistatin; canstatin; anecortave acetate; acetamide; triamcinolone; tetrathiomolybdate; RNA silencing or RNA interference (RNAi) of angiogenic factors, including ribozymes that target VEGF expression; Accutane™ (13-*cis* retinoic acid); ACE inhibitors, including but not limited to quinopril, captopril, and perindozril; inhibitors of mTOR (mammalian target of rapamycin); 3-aminothalidomide; pentoxifylline; 2-methoxyestradiol; colchicines; AMG-1470; cyclooxygenase inhibitors such as nepafenac, rofecoxib, diclofenac, rofecoxib, NS398, celecoxib, vioxx, and (E)-2-alkyl-2-(4-methanesulfonylphenyl)-1-phenylethene; t-RNA synthase modulator; metalloprotease 13 inhibitor; acetylcholinesterase inhibitor; potassium channel blockers; endorepellin; purine analog of 6-thioguanine; cyclic peroxide ANO-2; (recombinant) arginine deiminase; epigallocatechin-3-gallate; cerivastatin; analogues of suramin; VEGF trap molecules; inhibitors of hepatocyte growth factor (antibodies to the growth factor or its

receptors, small molecular inhibitors of the c-met tyrosine kinase, truncated versions of HGF e.g. NK4); apoptosis inhibiting agents; Visudyne™, snET2 and other photo sensitizers with photodynamic therapy (PDT); and laser photocoagulation.

Diseases and conditions that may be treated, prevented, inhibited, onset delayed, or regression caused

[0069] Herein are described diseases and conditions that may be treated, prevented, inhibited, onset delayed, or regression caused using the therapeutic agents and the self-emulsifying formulations and methods described herein. In some variations, the diseases or conditions are treated using the therapeutic agents and the self-emulsifying formulations and methods described herein.

[0070] In some variations, the diseases or conditions treated using the therapeutic agents and the self-emulsifying formulations and methods described herein are not diseases or conditions of the eye.

[0071] The following references, each of which is incorporated herein by reference in its entirety, show one or more formulations, including but not limited to rapamycin formulations, and which describe use of rapamycin at various doses and other therapeutic agents for treating various diseases or conditions: US 60/651,790, filed 2/9/2005, titled FORMULATIONS FOR OCULAR TREATMENT, attorney docket number 57796-30002.00; US 60/664,040, filed 2/9/2005, attorney docket number 57796-30004.00, titled LIQUID FORMULATIONS FOR TREATMENT OF DISEASES OR CONDITIONS; US 60/664,119, filed 3/21/2005, attorney docket number 57796-30005.00, titled DRUG DELIVERY SYSTEMS FOR TREATMENT OF DISEASES OR CONDITIONS; US 60/664,306, filed 3/21/2005, attorney docket number 57796-30006.00 titled IN SITU GELLING FORMULATIONS AND LIQUID FORMULATIONS FOR TREATMENT OF DISEASES OR CONDITIONS; US __/__, filed 2/9/2006, titled FORMULATIONS FOR OCULAR TREATMENT, attorney docket number 57796-20002.00; __/__, filed 2/9/2006, attorney docket number 57796-20004.00, titled LIQUID FORMULATIONS FOR TREATMENT OF DISEASES OR CONDITIONS; US 2005/0187241, and US 2005/0064010.

[0072] Generally, any diseases or condition of the eye susceptible to treatment, prevention, inhibition, delaying the onset of, or causing the regression of using the

therapeutic agents and the self-emulsifying formulations and methods described herein may be treated, prevented, inhibited, onset delayed, or regression caused treated or prevented. Examples of diseases or conditions of the eye include, but are not limited to, diseases or conditions associated with neovascularization including retinal and/or choroidal neovascularization.

[0073] Diseases or conditions associated with retinal and/or choroidal neovascularization that can be treated, prevented inhibited, have onset delayed, or be caused to regress using the self-emulsifying formulations and methods described herein include, but are not limited to, diabetic retinopathy, macular degeneration, wet and dry AMD, retinopathy of prematurity (retrolental fibroplasia), infections causing a retinitis or choroiditis, presumed ocular histoplasmosis, myopic degeneration, angioid streaks, and ocular trauma. Other non-limiting examples of diseases and conditions of the eye that may be treated, prevented inhibited, have onset delayed, or be caused to regress using the self-emulsifying formulations and methods described herein include, but are not limited to, pseudoxanthoma elasticum, vein occlusion, artery occlusion, carotid obstructive disease, Sickle Cell anemia, Eales disease, myopia, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, trauma, polypoidal choroidal vasculopathy, post-laser complications, complications of idiopathic central serous chorioretinopathy, complications of choroidal inflammatory conditions, rubeosis, diseases associated with rubeosis (neovascularization of the angle), neovascular glaucoma, uveitis and chronic uveitis, macular edema, proliferative retinopathies and diseases or conditions caused by the abnormal proliferation of fibrovascular or fibrous tissue, including all forms of proliferative vitreoretinopathy (including post-operative proliferative vitreoretinopathy), whether or not associated with diabetes.

[0074] In some variations, the formulations and pharmaceutical formulations described herein are used to treat, prevent, or delay onset of CNV, including but not limited to in the fellow eye of a subject with AMD in one eye. In some variations, the formulations and pharmaceutical formulations described herein are used to treat, prevent, or delay onset of CNV or AMD in the fellow eye of a subject with wet AMD in one eye. In some variations, the formulations and pharmaceutical formulations comprise a limus compound, including but not limited to rapamycin. In some variations the formulations and pharmaceutical formulations are administered periocularly, including but not limited to subconjunctivally,

to an eye with vision of 20/40 or better. In some variations, the formulations and pharmaceutical formulations are administered periocularly, including without limitation subconjunctivally, to the eye of a human subject where the eye to which the formulation is administered has vision of 20/40 or better.

[0075] In some variations, the formulations and pharmaceutical formulations described herein are used to prevent or delay onset of a disease or condition of the eye where the subject, including but not limited to a human subject, is at heightened risk of developing the disease or condition of the eye. A subject with a heightened risk of developing a disease or condition is a subject with one or more indications that the disease or condition is likely to develop in the particular subject. In some variations the subject with a heightened risk of developing wet AMD is a subject with dry AMD in at least one eye. In some variations the subject with a heightened risk of developing wet AMD in a fellow eye is a subject with wet AMD in the other eye. In some variations, the formulations and pharmaceutical formulations described herein are used to prevent or delay onset of CNV in a subject at heightened risk of developing CNV, including but not limited to prevention or delaying onset of CNV in the fellow eye of a subject, including but not limited to a human subject with AMD in one eye. In some variations, the formulations and pharmaceutical formulations described herein are used to prevent or delay onset of CNV in the fellow eye of a subject with wet AMD in one eye. In some variations, the formulations and pharmaceutical formulations comprise a limus compound, including but not limited to rapamycin. In some variations the formulations and pharmaceutical formulations are administered subconjunctivally to an eye with vision of 20/40 or better.

[0076] In some variations, the formulations and pharmaceutical formulations described herein are used to treat, prevent, or delay onset of AMD. In some variations, the formulations and pharmaceutical formulations described herein are used to treat, prevent, or delay onset of dry AMD. In some variations, subjects with non-central geographic atrophy are administered a formulation or pharmaceutical formulations described herein to treat, prevent, or delay onset of central geographic atrophy. In some variations, the formulations and pharmaceutical formulations comprise a limus compound, including but not limited to rapamycin. In some variations the formulations and pharmaceutical formulations are administered subconjunctivally to an eye with vision of 20/40 or better. In some variations, the formulations and pharmaceutical formulations described herein are administered and

the subject is also treated with a second therapy for treating the disease or disorder. In some variations, the formulations and pharmaceutical formulations described herein are used to treat, prevent, or delay onset of wet or dry AMD and the subject is also treated with laser therapy such as photodynamic laser therapy, either before, during, or after treatment with the formulations or pharmaceutical formulations described herein.

[0077] In some variations, the formulations and pharmaceutical formulations described herein are used to treat one or more of uveitis, allergic conjunctivitis, or dry eye.

[0078] In some variations, a formulations or pharmaceutical formulation comprises a limus compound such as rapamycin, and is administered to treat, prevent, or delay onset of dry eye. In some variations, a formulations or pharmaceutical formulation comprises a limus compound such as rapamycin, and is administered to treat, prevent, or delay onset of allergic conjunctivitis.

[0079] In some variations, the formulations and pharmaceutical formulations described herein are used to treat glaucoma. In some variations, the formulations and pharmaceutical formulations described herein for treating glaucoma comprise a limus compound such as rapamycin, and are used as a surgical adjuvant to prevent, reduce or delay surgical complications. In some variations, the formulations and pharmaceutical formulations described herein for treating glaucoma comprise a limus compound such as rapamycin, and are used to improve or prolong surgical implant success. In some variations, the formulations and pharmaceutical formulations described herein for treating glaucoma comprise a limus compound such as rapamycin, and are used to improve or prolong success of an argon laser trabeculectomy or other glaucoma-related surgery. In some variations, the formulations and pharmaceutical formulations described herein have a neuroprotective effect and are used to treat glaucoma.

[0080] In some variations, the formulations and pharmaceutical formulations described herein are used to treat retinitis pigmentosa. In some variations, the formulations and pharmaceutical formulations described herein for treating glaucoma comprise a limus compound such as rapamycin, and are used to treat, prevent, or delay onset of retinitis pigmentosa. In some variations, the formulations and pharmaceutical formulations described herein have a neuroprotective effect and are used to treat retinitis pigmentosa.

[0081] In some variations, the formulations and pharmaceutical formulations described herein are used to treat one or more of central retinal vein occlusive diseases (CRVO),

branch retinal venous occlusion (BRVO), retinal vascular diseases and conditions, macular edema, diabetic macular edema, iris neovascularization, diabetic retinopathy, or corneal graft rejection. In some variations, a formulations or pharmaceutical formulation comprises a limus compound such as rapamycin, and is administered to treat, prevent, or delay onset of one or more of these diseases or conditions. In some variations the formulations and pharmaceutical formulations are administered subconjunctivally to an eye with vision of 20/40 or better.

[0082] When used to treat, prevent, inhibit, delay the onset of, or cause regressions of uveitis, the formulations and pharmaceutical formulations described herein may be administered by a variety of routes as is known in the art, including but not limited to by ocular or oral administration. Other routes of administration are known and are routine in the art. In some variations, the formulations described herein comprise rapamycin and are used to treat uveitis.

[0083] One disease that may be treated, prevented, inhibited, have onset delayed, or be caused to regress using the self-emulsifying formulations and methods described herein is the wet form of AMD. In some variations wet AMD is treated using the self-emulsifying formulations and methods described herein. The wet form of AMD is characterized by blood vessels growing from their normal location in the choroid into an undesirable position under the retina. Leakage and bleeding from these new blood vessels results in vision loss and possibly blindness.

[0084] The self-emulsifying formulations and methods described herein may also be used to prevent or slow the transition from the dry form of AMD (wherein the retinal pigment epithelium or RPE degenerates and leads to photoreceptor cell death and the formation of yellow deposits called drusen under the retina) to the wet form of AMD.

[0085] "Macular degeneration" is characterized by the excessive buildup of fibrous deposits in the macula and retina and the atrophy of the retinal pigment epithelium. As used herein, an eye "afflicted" with macular degeneration is understood to mean that the eye exhibits at least one detectable physical characteristic associated with the disease of macular degeneration. The administration of rapamycin appears to limit and regress angiogenesis, such as choroidal neovascularization in age-related macular degeneration (AMD), which may occur without treatment. As used herein, the term "angiogenesis" means the generation of new blood vessels ("neovascularization") into a tissue or organ.

An “angiogenesis-mediated disease or condition” of the eye or retina is one in which new blood vessels are generated in a pathogenic manner in the eye or retina, resulting in diminution or loss of vision or other problem, e.g., choroidal neovascularization associated with AMD.

[0086] The self-emulsifying formulations described herein, including but not limited to rapamycin-containing self-emulsifying formulations, may also be used to treat, prevent, inhibit, delay the onset of, or cause regression of various immune-related diseases and conditions, including but not limited to organ transplant rejection in a host, graft vs. host disease, autoimmune diseases, diseases of inflammation, hyperproliferative vascular disorders, solid tumors, and fungal infections. In some variations, the self-emulsifying formulations described herein, including but not limited to rapamycin-containing self-emulsifying formulations, are used to treat various immune-related diseases and conditions, including but not limited to organ transplant rejection in a host, graft vs. host disease, autoimmune diseases, diseases of inflammation, hyperproliferative vascular disorders, solid tumors, and fungal infections. The self-emulsifying formulations described herein, including but not limited to rapamycin-containing formulations, may be used as immunosuppressants. The self-emulsifying formulations described herein, including but not limited to rapamycin-containing formulations, may be used to treat, prevent, inhibit, or delay the onset of rejection of transplanted organs or tissues including but not limited to transplanted heart, liver, kidney, spleen, lung, small bowel, pancreas, and bone marrow. In some variations, the self-emulsifying formulations described herein are used to treat the onset of rejection of transplanted organs or tissues including but not limited to transplanted heart, liver, kidney, spleen, lung, small bowel, pancreas, and bone marrow. When used to treat, prevent, inhibit, delay the onset of, or cause regressions of immune-related diseases, including but not limited to transplant rejection, the self-emulsifying formulations described herein may be administered by a variety of routes as is known in the art, including but not limited to by oral administration.

[0087] Systemic administration may be achieved by oral administration of the self-emulsifying formulation. Other systemic routes of administration are known and are routine in the art. Some examples thereof are listed in the Detailed Description section.

[0088] As used herein, to “inhibit” a disease or condition by administration of a therapeutic agent means that the progress of at least one detectable physical characteristic or

symptom of the disease or condition is slowed or stopped following administration of the therapeutic agent as compared to the progress of the disease or condition without administration of the therapeutic agent.

[0089] As used herein, to “prevent” a disease or condition by administration of a therapeutic agent means that the detectable physical characteristics or symptom of the disease or condition do not develop following administration of the therapeutic agent.

[0090] As used herein, to “delay onset of” a disease or condition by administration of a therapeutic agent means that at least one detectable physical characteristic or symptom of the disease or condition develops later in time following administration of the therapeutic agent as compared to the progress of the disease or condition without administration of the therapeutic agent.

[0091] As used herein, to “treat” a disease or condition by administration of a therapeutic agent means that the progress of at least one detectable physical characteristic or symptom of the disease or condition is slowed, stopped, or reversed following administration of the therapeutic agent as compared to the progress of the disease or condition without administration of the therapeutic agent.

[0092] As used herein, to “cause regression of” a disease or condition by administration of a therapeutic agent means that the progress of at least one detectable physical characteristic or symptom of the disease or condition is reversed to some extent following administration of the therapeutic agent.

[0093] A subject having a predisposition for or in need of prevention may be identified by the skilled practitioner by established methods and criteria in the field given the teachings herein. The skilled practitioner may also readily diagnose individuals as in need of inhibition or treatment based upon established criteria in the field for identifying angiogenesis and/or neovascularization given the teachings herein.

[0094] As used herein, a “subject” is generally any animal that may benefit from administration of the therapeutic agents described herein. The therapeutic agents may be administered to a mammal subject. The therapeutic agents may be administered to a human subject. The therapeutic agents may be administered to a veterinary animal subject. The therapeutic agents may be administered to a model experimental animal subject.

[0095] Other diseases and conditions that may be treated, prevented, inhibited, have the onset delayed, or be caused to regress using the methods described herein include those

disclosed in the following patents and publications, the contents of each of which is incorporated herein in its entirety: PCT publication WO 2004/027027, published April 1, 2004, titled Method of inhibiting choroidal neovascularization, assigned to Trustees of the University of Pennsylvania; US patent number 5,387,589, issued February 7, 1995, titled Method of Treating Ocular Inflammation, with inventor Prasad Kulkarni, assigned to University of Louisville Research Foundation; US patent number 6,376,517, issued April 23, 2003, titled Pipecolic acid derivatives for vision and memory disorders, assigned to GPI NIL Holdings, Inc; PCT publication WO 2004/028477, published April 8, 2004, titled Method subretinal administration of therapeutics including steroids: method for localizing pharmacodynamic action at the choroid and retina; and related methods for treatment and or prevention of retinal diseases, assigned to Innorx, Inc; US patent number 6,416,777, issued July 9, 2002, titled Ophthalmic drug delivery device, assigned to Alcon Universal Ltd; US patent number 6,713,081, issued March 30, 2004, titled Ocular therapeutic agent delivery device and methods for making and using such devices, assigned to Department of Health and Human Services; and U.S. Pat. No. 5,536,729, issued July 16, 1996, titled Rapamycin Formulations for Oral Administration, assigned to American Home Products Corp., U.S. Pat. App. Nos. 60/503,840 and 10/945,682.

Self-emulsifying formulations for delivery of therapeutic agents

[0096] Unless the context clearly indicates otherwise, it is intended that any one or more of the therapeutic agents described herein may be used in the self-emulsifying formulations described herein. Unless the context clearly indicates otherwise, it is intended that any one or more of the self-emulsifying formulations described herein may be used to treat, prevent, inhibit, or delay onset of any one or more of the diseases or conditions described herein.

[0097] In some variations, prior to administration the self-emulsifying formulation is a solution. In some variations, the self-emulsifying formulation is stable for a period of time that is greater than a formulation that is an emulsion.

[0098] As used herein, an “aqueous medium” or “aqueous environment” is one that contains at least about 50% water.

[0099] Examples of aqueous media include but are not limited to the vitreous, extracellular fluid, conjunctiva, sclera, the area between the sclera and the conjunctiva, aqueous humor, gastric fluid, and any tissue or body fluid comprised of at least about 50%

of water. Aqueous media include but are not limited to gel structures, including but not limited to those of the conjunctiva and sclera.

[00100] Herein are described how the self-emulsifying formulations may be used to deliver amounts of the therapeutic agents effective for treating, preventing, inhibiting, delaying on set of, or causing the regression of the diseases and conditions described in the *Diseases and Conditions* section, including a description of how the self-emulsifying formulations may be used for extended release of the therapeutic agents.

[0100] An “effective amount,” which is also referred to herein as a “therapeutically effective amount,” of a therapeutic agent for administration as described herein is that amount of the therapeutic agent that provides the therapeutic effect sought when administered to the subject. The achieving of different therapeutic effects may require different effective amounts of therapeutic agent. For example, the therapeutically effective amount of a therapeutic agent used for preventing a disease or condition may be different from the therapeutically effective amount used for treating, inhibiting, delaying the onset of, or causing the regression of the disease or condition. In addition, the therapeutically effective amount may depend on the age, weight, and other health conditions of the subject as is well known to those versed in the disease or condition being addressed. Thus, the therapeutically effective amount may not be the same in every subject to which the therapeutic agent is administered.

[0101] An effective amount of a therapeutic agent for treating, preventing, inhibiting, delaying the onset of, or causing the regression of a specific disease or condition is also referred to herein as the amount of therapeutic agent effective to treat, prevent, inhibit, delay the onset of, or cause the regression of the disease or condition.

[0102] To determine whether a level of therapeutic agent is a “therapeutically effective amount” to treat, prevent, inhibit, delay on set of, or cause the regression of the diseases and conditions described in the *Diseases and Conditions* section, self-emulsifying formulations may be administered in animal models for the diseases or conditions of interest, and the effects may be observed.

[0103] Delivery of a therapeutically effective amount of the therapeutic agent for an extended period may be achieved via a single administration of a self-emulsifying formulation or may be achieved by administration of two or more doses of a self-emulsifying formulation. As a non-limiting example of such multiple applications,

maintenance of the therapeutic amount of rapamycin for 3 months for treatment, prevention, inhibition, delay of onset, or cause of regression of wet AMD may be achieved by administration of one dose of self-emulsifying formulation delivering a therapeutic amount for 3 months or by sequential application of a plurality of doses of a self-emulsifying formulation. The optimal dosage regime will depend on the therapeutic amount of the therapeutic agent needing to be delivered, the period over which it need be delivered, and the delivery kinetics of the self-emulsifying formulation. Those versed in such extended therapeutic agent delivery dosing will understand how to identify dosing regimes that may be used based on the teachings described herein.

[0104] When using certain therapeutic agents for the treatment, prevention, inhibition, delaying the onset of, or causing the regression of certain diseases, it may be desirable for delivery of the therapeutic agent not to commence immediately upon placement of the formulation into the eye region, but for delivery to commence after some delay. For example, but in no way limiting, such delayed release may be useful where the therapeutic agent inhibits or delays wound healing and delayed release is desirable to allow healing of any wounds occurring upon placement of the formulation. Depending on the therapeutic agent being delivered and/or the diseases and conditions being treated, prevented, inhibited, onset delayed, and regression caused this period of delay before delivery of the therapeutic agent commences may be about 1 hour, about 6 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, or about 42 days. Other delay periods may be possible. Delayed release formulations that may be used are known to those of skill in the art given the teachings herein.

[0105] Generally, the therapeutic agent may be formulated in any self-emulsifying formulation capable of delivery of a therapeutically effective amount of the therapeutic agent to a subject or to the eye of a subject for the required delivery period.

Solubilization of therapeutic agents

[0106] One formulation that may be used is a formulation in which the therapeutic agent is dissolved in a solvent. Generally, any solvent that has the desired effect may be used in which the therapeutic agent dissolves and which can be administered to the subject.

Generally, any concentration of solubilized therapeutic agent that has the desired effect can be used. The solvent may be a single solvent or may be a mixture of solvents. Solvent and types of solutions that may be used are well known to those versed in such drug delivery technologies. The solvent component may be a single solvent or may be a mixture of solvents. Solvents are well known to those versed in such drug delivery technologies. See for example, Remington: The Science and Practice of Pharmacy, Twentieth Edition, Lippincott Williams & Wilkins; 20th edition (December 15, 2000); Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Eighth Edition, Lippincott Williams & Wilkins (August 2004); Handbook Of Pharmaceutical Excipients 2003, American Pharmaceutical Association, Washington, DC, USA and Pharmaceutical Press, London, UK; and Strickley, solubilizing Excipients in Oral and Injectable Formulations, Pharmaceutical Research, Vol. 21, No. 2, February 2004.

[0107] Solvents that may be used include but are not limited to any one or more of DMSO, ethanol, methanol, isopropyl alcohol; castor oil, propylene glycol, glycerin, polysorbate 80, benzyl alcohol, dimethyl acetamide (DMA), dimethyl formamide (DMF), triacetin, diacetin, corn oil, acetyl triethyl citrate (ATC), ethyl lactate, glycerol formal, ethoxy diglycol (Transcutol, Gattefosse), triethylene glycol dimethyl ether (Triglyme), dimethyl isosorbide (DMI), γ -butyrolactone, N-Methyl-2-pyrrolidinone (NMP), polyethylene glycol of various molecular weights, including but not limited to PEG 300 and PEG 400, and polyglycolated capryl glyceride (Labrasol, Gattefosse), combinations of any one or more of the foregoing, or analogs or derivatives of any one or more of the foregoing.

[0108] In some variations, the solvent is polyethylene glycol. Polyethylene glycol is known by various names and is available in various preparations, including but not limited to macrogels, macrogel 400, macrogel 1500, macrogel 4000, macrogel 6000, macrogel 20000, macrogola, breox PEG; carbowax; carbowax sentry; Hodag PEG; Lipo; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol, and α -Hydro- ω -hydroxy-poly(oxy-1,2-ethanediyl).

[0109] Other solvents include an amount of a C₆-C₂₄ fatty acid sufficient to solubilize a therapeutic agent.

[0110] Phospholipid solvents may also be used, such as lecithin, phosphatidylcholine, or a mixture of various diglycerides of stearic, palmitic, and oleic acids, linked to the choline ester of phosphoric acid; hydrogenated soy phosphatidylcholine (HSPC),

distearoylphosphatidylglycerol (DSPG), L- α -dimyristoylphosphatidylcholine (DMPC), L- α -dimyristoylphosphatidylglycerol (DMPG).

[0111] Further examples of solvents include, for example, components such as alcohols, propylene glycol, polyethylene glycol of various molecular weights, propylene glycol esters, propylene glycol esterified with fatty acids such as oleic, stearic, palmitic, capric, linoleic, etc; medium chain mono-, di-, or triglycerides, long chain fatty acids, naturally occurring oils, and a mixture thereof. The oily components for the solvent system include commercially available oils as well as naturally occurring oils. The oils may further be vegetable oils or mineral oils. The oils can be characterized as non-surface active oils, which typically have no hydrophile lipophile balance value. Commercially available substances comprising medium chain triglycerides include, but are not limited to, Captex 100, Captex 300, Captex 355, Miglyol 810, Miglyol 812, Miglyol 818, Miglyol 829, and Dynacerin 660. Propylene glycol ester compositions that are commercially available encompass Captex 200 and Miglyol 840, and the like. The commercial product, Capmul MCM, is one of many possible medium chain mixtures comprising monoglycerides and diglycerides.

[0112] Other solvents include naturally occurring oils such as seed oils. Exemplary natural oils include oleic acid, castor oil, safflower seed oil, soybean oil, olive oil, sunflower seed oil, sesame oil and peanut oil. Soy fatty acids may also be used. Examples of fully saturated non-aqueous solvents include, but are not limited to, esters of medium to long chain fatty acids (such as fatty acid triglycerides with a chain length of about C₆ to about C₂₄). Mixtures of fatty acids may be split from the natural oil (for example coconut oil, palm kernel oil, babassu oil, or the like) and are refined. In some embodiments, medium chain (about C₈ to about C₁₂) triglycerides, such as caprylic/capric triglycerides derived from coconut oil or palm seed oil, may be used. Medium chain mono- and diglycerides may also be used. Other fully saturated non-aqueous solvents include, but are not limited to, saturated coconut oil (which typically includes a mixture of lauric, myristic, palmitic, capric and caproic acids), including those sold under the Miglyol™ trademark from Huls and bearing trade designations 810, 812, 829 and 840). Also noted are the NeoBee™ products sold by Drew Chemicals. Non-aqueous solvents include isopropyl myristate. Examples of synthetic oils include triglycerides and propylene glycol diesters of saturated or unsaturated fatty acids having 6 to 24 carbon atoms such as, for example hexanoic acid, octanoic

(caprylic), nonanoic (pelargonic), decanoic (capric), undecanoic, lauric, tridecanoic, tetradecanoic (myristic), pentadecanoic, hexadecanoic (palmitic), heptadecanoic, octadecanoic (stearic), nonadecanoic, heptadecanoic, eicosanoic, heneicosanoic, docosanoic and lignoceric acids, and the like. Examples of unsaturated carboxylic acids include oleic, linoleic and linolenic acids, and the like. The non-aqueous solvent can comprise the mono-, di- and triglyceryl esters of fatty acids or mixed glycerides and/or propylene glycol mono- or diesters wherein at least one molecule of glycerol has been esterified with fatty acids of varying carbon atom length. A non-limiting example of a "non-oil" useful as a solvent is polyethylene glycol.

[0113] Exemplary vegetable oils include cottonseed oil, corn oil, sesame oil, soybean oil, olive oil, fractionated coconut oil, peanut oil, sunflower oil, safflower oil, almond oil, avocado oil, palm oil, palm kernel oil, babassu oil, beechnut oil, linseed oil, rape oil and the like. Mono-, di-, and triglycerides of vegetable oils, including but not limited to corn, may also be used.

[0114] Polyvinyl pyrrolidone (PVP), cross-linked or not, may also be used as a solvent. Further solvents include but are not limited to C₆-C₂₄ fatty acids, oleic acid, Imwitor 742, Capmul, F68, F68 (Lutrol), PLURONICS including but not limited to PLURONICS F108, F127, and F68, Poloxamers, Jeffamines), Tetronics, F127; cyclodextrins such as α -cyclodextrin, β -cyclodextrin, hydroxypropyl- β -cyclodextrin, sulfobutylether- β -cyclodextrin (Captisol); CMC, polysorbitan 20, Cavitron, polyethylene glycol of various molecular weights including but not limited to PEG 300 and PEG 400.

[0115] Beeswax and *d*- α -tocopherol (Vitamin E) may also be used as solvents.

[0116] Solvents for use in the self-emulsifying formulations can be determined by a variety of methods known in the art, including but not limited to (1) theoretically estimating their solubility parameter values and choosing the ones that match with the therapeutic agent, using standard equations in the field; and (2) experimentally determining the saturation solubility of therapeutic agent in the solvents, and choosing the ones that exhibit the desired solubility.

Solubilization of rapamycin

[0117] Where the therapeutic agent is rapamycin, nonlimiting examples of solvents for use in the self emulsifying formulations described herein include any solvent described

herein, including but not limited to any one or more of DMSO, ethanol, methanol, isopropyl alcohol; castor oil, propylene glycol, glycerin, polysorbate 80, benzyl alcohol, dimethyl acetamide (DMA), dimethyl formamide (DMF), triacetin, diacetin, corn oil, acetyl triethyl citrate (ATC), ethyl lactate, glycerol formal, ethoxy diglycol (Transcutol, Gattefosse), triethylene glycol dimethyl ether (Triglyme), dimethyl isosorbide (DMI), γ -butyrolactone, N-Methyl-2-pyrrolidinone (NMP), polyethylene glycol of various molecular weights, including but not limited to PEG 300 and PEG 400, and polyglycolated capryl glyceride (Labrasol, Gattefosse), combinations of any one or more of the foregoing, or analogs or derivatives of any one or more of the foregoing.

[0118] Further solvents include but are not limited to C₆-C₂₄ fatty acids, oleic acid, Imwitor 742, Capmul, F68, F68 (Lutrol), PLURONICS including but not limited to PLURONICS F108, F127, and F68, Poloxamers, Jeffamines), Tetronics, F127, beta-cyclodextrin, CMC, polysorbitan 20, Cavitron, softigen 767, captisol, and sesame oil.

[0119] Other methods that may be used to solubilize rapamycin are described in solubilization of rapamycin, P. Simamora et al. *Int'l J. Pharma* 213 (2001) 25-29, the contents of which is incorporated herein in its entirety.

[0120] As a nonlimiting example, rapamycin can be dissolved in 5% DMSO or methanol in a balanced salt solution. The rapamycin solution can generally contain any concentration of rapamycin that has the desired effect. The rapamycin solution can be a saturated or supersaturated solution of rapamycin. The rapamycin solution can be in contact with solid rapamycin. In one nonlimiting example, rapamycin can be dissolved in a concentration of up to about 400 mg/ml. Rapamycin can also, for example, be solubilized with propylene glycol esterified with fatty acids such as oleic, stearic, palmitic, capric, linoleic, etc.

[0121] Many other solvents are possible. Those of ordinary skill in the art, based on the teachings herein, will find it routine to identify which solvents may be used for rapamycin.

Surfactants

[0122] Generally, any surfactant or combination of surfactants may be used in the self-emulsifying formulations described herein, provided the surfactant when combined with the other components in the formulation gives a self-emulsifying formulation. Many surfactants are possible. Combinations of surfactants, including combinations of various types of surfactants, may also be used. For instance, surfactants which are nonionic,

anionic (i.e. soaps, sulfonates), cationic (i.e. CTAB), zwitterionic, or amphoteric may be, provided the surfactant when combined with the other components in the formulation gives a self-emulsifying formulation.

[0123] Surfactants that can be used may be determined by mixing a therapeutic agent of interest with a putative solvent and a putative surfactant, and observing the characteristics of the formulation after exposure to an aqueous medium.

[0124] Examples of surfactants include but are not limited to fatty acid esters or amides or ether analogues, or hydrophilic derivatives thereof; monoesters or diesters, or hydrophilic derivatives thereof; or mixtures thereof; monoglycerides or diglycerides, or hydrophilic derivatives thereof; or mixtures thereof; mixtures having enriched mono- or/and diglycerides, or hydrophilic derivatives thereof; surfactants with a partially derivatized with a hydrophilic moiety; monoesters or diesters or multiple-esters of other alcohols, polyols, saccharides or oligosaccharides or polysaccharides, oxyalkylene oligomers or polymers or block polymers, or hydrophilic derivatives thereof, or the amide analogues thereof; fatty acid derivatives of amines, polyamines, polyimines, aminoalcohols, aminosugars, hydroxyalkylamines, hydroxypolyimines, peptides, polypeptides, or the ether analogues thereof.

[0125] Hydrophilic Lipophilic Balance ("HLB") is an expression of the relative simultaneous attraction of a surfactant for water and oil (or for the two phases of the emulsion system being considered).

[0126] Surfactants are characterized according to the balance between the hydrophilic and lipophilic portions of their molecules. The hydrophilic-lipophilic balance (HLB) number indicates the polarity of the molecule in an arbitrary range of 1 - 40, with the most commonly used emulsifiers having a value between 1 - 20. The HLB increases with increasing hydrophilicity.

[0127] Surfactants that may be used include but are not limited to those with an HLB greater than 10, 11, 12, 13 or 14. Examples of surfactants include polyoxyethylene products of hydrogenated vegetable oils, polyethoxylated castor oils or polyethoxylated hydrogenated castor oil, polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene castor oil derivatives and the like, for example, NIKKOL HCO-50, NIKKOL HCO-35, NIKKOL HCO-40, NIKKOL HCO-60 (from Nikko Chemicals Co. Ltd.); CREMOPHOR (from BASF) such as CREMOPHOR RH40, CREMOPHOR RH60, CREMOPHOR EL,

TWEENS (from ICI Chemicals) e.g., TWEEN 20, TWEEN 21, TWEEN 40, TWEEN 60, TWEEN 80, TWEEN 81, CREMOPHOR RH 410, CREMOPHOR RH 455 and the like.

[0128] The surfactant component may be selected from compounds having at least one ether formed from at least about 1 to 100 ethylene oxide units and at least one fatty alcohol chain having from at least about 12 to 22 carbon atoms; compounds having at least one ester formed from at least about 1 to 100 ethylene oxide units and at least one fatty acid chain having from at least about 12 to 22 carbon atoms; compounds having at least one ether, ester or amide formed from at least about 1 to 100 ethylene oxide units and at least one vitamin or vitamin derivative; and combinations thereof consisting of no more than two surfactants.

[0129] Other examples of surfactants include Lumulse GRH-40, TGPS, Polysorbate-80 (TWEEN-80), polysorbate-20 (TWEEN-20), polyoxyethylene 20, sorbitan mono-oleate, glyceryl glycol esters, polyethylene glycol esters, polyglycolized glycerides, and the like, or mixtures thereof; polyethylene sorbitan fatty acid esters, polyoxyethylene glycerol esters, such as Tagat TO, Tagat L, Tagat I, tagat I2 and Tagat 0 (commercially available from Goldschmidt Chemical Co., Essen, Germany); ethylene glycol esters, such as glycol stearate and distearate; propylene glycol esters, such as propylene glycol myristate; glyceryl esters of fatty acids, such as glyceryl stearates and monostearates; sorbitan esters, such as spans and TWEENS; polyglyceryl esters, such as polyglyceryl 4-oleate; fatty alcohol ethoxylates, such as Brij type emulsifiers; ethoxylated propoxylated block copolymers, such as poloxamers; polyethylene glycol esters of fatty acids, such as PEG 300 linoleic glycerides or Labrafil 2125 CS, PEG 300 oleic glycerides or Labrafil M 1944 CS, PEG 400 caprylic/capric glycerides or Labrasol; and PEG 300 caprylic/capric glycerides or Softigen 767; cremophors, such as Cremophor E, polyoxyl 35 castor oil or Cremophor EL, Cremophor EL-P, Cremophor RH 4OP, polyoxyl 40 hydrogenated castor oil, Cremophor RH40; polyoxyl 60 hydrogenated castor oil or Cremophor RH 60, glycerol monocaprylate/caprate, such as Campmul CM 10; polyoxyethylated fatty acids (PEG-stearates, PED-laurates, Brij®), polyoxylated glycerides of fatty acid, polyoxylated glycerol fatty acid esters i.e. Solutol HS-15; PEG-ethers (Mirj®), sorbitan derivatives (TWEENS), sorbitan monooleate or Span 20, aromatic compounds (Tritons®), PEG-glycerides (PECEOL™), PEG-PPG (polypropylene glycol) copolymers (PLURONICS including but not limited to PLURONICS F108, F127 and F68, poloxamers, Jeffamines), Tetronics,

Polyglycerines, PEG-tocopherols, PEG-LICOL 6-oleate; propylene glycol derivatives, sugar and polysaccharide alkyl and acyl derivatives (octylsucrose, sucrose stearate, laurolydextran etc.) and/or a mixture thereof; surfactants based on an oleate or laureate ester of a polyalcohol copolymerized with ethylene oxide; Labrasol Gelucire 44/14 polyoxyethylene stearates; saturated polyglycolized glycerides; or poloxamers; all of which are commercially available. Polyoxyethylene sorbitan fatty acid esters can include polysorbates, for example, polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80. Polyoxyethylene stearates can include polyoxyl 6 stearate, polyoxyl 8 stearate, polyoxyl 12 stearate and polyoxyl 20 stearate. Saturated polyglycolized glycerides are, for example, GELUCIRE™ 44/14 or GELUCIRE™ 50/13 (Gattefosse, Westwood, N.J., U.S.A.). Poloxamers used herein include poloxamer 124 and poloxamer 188.

[0130] Surfactants include *d*- α -tocopheryl polyethylene glycol 1000 succinate (TPGS), polyoxyl 8 stearate (PEG 400 monostearate), polyoxyl 40 stearate (PEG 1750 monostearate) and peppermint oil.

[0131] In some variations, surfactants having an HLB lower than 10 may also be used. Such surfactants may optionally be used in combination with other surfactants as co-surfactants. Examples of some surfactants, mixtures, and other equivalent compositions having an HLB less than or equal to 10 are propylene glycols, glyceryl fatty acids, glyceryl fatty acid esters, polyethylene glycol esters, glyceryl glycol esters, polyglycolized glycerides and polyoxyethyl steryl ethers. Propylene glycol esters or partial esters form the composition of commercial products, such as Lauroglycol FCC, which contains propylene glycol laureate. The commercially available excipient Maisine 35-1 comprises long chain fatty acids, for example glyceryl linoleate. Products, such as Acconon E, which comprise polyoxyethylene stearyl ethers, may also be used. Labrafil M 1944 CS is one example of a surfactant wherein the formulation contains a mixture of glyceryl glycol esters and polyethylene glycol esters.

Surfactants for rapamycin

[0132] Nonlimiting examples of surfactants that may be used for rapamycin include but are not limited to surfactants with an HLB greater than 10, 11, 12, 13 or 14. One nonlimiting example is Cremophor EL. Many other surfactants are possible, such as those in the Surfactants section above. As noted above, some solvents may also serve as

surfactants. Those of ordinary skill in the art, based on the teachings herein, will find it routine to identify which surfactants may be used for rapamycin.

Pharmaceutical formulations

[0133] Unless the context clearly indicates otherwise, the pharmaceutical formulations may comprise any of the self-emulsifying formulations described herein.

[0134] The formulations described herein may further comprise various other components appropriate for use in pharmaceutical formulations. Such components include, for example, stabilizers. Stabilizers for use in the formulations described herein include but are not limited to agents that will (1) improve the compatibility of excipients with the encapsulating materials such as gelatin, (2) improve the stability (e.g. prevent crystal growth of a therapeutic agent such as rapamycin) of a therapeutic agent such as rapamycin and/or rapamycin derivatives, and/or (3) improve formulation stability. Note that there is overlap between components that are stabilizers and those that are solvents or surfactants, and the same component can carry out more than one role.

[0135] Stabilizers may be selected from fatty acids, fatty alcohols, alcohols, long chain fatty acid esters, long chain ethers, hydrophilic derivatives of fatty acids, polyvinylpyrrolidones, polyvinylethers, polyvinyl alcohols, hydrocarbons, hydrophobic polymers, moisture-absorbing polymers, and combinations thereof. Amide analogues of the above stabilizers can also be used. The chosen stabilizer may change the hydrophobicity of the formulation (e.g. oleic acid, waxes), or improve the mixing of various components in the formulation (e.g. ethanol), control the moisture level in the formula (e.g. PVP), control the mobility of the phase (substances with melting points higher than room temperature such as long chain fatty acids, alcohols, esters, ethers, amides etc. or mixtures thereof; waxes), and/or improve the compatibility of the formula with encapsulating materials (e.g. oleic acid or wax). Some of these stabilizers may be used as solvents/co-solvents (e.g. ethanol). Stabilizers may be present in sufficient amount to inhibit the therapeutic agent's (such as rapamycin's) crystallization.

[0136] Examples of stabilizers include, but are not limited to, saturated, monoenoic, polyenoic, branched, ring-containing, acetylenic, dicarboxylic and functional-group-containing fatty acids such as oleic acid, caprylic acid, capric acid, caproic acid, lauric acid, myristic acid, palmitic acid, stearic acid, behenic acid, linoleic acid, linolenic acid, EPA,

DHA; fatty alcohols such as stearyl alcohol, cetyl alcohol, ceteryl alcohol; other alcohols such as ethanol, isopropyl alcohol, butanol; long chain fatty acid esters, ethers or amides such as glyceryl stearate, cetyl stearate, oleyl ethers, stearyl ethers, cetyl ethers, oleyl amides, stearyl amides; hydrophilic derivatives of fatty acids such as polyglyceryl fatty acids, polyethylene glycol fatty acid esters; PVPs, PVAs, waxes etc.

[0137] The formulations described may further contain a gelling agent that alters the texture of the final formulation through formation of a gel.

[0138] Gelling agents that may be used include but are not limited to carrageenan, cellulose gel, colloidal silicon dioxide, gelatin, propylene carbonate, carbonic acid, alginic acid, agar, carboxyvinyl polymers or carbomers and polyacrylamides, acacia, ester gum, guar gum, gum arabic, ghatti, gum karaya, tragacanth, terra, pectin, tamarind seed, larch arabinogalactan, alginates, locust bean, xanthan gum, starch, veegum, tragacanth, polyvinyl alcohol, gellan gum, hydrocolloid blends, and povidone.

[0139] The therapeutic agents for use as described herein, such as rapamycin, may be subjected to conventional pharmaceutical operations, such as sterilization and compositions containing the therapeutic agent may also contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. The therapeutic agents may also be formulated with pharmaceutically acceptable excipients for clinical use to produce a pharmaceutical composition. The therapeutic agents may be used to prepare a medicament to treat, prevent, inhibit, delay onset, or cause regression of any of the conditions described herein. Further, the pharmaceutical formulations described herein are also intended for use in the manufacture of a medicament for use in treatment of the diseases or conditions described herein according to one or more of the methods described herein.

[0140] A formulation containing a therapeutic agent such as rapamycin may contain one or more adjuvants appropriate for the indicated route of administration. Adjuvants with which the therapeutic agent may be admixed with include but are not limited to lactose, sucrose, starch powder, cellulose esters of alkanolic acids, stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol. When a solubilized formulation is required the therapeutic agent may be in a solvent including but not limited to polyethylene glycol of various molecular weights, propylene glycol,

carboxymethyl cellulose colloidal solutions, methanol, ethanol, DMSO, corn oil, peanut oil, cottonseed oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of administration are well known in the pharmaceutical art and may be used in the practice of the methods and self-emulsifying formulations described herein. The carrier or diluent may include time delay material, such as glyceryl monostearate or glyceryl distearate alone or with a wax, or other materials well known in the art. The formulations for use as described herein may also include gel formulations, erodible and non-erodible polymers, micropsheres, and liposomes.

[0141] Other adjuvants and excipients that may be used include but are not limited to C₈-C₁₀ fatty acid esters such as softigen 767, polysorbate 80, Pluronic, Tetronics, Miglyol, and Transcutol.

[0142] Additives and diluents normally utilized in the pharmaceutical arts can optionally be added to the pharmaceutical formulations described herein. These include thickening, granulating, dispersing, flavoring, sweetening, coloring, and stabilizing agents, including pH stabilizers, other excipients, anti-oxidants (e.g., tocopherol, BHA, BHT, TBHQ, tocopherol acetate, ascorbyl palmitate, ascorbic acid propyl gallate, and the like), preservatives (e.g., parabens), and the like. Exemplary preservatives include, but are not limited to, benzylalcohol, ethylalcohol, benzalkonium chloride, phenol, chlorobutanol, and the like. Some useful antioxidants provide oxygen or peroxide inhibiting agents for the formulation and include, but are not limited to, butylated hydroxytoluene, butylhydroxyanisole, propyl gallate, ascorbic acid palmitate, α -tocopherol, and the like. Thickening agents, such as lecithin, hydroxypropylcellulose, aluminum stearate, and the like, may improve the texture of the formulation.

[0143] In addition, a viscous polymer may be added to the formulation, assisting the localization in the sclera and ease of placement and handling. In some uses of the self-emulsifying formulations, a pocket in the sclera may be surgically formed to receive an injection of the self-emulsifying formulations. The hydrogel structure of the sclera can act as a rate-controlling membrane. Particles of therapeutic agent substance for forming a suspension can be produced by known methods including but not limited to via ball milling, for example by using ceramic beads. For example, a Cole Parmer ball mill such as Labmill 8000 may be used with 0.8 mm YTZ ceramic beads available from Tosoh or Norstone Inc.

[0144] The formulations may conveniently be presented in unit dosage form and may be prepared by conventional pharmaceutical techniques. Such techniques include the step of bringing into association the therapeutic agent and the pharmaceutical carrier(s) or excipient(s). The formulations may be prepared by uniformly and intimately bringing into associate the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0145] In some variations, the formulations described herein are provided in one or more unit dose forms, wherein the unit dose form contains an amount of a liquid rapamycin formulations described herein that is effective to treat or prevent the disease or condition for which it is being administered.

[0146] In some embodiments, the unit dose form is prepared in the concentration at which it will be administered. In some variations, the unit dose form is diluted prior to administration to a subject.

[0147] In a further aspect, provided herein are kits comprising one or more unit dose forms as described herein. In some embodiments, the kit comprises one or more of packaging and instructions for use to treat one or more diseases or conditions. In some embodiments, the kit comprises a diluent which is not in physical contact with the formulation or pharmaceutical formulation. In some embodiments, the kit comprises any of one or more unit dose forms described herein in one or more sealed vessels. In some embodiments, the kit comprises any of one or more sterile unit dose forms.

[0148] In some variations, the unit dose form is in a container, including but not limited to a sterile sealed container. In some variations the container is a vial, ampule, or low volume applicator, including but not limited to a syringe. In some variations, a low-volume applicator is pre-filled with a therapeutic agent for treatment of an ophthalmic disease or condition, including but not limited to a limus compound for treatment of age-related macular degeneration. Described herein is a pre-filled low-volume applicator pre-filled with a formulation comprising rapamycin. In some variations a low-volume applicator is pre-filled with a self-emulsifying formulation comprising rapamycin and a polyethylene glycol, and optionally further comprises one or more additional components including but not limited to ethanol. In some variations a pre-filled low-volume applicator is pre-filled with a self-emulsifying formulation comprising about 2% rapamycin, about 94% PEG-400, about 4% ethanol.

[0149] Described herein are kits comprising one or more containers. In some variations a kit comprises one or more low-volume applicators pre-filled with one or more formulations in liquid form comprising one or more therapeutic agents, including but not limited to formulations in liquid form comprising rapamycin, formulations in liquid form comprising rapamycin and a polyethylene glycol, and optionally further comprises one or more additional components including but not limited to ethanol, and formulations in liquid form comprising about 2% rapamycin, about 94% PEG-400, about 4% ethanol. In some variations the kit comprises one or more containers, including but not limited to pre-filled low-volume applicators, with instructions for its use. In a further variation a kit comprises one or more low-volume applicators pre-filled with rapamycin, with instructions for its use in treating a disease or condition of the eye.

[0150] In some variations, the containers described herein are in a secondary packaging.

Routes of Administration

[0151] The methods and self-emulsifying formulations described herein may be administered via one or more of the administration routes described herein.

[0152] In some variations, the self-emulsifying formulations described herein deliver one or more therapeutic agents to an aqueous medium in or proximal to an area where a disease or condition is to be treated, prevented, inhibited, onset delayed, or regression caused.

[0153] In some variations, the formulations and methods described herein deliver one or more therapeutic agents to an eye of a subject, including the macula and the retina choroid tissues, in an amount and for a duration effective to treat, prevent, inhibit, delay the onset of, or cause the regression of the diseases and conditions described in the Diseases and Conditions section.

[0154] When a certain volume is administered, it is understood that there is some imprecision in the accuracy of various devices that may be used to administer the liquid formulation. Where a certain volume is specified, it is understood that this is the target volume. However, certain devices such as insulin syringes are inaccurate to greater than 10%, and sometimes inaccurate up to 20% or more. Hamilton HPLC type syringes are generally considered precise to within 10%, and are recommended for volumes at or below 10 μ l.

[0155] In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or a subject's eye that is less than about 200 μl , less than about 100 μl , less than about 90 μl , less than about 80 μl , less than about 70 μl , less than about 60 μl , less than about 50 μl , less than about 40 μl , less than about 30 μl , less than about 20 μl , less than about 10 μl , less than about 5 μl , less than about 3 μl , or less than about 1 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or subject's eye that is less than about 20 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous that is less than about 10 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or a subject's eye that is between about 0.1 μl and about 200 μl , between about 50 μl and about 200 μl , between about 50 μl and about 150 μl , between about 0.1 μl and about 100 μl , between about 0.1 μl and about 50 μl , between about 1 μl and about 40 μl , between about 1 μl and about 30 μl , between about 1 μl and about 20 μl , between about 1 μl and about 10 μl , or between about 1 μl and about 5 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or a subject's eye that is between about 1 μl and about 10 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or a subject's eye that is between about 1 μl and about 5 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or a subject's eye that is between about 1 μl and about 5 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to the vitreous of a rabbit eye or a subject's eye that is between about 0.1 μl and about 200 μl .

[0156] In some variations, a total volume of a self-emulsifying formulation described herein is subconjunctivally administered to a rabbit eye or a subject's eye that is less than about 1000 μl , less than about 900 μl , less than about 800 μl , less than about 600 μl , less than about 500 μl , less than about 400 μl , less than about 300 μl , less than about 200 μl , less than about 100 μl , less than about 90 μl , less than about 80 μl , less than about 70 μl , less than about 60 μl , less than about 50 μl , less than about 40 μl , less than about 30 μl , less than about 20 μl , less than about 10 μl , less than about 5 μl , less than about 3 μl , or less than about 1 μl . In some variations, a volume of a self-emulsifying formulation described herein is subconjunctivally administered to a rabbit eye or a subject's eye that is less than about 20

μl . In some variations, a volume of a self-emulsifying formulation described herein is subconjunctivally administered to a rabbit eye or a subject's eye that is less than about 10 μl . In some variations, a volume of a self-emulsifying formulation described herein is subconjunctivally administered to a rabbit eye or a subject's eye that is between about 0.1 μl and about 200 μl , between about 50 μl and about 200 μl , between about 200 μl and about 300 μl , between about 300 μl and about 500 μl , between about 500 μl and about 700 μl , between about 700 μl and about 900 μl , between about 800 μl and about 1000 μl , between about 50 μl and about 150 μl , between about 0.1 μl and about 100 μl , between about 0.1 μl and about 50 μl , between about 1 μl and about 40 μl , between about 1 μl and about 30 μl , between about 1 μl and about 20 μl , between about 1 μl and about 10 μl , or between about 1 μl and about 5 μl . In some variations, a volume of a self-emulsifying formulation described herein is subconjunctivally administered to a rabbit eye or a subject's eye that is between about 1 μl and about 10 μl . In some variations, a volume of a self-emulsifying formulation described herein is subconjunctivally administered to a rabbit eye or a subject's eye that is between about 1 μl and about 5 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to subconjunctivally administered to a rabbit eye or a subject's eye that is between about 1 μl and about 5 μl . In some variations, a volume of a self-emulsifying formulation described herein is administered to subconjunctivally administered to a rabbit eye or a subject's eye that is between about 0.1 μl and about 200 μl .

[0157] In some variations the liquid formulations described herein contain no greater than about 250 μl of polyethylene glycol. In some variations the liquid formulations described herein contain no greater than about 250 μl , no greater than about 200 μl , no greater than about 150 μl , no greater than about 125 μl , no greater than about 100 μl , no greater than about 75 μl , no greater than about 50 μl , no greater than about 25 μl , no greater than about 20 μl , no greater than about 15 μl , no greater than about 10 μl , no greater than about 7.5 μl , no greater than about 5 μl , no greater than about 2.5 μl , no greater than about 1.0 μl , or no greater than about 0.5 μl of polyethylene glycol. Formulations containing polyethylene glycol may contain, for example, PEG 300 or PEG 400.

[0158] In some variations the self-emulsifying formulations described herein are administered in multiple subconjunctival locations within a period of time of one another, including but not limited to within an hour of one another. Without being bound by theory,

it is thought that such multiple administrations, such as multiple injections, allow for a greater total dose to be administered subconjunctivally than a single dose due to a potentially limited ability of the local ocular tissues to absorb larger volumes.

[0159] “Retina choroid” and “retina choroid tissues,” as used herein, are synonymous and refer to the combined retina and choroid tissues of the eye.

[0160] “Subconjunctival” placement or injection, as used herein, refers to placement or injection between the sclera and conjunctiva.

[0161] As a non-limiting example, the self-emulsifying formulations, and methods described herein may be administered to the vitreous, aqueous humor, sclera, conjunctiva, between the sclera and conjunctiva, the retina choroid tissues, macula, or other area in or proximate to the eye of a subject, in amounts and for a duration effective to treat, prevent, inhibit, delay the onset of, or cause the regression of CNV, wet AMD and dry AMD. The effective amounts and durations may be different for each of treating, preventing, inhibiting, delaying the onset of, or causing the regression of CNV, wet AMD and dry AMD, and for each of the different sites of delivery. For a description of exemplary periocular routes for retinal drug delivery, see Periocular routes for retinal drug delivery, Raghava et al. (2004), Expert Opin. Drug Deliv. 1(1):99-114, which is incorporated herein by reference in its entirety.

[0162] Intravitreal administration is more invasive than some other types of ocular procedures. Because of the potential risks of adverse effects, intravitreal administration may not be optimal for treatment of relatively healthy eyes. By contrast, periocular administration, such as subconjunctival administration, is much less invasive than intravitreal administration. When a therapeutic agent is delivered by a periocular route, it may be possible to treat patients with healthier eyes than could be treated using intravitreal administration. In some variations, subconjunctival injection is used to prevent or delay onset of a disease or condition of the eye, where the eye of the subject has visual acuity of 20/40 or better.

[0163] Routes of administration that may be used to administer a self-emulsifying formulation include but are not limited to placement of the self-emulsifying formulation, for example by injection, into an aqueous medium in the subject, including but not limited to placement, for example by injection, into the eye of a subject. The self-emulsifying formulation may be administered systemically, including but not limited to the following

delivery routes: rectal, vaginal, infusion, intramuscular, intraperitoneal, intraarterial, intrathecal, intrabronchial, intracisternal, cutaneous, subcutaneous, intradermal, transdermal, intravenous, intracervical, intraabdominal, intracranial, intraocular, intrapulmonary, intrathoracic, intratracheal, nasal, buccal, sublingual, oral, parenteral, or nebulised or aerosolized using aerosol propellants.

[0164] Self-emulsifying formulations comprising therapeutic agent can be administered directly to the eye using a variety of procedures, including but not limited to procedures in which (1) the therapeutic agent is administered by injection using a syringe and hypodermic needle, (2) a specially designed device is used to inject the therapeutic agent, (3) prior to injection of the therapeutic agent, a pocket is surgically formed within the sclera to serve as a receptacle for the therapeutic agent or therapeutic agent formulation. For example, in one administration procedure a surgeon forms a pocket within the sclera of the eye followed by injection of a self-emulsifying formulation comprising the therapeutic agent into the pocket.

[0165] Other administration procedures include, but are not limited to procedures in which (1) a formulation of the therapeutic agent is injected through a specially designed curved cannula to place the therapeutic agent directly against a portion of the eye, (2) a compressed form of the therapeutic agent is placed directly against a portion of the eye, (3) the therapeutic agent is inserted into the sclera by a specially designed injector or inserter, (4) the self-emulsifying formulation comprising the therapeutic agent is incorporated within a polymer, (5) a surgeon makes a small conjunctival incision through which to pass a suture and any therapeutic agent delivery structure so as to secure the structure adjacent to the sclera, (6) a needle is used for injection directly into the vitreous of an eye, or into any other site described.

[0166] The self-emulsifying formulations described herein may be used directly, for example, by injection, as an elixir, for topical administration including but not limited to via eye drops, or in hard or soft gelatin or starch capsules. The capsules may be banded to prevent leakage.

[0167] Some variations that may be used to deliver the self-emulsifying formulations described herein is delivery by injection. In this method self-emulsifying formulations may be injected into a subject or into a position in or proximate to an eye of the subject for delivery to a subject or to the eye of a subject. Nonlimiting examples of positions that are in or proximate to an eye of a subject follow.

[0168] Injection of therapeutic agent into the vitreous may provide a high local concentration of therapeutic agent in the vitreous and retina. Further, it has been found that in the vitreous the clearance half-life of a drug increases with molecular weight.

[0169] Intracameral injection, or injection into the anterior chamber of the eye, may also be used. In one example, up to about 100 μ l may be injected intracamerally.

[0170] Periocular routes of delivery may deliver therapeutic agent to the retina without some of the risks of intravitreal delivery. Periocular routes include but are not limited to subconjunctival, subtenon, retrobulbar, peribulbar and posterior juxtasceral delivery. A "periocular" route of administration means placement near or around the eye. For a description of exemplary periocular routes for retinal drug delivery, see *Periocular routes for retinal drug delivery*, Raghava et al. (2004), *Expert Opin. Drug Deliv.* 1(1):99-114, which is incorporated herein by reference in its entirety.

[0171] In some variations the liquid formulations described herein are administered intraocularly. Intraocular administration includes placement or injection within the eye, including in the vitreous.

[0172] Subconjunctival injection may be by injection of therapeutic agent underneath the conjunctiva, or between the sclera and conjunctiva. In one example, up to about 500 μ l may be injected subconjunctivally. As one nonlimiting example, a needle of up to about 25 to about 30 gauge and about 30 mm long may be used. Local pressure to the subconjunctival site of therapeutic agent administration may elevate delivery of the therapeutic agent to the posterior segment by reducing local choroidal blood flow.

[0173] Subtenon injection may be by injection of therapeutic agent into the tenon's capsule around the upper portion of the eye and into the "belly" of the superior rectus muscle. In one example, up to about 4 ml may be injected subtenon. As one nonlimiting example, a blunt-tipped cannula about 2.5 cm long may be used.

[0174] Retrobulbar injection refers to injection into the conical compartment of the four rectus muscles and their intermuscular septa, behind the globe of the eye. In one example, up to about 5 ml may be injected retrobulbarly. As one nonlimiting example, a blunt needle of about 25 - or about 27-gauge may be used.

[0175] Peribulbar injection may be at a location external to the confines of the four rectus muscles and their intramuscular septa, i.e., outside of the muscle cone. A volume of, for

example, up to about 10 ml may be injected peribulbarly. As one nonlimiting example, a blunt-tipped cannula about 1.25 inches long and about 25-gauge may be used.

[0176] Posterior juxtasceral delivery refers to placement of a therapeutic agent near and above the macula, in direct contact with the outer surface of the sclera, and without puncturing the eyeball. In one example, up to about 500 ml may be injected posterior juxtasclerally. As one nonlimiting example, a blunt-tipped curved cannula, specially designed at 56°, is used to place the therapeutic agent in an incision in the sclera.

[0177] Sites to which the self-emulsifying formulations may be administered include but are not limited to the vitreous, aqueous humor, sclera, conjunctiva, between the sclera and conjunctiva, the retina choroid tissues, macula, or other area in or proximate to the eye of a subject. Methods that may be used for placement of the self-emulsifying formulations include but are not limited to injection.

[0178] The self-emulsifying formulations described herein may be delivered to a variety of positions in the ocular region to enable delivery of the therapeutic agent, including but not limited to intraocular or periocular delivery; delivery to the vitreous, aqueous humor, sclera, conjunctiva, between the sclera and conjunctiva, the retina choroid tissues, macula, periocular tissue, tenons areas, and other area in or proximate to the eye of a subject or other environment. Other sites of delivery and routes of administration, such as systemic routes, are described above.

[0179] Self-emulsifying formulations comprising therapeutic agent can be administered directly to the eye using a variety of procedures, including but not limited to procedures in which (1) the therapeutic agent is administered by injection using a syringe and hypodermic needle, (2) a specially designed device is used to inject the therapeutic agent, (3) prior to injection of the therapeutic agent, a pocket is surgically formed within the sclera to serve as a receptacle for the therapeutic agent or therapeutic agent formulation. For example, in one administration procedure a surgeon forms a pocket within the sclera of the eye followed by injection of a formulation comprising the therapeutic agent into the pocket.

[0180] Other administration procedures include, but are not limited to procedures in which (1) a formulation of the therapeutic agent is injected through a specially designed curved cannula to place the therapeutic agent directly against a portion of the eye, (2) a compressed form of the therapeutic agent is placed directly against a portion of the eye, (3) the therapeutic agent is inserted into the sclera by a specially designed injector or inserter,

(4) the formulation comprising the therapeutic agent is incorporated within a polymer, (5) a surgeon makes a small conjunctival incision through which to pass a suture and any therapeutic agent delivery structure so as to secure the structure adjacent to the sclera, (6) a needle is used for injection directly into the vitreous of an eye, or into any other site described.

Intravitreal and subconjunctival delivery of rapamycin for treatment, prevention, inhibition, delay of onset, or cause of regression of AMD

[0181] In some variations described herein, a self-emulsifying formulation comprising rapamycin is delivered subconjunctivally or to the vitreous of an eye of a subject, including but not limited to a human subject, to prevent, treat, inhibit, delay onset of, or cause regression of angiogenesis in the eye, including but not limited to treating CNV as observed, for example, in AMD. In some variations, the self-emulsifying formulation is used to treat angiogenesis in the eye, including but not limited to treating CNV as observed, for example, in AMD. Rapamycin has been shown to inhibit CNV in rat and mice models, as described in U.S. Application No. 10/665,203, which is incorporated herein by reference in its entirety. Rapamycin has been observed to inhibit MatrigelTM and laser-induced CNV when administered systemically and subretinally.

[0182] Other therapeutic agents that may be delivered to the eye, including without limitation the vitreous of an eye, for treatment, prevention, inhibition, delaying onset, or causing regression of angiogenesis in the eye (such as CNV) are members of the limus family of compounds other than rapamycin including but not limited to everolimus and tacrolimus (FK-506).

[0183] As described herein, the dosage of the therapeutic agent will depend on the condition being addressed, whether the condition is to be treated, prevented, inhibited, have onset delayed, or be caused to regress, the particular therapeutic agent, and other clinical factors such as weight and condition of the subject and the route of administration of the therapeutic agent. It is to be understood that the methods and formulations described herein have application for both human and veterinary use, including but not limited to laboratory, experimental, pet, or agriculturally important animals. As described herein, tissue concentrations of therapeutic agents expressed in units of mass per volume generally refer to tissues that are primarily aqueous such as the vitreous, for example. Tissue

concentrations of therapeutic agents expressed in unit of mass per mass generally refer to other tissues such as the sclera or retina choroid tissues, for example.

[0184] When the therapeutic agent is rapamycin, the self-emulsifying formulations may be used to deliver or maintain an effective amount of rapamycin in the vitreous. In one nonlimiting example, it is believed that a delivery system delivering rapamycin to give a concentration of rapamycin of about 10 pg/ml to about 2 μ g/ml in the vitreous may be used for the treatment of wet AMD. When the rapamycin is administered intravitreally, calculation of the concentration of rapamycin in the vitreous excludes the initially administered contiguous emulsion bolus. In another nonlimiting example, it is believed that a delivery system delivering rapamycin to give a concentration of rapamycin of about 0.01 pg/mg to about 10 ng/mg in the retina choroid may be used for treatment of wet AMD. Other therapeutically effective amounts of therapeutic agent are also possible, and can be readily determined by one of skill in the art given the teachings herein.

[0185] When the therapeutic agent is rapamycin, the self-emulsifying formulations and other delivery systems described herein may be used to deliver a dose of rapamycin to a subject or to the eye of a subject. In one nonlimiting example, it is believed that a delivery system containing an initial dose of about 20 μ g to about 4 mg may be used for the treatment of wet AMD or dry AMD. Other delivery doses that may be used are described in the *Detailed Description*.

[0186] One concentration of rapamycin that may be used in the methods described herein is one that provides to a subject about 0.01 pg/ml or pg/mg or more of rapamycin at the tissue level. In some variations, a dose is used that provides to a subject greater than any one or more of about 0.1 pg/ml or ng/mg, about 1 pg/ml or ng/mg, about 0.01 ng/ml or ng/mg or more at the tissue level, about 0.1 ng/ml or ng/mg, about 0.5 ng/ml or ng/mg, about 1 ng/ml or or ng/mg, about 2 ng/ml or ng/mg, about 3 ng/ml or ng/mg, about 5 ng/ml or ng/mg, about 10 ng/ml or ng/mg, about 15 ng/ml or ng/mg, about 20 ng/ml or ng/mg, about 30 ng/ml or ng/mg, about 50 ng/ml or ng/mg, about 100 ng/ml or ng/mg, about 200 ng/ml or ng/ml, about 300 ng/ml or ng/mg, about 400 ng/ml or ng/mg, about 500 ng/ml or ng/mg, about 1 μ g/ml or μ g/mg, about 10 μ g/ml or μ g/mg, about 50 μ g/ml or μ g/mg, about 100 μ g/ml or μ g/mg, about 150 μ g/ml or μ g/mg, about 200 μ g/ml or μ g/mg, about 250 μ g/ml or μ g/mg, about 300 μ g/ml or μ g/mg, about 350 μ g/ml or μ g/mg, about 400 μ g/ml or μ g/mg, about 450 μ g/ml or μ g/mg, or about 400 μ g/ml or μ g/mg at the tissue level. One of

ordinary skill in the art would know how to arrive at an appropriate concentration depending on the route and duration of administration utilized, given the teachings herein.

[0187] In some variations, a total amount of rapamycin less than about 5 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 5.0 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 4.5 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 4.0 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 3.5 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 3.0 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 2.5 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 2 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 1.2 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 1.0 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 0.8 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 0.6 mg is administered subconjunctivally. In some variations, a total amount of rapamycin less than about 0.4 mg is administered subconjunctivally. In some variations, a volume of a formulation is administered that contains an amount of rapamycin described herein.

[0188] In some variations, a total amount of rapamycin less than about 200 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 200 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 300 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 400 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 500 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 600 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 800 μg is administered intravitreally. In some variations, a total amount of rapamycin less than about 1 mg is administered intravitreally. In some variations, a total amount of rapamycin less than about 2 mg is administered intravitreally. In some variations, a total amount of rapamycin less than about 2.5 mg is administered intravitreally. In some variations, a total

amount of rapamycin less than about 3 mg is administered intravitreally. In some variations, a total amount of rapamycin less than about 3.5 mg is administered intravitreally. In some variations, a total amount of rapamycin less than about 4 mg is administered intravitreally. In some variations, a volume of a formulation is administered that contains an amount of rapamycin described herein.

[0189] In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 μ g and about 5 mg is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μ g and about 4 mg is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μ g and about 1.2 mg is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 10 μ g and about 0.5 mg is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 10 μ g and 90 μ g is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 60 μ g and about 120 μ g is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 100 μ g and about 400 μ g is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 400 μ g and about 1 mg is administered to a human subject for treatment of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 mg and about 5 mg is administered to a human subject for treatment of wet AMD. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 3 mg and about 7 mg is administered to a human subject for treatment of wet AMD. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 5 mg and about 10 mg is administered to a human subject for treatment of wet AMD.

[0190] In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 μg and about 5 mg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μg and about 4 mg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μg and about 1.2 mg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 10 μg and about 0.5 mg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 10 μg and 90 μg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 60 μg and about 120 μg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 100 μg and about 400 μg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 400 μg and about 1 mg is administered to a human subject for prevention of wet AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 mg and about 5 mg is administered to a human subject for prevention of wet AMD. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 3 mg and about 7 mg is administered to a human subject for prevention of wet AMD. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 5 mg and about 10 mg is administered to a human subject for prevention of wet AMD.

[0191] In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 μg and about 5 mg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μg and about 4 mg is administered to a human subject for treatment of dry AMD. In some variations a self-

emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μg and about 1.2 mg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 10 μg and about 0.5 mg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 10 μg and 90 μg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 60 μg and about 120 μg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 100 μg and about 400 μg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 400 μg and about 1 mg is administered to a human subject for treatment of dry AMD. In some variations a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 mg and about 5 mg is administered to a human subject for treatment of dry AMD. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 3 mg and about 7 mg is administered to a human subject for treatment of dry AMD. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 5 mg and about 10 mg is administered to a human subject for treatment of dry AMD.

[0192] In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 1 μg and about 5 mg is administered to a human subject for treatment of angiogenesis, including but not limited to choroidal neovascularization. In some variations, a self-emulsifying formulation as described herein containing an amount of rapamycin of between about 20 μg and about 4 mg is administered to the human subject; between about 20 μg and about 1.2 mg; between about 10 μg and about 0.5 mg, between about 10 μg and 90 μg , between about 60 μg and 120 μg is administered to the human subject; between about 100 μg and 400 μg , between about 400 μg and 1 mg, between about 1 mg and 5 mg, between about 3 mg and 7 mg, or between about 5 mg and 10 mg is administered to the human subject for treatment of angiogenesis, including but not limited to choroidal neovascularization.

[0193] In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of between about 0.5% and about 6% is subconjunctivally administered to a human subject by administering between about 0.1 μ l and about 200 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of between about 0.5% and about 4% is subconjunctivally administered to a human subject by administering between about 1 μ l and about 50 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of between about 1.5% and about 3.5% is subconjunctivally administered to a human subject by administering between about 1 μ l and about 15 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of about 2% is subconjunctivally administered to a human subject by administering between about 1 μ l and about 15 μ l of a self-emulsifying formulation described herein.

[0194] In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 0.5 μ g and about 4 mg is subconjunctivally administered to a human subject by administering between about 0.1 μ l and about 200 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 5 μ g and about 2 mg is subconjunctivally administered to a human subject by administering between about 1 μ l and about 100 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 5 μ g and about 1 mg is subconjunctivally administered to a human subject by administering between about 1 μ l and about 50 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 15 μ g and about 500 μ g is subconjunctivally administered to a human subject by administering between about 1 μ l and about 25 μ l of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 20 μ g and about 300 μ g is subconjunctivally administered to a human subject by administering between about 1 μ l and about 15 μ l of a self-emulsifying formulation described herein.

[0195] In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of between about 0.5% and about 6% is intravitreally administered to a human subject by administering between about 0.1 μl and about 200 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of between about 0.5% and about 4% is intravitreally administered to a human subject by administering between about 1 μl and about 50 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of between about 1.5% and about 3.5% is intravitreally administered to a human subject by administering between about 1 μl and about 15 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing a concentration of rapamycin by weight of the total of about 2% is intravitreally administered to a human subject by administering between about 1 μl and about 15 μl of a self-emulsifying formulation described herein.

[0196] In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 2 μg and about 4 mg is intravitreally administered to a human subject by administering between about 0.1 μl and about 200 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 20 μg and about 2 mg is intravitreally administered to a human subject by administering between about 1 μl and about 100 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 20 μg and about 1 mg is intravitreally administered to a human subject by administering between about 1 μl and about 50 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 20 μg and about 500 μg is intravitreally administered to a human subject by administering between about 1 μl and about 25 μl of a self-emulsifying formulation described herein. In some variations, a self-emulsifying formulation containing an amount of rapamycin of between about 20 μg and about 300 μg is intravitreally administered to a human subject by administering between about 1 μl and about 15 μl of a self-emulsifying formulation described herein.

[0197] In some variations, a self-emulsifying formulation is described herein as containing an amount of a therapeutic agent equivalent to an amount of rapamycin. The therapeutic agent component may also be represented as a concentration equivalent to rapamycin. As used herein, an amount or concentration of a therapeutic agent “equivalent to rapamycin” refers to an amount or concentration of the therapeutic agent that will have approximately the same efficacy in vivo as a particular dose of rapamycin for treating, preventing, delaying, or inhibiting a disease or condition, including but not limited to the diseases and conditions described herein.

[0198] Those of skill in the art, based on the teachings herein, can determine what amount or concentration of a given therapeutic agent is equivalent to an amount or concentration of rapamycin by, for example, administering the therapeutic agent at various amounts or concentrations to a disease model system, such as an in vivo or in vivo model system, and comparing the results in the model system relative to the results of various amounts or concentrations of rapamycin. Those of skill in the art, based on the teachings herein, can also determine what amount or concentration of a given therapeutic agent is equivalent to an amount or concentration of rapamycin by reviewing the scientific literature for experiments performed comparing rapamycin to other therapeutic agents. It is understood that even the same therapeutic agent may have a different equivalent level of rapamycin when, for example, a different disease or disorder is being evaluated, or a different type of formulation is used. Nonlimiting examples of scientific references with comparative studies of rapamycin and other therapeutic agents on ocular disease are Ohia et al., *Effects of steroids and immunosuppressive drugs on endotoxin-uveitis in rabbits*, J. Ocul. Pharmacol. 8(4):295-307 (1992); Kulkarni, *Steroidal and nonsteroidal drugs in endotoxin-induced uveitis*, J. Ocul. Pharmacol. 10(1):329-34 (1994); Hafizi et al., *Differential effects of rapamycin, cyclosporine A, and FK506 on human coronary artery smooth muscle cell proliferation and signaling*, Vascul Pharmacol. 41(4-5):167-76 (2004); and US 2005/0187241.

[0199] For example, in a model for wet AMD, if a therapeutic agent is found to be approximately 10-fold less potent or efficacious than rapamycin in the treatment of wet AMD, a concentration of 10 ng/ml of the therapeutic agent would be equivalent to a 1 ng/ml concentration of rapamycin. Or if a therapeutic agent is found to be approximately

10-fold less potent or efficacious than rapamycin in the treatment of wet AMD, a 10-fold amount of the therapeutic agent would be administered relative to the amount of rapamycin.

[0200] In some variations, a self-emulsifying formulation as described herein containing an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 μg and about 5 mg is administered to a human subject for treatment of wet AMD. In some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 μg and about 5 mg is administered to the human subject; between about 20 μg and about 1.2 mg; between about 10 μg and about 0.5 mg is administered to a human subject for treatment of wet AMD, between about 10 μg and 90 μg , between about 60 μg and 120 μg is administered to the human subject; between about 100 μg and 400 μg , between about 400 μg and 1 mg is administered to the human subject is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 mg and 5 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 3 mg and 7 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 5 mg and 10 mg is administered to the human subject.

[0201] In some variations, a self-emulsifying formulation as described herein containing an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 μg and about 5 mg is administered to a human subject for treatment of dry AMD. In some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 20 μg and about 4 mg is administered to the human subject; between about 20 μg and about 1.2 mg; between about 10 μg and about 0.5 mg is administered to a human subject for treatment of wet AMD, between about 10 μg and 90 μg , between about 60 μg and 120 μg is administered to the human subject; between about 100 μg and 400 μg , between about 400 μg and 1 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 400 μg and 1 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 mg and 5 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 3 mg and 7 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an

amount of rapamycin of between about 5 mg and 10 mg is administered to the human subject to treat dry AMD.

[0202] In some variations, a self-emulsifying formulation as described herein containing an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 μ g and about 5 mg is administered to a human subject for prevention of wet AMD. In some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 20 μ g and about 4 mg is administered to the human subject; between about 20 μ g and about 1.2 mg; between about 10 μ g and about 0.5 mg is administered to a human subject for prevention of wet AMD, between about 10 μ g and 90 μ g, between about 60 μ g and 120 μ g is administered to the human subject; between about 100 μ g and 400 μ g, between about 400 μ g and 1 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 400 μ g and 1 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 1 mg and 5 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 3 mg and 7 mg is administered to the human subject; in some variations, an amount of a therapeutic agent equivalent to an amount of rapamycin of between about 5 mg and 10 mg is administered to the human subject to prevent wet AMD.

[0203] In some variations, any one or more of the formulations described herein are administered intravitreally every 3 or more months, every 6 or more months, every 9 or more months, or every 12 or more months, or longer, to treat one or more of choroidal neovascularization, wet AMD, dry AMD, or to prevent wet AMD. In some variations, any one or more of the formulations described herein are administered subconjunctivally every 3 or more months, every 6 or more months, every 9 or more months, or every 12 or more months, or longer, to treat one or more of choroidal neovascularization, wet AMD, dry AMD, or to prevent wet AMD.

[0204] In some variations, any one or more of the rapamycin formulations described herein are administered intravitreally every 3 or more months, every 6 or more months, every 9 or more months, or every 12 or more months, or longer, to treat one or more of choroidal neovascularization, wet AMD, dry AMD, or to prevent wet AMD. In some variations, any one or more of the rapamycin formulations described herein are

administered subconjunctivally every 3 or more months, every 6 or more months, every 9 or more months, or every 12 or more months, or longer, to treat one or more of choroidal neovascularization, wet AMD, dry AMD, or to prevent wet AMD. In some variations, the effect of the rapamycin persists beyond the period during which it is measurable in the ocular tissues by LCMS.

[0205] Delivery of the therapeutic agents described herein may, for example, be delivered at a dosage range between about 1 ng/day and about 100 µg/day, or at dosages higher or lower than this range, depending on the route and duration of administration. In some variations of self-emulsifying formulation used in the methods described herein, the therapeutic agents are delivered at a dosage range of between about 0.1 µg/day and about 10 µg/day. In some variations of formulation used in the methods described herein, the therapeutic agents are delivered at a dosage range of between about 1 µg/day and about 5 µg/day. Dosages of various therapeutic agents for treatment, prevention, inhibition, delay of onset, or cause of regression of various diseases and conditions described herein can be refined by the use of clinical trials.

[0206] When a therapeutically effective amount of rapamycin is administered to a subject suffering from wet AMD, the rapamycin may treat, inhibit, or cause regression of the wet AMD. Different therapeutically effective amounts may be required for treatment, inhibition or causing regression. A subject suffering from wet AMD may have CNV lesions, and it is believed that administration of a therapeutically effective amount of rapamycin may have a variety of effects, including but not limited to causing regression of the CNV lesions, stabilizing the CNV lesion, and preventing progression of an active CNV lesion.

Tissue Levels Achieved by Injection of the Formulations Described Herein

[0207] When the therapeutic agent is rapamycin, the self-emulsifying formulations may be used to deliver or maintain an effective amount of rapamycin in the vitreous. In one nonlimiting example, it is believed that a delivery system delivering rapamycin in an amount capable of providing a concentration of rapamycin of about 1 pg/ml to about 2 µg/ml in the vitreous may be used for treatment of wet AMD. When the rapamycin is administered intravitreally, calculation of the concentration of rapamycin in the vitreous excludes the initially administered contiguous emulsion bolus. In another nonlimiting example, it is believed that a delivery system delivering a concentration of rapamycin of

about 1 pg/mg to about 1 ng/mg in the retina or choroid may be used for treatment of wet AMD. Other effective concentrations are readily ascertainable by those of skill in the art given the teachings herein.

[0208] Described herein are self-emulsifying formulations showing in vivo clearance profiles with one or more of the following characteristics. The clearance profiles are for clearance of the therapeutic agent in vivo after injection of the self-emulsifying formulations into the vitreous of a rabbit eye. The volume of the rabbit vitreous is approximately 30-40% of the volume of the human vitreous. The amount of therapeutic agent is measured using techniques as described in Example 2, but without limitation to the formulation and therapeutic agent described in Example 2.

[0209] The average concentration of a therapeutic agent in the tissue of a rabbit eye at a given time after administration of a formulation containing the therapeutic agent may be measured according to the following method. Where volumes below 10 μ l are to be injected, a Hamilton syringe is used.

[0210] The liquid formulations are stored at a temperature of 2-8°C prior to use.

[0211] The experimental animals are specific pathogen free (SPF) New Zealand White rabbits. A mixed population of about 50% male, about 50% female is used. The rabbits are at least 12 weeks of age, usually at least 14 weeks of age, at the time of dosing. The rabbits each weigh at least 2.2 kg, usually at least 2.5 kg, at the time of dosing. Prior to the study, the animals are quarantined for at least one week and examined for general health parameters. Any unhealthy animals are not used in the study. At least 6 eyes are measured and averaged for a given timepoint.

[0212] Housing and sanitation are performed according to standard procedures used in the industry. The animals are provided approximately 150 grams of Teklad Certified Hi-Fiber Rabbit Diet daily, and are provided tap water ad libitum. No contaminants are known to exist in the water and no additional analysis outside that provided by the local water district is performed. Environmental Conditions are monitored.

[0213] Each animal undergoes a pre-treatment ophthalmic examination (slit lamp and ophthalmoscopy), performed by a board certified veterinary ophthalmologist. Ocular findings are scored according to the McDonald and Shadduck scoring system as described in *Dermatotoxicology*, F.N. Marzulli and H.I. Maibach, 1977 "Eye Irritation," T.O. McDonald and J.A. Shadduck (pages 579-582). Observations are recorded using a

standardized data collection sheet. Acceptance criteria for placement on study are as follows: scores of ≤ 1 for conjunctival congestion and swelling; scores of 0 for all other observation variables.

[0214] Gentamicin ophthalmic drops are placed into both eyes of each animal twice daily on the day prior to dosing, on the day of dosing (Day 1), and on the day after dosing (Day 2). Dosing is performed in two phases, the first including one set of animals and the second including the other animals. Animals are randomized separately into masked treatment groups prior to each phase of dosing according to modified Latin squares. Animals are fasted at least 8 hours prior to injection. The start time of the fast and time of injection are recorded.

[0215] Animals are weighed and anesthetized with an intravenous injection of a ketamine/xylazine cocktail (87 mg/mL ketamine, 13 mg/mL xylazine) at a volume of 0.1-0.2 mL/kg. Both eyes of each animal are prepared for injection as follows: approximately five minutes prior to injection, eyes are moistened with an ophthalmic Betadine solution. After five minutes, the Betadine is washed out of the eyes with sterile saline. Proparacaine hydrochloride 0.5% (1-2 drops) is delivered to each eye. For eyes to be intravitreally injected, 1% Tropicamide (1 drop) is delivered to each eye.

[0216] On Day 1, both eyes of each animal receive an injection of test or control article. Animals in selected groups are dosed a second time on Day 90 ± 1 . Dosing is subconjunctival or intravitreal. Actual treatments, injection locations, and dose volumes are masked and revealed at the end of the study.

[0217] Subconjunctival injections are given using an insulin syringe and 30 gauge x 1/2-inch needle. The bulbar conjunctiva in the dorsotemporal quadrant is elevated using forceps. Test article is injected into the subconjunctival space.

[0218] Intravitreal injections are given using an Insulin syringe and 30 gauge x 1/2-inch needle. For each injection, the needle is introduced through the ventral-nasal quadrant of the eye, approximately 2-3 mm posterior to the limbus, with the bevel of the needle directed downward and posteriorly to avoid the lens. Test article is injected in a single bolus in the vitreous near the retina.

[0219] Animals are observed for mortality/morbidity twice daily. An animal determined to be moribund is euthanized with an intravenous injection of commercial euthanasia solution. Both eyes are removed and stored frozen at -70°C for possible future evaluation.

If an animal is found dead prior to onset of rigor mortis, both eyes are removed and stored frozen at -70°C for possible future evaluation. Animals found after the onset of rigor mortis are not necropsied.

[0220] Animals are weighed at randomization, on Day 1 prior to dosing, and prior to euthanasia.

[0221] Ophthalmic observations (slit lamp and indirect ophthalmoscopy) are performed on all animals on Days 5 ± 1 , 30 ± 1 , 60 ± 1 , 90 ± 1 , and at later dates in some variations. Observations are performed by a board certified veterinary ophthalmologist. For animals to be dosed on Day 90 ± 1 , ophthalmic observations are performed prior to dosing. Ocular findings are scored according to the McDonald and Shadduck scoring system as described in *Dermatotoxicology*, F.N. Marzulli and H.I. Maibach, 1977 "Eye Irritation", T.O. McDonald and J.A. Shadduck (pages 579-582), and observations are recorded using a standardized data collection sheet.

[0222] Whole blood samples (1-3 mL per sample) are collected from each animal prior to necropsy in vacutainer tubes containing EDTA. Each tube is filled at least $2/3$ full and thoroughly mixed for at least 30 seconds. Tubes are stored frozen until shipped on dry ice.

[0223] Animals are euthanized with an intravenous injection of commercial euthanasia solution. Euthanasia is performed according to standard procedures used in the industry.

[0224] For treatment groups dosed intravitreally or subconjunctivally with placebo, all eyes from each of these groups are placed into Davidsons solution for approximately 24 hours. Following the 24-hour period, the eyes are transferred to 70% ethanol; these globes are submitted for masked histopathological evaluation by a board certified veterinary pathologist. The time that eyes are placed into Davidsons and the time of removal are recorded.

[0225] For treatment groups dosed intravitreally or subconjunctivally with test article, some eyes from each of these groups are frozen at -70°C and submitted for pharmacokinetic analysis. The remaining eyes from each of these groups are placed into Davidsons solution for approximately 24 hours. Following the 24-hour period, the eyes are transferred to 70% ethanol; these globes are submitted for masked histopathological evaluation by a board certified veterinary pathologist. The time that eyes are placed into Davidsons and the time of removal are recorded.

[0226] Frozen samples submitted for pharmacokinetic analysis are dissected with disposable instruments. One set of instruments is used per eye, and then discarded. The samples are thawed at room temperature for 1 to 2 minutes to ensure that the frost around the tissue has been removed. The sclera is dissected into 4 quadrants, and the vitreous is removed. If a non-dispersed mass (NDM) is clearly visible within the vitreous, the vitreous is separated into two sections. The section with the NDM is approximately two-thirds of the vitreous. The section without the NDM is the portion of the vitreous that is the most distant from the NDM. The aqueous humor, lens, iris, and cornea are separated. The retina choroid tissue is removed using a forceps and collected for analysis. The conjunctiva is separated from the sclera.

[0227] The various tissue types are collected into separate individual pre-weighed vials which are then capped and weighed. The vials of tissue are stored at -80°C until analyzed.

[0228] The sirolimus content of the retina choroid, sclera, vitreous humor, and whole anti-coagulated blood is determined by high-pressure liquid chromatography/tandem mass spectroscopy (HPLC/MS/MS) using 32-O-desmethoxyrapamycin as an internal standard. Where an NDM was observed in the vitreous, the section of the vitreous containing the NDM and the section of the vitreous not containing the NDM are analyzed separately.

[0229] The average concentration of a therapeutic agent over a period of time means for representative timepoints over the period of time the average concentration at each time point. For example, if the time period is 30 days, the average concentration may be measured at 5 day intervals: for the average concentration at day 5, the average of a number of measurements of concentration at day 5 would be calculated; for the average concentration at day 10, the average of a number of measurements of the concentration at day 10 would be calculated, etc.

[0230] "Average percentage in vivo" level means that an average concentration of therapeutic agent is obtained across multiple rabbit eyes for a given timepoint, and the average concentration of therapeutic agent at one timepoint is divided by the average concentration of therapeutic agent at another timepoint. In some variations of the average percentage in vivo levels, the therapeutic agent is rapamycin.

[0231] At five hours after injection into the vitreous of a rabbit eye, the average percentage in vivo clearance results in a level of therapeutic agent in the vitreous of between about 70% and about 150%, and more usually between about 90% and about

130%, and more usually between about 110% and about 120%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection. At five hours after injection into the vitreous of a rabbit eye, the average percentage therapeutic agent in the vitreous may be less than about 150%, and more usually less than about 120%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection.

[0232] At 24 hours after injection into the vitreous of a rabbit eye, the average percentage in vivo clearance results in a level of therapeutic agent in the vitreous of between about 50% and about 110%, and more usually between about 60% and about 100%, and more usually between about 70% and about 90%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection. At five hours after injection into the vitreous of a rabbit eye, the average percentage therapeutic agent in the vitreous may be less than about 100%, and more usually less than about 90%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection.

[0233] At 72 hours after injection into the vitreous of a rabbit eye, the average percentage in vivo clearance results in a level of therapeutic agent in the vitreous of between about 0.1% and about 20%, and more usually between about 1% and about 10%, and more usually between about 3% and about 7%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection. At five hours after injection into the vitreous of a rabbit eye, the average percentage therapeutic agent in the vitreous may be less than about 20%, and more usually less than about 10%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection.

[0234] At 168 hours after injection into the vitreous of a rabbit eye, the average percentage in vivo clearance results in a level of therapeutic agent in the vitreous of between about 0.01% and about 10%, and more usually between about 0.1% and about 5%, and more usually between about 0.1% and about 1%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection. At five hours after injection into the vitreous of a rabbit eye, the average percentage therapeutic agent in the vitreous may be less than about 5%, and more usually less than about 1%, as compared to the level of therapeutic agent in the vitreous 1 hour after injection.

[0235] Described is a self-emulsifying formulation for which the average percentage in vivo clearance has the following characteristics as compared to one hour after injection into the vitreous of a rabbit eye: 5 hours after injection the level of therapeutic agent is less than

about 150%; 24 hours after injection the level of therapeutic agent is less than about 100%; 72 hours after injection the level of therapeutic agent is less than about 25%; 168 hours after injection the level of therapeutic agent less than about 1%.

[0236] In some variations, the self-emulsifying formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye of at least about 10 ng/mL for at least about 3, at least about 6, at least about 9, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye of at least about 100 ng/mL for at least about 3, at least about 6, at least about 9, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye of at least about 1 $\mu\text{g/mL}$ for at least about 3, at least about 6, at least about 9, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye of at least about 10 $\mu\text{g/mL}$ for at least about 3, at least about 6, at least about 9, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye of at least about 100 $\mu\text{g/mL}$ for at least about 3, at least about 6, at least about 9, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the therapeutic agent is rapamycin.

[0237] In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye between about 10 ng/mL and about 10 $\mu\text{g/mL}$ for day 1 to at least about 2, at least about 4, at least about 6, at least about 8, at least about 10, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a

rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye between about 100 ng/mL and about 10 μ g/mL for day 1 to at least about day 2, at least about 4, at least about 6, at least about 8, at least about 10, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the therapeutic agent is rapamycin.

[0238] “Approximately constant,” as used herein, means that the average level does not vary by more than one order of magnitude over the extended period of time, i.e., the difference between the maximum and minimum is less than 10-fold for measurements of the average concentration at times in the relevant period of time.

[0239] In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye that is approximately constant at a value greater than about 10 ng/mL for day 1 to at least about 2, at least about 4, at least about 6, at least about 8, at least about 10, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye that is approximately constant at a value greater than about 100 ng/mL for day 1 to at least about 2, at least about 4, at least about 6, at least about 8, at least about 10, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye that is approximately constant at a value greater than about 1 μ g/mL for day 1 to at least about 2, at least about 4, at least about 6, at least about 8, at least about 10, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the liquid formulation when injected into the vitreous of a rabbit eye delivers therapeutic agent giving an average concentration of therapeutic agent in the vitreous of the rabbit eye that is approximately constant at a value greater than about 10 μ g/mL for day 1 to at least about 2, at least about 4, at least about 6, at least about 8, at least about 10, at least about 12, or at least about 15 days after administration of the liquid formulation to the rabbit eyes. In some variations, the therapeutic agent is rapamycin.

[0240] Described is a self-emulsifying formulation for which the average percentage in vivo clearance has the following characteristics as compared to one hour after injection: 5 hours after injection the level of therapeutic agent is less than about 125%; 24 hours after injection the level of therapeutic agent is less than about 90%; 72 hours after injection the level of therapeutic agent is less than about 10%; 168 hours after injection the level of therapeutic agent is less than about 0.5%.

[0241] Described is a self-emulsifying formulation for which the average percentage in vivo clearance has the following characteristics as compared to one hour after injection: 5 hours after injection the level of therapeutic agent is greater than about 90%; 24 hours after injection the level of therapeutic agent is greater than about 70%; 72 hours after injection the level of therapeutic agent is greater than about 5%; 168 hours after injection the level of therapeutic agent is greater than about 0.1%.

[0242] For treatment, prevention, inhibition, delaying the onset of, or causing the regression of certain diseases or conditions, it may be desirable to maintain delivery of a therapeutically effective amount of the therapeutic agent for an extended period of time. Depending on the disease or condition being treated, prevented, inhibited, having onset delayed, or being caused to regress this extended period of time may be up to 1 week, up to 2 weeks, up to 3 weeks, up to 1 month, up to 3 months, up to 6 months, up to 9 months, or up to 1 year. Generally, however, any extended period of delivery may be possible. A therapeutically effective amount of agent may be delivered for an extended period by a self-emulsifying formulation that maintains for the extended period a concentration of agent in the eye sufficient to deliver a therapeutically effective amount of agent for the extended time.

[0243] Delivery of a therapeutically effective amount of the therapeutic agent for an extended period may be achieved using application of one self-emulsifying formulation or may be achieved by application of two or more doses of self-emulsifying formulations. As a non-limiting example of such multiple applications, maintenance of the therapeutic amount of rapamycin for 3 months for treatment of wet or dry AMD may be achieved by application of one self-emulsifying formulation delivering a therapeutic amount for 3 months or by sequential application of a plurality of self-emulsifying formulations. The optimal dosage regime will depend on the therapeutic amount of the therapeutic agent needing to be delivered, and the period over which it need be delivered. Those versed in

such extended therapeutic agent delivery dosing will understand how to identify dosing regimes that may be used.

[0244] When using certain therapeutic agents or for the treatment, prevention, inhibition, delaying the onset of, or causing the regression of certain diseases, it may be desirable for delivery of the therapeutic agent not to commence immediately upon placement of the formulation into the eye region, but for delivery to commence after some delay. For example, but in no way limiting, such delayed release may be useful where the therapeutic agent inhibits or delays wound healing and delayed release is desirable to allow healing of any wounds occurring upon placement of the formulation. Depending on the therapeutic agent being delivered and/or the diseases and conditions being treated or prevented this period of delay before delivery of the therapeutic agent commences may be about 1 hour, about 6 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 21 days, about 28 days, about 35 days, or about 42 days. Other delay periods may be possible. Delayed release formulations that may be used are described herein and other delayed release formulations that may be used will be clear to people versed in the technology given the teachings herein.

Method of preparing self-emulsifying formulations

[0245] One nonlimiting method that may be used for preparing the self-emulsifying formulations described herein, including but not limited to self-emulsifying formulations comprising rapamycin, is by mixing a solvent, a therapeutic agent, and a surfactant together at room temperature or at slightly elevated temperature until a relatively clear solution is obtained, and then cooling the formulation. Other optional additives such as those described above may then be mixed with the formulation. Other methods may be used, and will be familiar to those of skill in the art given the teachings herein.

Intravitreal delivery of rapamycin for treatment of AMD

[0246] In some variations described herein, a self-emulsifying formulation comprising rapamycin is delivered to the vitreous of an eye to prevent, treat, inhibit, delay onset of, or cause regression of angiogenesis in the eye, such as to prevent, treat, inhibit, delay onset of,

or cause regression of CNV as observed, for example, in AMD. Rapamycin has been shown to inhibit CNV in rat and mice models, as described in U.S. Application No. 10/665,203, which is incorporated herein by reference in its entirety. Rapamycin has been observed to inhibit MatrigelTM and laser-induced CNV when administered systemically and subretinally. Also, periocular injection of rapamycin inhibits laser-induced CNV.

[0247] Other therapeutic agents that may be delivered to the eye, particularly the vitreous of an eye, for treatment, prevention, inhibition, delaying onset, or causing regression of angiogenesis in the eye (such as CNV) are members of the limus family of compounds other than rapamycin including but not limited to everolimus and tacrolimus (FK-506).

[0248] As described herein, the dosage of the therapeutic agent will depend on the condition being addressed, whether the condition is to be treated, prevented, inhibited, have onset delayed, or be caused to regress, the particular therapeutic agent, and other clinical factors such as weight and condition of the subject and the route of administration of the therapeutic agent. It is to be understood that the methods and self-emulsifying formulations described herein have application for both human and veterinary use, as well as uses in other possible animals. In the case of delivering rapamycin to a human in order to inhibit CNV, one inhibiting amount of the compound has been demonstrated to be one that provides about 10 ng/ml at the tissue level. This concentration of rapamycin, as well as higher and lower concentrations may be used in the methods described herein. One concentration of rapamycin that may be used in the methods described herein is one that provides about 1 ng/ml or less of rapamycin at the tissue level; another concentration that may be used is one that provides about 2 ng/ml or less at the tissue level, another concentration that may be used is one that provides about 3 ng/ml or less at the tissue level; another concentration that may be used is one that provides about 5 ng/ml or less at the tissue level; another concentration that may be used is one that provides about 10 ng/ml or less at the tissue level; another concentration that may be used is one that provides about 15 ng/ml or less at the tissue level; another concentration that may be used is one that provides about 20 ng/ml or less at the tissue level; another concentration that may be used is one that provides about 30 ng/ml or less at the tissue level; another concentration that may be used is one that provides about 50 ng/ml or less at the tissue level. One of ordinary skill in the art would know how to arrive at an appropriate concentration depending on the route and duration of administration utilized, given the teachings herein.

[0249] Delivery of the disclosed therapeutic agents may, for example, be delivered at a dosage range of between about 1 picogram/kg/day and about 300 mg/kg/day (with reference to the body weight of the subject), or at dosages higher or lower than this range, depending on the route and duration of administration. In some methods of using the self-emulsifying formulation described herein, the therapeutic agents are delivered at a dosage range of between about 1 picogram/kg/day and about 3 mg/kg/day. Dosages of various therapeutic agents for treating various diseases and conditions described herein can be refined by the use of clinical trials.

[0250] The self-emulsifying formulations described herein may be used for delivery to the eye, particularly to aqueous media of the eye including but not limited to the vitreous, aqueous humor, sclera, conjunctiva, and the area in between the sclera and conjunctiva, and other aqueous environments, of therapeutically effective amounts of rapamycin for extended periods of time to treat, prevent, inhibit, delay the onset of, or cause regression of CNV, and thus may be used to treat, prevent, inhibit, delay the onset of, or cause regression of wet or dry AMD. It is believed that by changing certain characteristics of the self-emulsifying formulations described herein, including but not limited to the components of the self-emulsifying formulations, the location in the eye to which the formulation is delivered, including without limitation to the vitreous or between the sclera and conjunctiva, and the volume administered, the self-emulsifying formulations described herein may be used to deliver therapeutically effective amounts of rapamycin to the eye for a variety of extended time periods including delivery of therapeutic amounts for greater than about 1 week, for greater than about 2 weeks, for greater than about 3 weeks, for greater than about 1 month, for greater than about 3 months, for greater than about 6 months, for greater than about 9 months, for greater than about 1 year.

[0251] When a therapeutically effective amount of rapamycin is administered to a subject suffering from wet AMD, the rapamycin may treat, inhibit, or cause regression of the wet AMD. Different therapeutically effective amounts may be required for treatment, inhibition or causing regression. A subject suffering from wet AMD may have CNV lesions, and it is believed that administration of a therapeutically effective amount of rapamycin may have a variety of effects, including but not limited to causing regression of the CNV lesions, stabilizing the CNV lesion, and preventing progression of an active CNV lesion.

[0252] When a therapeutically effective amount of rapamycin is administered to a subject suffering from dry AMD, it is believed that the rapamycin may prevent or slow the progression of the dry AMD.

[0253] Described herein are self-emulsifying formulations showing in vivo clearance profiles with one or more of the following described characteristics. The clearance profiles are for clearance of rapamycin in vivo after injection of the self-emulsifying formulations into the vitreous of a rabbit eye. The volume of rabbit eyes is approximately 30-40% of human eyes. The amount of rapamycin is measured using techniques as described in Example 2, but without limitation to the formulation described in Example 2.

[0254] At five hours after injection, the average percentage in vivo clearance results in a level of rapamycin in the vitreous of between about 70% and about 150%, and more usually between about 90% and about 130%, and more usually between about 110% and about 120%, as compared to the level of rapamycin in the vitreous 1 hour after injection. At five hours after injection, the average percentage rapamycin in the vitreous may be less than about 150%, and more usually less than about 120%, as compared to the level of rapamycin in the vitreous 1 hour after injection.

[0255] At 24 hours after injection, the average percentage in vivo clearance results in a level of rapamycin in the vitreous of between about 50% and about 110%, and more usually between about 60% and about 100%, and more usually between about 70% and about 90%, as compared to the level of rapamycin in the vitreous 1 hour after injection. At five hours after injection, the average percentage of rapamycin in the vitreous may be less than about 100%, and more usually less than about 90%, as compared to the level of rapamycin in the vitreous 1 hour after injection.

[0256] At 72 hours after injection, the average percentage in vivo clearance results in a level of rapamycin in the vitreous of between about 0.1% and about 20%, and more usually between about 1% and about 10%, and more usually between about 3% and about 7%, as compared to the level of rapamycin in the vitreous 1 hour after injection. At five hours after injection, the average percentage rapamycin in the vitreous may be less than about 20%, and more usually less than about 10%, as compared to the level of rapamycin in the vitreous 1 hour after injection.

[0257] At 168 hours after injection, the average percentage in vivo clearance results in a level of rapamycin in the vitreous of between about 0.01% and about 10%, and more

usually between about 0.1% and about 5%, and more usually between about 0.1% and about 1%, as compared to the level of rapamycin in the vitreous 1 hour after injection. At five hours after injection, the average percentage rapamycin in the vitreous may be less than about 5%, and more usually less than about 1%, as compared to the level of rapamycin in the vitreous 1 hour after injection.

[0258] Described is a self-emulsifying formulation for which the average percentage in vivo clearance has the following characteristics as compared to one hour after injection: 5 hours after injection the level of rapamycin is less than about 150%; 24 hours after injection the level of rapamycin is less than about 100%; 72 hours after injection the level of rapamycin is less than about 25%; 168 hours after injection the level of rapamycin is less than about 1%.

[0259] Described is a self-emulsifying formulation for which the average percentage in vivo clearance has the following characteristics as compared to one hour after injection: 5 hours after injection the level of rapamycin is less than about 125%; 24 hours after injection the level of rapamycin is less than about 90%; 72 hours after injection the level of rapamycin is less than about 10%; 168 hours after injection the level of rapamycin is less than about 0.5%.

[0260] Described is a self-emulsifying formulation for which the average percentage in vivo clearance has the following characteristics as compared to one hour after injection: 5 hours after injection the level of rapamycin is greater than about 90%; 24 hours after injection the level of rapamycin is greater than about 70%; 72 hours after injection the level of rapamycin is greater than about 5%; 168 hours after injection the level of rapamycin is greater than about 0.1%.

EXAMPLES

[0261] Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Celsius, and pressure is at or near atmospheric. Unless the context indicates otherwise, the error bars in the charts show one standard deviation. Where ethanol is used, it is 200 proof ethanol from Gold Shield Distributors, Hayward, CA. Where rapamycin is used, it is from LC laboratories, Woburn, MA, or Chungwha Chemical Synthesis & Biotech Co., LTD (CCSB), Taipei Hsien, Taiwan, ROC. Where PEG 400 is used, it is from The Dow Chemical Company, New Milford, CT. By

w/w is meant the weight of a particular component relative to the final weight of the formulation.

Example 1 – Preparation and Characterization of a Rapamycin-Containing Self-Emulsifying Formulation

[0262] 1.47% rapamycin w/w was dissolved in 11.77% ethanol w/w, followed by gentle mixing with 43.44% Cremophor EL w/w and 43.44% Capmuls PG8 w/w. The formulation was translucent. When contacted with aqueous media, i.e. water or the vitreous of a rabbit eye, the formulation formed a microemulsion and turned “cloudy” or “milky,” as opposed to forming a non-dispersed mass.

Example 2 – Injection of a Rapamycin-Containing Self-emulsifying Formulation Into the Vitreous of an Eye

[0263] 50 μ l of the formulation described in Example 1 were injected into the vitreous of the eye of New Zealand white rabbits. The full vitreous, which included the area into which the self-emulsifying formulation was injected, was homogenized and analyzed at 1, 5, 24, 72 and 168 hours for the concentration of rapamycin remaining therein. The average concentration of the vitreous was calculated by dividing the mass of rapamycin measured by the volume of vitreous analyzed. The analysis was by liquid chromatography mass spectroscopy (LCMS). Each timepoint represents the average of two eyes of each of two rabbits (four eyes at each timepoint).

[0264] The average concentration of rapamycin at 1, 5, 24, 72 and 168 hours was about 347, about 401, about 273, about 18, and about 1 μ g/ μ l, respectively. These results are shown Figure 1.

Example 3 – Preparation and Characterization of a Rapamycin-Containing Self-Emulsifying Formulation

[0265] Rapamycin was dissolved in 100% ethanol, followed by gentle mixing with Caprol MPGO and Softigen 767. Final percentages by weight of the total were 2% w/w rapamycin, 4% w/w ethanol, 47% w/w Caprol MPGO and w/w 47% Softigen 767.

[0266] All references cited herein, including patents, patent applications, and publications, are hereby incorporated by reference in their entireties, whether previously specifically incorporated or not.

WHAT IS CLAIMED IS:

1. A method for treating age-related macular degeneration in a human, the method comprising administering to an eye of a subject a self-emulsifying formulation comprising a therapeutic agent in an amount effective to treat age-related macular degeneration.
2. The method of claim 1, wherein the self-emulsifying formulation when injected into the vitreous of a rabbit eye delivers an amount of the therapeutic agent sufficient to achieve an average concentration of therapeutic agent in the retina choroid of the rabbit eye equivalent to a rapamycin concentration of at least about 0.001 ng/ml for a period of time of at least about 7 days following administration of the self-emulsifying formulation to the rabbit eye.
3. The method of claim 2, wherein the self-emulsifying formulation when injected into the vitreous of a rabbit eye delivers an amount of the therapeutic agent sufficient to achieve an average concentration of therapeutic agent in the retina choroid of the rabbit eye equivalent to a rapamycin concentration of at least about 0.01 ng/ml for a period of time of at least about 7 days following administration of the self-emulsifying formulation to the rabbit eye.
4. The method of claim 3, wherein the self-emulsifying formulation when injected into the vitreous of a rabbit eye delivers an amount of the therapeutic agent sufficient to achieve an average concentration of therapeutic agent in the retina choroid of the rabbit eye equivalent to a rapamycin concentration of at least about 0.1 ng/ml for a period of time of at least about 7 days following administration of the self-emulsifying formulation to the rabbit eye.
5. The method of claim 2, wherein the self-emulsifying formulation when injected into the vitreous of a rabbit eye delivers an amount of the therapeutic agent sufficient to achieve an average concentration of therapeutic agent in the retina choroid of the

rabbit eye equivalent to a rapamycin concentration of at least about 1 ng/ml for a period of time of at least about 7 days following administration of the self-emulsifying formulation to the rabbit eye.

6. The method of claim 1, wherein the therapeutic agent is an immunophilin binding compound.
7. The method of claim 1, wherein the therapeutic agent is selected from the group consisting of rapamycin, SDZ-RAD, tacrolimus, everolimus, pimecrolimus, CCI-779, AP23841, ABT-578, and analogs, salts and esters thereof.
8. The method of claim 7, wherein the therapeutic agent is rapamycin.
9. The method of claim 1, wherein the self-emulsifying formulation is placed in an aqueous medium of the eye of the subject.
10. The method of claim 9, wherein the self-emulsifying formulation is placed into the vitreous of an eye of the subject.
11. The method of claim 9, wherein the self-emulsifying formulation is placed between the sclera and conjunctiva of an eye of the subject.
12. The method of claim 1, wherein the self-emulsifying formulation further comprises a solvent.
13. The method of claim 12, wherein the self-emulsifying formulation further comprises a surfactant.
14. The method of claim 13, wherein the surfactant is a nonionic surfactant.
15. The method of claim 14, wherein the nonionic surfactant has an HLB value greater than about 10.

16. The method of claim 15, wherein, wherein the nonionic surfactant is Cremophor EL.
17. The method of claim 12, wherein the solvent is a fatty acid.
18. The method of claim 12, wherein the solvent is selected from the group consisting of oleic acid, Imwitor 742, Softigen 767, or Capmuls PG8.
19. A method for treating a disease or disorder in a human, the method comprising administering to an eye of a human subject a self-emulsifying formulation comprising rapamycin in an amount effective to treat one or more of choroidal neovascularization, iris neovascularization, macular degeneration, wet AMD, dry AMD, uveitis, allergic conjunctivitis, dry eye, glaucoma, retinitis pigmentosa, central retinal vein occlusive diseases, macular edema, diabetic retinopathy, and corneal graft disease.
20. The method of claim 19, wherein the rapamycin is present in an amount effective to treat wet AMD.
21. The method of claim 19, wherein the rapamycin is present in an amount effective to prevent wet AMD.
22. The method of either of claims 20 or 21, wherein the self-emulsifying formulation is placed in the vitreous of the subject's eye.
23. The method of either of claims 20 or 21, wherein the self-emulsifying formulation is placed between the sclera and conjunctiva of the subject's eye.
24. The method of claim 22, wherein the self-emulsifying formulation contains between about 20 μg and about 4 mg.

25. The method of claim 23, wherein the self-emulsifying formulation contains between about 20 μg and about 4 mg.
26. The method of either of claims 22 or 23, wherein the self-emulsifying formulation contains between about 20 μg and about 1 mg.
27. A self-emulsifying formulation comprising an amount of an immunophilin binding compound effective to treat wet AMD, dry AMD, or CNV; a solvent; and a surfactant, wherein the self-emulsifying formulation is formulated for placement in an aqueous medium of an eye of a subject.
28. A self-emulsifying formulation comprising an amount of an immunophilin binding compound effective to prevent wet AMD; a solvent; and a surfactant, wherein the self-emulsifying formulation is formulated for placement in an aqueous medium of an eye of a subject.
29. The self-emulsifying formulation of claim 28, wherein the compound is selected from the group consisting of rapamycin, SDZ-RAD, tacrolimus, everolimus, pimecrolimus, CCI-779, AP23841, ABT-578, and analogs, salts and esters thereof.
30. The self-emulsifying formulation of claim 29, wherein the compound is rapamycin.
31. The self-emulsifying formulation of claim 30, wherein the self-emulsifying formulation when administered to a subject delivers an amount of rapamycin effective to treat choroidal neovascularization in the subject.
32. The self-emulsifying formulation of claim 30, wherein the self-emulsifying formulation when administered to a subject delivers an amount of rapamycin effective to treat wet age-related macular degeneration in the subject.

33. The self-emulsifying formulation of claim 30, wherein the self-emulsifying formulation when administered to a subject delivers an amount of rapamycin effective to prevent wet age-related macular degeneration in the subject.
34. The self-emulsifying formulation of claim 30, wherein the surfactant is nonionic.
35. The self-emulsifying formulation of claim 30, wherein the surfactant has an HLB value greater than about 10.
36. The self-emulsifying formulation of claim 30, wherein the solvent is a fatty acid.
37. The self-emulsifying formulation of claim 30, wherein the solvent is selected from the group consisting of oleic acid, Imwitor 742, Softigen 767, or Capmuls PG8.
38. The self-emulsifying formulation of claim 34, wherein the nonionic surfactant is Cremophor EL.
39. The self-emulsifying formulation of claim 34, wherein the self-emulsifying formulation contains between 0.1 to 5% w/w rapamycin; between about 40 to 50% w/w solvent; and between 40 to 50% w/w non-ionic surfactant.
40. The self-emulsifying formulation of claim 39, further comprising ethanol.

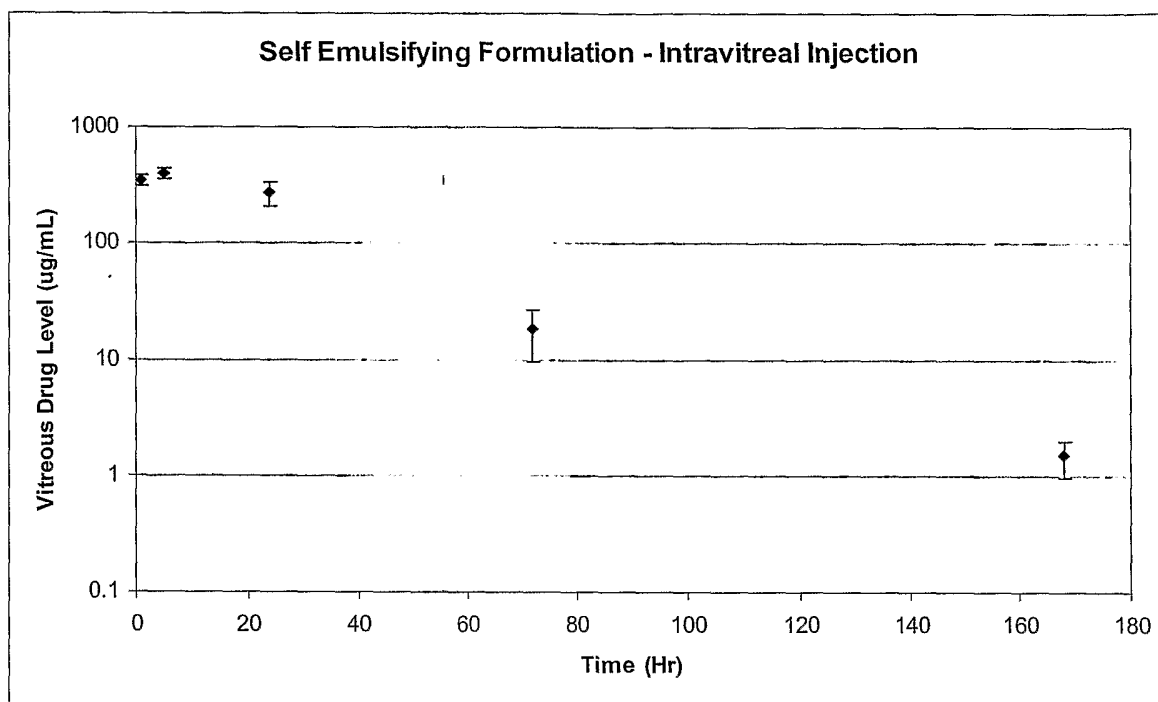


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US06/04955

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 31/44(2006.01)

USPC: 514/291

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/291

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,387,589 A (KULKARNI) 07 February 1995 (07.02.1995), see the entire document.	1-40

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

<p>“A” document defining the general state of the art which is not considered to be of particular relevance</p> <p>“E” earlier application or patent published on or after the international filing date</p> <p>“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>“O” document referring to an oral disclosure, use, exhibition or other means</p> <p>“P” document published prior to the international filing date but later than the priority date claimed</p>	<p>“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>“&” document member of the same patent family</p>
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Date of the actual completion of the international search

30 April 2006 (30.04.2006)

Date of mailing of the international search report

30 MAY 2006

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