LIQUID DEPOT FOR NON-INVASIVE SUSTAINED DELIVERY OF AGENTS TO THE EYE

RELATED APPLICATION

[0001] This Application claims priority benefit of U.S. Provisional Application No. 62/665,367, filed May 1, 2018, which is incorporated fully herein for all purposes.

[0002] The present embodiments provide compositions and methods for the treatment of ocular conditions or maladies.

BACKGROUND

[0003] There remains a need for noninvasive, sustained delivery of pharmaceutical agents to tissues and liquid portions of the eye, such as the conjunctiva, cornea, or aqueous humor.

SUMMARY

[0003a] In one aspect, the present disclosure refers to a liquid depot for sustained release of an active agent in the eye, the liquid depot comprising: a tocopherol; an ocular film-forming excipient which are triglycerides or glycerides, wherein the tocopherol:ocular film-forming excipient is at a weight ratio of 90:10 to 60:40; and an active agent, which is a corticosteroid; wherein the liquid depot has a viscosity of ~~about~~ 850 cP to ~~about~~ 1100 cP, inclusive and water has a viscosity of 1.00 cP.

[0003b] In another aspect, the present disclosure refers to a kit comprising at least one single-use dispenser, wherein the at least single-use dispenser comprises the liquid depot disclosed herein.

[0003c] In yet another aspect, the present disclosure refers to a use of a liquid depot comprising (a) at least one active agent, which is a corticosteroid; and (b) a mixture of ~~mixture of~~ tocopheryl acetate:medium-chain triglycerides at a weight ratio of ~~about~~ 90:10 to ~~about~~ 60:40, in the manufacture of a medicament for treating a malady of the eye in a subject, wherein the medicament is to be topically administered to the eye of the subject.

~~**[0003d]** In a further aspect, the present disclosure refers to a liquid depot comprising: a tocopherol; an ocular film-forming excipient; and, optionally, an active agent;~~

~~wherein the liquid depot has a viscosity of about 850 cP to about 1100 cP, inclusive.~~

~~**[0003e]** In another aspect, the present disclosure refers to a use of a liquid depot disclosed herein in the manufacture of a medicament for providing a protective coating to the eye, wherein the medicament is to be instilled into the eye.~~

~~**[0003f]** In yet another aspect, the present disclosure refers to a liquid depot comprising (a) at least one active agent; and (b) a mixture of mixture of tocopheryl acetate:medium-chain~~

~~triglycerides at a weight ratio of about 90:10 to about 60:40, for use in treating a malady of the eye in a subject.~~

~~**[0003g]** In a further aspect, the present disclosure refers to a liquid depot disclosed herein for use in providing a protective coating to the eye.~~

[0004] The present examples provide compositions and methods for treating or preventing ocular ailments via a non-invasive liquid depot capable of delivering at least one pharmaceutical agent to the eye for days or weeks. This liquid depot is biocompatible and adapts to the shape of the eye, forming a thin film or flat bubble that covers the exterior tissues of the eye (e.g., conjunctiva, corneal surface) and is resistant to lacrimation (e.g., tears); although this film remains in place for days or over a week, it does not impair vision after initial instillation; and instillation is mediated, at least in part, by viscosity of the liquid depot; this depot formulation can be used to deliver pharmaceutical agent(s) to various parts of the eye where it can be detected for over the course of days or in some circumstances, over three weeks after a single administration. Remarkably, although this liquid depot remains on the outside of the eye, pharmaceutical agent(s) can be delivered into ocular tissues (e.g., cornea) and fluids (e.g., the aqueous humor) inside the eye for at least an entire day, at least three (3) days, and in some examples, at least seven (7) days. As such, effective intermittent administration (e.g., once a day, once every 3 days, or longer) of a single-dose liquid depot comprising at least one pharmaceutical agent is made possible with the present examples, in marked contrast to the multiple daily doses required with current commercial ocular formulations.

[0005] The liquid depot described herein provides sustained release of pharmaceutical agent(s) at a steadier release rate (i.e., decreased “spike”), fewer side effects, and/or with superior efficacy compared with current aqueous-based eye drops. In some examples, the continuous levels of pharmaceutical agent released from the liquid depot provides efficacious

CLAIMS

1. A liquid depot for sustained release of an active agent in the eye, the liquid depot comprising: a tocopherol; an ocular film-forming excipient which are triglycerides or glycerides, wherein the tocopherol:ocular film-forming excipient is at a weight ratio of 90:10 to 60:40; and an active agent, which is a corticosteroid; wherein the liquid depot has a viscosity of ~~about~~ 850 cP to ~~about~~ 1100 cP, inclusive and water has a viscosity of 1.00 cP.

2. The liquid depot of claim 1, wherein the tocopherol is α-, β-, γ- or δ-tocopherol, or α-, β-, γ- or δ-tocotrienol.

3. The liquid depot of any one of claims 1-2, wherein the tocopherol is an α-, β-, γ-, or δ-tocopherol.

4. The liquid depot of any one of claims 1-3, wherein the tocopherol is tocopheryl acetate.

5. The liquid depot of any one of claims 1-4, wherein the ocular film-forming excipient consists of medium-chain triglycerides.

~~6. The liquid depot of any one of claims 1-5, wherein the active agent is a corticosteroid.~~

~~7~~6. The liquid depot of claim ~~6~~1, wherein the corticosteroid is a member selected from the group consisting of dexamethasone, prednisolone, prednisone, loteprednol, triamcinolone and fluorometholone.

~~8~~7. The liquid depot of claim 7, wherein the liquid depot comprises (a) ~~about~~ 10% dexamethasone; and (b) ~~about~~ 90% of a mixture of tocopheryl acetate:medium-chain triglycerides at a ratio of ~~about~~ 90:10 to ~~about~~ 60:40.

~~9~~8. The liquid depot of claim 5, wherein the liquid depot comprises, on a wt% basis, (a) ~~about~~ 10% prednisolone and (b) ~~about~~ 90% of a mixture of tocopheryl acetate:medium-chain triglycerides at wt/wt a ratio of ~~about~~ 80:20.

~~10~~9. The liquid depot of claim 7, wherein the liquid depot comprises, on a wt% basis, (a) ~~about~~ 10% loteprednol and (b) ~~about~~ 90% of a mixture of tocopheryl acetate:medium-chain triglycerides at wt/wt a ratio of ~~about~~ 80:20.

~~11~~10. The liquid depot of any one of claims 1-5, wherein the active agent is an anti-infective.

~~12~~11. The liquid depot of any one of claims 1-~~7~~ 6 further comprising an anti-infective.

~~13~~12. The liquid depot of claim ~~11~~ 10 or ~~12~~11, wherein the anti-infective is moxifloxacin.

~~14~~13. The liquid depot of claim ~~12~~11, wherein the liquid depot comprises (a) ~~about~~ 10%-20% moxifloxacin; and (b) ~~about~~ 80%-90% of a mixture of tocopheryl acetate:medium-chain triglycerides at a ratio of ~~about~~ 70:30.

~~15~~14. The liquid depot of claim ~~12~~11, wherein the liquid depot comprises, on a wt% basis (a) ~~about~~ 15% ciprofloxacin; and (b) ~~about~~ 85% of a mixture of tocopheryl acetate:medium-chain triglycerides at a ratio of ~~about~~ 70:30.

~~16~~15. The liquid depot of claim ~~12~~11, wherein the liquid depot comprises, on a wt% basis (a) ~~about~~ 10% gatifloxacin; and (b) ~~about~~ 90% of a mixture of tocopheryl acetate:medium-chain triglycerides at a ratio of ~~about~~ 70:30.

~~17~~16. The liquid depot of any one claim claims 1-~~6~~5, comprising dexamethasone and moxifloxacin in a mixture of tocopheryl acetate:medium-chain triglycerides at a ratio of ~~about~~ 90:10 to ~~about~~ 60:40.

~~18~~17. The liquid depot of any one of the preceding claims, wherein the liquid depot is disposed within a single-use dispenser.

~~19~~18. A kit comprising at least one single-use dispenser, wherein the at least single-use dispenser comprises the liquid depot of any one of claims 1-~~18~~17.

~~20~~19. Use of a liquid depot comprising (a) at least one active agent, which is a corticosteroid; and (b) a mixture of ~~mixture of~~ tocopheryl acetate:medium-chain triglycerides at a weight ratio of ~~about~~ 90:10 to ~~about~~ 60:40, in the manufacture of a medicament for treating a malady of the eye in a subject, wherein the medicament is to be topically administered to the eye of the subject.

~~21~~20. The use of claim ~~20~~19, wherein the medium-chain triglycerides is at least one MIGLYOL® neutral oil.

~~22~~21. The use of claim ~~20~~ 19 or ~~21~~20, wherein the malady of the eye is inflammation, infection, allergic reaction, or glaucoma.

~~23~~22. The use of claim ~~20~~ 19 or ~~21~~20, wherein the malady of the eye is infection, corneal abrasion or other trauma to the eye surface, blepharitis, inflammatory meibomian gland disease, meibomian gland dysfunction, allergic conjunctivitis, chronic conjunctivitis, Sjögren's syndrome, dry eye (keratoconjunctivitis sicca), aqueous-deficient dry eye, mucin-deficient dry eye (punctate epithelial keratitis), episcleritis, keratitis (corneal ulcers), pterigia, Stevens-Johnson syndrome, ocular citatrical pemphigoid/mucous membrane pemphigoid, irregular cornea condition or other surface abnormalities, epitheliopathy, neurotrophic cornea, corneal dystrophy such as Fuch's dystrophy, peripheral or marginal degeneration of the cornea, conjunctivochalasis, glaucoma, conjunctival degeneration such as pinguecula, or pingueculitis.

~~24~~23. The use of any one of claims ~~20-21~~19-20, wherein the medicament is to be intermittently administered.

~~25~~24. The use of claim ~~24~~23, wherein the medicament is to be intermittently administered for at least ~~about~~ 24 hours, 48 hours, 72 hours (3 days), 4 days, 5 days, 6 days, 7 days (1 week), 14 days (2 weeks), or 21 days (3 weeks).

~~26~~25. The use of claim ~~24~~23, wherein the medicament is to be intermittently administered for at least ~~about~~ 24 hours.

~~27. A liquid depot comprising: a tocopherol; an ocular film-forming excipient; and, optionally, an active agent;~~

~~wherein the liquid depot has a viscosity of about 850 cP to about 1100 cP, inclusive.~~

~~28. The liquid depot of claim of claim 27, consisting of a tocopherol; an ocular film-forming excipient, wherein the ocular film-forming excipient is a triglyceride or mixture of triglycerides.~~

~~29. The liquid depot of claim of claim 27, wherein the ocular film-forming excipient is MIGLYOL® decanoyl/octanoyl glycerides.~~

~~30. The liquid depot of any one of claims 27-30, wherein the tocopherol is tocopheryl acetate.~~

~~31. The liquid depot of any one of claims 27-30, wherein the weight ratio of tocopherol to film-forming agent is in a range of about 60:40 to about 90:10.~~

~~32. Use of a liquid depot of any one of claims 27-31 in the manufacture of a medicament for providing a protective coating to the eye, wherein the medicament is to be instilled into the eye.~~

~~33. The use of claim 32, wherein the instilling into the eye is to be intermittently repeated.~~

~~34. A liquid depot comprising (a) at least one active agent; and (b) a mixture of mixture of tocopheryl acetate:medium-chain triglycerides at a weight ratio of about 90:10 to about 60:40, for use in treating a malady of the eye in a subject.~~

~~35. A liquid depot of any one of claims 27-31 for use in providing a protective coating to the eye.~~