Tear is comprised of aqueous, mucin and lipid components. With each and every blink, the aqueous and lipid components are intimately mixed and the aqueous and lipid components self sort into the inner aqueous and outer lipid layers of the tear film. Within the lipid layer, polar and nonpolar lipids self sort with the polar lipids forming a monolayer at the aqueous layer interface and the non-polar lipids forming a thicker outer layer of the tear film lipid layer which directly interfaces with air. The non-polar outer layer of the tear film lipid layer (TFLL) can be from 5 to 50 molecules thick. An adequate and consistent layer of tear on the surface of the eye is essential to keep the eyes healthy, comfortable and seeing well. The tear film bathes the eye's surface to keep it moist and wash away dust, debris and microorganisms that could damage the cornea and lead to an eye inflammation and/or infection. As noted, a normal tear film consists of three important components: an oily (lipid) component; a watery (aqueous) component; and a mucous-like (mucin) component. Each component of the tear film serves a critical purpose. For example, tear lipids help keep the tear film aqueous layer from evaporating too quickly and increase lubrication, while mucins (soluble and cell associated) help anchor and spread the tears across the living surface of the corneal epithelium. The aqueous component is the thickest layer of the precorneal tear film and contains a variety of proteins including immunoglobulins and lysozyme that serve in preventing microbial colonization. The tear film is described in Yanez-Soto et al., Interfacial phenomena and the ocular surface, Ocul Surf. 2014 Jul;12(3):178-201, which is incorporated herein by reference in its entirety.

Each tear component is produced by different glands on or near the eye. The oily component is produced by meibomian glands in the eyelids as well as from harderian glands in species that possess one (e.g. rabbits). The aqueous component is produced by lacrimal glands located behind the outer aspect of the upper eyelids (in humans). Many vertebrate species also possess accessory lacrimal glands (e.g., the accessory lacrimal gland associated with the third eyelid of dogs). The soluble mucin component is produced by goblet cells in the conjunctiva that covers the white of the eye (sclera). A problem with any of these sources of tear film components can result in tear instability and dry eye.

What is needed in the art are effective treatments for dry eye, as well as effective delivery systems for those treatments.

SUMMARY

The present disclosure relates to drug delivery vehicles comprising micronized particles that include an active lipid agent, and in particular to micronized lipid particles that

comprise an ether lipid such as *sn*-1-O-eicosanyl-*sn*-2-palmitoyl-glycerol and its isomers, analogs and homologs as both the drug delivery vehicle and active lipid agent.

In an aspect, there is provided a lipid particle composition comprising solid non-polar lipid particles comprising an active lipid agent and having an average particle size of less than 50 microns stably suspended in a buffered aqueous vehicle suitable for topical administration.

In another aspect, there is provided the use of a lipid particle composition as defined above in the manufacture of a medicament in treating a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment.

In another aspect, there is provided a drug delivery vehicle comprising solid non-polar lipid particles having an average particle size of less than 50 microns, the particles comprising an active agent other than the lipids forming the solid non-polar lipid particles.

In another aspect, there is provided the use of a drug delivery vehicle as defined above in the manufacture of a medicament in treating a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment.

In some preferred examples, the present disclosure provides a drug delivery vehicle comprising crystalline and amorphous solid micronized lipid particles having an average particle size of less than 100 microns, the particles comprising an active agent and wherein the drug delivery vehicle is selected from the group selected from a therapeutic composition, a physiologically compatible carrier and a medical insert device.

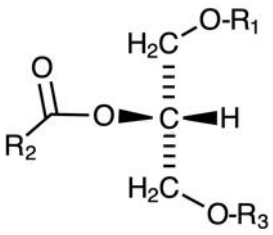
In an example, the present disclosure provides a lipid particle composition comprising solid non-polar lipid particles comprising an active lipid agent and having an average particle size of less than 50 microns stably suspended in a buffered aqueous vehicle suitable for topical administration.

In some preferred examples, the solid non-polar lipid particles have a melting point of less than 80 degrees C. In some preferred examples, the solid

non-polar lipid particles have a melting point of from 20 to 80 degrees C. In some preferred examples, the solid non-polar lipid particles have a melting point of from 30 to 60 degrees C. In some preferred examples, the solid non-polar lipid particles have an average particle size of less than 20 microns. In some preferred examples, the solid non-polar lipid particles have an average particle size of less than 10 microns.

In some preferred examples, the active lipid agent is a non-polar ether lipid.

In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of:

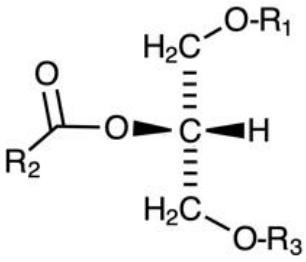


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H)

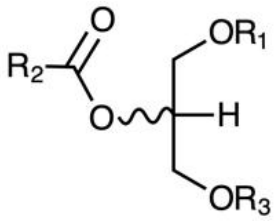


wherein

R_1 is a hydrogen (i.e., H);

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



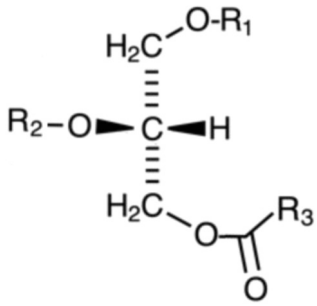
wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H).

In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of:

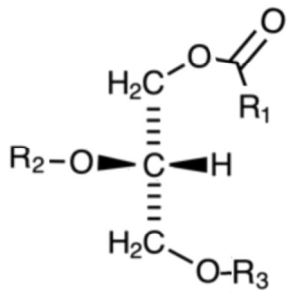


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl;

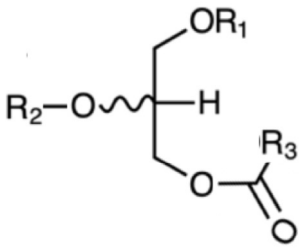


wherein

R_1 is an unsubstituted C5 to C29 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl.

In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG), *sn*-1-O-eicosanyl-2-palmitoyl-glycerol, *sn*-2-palmitoyl-3-O-eicosanyl-glycerol, 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG), *sn*-1-O-eicosanyl-3-palmitoyl-glycerol, *sn*-1-palmitoyl-3-O-eicosanyl-glycerol and mixtures thereof. In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) or 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) and mixtures thereof.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG)

is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 95% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 98% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 98% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 99% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 99% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 50% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 50% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising no greater than 50% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and more than 50% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 5% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 98% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 2% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 99% (mole percent) of the 1-O-eicosanyl-2-

palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 1% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the solid non-polar lipid particles further comprise one or more additional lipids selected from the group consisting of a nonpolar mono-, di- or tri- glyceride, a wax ester including cholesterol esters, a sterol, a free fatty acid and combinations thereof. In some preferred examples, the aqueous buffered vehicle comprises phosphate buffered saline (PBS), 3% or less (w/w of the vehicle) polysorbate 80 and 0.3% or less (w/w of the vehicle) xanthan gum and has a pH of from 6.5-8.0 and an osmolality of from 260 to 320 mOsm/L.

In some preferred examples, the suspended particles are stable to phase separation from the suspension for 6 months at room temperature. In some preferred examples, the suspended particles are chemically stable to <5% isomerization of 1,2-EPRG to the isomeric 1,3-EPRG during storage at room temperature for 6 months. In some preferred examples, the suspended particles are stable to phase separation from the suspension for 24 months at room temperature. In some preferred examples, the suspended particles are chemically stable to <5% isomerization of 1,2-EPRG to the isomeric 1,3-EPRG during storage at room temperature for 24 months.

In some preferred examples, the composition is sterile. In some preferred examples, the composition comprises a preservative. In some preferred examples, the suspension is preservative-free. In some preferred examples, the aqueous buffered vehicle is an ophthalmologically acceptable carrier. In some preferred examples, the aqueous buffered vehicle further comprises an agent selected from the group consisting of a buffering agent, a tonicity agent, a wetting agent, a thickening and viscosity agent, a density adjusting agent and combinations thereof.

In some preferred examples, the active lipid agent in the solid non-polar lipid particles is released from the solid non-polar lipid particles as individual molecules for a period of time after administration as an ophthalmic drop. In some preferred examples, the individual molecules are released for a period of from 1 up to 24 hours. In some preferred examples, the suspension is provided in a drop dispenser.

In some preferred examples, the present disclosure provides methods of treating a disease or disorder of the eye selected from the group consisting of evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an

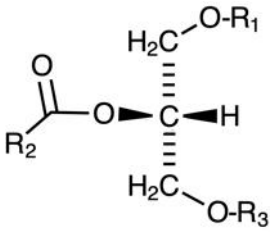
animal or human subject in need of such treatment, comprising topically administering a lipid particle composition as described above comprising an effective amount of the active lipid agent to the eye of the subject. In some preferred examples, the subject in need of treatment has a tear film breakup time less than the normal clinical range of TBUT (tear break-up time) for the normal healthy population, e.g., in the United States or another country. In some preferred examples, the methods provide improvement (e.g., as compared to a control or reported by the patient) in one or more symptoms or measures selected from the group consisting of TBUT, eye comfort, eye dryness, vital conjunctival or corneal staining and Schirmer tear tests).

In some preferred examples, the present disclosure provides a lipid particle composition as described above for use in treating a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment. In some preferred examples, administration of the compositions results in improvement (e.g., as compared to a control or reported by the patient) in one or more symptoms or measures selected from the group consisting of TBUT, eye comfort, eye dryness, vital conjunctival or corneal staining and Schirmer tear tests).

In an example, the present disclosure provides drug delivery vehicles comprising solid non-polar lipid particles having an average particle size of less than 100 microns, and preferable less than 50 microns, the particles comprising an active agent (which can be denominated a second active agent where the lipids in the particle, for example the ether lipids described herein are denominated the first active agent) other than the lipids forming the solid non-polar lipid particles.

In some preferred examples, the solid non-polar lipid particles have a melting point of less than 80 degrees C. In some preferred examples, the solid non-polar lipid particles have a melting point of from 20 to 80 degrees C. In some preferred examples, the solid non-polar lipid particles have a melting point of from 30 to 60 degrees C. In some preferred examples, the solid non-polar lipid particles have an average particle size of less than 20 microns. In some preferred examples, the solid non-polar lipid particles have an average particle size of less than 10 microns.

In other preferred examples, the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of:

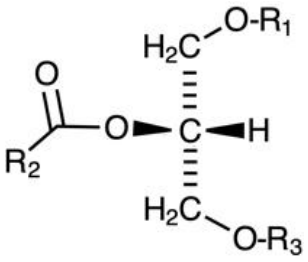


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H);

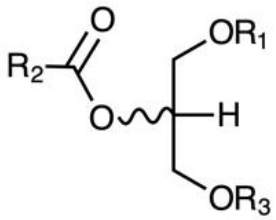


wherein

R_1 is a hydrogen (i.e., H);

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H).

In some preferred examples, the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of:

In some preferred examples, the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG), *sn*-1-O-eicosanyl-2-palmitoyl-glycerol, *sn*-2-palmitoyl-3-O-eicosanyl-glycerol, 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG), *sn*-1-O-eicosanyl-3-palmitoyl-glycerol, *sn*-1-palmitoyl-3-O-eicosanyl-glycerol and mixtures thereof . In some preferred examples, the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) or 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) and mixtures thereof.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) and mixtures thereof is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 95% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG)isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 98% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 98% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 99% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 99% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 5% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 98% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 2% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 99% (mole percent) of the 1-O-eicosanyl-2-

palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 1% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the solid non-polar lipid particles further comprise one or more additional lipids selected from the group consisting of a nonpolar mono-, di- or tri- glyceride, a wax ester including cholesterol esters, a sterol, a free fatty acid and combinations thereof.

In some preferred examples, the active agent is selected from the group consisting of over the counter (OTC) or prescription topical ophthalmics, OTC or prescription topical ophthalmics for the treatment of dry eye, NMDA antagonists, anti-bacterials, antihistamines, decongestants, anti-inflammatories, antiparasitics, miotics, sympathomimetics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics, adrenergic anesthetics, beta blockers, alpha-2-agonists, cycloplegics, prostaglandins and combinations thereof.

In some preferred examples, the solid non-polar lipid particles are formulated as an aqueous suspension in a physiologically acceptable carrier. In some preferred examples, the liquid composition is a suspension of the solid micronized lipid particles in water containing phosphate buffered saline (PBS), 3% or less (w/w of the vehicle) polysorbate 80 and 0.3% or less (w/w of the vehicle) xanthan gum and has a pH of from 6.5-8.0 and an osmolality of from 260 to 320 mOsm/L.

In some preferred examples, the suspension is stable to phase separation of the solid non-polar lipid particles in the suspension for 6 months at room temperature. In some preferred examples, the suspension is chemically stable to <5% isomerization of 1,2-EPRG to the isomeric 1,3-EPRG during storage at room temperature for 6 months. In some preferred examples, the suspension is stable to phase separation of the solid non-polar lipid particles in the suspension for 24 months at room temperature. In some preferred examples, the suspension is chemically stable to <5% isomerization of 1,2-EPRG to the isomeric 1,3-EPRG during storage at room temperature for 24 months.

In some preferred examples, the suspension is sterile. In some preferred examples, the suspension comprises a preservative. In some preferred examples, the suspension is preservative-free. In some preferred examples, the physiologically acceptable carrier is an ophthalmologically acceptable carrier. In some preferred

examples, the ophthalmologically acceptable carrier comprises an agent selected from the group consisting of a buffering agent, a tonicity agent, a wetting agent, a thickening and viscosity agent, a density adjusting agent and combinations thereof.

In some preferred examples, the active agent is released from the solid non-polar lipid particles as individual molecules of the active agent for a period of time after administration as an ophthalmic drop. In some preferred examples, the individual molecules are released for a period of from 1 up to 24 hours.

In some preferred examples, the suspension is provided in a drop dispenser.

In some preferred examples, the drug delivery vehicle is a medical insert device. In some preferred examples, the medical insert device is formed from a physiologically acceptable material. In some preferred examples, the physiologically acceptable material is a polymer. In some preferred examples, the physiologically acceptable material is selected from the group consisting of hydroxypropyl cellulose, a hydrogel, polymethyl methacrylate, and silicone acrylate. In some preferred examples, the medical insert device is selected from the group consisting of a punctal plug, a contact lens, and an ophthalmic insert. In some preferred examples, the medical insert device is rechargeable. In some preferred examples, the medical insert device is single use. In some preferred examples, the medical insert device is compatible with a mucosal surface. In some preferred examples, the mucosal surface is selected from the group consisting of an ocular mucosal surface, a vaginal mucosal surface, a nasal mucosal surface, an oropharyngeal mucosal surface, an oral cavity mucosal surface, and a rectal mucosal surface.

In some preferred examples, the present disclosure provides methods of delivering an active agent to a subject in need thereof comprising topically administering the drug delivery vehicle as described above to a subject. In some preferred examples, the drug delivery vehicle is administered to a mucosal surface of the subject. In some preferred examples, the mucosal surface is selected from the group consisting of an ocular mucosal surface, a vaginal mucosal surface, an oviduct mucosal surface, a respiratory system mucosal surface, a nasal mucosal surface, an oropharyngeal mucosal surface, an oral cavity mucosal surface, a rectal mucosal surface, a digestive system mucosal surface, and an esophageal mucosal surface. In some preferred examples, the drug delivery vehicle is applied or implanted under the mucosal surface. In some preferred examples, the mucosal surface is an ocular mucosal surface and the drug delivery vehicle is implanted or applied under the conjunctival or tenons capsule. In some preferred examples, the drug delivery vehicle is

applied to an ocular mucosal surface by a route of delivery selected from the group consisting of retrobulbar, intracameral, intravitreal, suprachoroidal and subretinal routes of delivery.

In some preferred examples, the present disclosure provides methods of treating a disease or disorder of the eye selected from the group consisting of evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment, comprising topically administering a drug delivery vehicle as described above comprising an effective amount of the active lipid agent to the eye of the subject. In some preferred examples, the subject in need of treatment has a tear film breakup time less than the normal clinical range of TBUT (tear break-up time) for the normal healthy population, e.g., in the United States or another country. In some preferred examples, the methods provide improvement (e.g., as compared to a control or reported by the patient) in one or more symptoms or measures selected from the group consisting of TBUT, eye comfort, eye dryness, vital conjunctival or corneal staining and Schirmer tear tests).

In some preferred examples, the present disclosure provides a drug delivery vehicle as described above for use in treating a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment. In some preferred examples, administration of the compositions results in improvement (*e.g.*, as compared to a control or reported by the patient) in one or more symptoms or measures selected from the group consisting of TBUT, eye comfort, eye dryness, vital conjunctival or corneal staining and Schirmer tear tests).

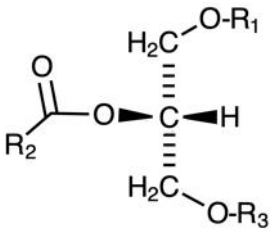
In still other preferred examples, the present disclosure provides a lipid particle composition or drug delivery vehicle as described above for use in treating an animal or human subject in need of such treatment can be identified with a tear film breakup time (TBUT) below the clinically recognized normal range in that animal species or humans.

In an example, the present disclosure provides a lipid particle composition comprising solid non-polar lipid particles comprising an active lipid agent and having an average particle size of less than 50 microns.

In some preferred examples, the solid non-polar lipid particles have a melting point of less than 80 degrees C. In some preferred examples, the solid non-polar lipid particles have a melting point of from 20 to 80 degrees C. In some preferred examples, the solid non-polar lipid particles have a melting point of from 30 to 60 degrees C. In some preferred examples, the solid non-polar lipid particles have an average particle size of less than 20 microns. In some preferred examples, the solid non-polar lipid particles have an average particle size of less than 10 microns.

In some preferred examples, the active lipid agent is a non-polar ether lipid.

In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of:

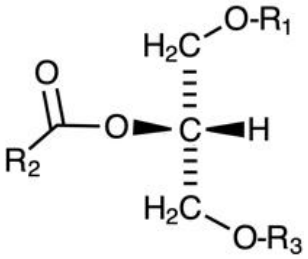


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H);

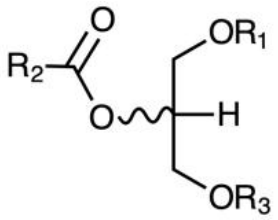


wherein

R_1 is a hydrogen (i.e., H);

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



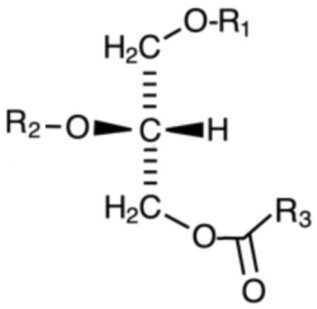
wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H).

In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of:

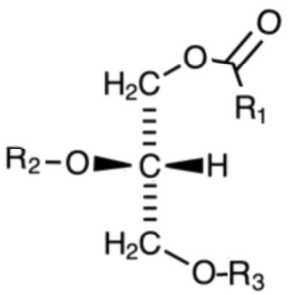


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl;

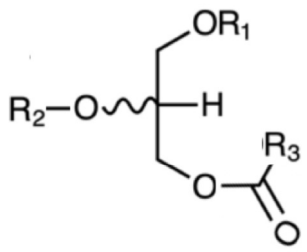


wherein

R_1 is an unsubstituted C5 to C29 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl.

In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG), *sn*-1-O-eicosanyl-2-palmitoyl-glycerol, *sn*-2-palmitoyl-3-O-eicosanyl-glycerol, 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG), *sn*-1-O-eicosanyl-3-palmitoyl-glycerol, *sn*-1-palmitoyl-3-O-eicosanyl-glycerol and mixtures thereof. In some preferred examples, the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) or 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) and mixtures thereof.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 95% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 98% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 98% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 99% (mole percent) of the 1-O-eicosanyl-2-

palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 99% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 5% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 98% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 2% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer. In some preferred examples, the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 99% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 1% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

In some preferred examples, the solid non-polar lipid particles further comprise one or more additional lipids selected from the group consisting of a nonpolar mono-, di- or tri- glyceride, a wax ester including cholesterol esters, a sterol, a free fatty acid and combinations thereof.

In some preferred examples, the solid non-polar lipid particles are formulated as a suspension.

In some preferred examples, the solid non-polar lipid particles are provided as a medical insert device. In some preferred examples, the medical insert device is formed from a physiologically acceptable material. In some preferred examples, the physiologically acceptable material is a polymer. In some preferred examples, the physiologically acceptable material is selected from the group consisting of hydroxypropyl cellulose, a hydrogel, polymethyl methacrylate, and silicone acrylate. In some preferred examples, the medical insert device is selected from the group consisting of a punctal plug, a contact lens, and an ophthalmic insert. In some preferred examples, the medical insert device is rechargeable. In some preferred examples, the medical insert device is single use. In some preferred examples, the medical insert device is compatible with a mucosal surface. In some preferred examples, the mucosal surface is selected from the group consisting of an ocular mucosal surface, a vaginal mucosal surface, a nasal mucosal

surface, an oropharyngeal mucosal surface, an oral cavity mucosal surface, and a rectal mucosal surface.

In some preferred examples, the lipid particle may preferably comprise a second active agent in addition to the first active agent (i.e., the ether lipid). In some preferred examples, the active agent is selected from the group consisting of over the counter (OTC) or prescription topical ophthalmics, OTC or prescription topical ophthalmics for the treatment of dry eye, NMDA antagonists, anti-bacterials, antihistamines, decongestants, anti-inflammatories, antiparasitics, miotics, sympathomimetics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics, adrenergic anesthetics, beta blockers, alpha-2-agonists, cycloplegics, prostaglandins and combinations thereof.

In some preferred examples, the present disclosure provides methods of treating a disease or disorder associated with a mucous membrane comprising administering a lipid particle composition as described above to a subject in need thereof. In some preferred examples, the disease or disorder is a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment. In some preferred examples, administration of the compositions results in improvement (e.g., as compared to a control or reported by the patient) in one or more symptoms or measures selected from the group consisting of TBUT, eye comfort, eye dryness, vital conjunctival or corneal staining and Schirmer tear tests).

In some preferred examples, the present disclosure provides for use of a lipid particle composition as described above to treat a disease or disorder of the mucous membrane of a subject. In some preferred examples, the disease or disorder is a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment. In some preferred examples, administration of the compositions results in improvement (e.g., as

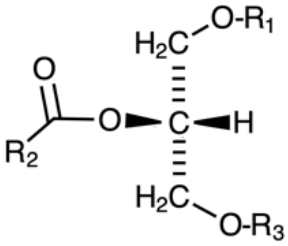
WHAT IS CLAIMED IS:

1. A lipid particle composition comprising solid non-polar lipid particles comprising an active lipid agent and having an average particle size of less than 50 microns stably suspended in a buffered aqueous vehicle suitable for topical administration.

2. The lipid particle composition of claim 1, wherein the solid non-polar lipid particles have a melting point of from 30 to 60 degrees C.

3. The lipid particle composition of any one of claims 1 to 2, wherein the solid non-polar lipid particles have an average particle size of less than 20 microns.

4. The lipid particle composition of any one of claims 1 to 3, wherein the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of:

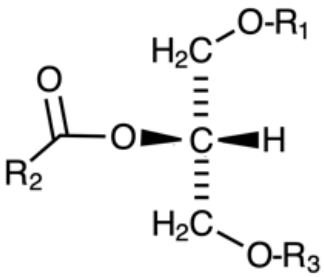


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H);

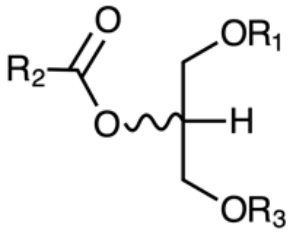


wherein

R_1 is a hydrogen (i.e., H);

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



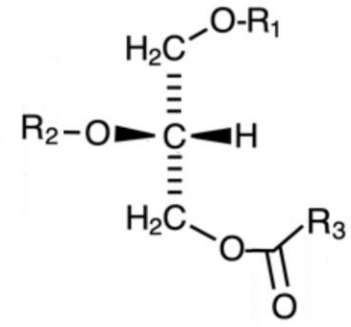
wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H).

5. The lipid particle composition of any one of claims 1 to 4, wherein the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of:

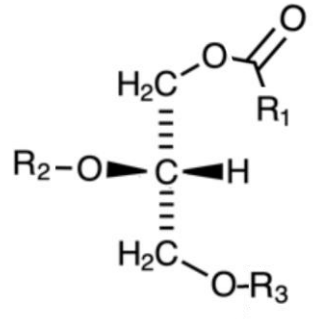


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl;

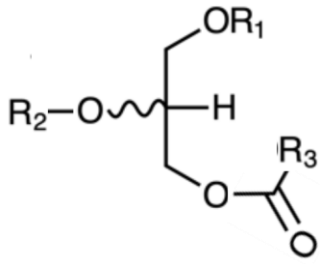


wherein

R_1 is an unsubstituted C5 to C29 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl.

6. The lipid particle composition of any one of claims 1 to 5, wherein the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG), *sn*-1-O-eicosanyl-2-palmitoyl-glycerol, *sn*-2-palmitoyl-3-O-eicosanyl-glycerol, 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG), *sn*-1-O-eicosanyl-3-palmitoyl-glycerol, *sn*-1-palmitoyl-3-O-eicosanyl-glycerol and mixtures thereof .

7. The lipid particle composition of claim 6, wherein the solid non-polar lipid particles comprise an active lipid agent selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) or 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) and mixtures thereof.

8. The lipid particle composition of claim 7, wherein the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 95% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

9. The lipid particle composition of claim 7, wherein the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer and no greater than 5% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) isomer.

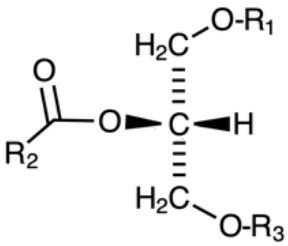
10. The lipid particle composition of any one of claims 1 to 9, wherein the suspended particles are stable to phase separation from the suspension for 6 months at room temperature.

11. The lipid particle composition of any one of claims 1 to 10, wherein the aqueous buffered vehicle is an ophthalmologically acceptable carrier.

12. Use of a lipid particle composition of any one of claims 1 to 11 in the manufacture of a medicament in treating a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms, clinical signs or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment.

13. A drug delivery vehicle comprising solid non-polar lipid particles having an average particle size of less than 50 microns, the particles comprising an active agent other than the lipids forming the solid non-polar lipid particles.

14. The drug delivery vehicle of claim 13, wherein the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of:

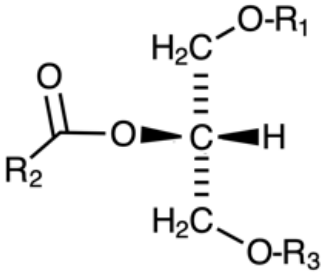


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H);

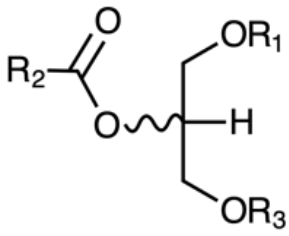


wherein

R_1 is a hydrogen (i.e., H);

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



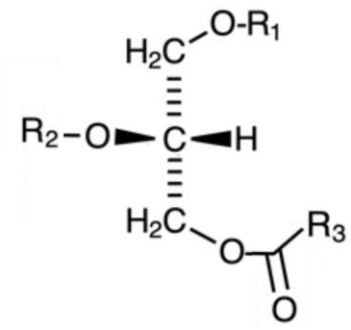
wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is an unsubstituted C5 to C29 alkyl or alkenyl; and

R_3 is a hydrogen (i.e., H).

15. The drug delivery vehicle of claim 13, wherein the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of:

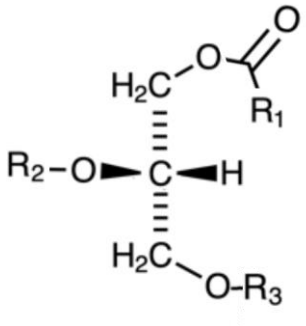


wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl;

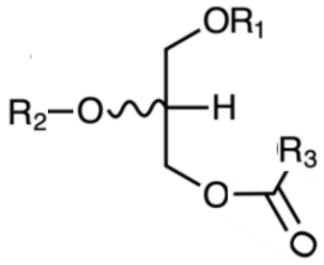


wherein

R_1 is an unsubstituted C5 to C29 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C6 to C30 alkyl or alkenyl; and



wherein

R_1 is an unsubstituted C6 to C30 alkyl or alkenyl;

R_2 is a hydrogen (i.e., H); and

R_3 is an unsubstituted C5 to C29 alkyl or alkenyl.

16. The drug delivery vehicle of any one of claims 13 to 15, wherein the solid non-polar lipid particles comprise an ether lipid selected from the group consisting of 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG), *sn*-1-O-eicosanyl-2-palmitoyl-glycerol, *sn*-2-palmitoyl-3-O-eicosanyl-glycerol, 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG), *sn*-1-O-eicosanyl-3-palmitoyl-glycerol, *sn*-1-palmitoyl-3-O-eicosanyl-glycerol and mixtures thereof .

17. The drug delivery vehicle of claim 16, wherein the mixture of ether lipid isomers 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) and 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG) and mixtures thereof is characterized in comprising greater than 95% (mole percent) of the 1-O-eicosanyl-2-palmitoyl-*rac*-glycerol (1,2-EPRG) isomer or greater than 95% (mole percent) of the 1-O-eicosanyl-3-palmitoyl-*rac*-glycerol (1,3-EPRG)isomer.

18. The drug delivery vehicle of any one of claims 13 to 17, wherein the active agent is selected from the group consisting of over the counter (OTC) or prescription topical ophthalmics, OTC or prescription topical ophthalmics for the treatment of dry eye, NMDA antagonists, anti-bacterials, antihistamines, decongestants, anti-inflammatories, antiparasitics, miotics, sympathomimetics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics, adrenergic anesthetics, beta blockers, alpha-2-agonists, cycloplegics, prostaglandins and combinations thereof.

19. The drug delivery vehicle of any one of claims 13 to 18, wherein the suspension is stable to phase separation of the solid non-polar lipid particles in the suspension for 6 months at room temperature.

20. Use of a drug delivery vehicle of any one of claims 13 to 20 in the manufacture of a medicament in treating a disease or disorder of the eye selected from the group consisting of dry eye, inflammatory dry eye, evaporative dry eye, meibomian gland dysfunction and symptoms or conditions associated therewith, an unstable tear film resulting in rapid aqueous tear evaporation and keratoconjunctivitis sicca (dry eye) and symptoms or clinical signs associated therewith, in an animal or human subject in need of such treatment.