[0008] While steroid ointments/creams are extensively prescribed to control long term or chronic non-ophthalmic inflammatory conditions (due to their low penetration/permeation), the long term use of current steroid ointment/cream formulations on or near the eyes is strongly disfavored, as ophthalmic use of these formulations is likely to induce serious adverse events, such as increased IOP (which may result in ocular hypertension or glaucoma, or induce loss of sight), posterior subcapsular cataracts, retardation of corneal epithelial healing, corticosteroid uveitis, mydriasis and ptosis, infection, and other possible side effects (*e.g.,* transient ocular discomfort, steroid-induced calcium deposits, *etc.*). In fact, topical application of a typical dexamethasone ointment formulation to the eyelids of children was shown to sharply increase IOP. "Ocular hypertensive response after dexamethasone ointment to the eyelids occurred frequently in children, especially those 5 years old or younger" (*See* page 166 of Lee *et al.,* Korean J Ophthalmol. 2006 Sep;20(3):166-70). Thus, steroid formulations/routes of administration appropriate for the long term or even chronic therapy of inflammatory conditions of the eye are lacking.

[0009] All references cited herein, including patent applications, patent publications, and non-patent literature are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0010] To meet the above and other needs, disclosed herein are pharmaceutical compositions adapted for peri-ocular transdermal delivery of one or more lipophilic compounds. In some examples, the pharmaceutical compositions are adapted for peri-ocular transdermal delivery to significantly enhance the ocular safety of the delivered lipophilic compound by: 1) decreasing the concentration of the permeation enhancer in the pharmaceutical composition relative to the concentration used in a standard ointment/cream or ophthalmic formulation; 2) using a permeation enhancer (not typically found in topical steroid ointment/cream formulations) that is suitable for transdermal delivery of the compound into the eyelid (*e.g.,* Tween-80); 3) formulating the pharmaceutical composition to achieve improved spreadability on the peri-ocular surface relative to an ointment base; 4) formulating the pharmaceutical composition to avoid flow from the peri-ocular surface onto the corneal surface; 5) using a novel steroid such as the compound of Formula I (which has been specifically developed with an ability to enable the glucocorticoid receptor to

transrepress gene activation with less or little transactivation) in an effort to reduce the side effects of glucocorticoids that are thought to be mediated through transactivation; 6) using the Meibomian glands, meibum, and other fatty structures in the eyelids as a drug depot of a lipophilic compound for sustained delivery to the ocular surface; and/or 7) use of the Meibomian glands and meibum as a novel drug delivery system for a pharmaceutical formulation of a lipophilic compound applied peri-ocularly to the outside of the upper and/or lower eyelid(s). Accordingly, the present disclosure is directed, in part, to a safer method for treating ocular surface conditions as well as within the peri-ocular glands and lids by transdermally administering a pharmaceutical formulation (*e.g.,* via topical application of the formulation to the outside of the upper and/or lower eyelids) as described herein in order to deliver a therapeutically active concentration of a lipophilic compound to the meibomian glands, the lacrimal glands, the accessory lacrimal glands, and the ocular surface. Without wishing to be bound by theory it is thought that lipophilic compounds (*e.g.,* steroids) will preferentially accumulate in/partition to lipid-producing (*e.g.,* meibum) peri-ocular glands (*e.g.,* the Meibomian glands) and other fatty/lipophilic structures in the eyelids. Consequently, the present disclosure is believed to provide a novel therapeutic strategy for treating inflammation within the lacrimal functional unit (LFU), other ocular inflammatory diseases, bacterial infections of the eye, glaucoma, and ocular hypertension by delivering anti-glaucoma agents, antibiotics and other lipophilic compounds via transdermal peri-ocular delivery that diminishes or avoids some or all of the adverse events associated with the use of standard topical formulations in an ophthalmic setting, such as increased IOP, BAK sensitivity, and disruption of the pre-corneal tear film (e.g., blurred vision). In addition, the present disclosure is believed to provide a novel strategy for longer term/chronic ophthalmic therapy than may be used with current short-term topical ocular regimens (e.g., corticosteroids).

[0011] Accordingly, in one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a lipophilic compound, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the lipophilic compound to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a lipophilic compound, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the lipophilic compound to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject, wherein the pharmaceutical

composition is specifically formulated for peri-ocular delivery. In some examples, the lipophilic compound is not delivered systemically to the subject. In some examples, the lipophilic compound is not delivered to a tear or tear duct of the subject. In some examples, the lipophilic compound is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the lipophilic compound is delivered to an ocular surface of the subject via the meibomian gland and meibum. In some examples, the lipophilic compound is selected from the group consisting of steroids, antibiotics, immunomodulatory drugs, integrin antagonists, anti-inflammatory agents, and anti-glaucoma or ocular anti-hypertension agents.

[0011a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising: a) a therapeutically effective amount of a lipophilic compound; and b) a pharmaceutically acceptable carrier adapted for peri-ocular transdermal delivery of the lipophilic compound to one or more peri-orbital glands of a subject; wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery.

[0012] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a steroid, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the steroid to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In some examples, the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the steroid is not delivered systemically to the subject. In some examples, the steroid is not delivered to a tear or tear duct of the subject. In some examples, the steroid is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the steroid is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0013] The steroid can be any steroid. In some examples that may be combined with any of the preceding examples, the steroid is selected from the compound of Formula I, fluocinolone, difluprednate, fluticasone, fluorometholone, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, rimexolone, cortisol, cortisone, hydrocortisone, testosterone, and ester derivatives thereof. In some examples, the steroid is selected from the compound of Formula I, difluprednate, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, and ester derivatives thereof. In some examples, the steroid is

the compound of Formula I. In some examples, the pharmaceutical composition comprises the steroid at a concentration between 0.001% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the steroid at a concentration between 0.01% and 2% w/w.

[0014] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an antibiotic, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the antibiotic to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an antibiotic, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the antibiotic to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject, wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the antibiotic is not delivered systemically to the subject. In some examples, the antibiotic is not delivered to a tear or tear duct of the subject. In some examples, the antibiotic is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the antibiotic is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0015] The antibiotic can be any antibiotic. In some examples, the antibiotic is selected from the group consisting of sulfonamides, macrolides, chloramphenicol, aminoglycosides, fluoroquinolones, vancomycin, and tetracyclines. In some examples, the antibiotic is selected from the group consisting of azithromycin, erythromycin, gentamicin, natamycin, neomycin, tobramycin, vancomycin, bacitracin, besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, oxifloxacin, chloramphenicol, doxycycline, tetracyclin, gramicidin, mupirocin, polymyxin B, and sulfacetamide. In some examples, the pharmaceutical composition comprises the antibiotic at a concentration between 0.01% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the antibiotic at a concentration between 0.1% and 2% w/w.

[0016] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an immunomodulatory drug, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the immunomodulatory drug to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an immunomodulatory drug, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the immunomodulatory drug to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject, wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the immunomodulatory drug is not delivered systemically to the subject. In some examples, the immunomodulatory drug is not delivered to a tear or tear duct of the subject. In some examples, the immunomodulatory drug is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the immunomodulatory drug is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0017] The immunomodulatory drug can be any immunomodulatory drug. In some examples, the immunomodulatory drug is selected from the group consisting of calcineurin inhibitors and thalidomide analogues. In some examples, the immunomodulatory drug is selected from the group consisting of cyclosporine A, voclosporine, tacrolimus, pimecrolimus, thalidomide, lenalidomide, and pomalidomide. In some examples, the immunomodulatory drug is cyclosporine A. In some examples, the pharmaceutical composition comprises the immunomodulatory drug at a concentration between 0.01% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the immunomodulatory drug at a concentration between 0.1% and 2% w/w.

[0018] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an integrin antagonist, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the integrin antagonist to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In one example, provided

herein are pharmaceutical compositions comprising a therapeutically effective amount of an integrin antagonist, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the integrin antagonist to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject, wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the integrin antagonist is not delivered systemically to the subject. In some examples, the integrin antagonist is not delivered to a tear or tear duct of the subject. In some examples, the integrin antagonist is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the integrin antagonist is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0019] The integrin antagonist can be any integrin antagonist. In some examples, the integrin antagonist is selected from the group consisting of lifitegrast and GW559090, and ester derivatives thereof. In some examples, the pharmaceutical composition comprises the integrin antagonist at a concentration between 0.01% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the integrin antagonist at a concentration between 0.1% and 5% w/w.

[0020] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an anti-inflammatory agent, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the anti-inflammatory agent to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an anti-inflammatory agent, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the anti-inflammatory agent to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject, wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the anti-inflammatory agent is not delivered systemically to the subject. In some examples, the anti-inflammatory agent is not delivered to a tear or tear duct of the subject. In some examples, the anti-inflammatory agent is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid

topical ocular suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the anti-inflammatory agent is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0021] The anti-inflammatory agent can be any anti-inflammatory agent. In some examples, the anti-inflammatory agent is selected from the group consisting of omega 3 fatty acids and non-steroidal anti-inflammatory drugs (NSAIDs). In some examples, the omega 3 fatty acids are selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and any combinations thereof. In some examples, the NSAIDs are selected from the group consisting of bromfenac, diclofenac, indomethacin, flurbiprofen, ketorolac, nepafenac, and any combinations thereof. In some examples, the anti-inflammatory agent is selected from flurbiprofen and ketorolac. In some examples, the pharmaceutical composition comprises the anti-inflammatory agent at a concentration between 0.001% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the anti-inflammatory agent at a concentration between 0.1% and 2% w/w.

[0022] In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an anti-glaucoma or ocular anti-hypertension agent, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the anti-glaucoma or ocular anti-hypertension agent to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject. In one example, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of an anti-glaucoma or ocular anti-hypertension agent, and a pharmaceutically acceptable carrier adapted for per-ocular transdermal delivery of the anti-glaucoma or ocular anti-hypertension agent to one or more peri-orbital (*e.g.,* oil-secreting peri-orbital) glands of a subject, wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery. In some examples, the anti-glaucoma or ocular anti-hypertension agent is not delivered systemically to the subject. In some examples, the anti-glaucoma or ocular anti-hypertension agent is not delivered to a tear or tear duct of the subject. In some examples, the anti-glaucoma or ocular anti-hypertension agent is not delivered by direct application to an ocular surface of the subject. In some examples, the pharmaceutical composition is not a liquid topical ocular

suspension, emulsion, or solution. In some examples, the one or more peri-orbital glands are selected from the group consisting of a meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof. In some examples, the anti-glaucoma or ocular anti-hypertension agent is delivered to an ocular surface of the subject via the meibomian gland and meibum.

[0023] The anti-glaucoma or ocular anti-hypertension agent can be any anti-glaucoma agent or any ocular anti-hypertension agent. In some examples, the anti-glaucoma or ocular anti-hypertension agent is selected from the group consisting of bimatoprost, latanoprost, travoprost, tafluprost, latanoprostene-bunod, timolol, betaxolol, levobunolol, dorzolamide, brinzolamide, and acetazolamide. In some examples, the anti-glaucoma or ocular anti-hypertension agent is selected from bimatoprost, latanoprost, travoprost, tafluprost, latanoprostene-bunod, timolol, betaxolol, levobunolol, metipranolol, brimonidine, clonidine, apraclonidine, dorzolamide, brinzolamide, acetazolamide, methazolamide, netarsudil, and any combinations thereof. In some examples the anti-glaucoma drug is selected from bimatoprost, latanoprost, travoprost, brimonidine, brinzolamide, netarsudil and timolol. In some examples the anti-glaucoma agent is bimatoprost. In some examples, the pharmaceutical composition comprises the anti-glaucoma drug at a concentration between 0.0001% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the anti-glaucoma drug or ocular anti-hypertension agent at a concentration between 0.01% and 2% w/w.

[0024] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition further comprises a therapeutically effective amount of an additional steroid. In some examples, the additional steroid is selected from the compound of Formula I, fluocinolone, difluprednate, fluticasone, fluorometholone, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, rimexolone, cortisol, cortisone, hydrocortisone, testosterone, and ester derivatives thereof. In some examples, the lipophilic compound and the additional steroid are different.

[0025] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition further comprises a therapeutically effective amount of one or more antibiotics. In some examples, the one or more antibiotics are selected from sulfonamides, macrolides, chloramphenicol, aminoglycosides, fluoroquinolones, vancomycin, tetracyclines, and any combinations thereof. In some

examples, the one or more antibiotics are selected from azithromycin, erythromycin, gentamicin, natamycin, neomycin, tobramycin, vancomycin, bacitracin, besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, oxifloxacin, chloramphenicol, doxycycline, tetracyclin, gramicidin, mupirocin, polymyxin B, sulfacetamide, and any combinations thereof. In some examples, the one or more antibiotics are selected from azithromycin, gentamicin, tobramycin, bacitracin, besifloxacin, gatifloxacin, moxifloxacin, chloramphenicol, and doxycycline. In some examples, the pharmaceutical composition comprises the one or more antibiotics at a concentration between 0.01% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the one or more antibiotics at a concentration between 0.1% and 2% w/w. In some examples, the lipophilic compound and the one or more antibiotics are different.

[0026] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition further comprises a therapeutically effective amount of one or more immunomodulatory drugs. In some examples, the one or more immunomodulatory drugs are selected from calcineurin inhibitors, thalidomide analogues, and any combinations thereof. In some examples, the one or more immunomodulatory drugs are selected from cyclosporine A, voclosporine, tacrolimus, pimecrolimus, thalidomide, lenalidomide, pomalidomide, and any combinations thereof. In some examples, the immunomodulatory drug is cyclosporine A. In some examples, the pharmaceutical composition comprises the one or more immunomodulatory drugs at a concentration between 0.01% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the one or more immunomodulatory drugs at a concentration between 0.1% and 2% w/w. In some examples, the lipophilic compound and the one or more immunomodulatory drugs are different.

[0027] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition further comprises a therapeutically effective amount of one or more integrin antagonists. In some examples, the one or more integrin antagonists are selected from lifitegrast, GW559090, ester derivatives thereof, and any combinations thereof. In some examples, the integrin antagonist is GW559090. In some examples, the pharmaceutical composition comprises the one or more integrin antagonists at a concentration between 0.01% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the one or more integrin

antagonists at a concentration between 0.1% and 5% w/w. In some examples, the lipophilic compound and the one or more integrin antagonists are different.

[0028] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition further comprises a therapeutically effective amount of one or more anti-inflammatory agents. In some examples, the one or more anti-inflammatory agents are selected from omega 3 fatty acids, non-steroidal anti-inflammatory drugs (NSAIDs), and any combinations thereof. In some examples, the omega 3 fatty acids are selected from eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and any combinations thereof. In some examples, the NSAIDs are selected from bromfenac, diclofenac, indomethacin, flurbiprofen, ketorolac, nepafenac, and any combinations thereof. In some examples, the one or more anti-inflammatory agents is selected from flurbiprofen and ketorolac. In some examples, the pharmaceutical composition comprises the one or more anti-inflammatory agents at a concentration between 0.001% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the one or more anti-inflammatory agents at a concentration between 0.1% and 2% w/w. In some examples, the lipophilic compound and the one or more anti-inflammatory agents are different.

[0029] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition further comprises a therapeutically effective amount of one or more anti-glaucoma drugs or ocular anti-hypertension agents. In some examples, the one or more anti-glaucoma drugs or ocular anti-hypertension agents are selected from bimatoprost, latanoprost, travoprost, tafluprost, latanoprostene-bunod, timolol, betaxolol, levobunolol, metipranolol, brimonidine, clonidine, apraclonidine, dorzolamide, brinzolamide, acetazolamide, methazolamide, netarsudil, and any combinations thereof. In some examples the anti-glaucoma drug or ocular anti-hypertension agent is selected from bimatoprost, latanoprost, travoprost, brimonidine, brinzolamide, netarsudil and timolol. In some examples the anti-glaucoma drug is bimatoprost. In some examples, the pharmaceutical composition comprises the one or more anti-glaucoma drugs or ocular anti-hypertension agents at a concentration between 0.0001% and 10% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the one or more anti-glaucoma drugs or ocular anti-hypertension agents at a concentration between 0.01% and 2%

w/w. In some examples, the lipophilic compound and the one or more anti-glaucoma drugs or ocular anti-hypertension agents are different.

[0030] In some examples that may be combined with any of the preceding examples, the pharmaceutically acceptable carrier is selected from an ointment, cream, lotion, gel, emulsion, suspension, oil, foam, transdermal patch, spray, and any combinations thereof. In some examples, the pharmaceutically acceptable carrier is an ointment. In some examples, the ointment comprises a paraffinic or a water-miscible ointment base. In some examples, the ointment comprises 61.5% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 5% w/w of St. cyclomethicone-5NF, 5% w/w of labrasol, 5% w/w of propylene carbonate, 2.5% w/w of steareth 2, 2.5% w/w of St. emulsifier 10, and 2.5% w/w of St. elastomer-10. In some examples, the pharmaceutically acceptable carrier is a cream. In some examples, the cream comprises an oil-in-water base or a water-in-oil base. In some examples, the cream comprises 48% w/w soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w ST-emulsifier-10, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w dibasic sodium phosphate, 0.05% w/w citric acid, 0.02% w/w propylparaben, and q.s. purified water. In some examples, the cream comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w propylparaben, and q.s. purified water. In some examples, the cream comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w benzalkonium chloride, and q.s. purified water. In some examples, the cream is preservative-free comprising 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, and q.s. purified water.

[0031] In some examples, one or more active pharmaceutical ingredients are incorporated at the desired final concentration (w/w) into a cream vehicle comprised of 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.08% w/w

methylparaben, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w propylparaben, and q.s. purified water. In some examples, the cream vehicle comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w benzalkonium chloride, and q.s. purified water. In some examples, the cream vehicle is preservative-free comprising 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, and q.s. purified water.

[0032] In some examples, one or more active pharmaceutical ingredients are incorporated at the desired final concentration by substituting an equal amount of white petrolatum or paraffin (w/w). As an example, one such example comprises 46% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w propylparaben, 2% w/w compound of Formula I and q.s. purified water. Another such example is preservative-free and comprises 46% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 2% w/w compound of Formula I and q.s. purified water.

[0033] In some examples, the pharmaceutical composition comprises the lipophilic compound at a concentration between about 0.001% and about 10% weight per weight (w/w), between about 0.0001% and about 10% weight per weight (w/w), or between about 0.0001% and about 5% weight per weight (w/w). In some examples, the pharmaceutical composition comprises the lipophilic compound at a concentration between about 0.01% and about 2% w/w.

[0034] In some examples, the pharmaceutically acceptable carrier comprises benzalkonium chloride (BAK). In some examples, the pharmaceutically acceptable carrier comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10,

0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w benzalkonium chloride, and purified water. In some examples, the pharmaceutically acceptable carrier is preservative-free. In some examples, the pharmaceutically acceptable carrier comprises white soft paraffin/petrolatum, mineral oil, propylene glycol, ST-cyclomethicone-5NF, ST-emulsifier-10, ST-elastomer-10, dibasic sodium phosphate, citric acid, and purified water. In some examples, the pharmaceutically acceptable carrier comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, and purified water.

[0035] In some examples that may be combined with any of the preceding examples, the subject is a human or a non-human animal. In some examples that may be combined with any of the preceding examples, the subject is suffering from, or is suspected and/or expected to be suffering from, inflammation of one or more peri-orbital glands. In some examples that may be combined with any of the preceding examples, the subject suffers from an ocular disease. In some examples, the ocular disease is selected from inflammation of the peri-ocular glands, meibomitis, dry eye disease, allergic eye disease, topical preservative toxicity, xerophthalmia, loss of homeostasis of the tear film, tear film instability and hyperosmolarity, ocular surface inflammation and damage, neuronal sensory abnormalities, meibomian gland dysfunction, exacerbated inflammatory ocular surface disease, phlyctenular keratitis, chalazion, anterior blepharitis, posterior blepharitis, bacterial infection, glaucoma, ocular hypertension, and any combinations thereof.

[0036] In another example, provided herein are methods of providing prophylactic palliative, or therapeutic relief of one or more signs or symptoms of an ocular disease in a subject comprising administering to the subject any of the pharmaceutical compositions described herein. In some examples, the subject is a human or a non-human animal. In some examples, the subject is suffering from, or is suspected and/or expected to be suffering from, inflammation of one or more peri-orbital glands. In some examples, the subject suffers from an ocular disease. In some examples, the ocular disease is selected from inflammation of the peri-ocular glands, meibomitis, dry eye disease, allergic eye disease, topical preservative toxicity, xerophthalmia, loss of homeostasis of the tear film, tear film instability and hyperosmolarity, ocular surface inflammation and damage, neuronal

sensory abnormalities, meibomian gland dysfunction, exacerbated inflammatory ocular surface disease, phlyctenular keratitis, chalazion, anterior blepharitis, posterior blepharitis, bacterial infection, glaucoma, ocular hypertension, and any combinations thereof.

[0036a] In another aspect, the present disclosure refers to use of a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for providing prophylactic, palliative, or therapeutic relief of one or more signs or symptoms of an ocular disease in a subject.

[0037] In some examples that may be combined with any of the preceding examples, the pharmaceutical composition is topically administered to an external portion of an eyelid of the subject, including the upper lateral region of an orbit of the subject. In some examples, the pharmaceutical composition is topically administered to the external portion of the upper and/or lower eyelid of the subject. In some examples, the lipophilic compound is delivered to an ocular surface of the subject via the meibomian gland. In some examples, the pharmaceutical composition is administered one, two, three, four, five, six or more times per day. In some examples, the pharmaceutical composition is administered for one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, 10 weeks, 11 weeks, 12 weeks or more, 24 weeks, 36 weeks, 48 weeks or more. In some examples, prolonged administration of the pharmaceutical composition does not result in an adverse ocular event in the subject. In some examples, the adverse ocular event is selected from elevated intraocular pressure, cataracts, ocular infection, and any combinations thereof. In some examples, the lipophilic compound is not delivered systemically to the subject by the administration of the pharmaceutical composition. In some examples, the lipophilic compound is not delivered to a tear or tear duct of the subject by the administration of the pharmaceutical composition. In some examples, the lipophilic compound is not delivered directly to an ocular surface of the subject by the administration of the pharmaceutical composition.

[0038] In another example, provided herein are articles of manufacture or kits comprising any of the pharmaceutical compositions described herein. In some examples, the article of manufacture or kit further comprises a package insert comprising instructions for administering the pharmaceutical composition.

[0038a] In another aspect, the present disclosure refers to a kit comprising: a) the pharmaceutical composition as disclosed herein; and b) a package insert comprising instructions for administering the pharmaceutical composition.

[0039] It is to be understood that one, some, or all of the properties of the various examples described above and herein may be combined to form other examples of the present disclosure. These and other examples of the present disclosure will become apparent to one of skill in the art. These and other examples of the present disclosure are further described by the detailed description that follows.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:

a) a therapeutically effective amount of a lipophilic compound; and

b) a pharmaceutically acceptable carrier adapted for peri-ocular transdermal delivery of the lipophilic compound to one or more peri-orbital glands of a subject;

wherein the pharmaceutical composition is specifically formulated for peri-ocular delivery.

2. The pharmaceutical composition of claim 1, wherein the lipophilic compound is not to be delivered systemically to the subject.

3. The pharmaceutical composition of claim 1 or claim 2, wherein the lipophilic compound is not to be delivered to a tear or tear duct of the subject.

4. The pharmaceutical composition of any one of claims 1-3, wherein the lipophilic compound is not to be delivered directly to an ocular surface of the subject.

5. The pharmaceutical composition of any one of claims 1-4, wherein the pharmaceutical composition is not a liquid topical ocular suspension, emulsion, or solution.

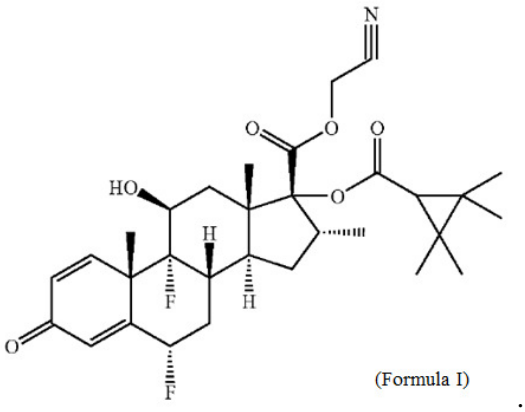
6. The pharmaceutical composition of any one of claims 1-5, wherein the one or more peri-orbital glands are selected from the group consisting of a Meibomian gland, a lacrimal gland, an accessory lacrimal gland, and any combinations thereof.

7. The pharmaceutical composition of any one of claims 1-6, wherein the lipophilic compound is to be delivered to an ocular surface of the subject via the Meibomian gland.

8. The pharmaceutical composition of any one of claims 1-7, wherein the lipophilic compound is a steroid.

9. The pharmaceutical composition of claim 8, wherein the steroid is selected from the group consisting of a compound of Formula I, fluocinolone, difluprednate, fluticasone, fluorometholone, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, rimexolone, cortisol, cortisone, hydrocortisone, testosterone, and ester derivatives thereof;

wherein the compound of Formula I comprises the structure:



(Formula I)

10. The pharmaceutical composition of claim 8 or claim 9, wherein the steroid is selected from the group consisting of the compound of Formula I, difluprednate, loteprednol, dexamethasone, prednisolone, triamcinolone acetonide, and ester derivatives thereof.

11. The pharmaceutical composition of any one of claims 8-10, wherein the steroid is the compound of Formula I.

12. The pharmaceutical composition of any one of claims 1-11, wherein the pharmaceutical composition comprises the lipophilic compound at a concentration between about 0.001% and about 10% weight per weight (w/w), between about 0.0001% and about 10% weight per weight (w/w), or between about 0.0001% and about 5% weight per weight (w/w).

13. The pharmaceutical composition of any one of claims 1-12, wherein the pharmaceutical composition comprises the steroid at a concentration between about 0.01% and about 2% w/w.

14. The pharmaceutical composition of any one of claims 1-13, further comprising a therapeutically effective amount of an additional steroid.

15. The pharmaceutical composition of claim 14, wherein the additional steroid is selected from the group consisting of the compound of Formula I, fluocinolone, difluprednate, fluticasone, fluorometholone, loteprednol, dexamethasone, prednisolone,

triamcinolone acetonide, rimexolone, cortisol, cortisone, hydrocortisone, testosterone, and ester derivatives thereof.

16. The pharmaceutical composition of claim 14 or claim 15, wherein the lipophilic compound and the additional steroid are different.

17. The pharmaceutical composition of any one of claims 1-16, further comprising a therapeutically effective amount of one or more antibiotics.

18. The pharmaceutical composition of claim 17, wherein the one or more antibiotics are selected from the group consisting of sulfonamides, macrolides, chloramphenicol, aminoglycosides, fluoroquinolones, vancomycin, tetracyclines, and any combinations thereof.

19. The pharmaceutical composition of claim 17 or claim 18, wherein the one or more antibiotics are selected from the group consisting of azithromycin, erythromycin, gentamicin, natamycin, neomycin, tobramycin, vancomycin, bacitracin, besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, oxifloxacin, chloramphenicol, doxycycline, tetracyclin, gramicidin, mupirocin, polymyxin B, sulfacetamide, and any combinations thereof.

20. The pharmaceutical composition of any one of claims 17-19, wherein the lipophilic compound and the one or more antibiotics are different.

21. The pharmaceutical composition of any one of claims 1-20, further comprising a therapeutically effective amount of one or more immunomodulatory drugs.

22. The pharmaceutical composition of claim 21, wherein the one or more immunomodulatory drugs are selected from the group consisting of calcineurin inhibitors, thalidomide analogues, and any combinations thereof.

23. The pharmaceutical composition of claim 21 or claim 22, wherein the one or more immunomodulatory drugs are selected from the group consisting of cyclosporine A, voclosporine, tacrolimus, pimecrolimus, thalidomide, lenalidomide, pomalidomide, and any combinations thereof.

24. The pharmaceutical composition of any one of claims 21-23, wherein the lipophilic compound and the one or more immunomodulatory drugs are different.

25. The pharmaceutical composition of any one of claims 1-24, further comprising a therapeutically effective amount of one or more integrin antagonists.

26. The pharmaceutical composition of claim 25, wherein the one or more integrin antagonists are selected from the group consisting of lifitegrast, GW559090, ester derivatives thereof, and any combinations thereof.

27. The pharmaceutical composition of claim 25 or claim 26, wherein the lipophilic compound and the one or more integrin antagonists are different.

28. The pharmaceutical composition of any of claims 1-27, further comprising a therapeutically effective amount of one or more anti-inflammatory agents.

29. The pharmaceutical composition of claim 28, wherein the one or more anti-inflammatory agents are selected from the group consisting of omega 3 fatty acids, non-steroidal anti-inflammatory drugs (NSAIDs), and any combinations thereof.

30. The pharmaceutical composition of claim 29, wherein the omega 3 fatty acids are selected from the group consisting of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and any combinations thereof.

31. The pharmaceutical composition of claim 29, wherein the NSAIDs are selected from the group consisting of bromfenac, diclofenac, indomethacin, flurbiprofen, ketorolac, nepafenac, and any combinations thereof.

32. The pharmaceutical composition of any of claims 28-31, wherein the lipophilic compound and the one or more anti-inflammatory agents are different.

33. The pharmaceutical composition of any of claims 1-32, further comprising a therapeutically effective amount of one or more anti-glaucoma or ocular anti-hypertension agents.

34. The pharmaceutical composition of claim 33, wherein the one or more anti-glaucoma or ocular anti-hypertension agents are selected from the group consisting of bimatoprost, latanoprost, travoprost, tafluprost, latanoprostene-bunod, timolol, betaxolol, levobunolol, metipranolol, brimonidine, clonidine, apraclonidine, dorzolamide, brinzolamide, acetazolamide, methazolamide, netarsudil, and any combinations thereof.

35. The pharmaceutical composition of claim 33 or claim 34, wherein the lipophilic compound and the one or more anti-glaucoma or ocular anti-hypertension agents are different.

36. The pharmaceutical composition of any one of claims 1-35, wherein the pharmaceutically acceptable carrier is selected from the group consisting of an ointment, cream, lotion, gel, emulsion, suspension, oil, foam, transdermal patch, spray, and any combinations thereof.

37. The pharmaceutical composition of claim 36, wherein the ointment comprises a paraffinic or a water-miscible ointment base.

38. The pharmaceutical composition of claim 36 or claim 37, wherein the ointment comprises 61.5% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 5% w/w of St. cyclomethicone-5NF, 5% w/w of labrasol, 5% w/w of propylene carbonate, 2.5% w/w of steareth 2, 2.5% w/w of St. emulsifier 10, and 2.5% w/w of St. elastomer-10.

39. The pharmaceutical composition of claim 36, wherein the cream comprises an oil-in-water base or a water-in-oil base.

40. The pharmaceutical composition of claim 36 or claim 39, wherein the cream comprises 48% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w ST-emulsifier, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w dibasic sodium phosphate, 0.05% w/w citric acid, 0.02% w/w propylparaben, and purified water.

41. The pharmaceutical composition of claim 36 or claim 39, wherein the cream comprises 48% w/w white soft paraffin, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w cyclomethicone, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.08% w/w methylparaben, 0.06% w/w sodium phosphate dibasic anhydrous, 0.046% w/w citric acid anhydrous, 0.02% w/w propylparaben, and purified water.

42. The pharmaceutical composition of any one of claims 36 and 39-41, wherein the cream comprises benzalkonium chloride (BAK).

43. The pharmaceutical composition of any one of claims 36 and 39-41, wherein the cream comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, 0.02% w/w benzalkonium chloride, and purified water.

44. The pharmaceutical composition of any one of claims 36 and 39-43, wherein the cream is preservative-free.

45. The pharmaceutical composition of claim 44, wherein the cream that is preservative-free comprises white soft paraffin/petrolatum, mineral oil, propylene glycol, ST-cyclomethicone-5NF, emulsifier-10, ST-elastomer-10, dibasic sodium phosphate, citric acid, and purified water.

46. The pharmaceutical composition of claim 44 or claim 45, wherein the cream that is preservative-free comprises 48% w/w white petrolatum, 8% w/w mineral oil, 8% w/w propylene glycol, 6.6% w/w ST-cyclomethicone-5NF, 3.3% w/w emulsifier 10, 2% w/w ST-elastomer-10, 0.06% w/w sodium phosphate dibasic anhydrous, 0.05% w/w citric acid anhydrous, and purified water.

47. The pharmaceutical composition of any one of claims 1-46, wherein the subject is a human or a non-human animal.

48. The pharmaceutical composition of any one of claims 1-47, wherein the subject suffers from an ocular disease.

49. The pharmaceutical composition of claim 48, wherein the ocular disease is selected from the group consisting of inflammation of the peri-ocular glands, meibomitis, dry eye disease, allergic eye disease, topical preservative toxicity, xerophthalmia, loss of homeostasis of the tear film, tear film instability and hyperosmolarity, ocular surface inflammation and damage, neuronal sensory abnormalities, Meibomian gland dysfunction, exacerbated inflammatory ocular surface disease, phlyctenular keratitis, chalazion, anterior blepharitis, posterior blepharitis, bacterial infection, glaucoma, ocular hypertension, and any combinations thereof.

50. A kit comprising:

a) the pharmaceutical composition of any one of claims 1-49; and

b) a package insert comprising instructions for administering the pharmaceutical composition.

51. Use of a pharmaceutical composition of any one of claims 1-49, in the manufacture of a medicament for providing prophylactic, palliative, or therapeutic relief of one or more signs or symptoms of an ocular disease in a subject.

52. The use of claim 51, wherein the subject is a human or a non-human animal.

53. The use of claim 51 or claim 52, wherein the ocular disease is selected from the group consisting of inflammation of the peri-ocular glands, meibomitis, dry eye disease, allergic eye disease, topical preservative toxicity, xerophthalmia, loss of homeostasis of the tear film, tear film instability and hyperosmolarity, ocular surface inflammation and damage, neuronal sensory abnormalities, Meibomian gland dysfunction, exacerbated inflammatory ocular surface disease, phlyctenular keratitis, chalazion, anterior blepharitis, posterior blepharitis, bacterial infection, glaucoma, ocular hypertension, and any combinations thereof.

54. The use of any one of claims 51-53, wherein the medicament is to be topically administered to an external portion of an eyelid of the subject, including the upper lateral region of an orbit of the subject.

55. The use of claim 54, wherein the medicament is to be topically administered to the external portion of the upper and/or lower eyelid of the subject.

56. The use of any one of claims 51-55, wherein the lipophilic compound of the medicament is to be delivered to an ocular surface of the subject via the Meibomian gland.

57. The use of any one of claims 51-56, wherein the medicament is to be administered one, two, three, four, five, six or more times per day.

58. The use of any one of claims 51-57, wherein the medicament is to be administered for one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, 10 weeks, 11 weeks, 12 weeks or more, 24 weeks, 36 weeks, 48 weeks or more.

59. The use of any one of claims 51-58, wherein prolonged administration of the medicament does not result in an adverse ocular event in the subject.

60. The use of claim 59, wherein the adverse ocular event is selected from the group consisting of elevated intraocular pressure, cataracts, ocular infection, and any combinations thereof.

61. The use of any one of claims 51-60, wherein the lipophilic compound of the medicament is not to be delivered systemically to the subject.

62. The use of any one of claims 51-61, wherein the lipophilic compound of the medicament is not to be delivered to a tear or tear duct of the subject.

63. The use of any one of claims 51-62, wherein the lipophilic compound of the medicament is not to be delivered directly to an ocular surface of the subject.