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(72) Feltaláló(k):

SINGER, Michael, S., Newton, MA 02459 (US)**KALAYOGLU, Murat, V., Silver Spring, MD 20910 (US)**

(73) Jogosult(ak):

**Topokine Therapeutics, Inc., Newton, MA
02459 (US)**

(74) Képviselő:

**Danubia Szabadalmi és Jogi Iroda Kft.,
Budapest**

(54)

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(54) **COMPOSITIONS AND METHODS FOR TOPICAL DELIVERY OF PROSTAGLANDINS TO
SUBCUTANEOUS FAT**

ZUSAMMENSETZUNGEN UND VERFAHREN ZUR TOPISCHEN VERABREICHUNG VON
PROSTAGLANDINEN IN SUBKUTANES FETT

COMPOSITIONS ET PROCÉDÉS PERMETTANT UNE ADMINISTRATION TOPIQUE DE
PROSTAGLANDINES À LA GRAISSE SOUS-CUTANÉE

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(73) Proprietor: **Topokine Therapeutics, Inc.**
Newton, MA 02459 (US)

(72) Inventors:

- **SINGER, Michael, S.**
Newton, MA 02459 (US)
- **KALAYOGLU, Murat, V.**
Silver Spring, MD 20910 (US)

(74) Representative: **D Young & Co LLP**

120 Holborn
London EC1N 2DY (GB)

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- **MAMTA SHAH ET AL: "A Cross-Sectional Survey of the Association between Bilateral Topical Prostaglandin Analogue Use and Ocular Adnexal Features", PLOS ONE, vol. 8, no. 5, 1 May 2013 (2013-05-01), pages 1-7, XP055134207, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0061638**
- **HEE YOUNG CHOI ET AL: "In Vitro Study of Antiadipogenic Profile of Latanoprost, Travoprost, Bimatoprost, and Tafluprost in Human Orbital Preadipocytes", JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS., vol. 28, no. 2, April 2012 (2012-04), pages 146-152, XP055131156, US ISSN: 1080-7683, DOI: 10.1089/jop.2011.0160**

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Description

Field of the Invention

[0001] The present invention relates to compositions for topically delivering a therapeutically effective amount of latanoprost, which is a prostaglandin FP receptor agonist (a PFPRA compound), to adipose tissue under the skin. The therapeutic effect is, for example, reduction of excess fat under the skin, for example, the skin of the face, eyelids, neck, chin, submental region, limbs, breast, abdomen, hips, etc. More specifically, the invention relates to new compositions comprising a PFPRA compound (latanoprost) and a fatty acid ester (isopropyl myristate), optionally further comprising an ointment base such as a hydrocarbon base (e.g., petroleum jelly), and/or optionally further comprising an organic alcohol (e.g., propylene glycol). The invention further relates to methods comprising applying the aforementioned composition(s) to the skin. The invention further relates to processes for manufacturing the aforementioned composition(s).

[0002] Experimentally, in comparison to a wide array of other compositions tested, the compositions disclosed herein demonstrate exceptional and surprising efficiency in delivering a certain PFPRA compound across *skin in vitro*, in delivering a therapeutically effective amount to fat below the skin *in vivo*, and/or in reducing subcutaneous fat *in vivo*. In theory, this surprising efficiency may owe to the similar structure and polarity between the PFPRA compound (latanoprost) and the fatty acid ester (isopropyl myristate), as described herein. The compositions are non-irritating, well-tolerated, and aesthetically pleasing. As a further advantage, they are considered suitable for application to the face, the eyelid, and/or periorbital skin. Furthermore, the compositions are stable and can be readily manufactured, where necessary in sterile form.

Background of the Invention

[0003] Excess body fat is an important cause of human disease, disability, and cosmetic disturbance. For many people excess body fat is also a source of psychosocial distress and reduced self-esteem.

[0004] Excess body fat may be diffuse or concentrated on particular portion(s) of the body. Of particular importance is excess body fat of the face, for example, of the eyelids, chin, or jowls. Other important sites of excess body fat can include, for example, the arms, abdomen, buttocks, hips, chest, thighs, and neck. Excess body fat can also involve excessive breast tissue on a woman or on a man, *i.e.*, gynecomastia. Excess body fat can be located within or near the eyelids, and topical treatment of such fat requires a composition that is safe for application near the eyes, *i.e.* an ophthalmic and/or ophthalmically compatible formulation. Local accumulations of body fat may result from constitutional factors, disease, hormonal status, or as side effects of medication or other substances. Even in the absence of disease, cosmetic considerations apply to individuals who nevertheless perceive an excess of fat and wish to have it corrected. For example, excess submental fat, commonly known as "double chin," is not considered a disease; however, people with excess submental fat often appear less attractive and less youthful, and can have lower self-esteem as a result. Likewise, an individual may have excess subcutaneous fat on the anterior abdomen, excess subcutaneous fat on the oblique abdomen, *e.g.* above the iliac crests ("love handles"), excess chest fat, excess breast fat, excess buttocks fat, excess hip fat, excess thigh fat, excess leg fat, excess upper arm fat, excess cheek fat, excess neck fat, *etc.*

[0005] A number of medical conditions are considered to be causes of excess body fat. Examples include drug-induced obesity, hypothyroidism, pseudohypoparathyroidism, hypothalamic obesity, polycystic ovarian disease, depression, binge eating, Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, Down syndrome, Turner syndrome, growth hormone deficiency, growth hormone resistance, and leptin deficiency or resistance. Disfiguring excess regional fat deposits, for example excess dorsocervical fat, may be found in conditions such as HIV lipodystrophy, Cushing syndrome and pseudo-Cushing syndrome (*i.e.*, characteristic syndrome of excess body fat and other findings due to excessive endogenous or exogenous corticosteroid levels), other acquired lipodystrophies, familial lipodystrophies, lipoma, lipomatosis, and Madelung disease.

[0006] Medications known to cause excess body fat include cortisol and analogs, other corticosteroids, megace, sulfonylureas, antiretrovirals, tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, oral contraceptives, insulin, risperidone, clozapine, and thiazolidinediones.

[0007] Changes in hormonal status, including physiologic changes such as pregnancy or menopause, may result in excess body fat in a subject. Smoking cessation commonly leads to weight gain and excess body fat. Trauma may favor the accumulation of excess body fat by virtue of immobility or disuse of an extremity. Similar problems may affect a subject who is immobilized, for example due to an injury. Some tumors, for example lipomas and liposarcomas, are characterized by local collections of fat cells. Lipomatosis is any condition characterized by the formation of multiple lipomas on the body, *e.g.*, familial multiple lipomatosis, adiposis dolorosa (Dercum's disease), pelvic lipomatosis, *etc.*

[0008] Even in the absence of underlying pathology, an individual may have cosmetic concerns about local or diffuse deposits of body fat. These can usually be attributed to constitutional or hereditary factors, developmental history, age, gender, diet, alcohol use, or other components of lifestyle. Individuals in such circumstances commonly wish to reduce

the amount of fat on the face, eyelids, chin, arms, neck, abdomen, chest, breast, buttocks, hips, thighs, and/or legs. In some cases a local excess of fat can be due to fat prolapse, displacement, and/or migration, as in age-related orbital fat prolapse or descent of malar fat pads. Grave's ophthalmopathy (thyroid-related eye disease) is a condition that can be treated by reducing the volume of orbital fat.

[0009] A number of methods have been developed to reduce or remove excess body fat. It is helpful to classify these methods as extractive, metabolic, or adipolytic. Extractive methods, such as lipoplasty (e.g., liposuction) or local excision, are methods whereby fat is physically removed from areas of interest. Such methods are costly and may involve scars, postsurgical deformity or regression, discomfort, infection, and other adverse reactions.

[0010] In contrast to extractive methods, metabolic methods, which include systemic medications, nutritional supplements, devices, and exercise or other body treatment, seek to modify the subject's metabolism (e.g., whether caloric consumption, expenditure, or both) such that the subject incurs a net loss of fat. A disadvantage is that these methods typically cannot be directed to a particular part of the body. Another drawback is potential concomitant loss of water, carbohydrates, protein, vitamins, minerals, and other nutrients. Furthermore, traditional diet medications may have undesired side effects, for example palpitations, tremor, insomnia, and/or irritability in a subject who uses stimulants as appetite suppressants. Despite salubrious value, the traditional metabolic methods of diet and exercise are not practical for everybody.

[0011] Adipolytic methods aim to cause breakdown of adipocytes and/or their lipid contents. For example, fat deposits can be reduced by exposure to cold temperature or to deoxycholate, a solubilizer that lyses cell membranes and results in local necrosis. Drawbacks of these methods can include poor discrimination between adipose and other nearby tissues, barriers to delivery that require hypodermic needles or special equipment, and adverse effects such as necrosis, inflammation, and pain.

[0012] Compounds of the prostaglandin FP receptor agonist (PFPR compound) class, e.g., latanoprost and tafluprost, can be administered to the skin to locally reduce adipose tissue under the skin, *i.e.*, subcutaneous fat. See, e.g., U.S. Patent 8,426,471 and U.S. Publication No. 2010/0234466. Developing topical delivery of the PFPR compound poses significant challenges, since delivery to subcutaneous fat comprises delivery across the stratum corneum, epidermis, dermis, and dermal microcirculation, and into the fat below.

[0013] For example, the skin, in particular the stratum corneum, presents a formidable physical barrier to drug penetration. See, e.g., Dayan N, *Delivery System Design in Topically Applied Formulations: An Overview*, in Rosen M, *Delivery System Handbook for Personal Care and Cosmetic Products*, William Andrew, 2005, pp. 103-104. For any particular drug, the formulation must be selected empirically. The formulation must be physically and chemically compatible with the drug.

[0014] Furthermore, provided that a formulation enables a drug to cross the skin, to reach the subcutaneous fat it must also circumvent what is known as the "sink condition" of the dermal circulation. See, e.g., Dayan N, *Delivery System Design in Topically Applied Formulations: An Overview*, in Rosen M, *Delivery System Handbook for Personal Care and Cosmetic Products*, William Andrew, 2005, pp. 103-104; Kao J, *In Vitro Assessment of Dermal Absorption*, in Hobson DW, *Dermal and Ocular Toxicology: Fundamentals and Methods*, CRC Press, 1991, pp. 272-273. Because the dermis is invested by a network of capillaries with rapid blood flow, for any solute (e.g., drug) that penetrates the dermis, a wide concentration gradient is created between the skin and bloodstream. Thus, there is a strong tendency for drugs that penetrate into the dermis to diffuse rapidly down this gradient into the bloodstream. This sink phenomenon favors systemic delivery (e.g., to the bloodstream, as with a nicotine patch), but undermines attempts at local delivery (e.g., to subcutaneous fat, as in the present invention). No method of reasoning or prediction is available in the art to suggest which formulations, if any, can circumvent the sink condition. Therefore, the artisan must search for such formulations empirically, and without prior knowledge that such formulation even exists.

[0015] The formulation must also have a favorable systemic drug exposure profile, e.g., that avoids excessive levels of drug in the bloodstream. This requirement is rendered more difficult by the sink condition.

[0016] Additionally, the formulation should deliver the active ingredient with reasonable efficiency. One measure of efficiency is the ability to minimize the concentration of active ingredient in the finished product and still maintain the desired therapeutic effect. This has implications for manufacturability, cost of goods, and local safety and tolerability. Another measure of efficiency is the ability to minimize the dose frequency and still maintain the desired therapeutic effect, which has implications for patient convenience and product marketability.

[0017] As well, the formulation must cause little or no skin irritation. If applied to skin near the eye, e.g., the eyelid, the formulation is considered an ophthalmic formulation. Generally, an ophthalmic formulation must be sterile, e.g., according to Chapter <71> of the U.S. Pharmacopeia. Preferably, an ophthalmic formulation must also be free or essentially free of bacterial endotoxin, e.g. according to Chapter <85> of the U.S. Pharmacopeia, e.g., an endotoxin level of <10 EU (endotoxin units) per gram of composition. If applied to skin near the eye, the formulation must be ophthalmically compatible, *i. e.*, the formulation must not cause clinically significant eye irritation, and must not be toxic to the eye, e.g., the ocular surface, e.g. the cornea. Irritation potential and ocular toxicity are studied empirically by standard preclinical models, or in human trials. Although the skin or eye irritation potential of individual inactive ingredients is generally

known, combinations of inactive and active ingredients can cause unexpected irritation, which must be tested empirically.

[0018] Furthermore, the formulation must possess other qualities necessary to make a topical formulation and market it to consumers: ease of manufacture, physical and chemical stability, and commercially acceptable appearance, odor, and tactile qualities.

EP 2228058 describes a colloidal anionic oil-in-water emulsion comprising a prostaglandin, an oil having an iodine value of ≤ 2 , a surfactant and water, provided the anionic oil-in-water emulsion does not contain polyvinyl alcohol. Also described is the use of said anionic oil-in-water emulsions for enhancing the stability of said prostaglandins, for the treatment of ocular hypertension and/or glaucoma, for promoting the growth of eyelashes and/or for treating eyelash hypotrichosis. Mamta Shah et al., PLoS ONE, 8(5), pp. 1-7, 2013 describes the relation between prostaglandin analogue use and ocular adnexal features.

[0019] Therefore, there is a need for new compositions for topically delivering a PFPPRA compound to adipose tissue under the skin.

Summary of the Invention

[0020] It has now been discovered experimentally that certain topical compositions comprising a PFPPRA compound (latanoprost) and certain fatty acid esters (isopropyl myristate) provide exceptionally efficient delivery of the compound and its active metabolite into subcutaneous fat, and thus have particular uses and advantages, as described herein. In theory, this efficiency may owe to the similar structure and polarity between the PFPPRA compound (latanoprost) and the fatty acid ester (isopropyl myristate), as described herein.

[0021] Thus, in one aspect, provided is a composition useful in the reduction of subcutaneous fat comprising a PFPPRA compound, which is latanoprost, and a fatty acid ester which is isopropyl myristate, wherein the composition comprises between 1 percent and 20 percent of isopropyl myristate by weight of the total weight of the composition. In certain embodiments, the concentration of latanoprost in the composition is between about 0.0001 percent to about 1 percent by weight, as a proportion of the total weight of the composition, e.g., between about 0.05 percent and about 0.5 percent by weight, or between about 0.01 percent and about 0.1 percent by weight of the final composition. The final concentration of the fatty acid ester (isopropyl myristate) is between 1 percent to 20 percent by weight, e.g., between about 1 percent and about 10 percent by weight of the composition. In certain embodiments, the composition further comprises an ointment base, e.g., a hydrocarbon base such as petroleum jelly. In some embodiments, the final concentration of the ointment base is between about 50 percent and about 99 percent by weight, e.g., between about 70 percent and about 99 percent by weight, of the total weight of the composition. In some embodiments, the composition further comprises an organic alcohol (e.g., propylene glycol). In some embodiments, the final concentration of the organic alcohol is between about 5 percent and about 50 percent by weight, e.g., between about 5 percent and about 20 percent by weight, of the total weight of the composition. In some embodiments, the composition is not an emulsion. In some embodiments, the composition is immiscible in water. In some embodiments, the composition is an ophthalmic composition and is ophthalmically compatible. In some embodiments, the composition is sterile.

[0022] Also described herein is a method of reducing body fat in a subject, comprising topically administering a composition as described herein to a subject in need thereof, wherein the method is a cosmetic method.

[0023] In another aspect, provided is a composition as described herein for use in reducing body fat in a subject.

[0024] In another aspect, provided is a composition for use in reducing fat in a subject suffering from steatoblepharon. In another aspect, provided is a composition as described herein for use in treating steatoblepharon in a subject. In another aspect, provided is use a composition as described herein in the manufacture of a medicament for treating steatoblepharon in a subject.

[0025] As described herein, there is provided a kit comprising a composition as described herein and instructions for use.

[0026] In another aspect, provided is a process for manufacturing one or more of the inventive compositions in a sterile fashion, whereby the composition is sterile, endotoxin-free, and ophthalmically compatible, and therefore suitable for use on the eyelid or near the eye. For example, in one embodiment, provided is a process for manufacturing a sterile ointment, comprising the steps of dissolving a PFPPRA compound (latanoprost) in a fatty acid ester (isopropyl myristate) to make a solution; microfiltration of the solution to make a filtrate; and combining the filtrate with an ointment base (e.g., a hydrocarbon base such as petroleum jelly). In certain embodiments, the method further comprises dissolving a preservative (e.g., chlorobutanol) in the fatty acid ester (isopropyl myristate).

[0027] Other objects and advantages will become apparent to those skilled in the art from consideration of the ensuing Detailed Description, Examples, and Claims.

Description of the Drawings

[0028] *Figure 1* depicts three-dimensional molecular models of isopropyl myristate and latanoprost in energy-minimized conformations (solved *in vacuo*). Carbon atoms are shown in gray and oxygen atoms in red; hydrogens are not shown.

Measured end-to-end distances (between heavy atom centers) are 19.9 Å for isopropyl myristate and 17.7 Å for latanoprost.

Definitions

Chemical definitions

[0029] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Organic Chemistry, Thomas Sorrell, University Science Books, Sausalito, 1999; Smith and March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0030] Certain compounds as described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. The compounds provided herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. In certain embodiments, the compounds as described herein are enantiopure compounds. In certain other embodiments, mixtures of stereoisomers are provided.

[0031] Furthermore, certain compounds, as described herein may have one or more double bonds that can exist as either the *cis* or *trans*, or the E or Z isomer, unless otherwise indicated. The invention additionally encompasses the compounds as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers, e.g., racemic mixtures of E/Z isomers or mixtures enriched in one E/Z isomer.

[0032] The terms "enantiomerically enriched," "enantiomerically pure" and "non-racemic," as used interchangeably herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (R)-enantiomer, more preferably at least 75% by weight, and even more preferably at least 80% by weight. In some embodiments, the enrichment can be much greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure" or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to other enantiomer, more preferably at least 90% by weight, and even more preferably at least 95% by weight. In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen, S.H., et al., Tetrahedron 33:2725 (1977); Eliel, E.L. Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, S.H. Tables of Resolving Agents and Optical Resolutions p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0033] When a range of values is listed, it is intended to encompass each value and sub-range within the range.

[0034] As used herein, the terms "salt", "acceptable salt", or "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge et al., describes pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences (1977) 66:1-19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts

derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

Other definitions

[0035] "Disease", "disorder," and "condition" are used interchangeably herein.

[0036] As used herein, an "individual" or "subject" to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)), other primates (*e.g.*, cynomolgus monkeys, rhesus monkeys) and commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs. In any aspect and/or embodiment of the invention, the mammal is a human.

[0037] As used herein, "local administration" or "administering locally" or "local effect" means administration/application of the active ingredient or active metabolite thereof directly, or in proximity to, a part of the body, tissue, or lesion where said active substance is intended to exert its action. This may include, for example, topical administration to a part of the skin.

[0038] As used herein, unless otherwise specified, "topical administration" or "topically" means application to the surface of the skin, *e.g.*, in a non-invasive manner.

[0039] As used herein, and unless otherwise specified, a "therapeutically effective amount" "an amount sufficient" or "sufficient amount" of a compound means the level, amount or concentration of the compound needed to treat a disease, disorder or condition, or to reduce or lower a particular parameter (*e.g.*, body fat) in the body of a subject, without causing significant negative or adverse side effects to body or the treated tissue. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease or condition, or enhances the therapeutic efficacy of another therapeutically active agent.

[0040] As used herein, the terms "reduce", "reduction", "reducing", "lower", or "lowering" means to diminish or lessen the volume, size, mass, bulk, density, amount, and/or quantity of a substance (*e.g.*, body fat, adipose tissue) in the body of a subject.

[0041] As used herein, the term "eliminate" means to completely remove any unwanted or undesired volume, size, mass, bulk, density, amount, and/or quantity of a substance (*e.g.*, excess body fat, excess adipose tissue) in the body of a subject.

[0042] As used herein, "suffer", "suffers" or "suffering from" refers to a subject diagnosed with a particular disease or condition. As used herein, "likely to suffer" refers to a subject who has not been diagnosed with a particular disease or condition by a medical practitioner, but has a predisposition (*e.g.*, genetic and/or physiologic predisposition), or exhibits signs or symptoms of the disease or condition.

[0043] As used herein, and unless otherwise specified, the terms "treat," "treating" and "treatment" contemplate an action that occurs while a subject is suffering from the specified disease or condition, which reduces the severity of the disease or condition, or retards or slows the progression of the disease or condition.

[0044] As used herein, unless otherwise specified, the terms "prevent," "preventing" and "prevention" contemplate an action that occurs before a subject begins to suffer from the specified disease or condition, which inhibits or reduces the severity of the disease or condition.

[0045] Conditions for which treatment and prevention are contemplated may be further classified as a medical condition or a cosmetic condition. A "medical condition," as used herein, refers to an abnormal condition that affects the body. A "cosmetic condition," as used herein, refers to a condition other than a medical condition that affects the physical appearance of the body. A cosmetic condition can occur, for example, due to normal processes in a body, such as aging, pregnancy, puberty, and exposure to the sun or the elements, or due to normal features of a body, such as inherited facial features or body shapes that are found in healthy individuals. Various medical and cosmetic conditions are described herein. A "cosmetic method" refers to a method or procedure intended to ameliorate a cosmetic condition in the subject, *e.g.*, for the beautification of the subject's body or a part thereof, and a "cosmetic composition" is contemplated useful for such purpose. A "therapeutic method" refers to a method or procedure intended to treat or prevent a medical condition, and a "pharmaceutical composition" is contemplated useful for such purpose. However, while pharmaceutical compositions are contemplated useful for therapeutic and prophylactic purposes, and cosmetic compositions are contemplated useful for cosmetic purposes, there is overlap between the two compositions in terms of use of the composition. For example, a pharmaceutical composition is also contemplated useful for beautification purposes.

[0046] As used herein, unless otherwise specified, "excess submental fat" means excess fat on the body region including the mentum, the underside of the jaw, and the anterior neck, for example to the level of the inferior border of the cricoid.

[0047] As used herein, unless otherwise specified, "steatoblepharon" refers to a condition characterized by excess fat of the eyelids and/or periorbital tissue. The excess fat can be due to prolapse of orbital or periorbital fat. Steatoblepharon can occur in the lower or upper eyelid, or both. Steatoblepharon can be considered a cause of "eye bags."

[0048] The presence, amount, or severity of excess fat can be assessed objectively, e.g., by magnetic resonance imaging, computed tomography, biopsy, or skin calipers, or subjectively, e.g., by a clinician, a patient, or other observer, optionally with reference to a photonumeric, verbal, or descriptive scale or classification system, e.g., a five-step severity scale.

Detailed Description of Certain Embodiments of the Invention

[0049] The present invention relates to new, stable, manufacturable, well-tolerated, aesthetically pleasing compositions that, when topically applied to the skin, delivers a therapeutically effective amount of latanoprost to subcutaneous fat. More specifically, the invention relates to compositions for delivery of latanoprost to subcutaneous fat comprising latanoprost and a fatty acid ester (isopropyl myristate). The formulations are useful for local reduction of subcutaneous fat, and for other therapeutic uses as described herein. The invention also related to a process for manufacturing one or more of the inventive compositions, e.g., in a sterile fashion, whereby the composition is sterile, endotoxin-free, and ophthalmically compatible, and therefore suitable for use on the eyelid or near the eye. A particular advantage of the inventive formulations is suitability for application on the face and/or periorbital skin.

[0050] As described herein, no theoretical framework was available to the inventors to select or improve a composition for delivering latanoprost to subcutaneous fat. Rather, the inventors found it necessary to test a wide range of conditions both *in vitro* and *in vivo*, with different formulation components at different concentrations and in different combinations. This testing led to the discovery that inclusion of a fatty acid ester (isopropyl myristate) in the composition conferred exceptionally better performance for delivery of latanoprost and reduction of subcutaneous fat compared to, for example, use of 1,3-butanediol, diethylene glycol monoethyl ether, dimethylsulfoxide, ethanol, glycerol monooleate, hydroxypropyl cellulose, lauryl lactate, methyl laurate, oleyl alcohol, polysorbate 80, propylene glycol, and combinations thereof.

[0051] Without wishing to be bound by any particular theory, the special properties conferred by combining a fatty acid ester (isopropyl myristate) and latanoprost may owe to certain similarities between the fatty acid ester (isopropyl myristate) and latanoprost, *i.e.*, similar structure and similar polarity.

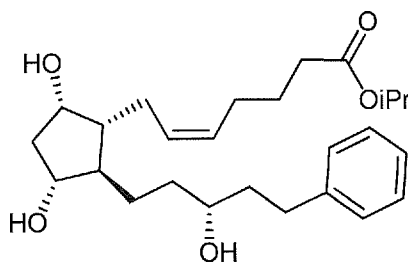
Latanoprost (*cf.* Examples 1-3) and isopropyl myristate are both isopropyl esters with parent acids comprising aliphatic tails of similar chain length (isopropyl myristate, 13 aliphatic carbons in the lipid tail; latanoprost, 13 aliphatic carbons if the cyclizing carbons 9 through 11 of the cyclopentyl ring are not counted). As shown in *Figure 1*, in their energy-minimized 3-dimensional conformations, both compounds are roughly linear and of similar length. Furthermore, according to this structural hypothesis, latanoprost *per se* could serve as a penetration enhancer in this context, in that the 5-*cis* double bond of latanoprost may lend particular improvement to the penetration characteristics of isopropyl myristate, as the structural kink of unsaturated molecules is known to interfere with close packing of the phospholipid bilayer and can thereby improve penetration.

[0052] In certain embodiments, the composition further comprises an ointment base. As used herein, an ointment is a homogeneous, viscous, semi-solid preparation, which comprises a greasy, ointment base having a medium-to-high viscosity, that is intended for topical application to the skin. Exemplary ointment bases include, but are not limited to, hydrocarbon bases/waxes (e.g., plant and animal waxes (e.g., beeswax, lanolin, carnauba wax), petroleum derived waxes (e.g., hard paraffin wax or soft paraffin wax, *i.e.*, petroleum jelly), microcrystalline wax, ceresine wax, white wax, yellow wax, and cetyl esters wax). In certain embodiments, the ointment base is a hydrocarbon base, e.g., soft paraffin wax, e.g., petroleum jelly. Petroleum jelly (also known as petrolatum, white petrolatum, soft paraffin or multi-hydrocarbon) is a semi-solid preparation typically comprising (or consisting of) one or more saturated hydrocarbons with carbon numbers mainly higher than 25 (typically 25 to 50, such as 25 to 40, such as 25 to 35). It typically has a boiling point of from about 250°C to about 350°C, such as about 280°C to about 320°C, preferably about 300°C, and a melting point typically from about 36°C to about 60°C. In certain embodiments, the petroleum jelly is obtained in sterile form or is sterilized prior to manufacturing the composition. In certain embodiments, the petroleum jelly is pure ultra white petroleum jelly.

[0053] In some embodiments, the composition further comprises an organic alcohol, e.g., methanol, ethanol, propanol, isopropanol, 1,3-butanediol, ethylene glycol, or propylene glycol. In certain embodiments, the organic alcohol is propylene glycol. However, in certain embodiments, 1,3-butanediol is excluded.

[0054] In clinical practice, topical delivery of compounds across the skin usually relies on the principle of passive diffusion. This principle dictates that a compound can only flow from an area of higher thermodynamic potential to one of lower thermodynamic potential. A solute held firmly by a vehicle will demonstrate little or no diffusion. Thus, the skilled artisan expects that latanoprost (which is an oil-soluble compound) will penetrate better from an aqueous vehicle than from an oily vehicle (See, e.g., Barrett CW, Skin penetration. J. Soc. Cosmetic Chemists 1969;20:487-499). Thus far, this theory has been borne out in practice, as PFPPRA compound formulations for topical use have repeatedly selected

water or ethanol as the preferred carrier for clinical use. See, e.g., prescribing inserts for Xalatan®, Travatan®, Lumigan®, and Zioptan®. See also Blume-Peytavi U et al, A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia, J Am Acad Dermatol 2012;66:794-800. Thus, another surprising aspect of the invention is that compositions comprising latanoprost formulated with a fatty acid ester (isopropyl myristate) and an ointment base, e.g., a hydrocarbon base such as petroleum jelly, delivers the latanoprost more effectively than an array of other vehicles, as disclosed herein. In certain embodiments, the composition does not include an aqueous or water-soluble component such as an organic alcohol. However, in certain embodiments, the composition does comprise an organic alcohol, e.g., propylene glycol, and, in certain embodiments, the composition comprises the organic alcohol in no greater than 50% by weight. In certain embodiments, the composition is hydrophobic, e.g., the composition is not miscible in water. In certain embodiments, the composition is not an emulsion. In certain embodiments, the composition does not contain mineral oil. The PFPPRA compound used in the composition of the invention is:



also referred to herein as latanoprost.

Composition and Formulations

[0055] In certain embodiments, the present invention provides compositions for topical administration of a composition comprising latanoprost, as described herein, and a fatty acid ester (isopropyl myristate). Compositions, as used herein, encompass pharmaceutical compositions as well as cosmetic compositions.

[0056] In certain embodiments, the composition comprises latanoprost, fatty acid ester (isopropyl myristate), and an ointment base. In some embodiments, the composition further comprises an organic alcohol, e.g., methanol, ethanol, propanol, isopropanol, 1,3-butanediol, ethylene glycol, or propylene glycol. In certain embodiments, the organic alcohol is propylene glycol. In certain embodiments, the composition comprises latanoprost, isopropyl myristate, and an ointment base. In certain embodiments, the composition consists essentially of the above-recited components. In certain embodiments, the composition is not irritating to the skin. In certain embodiments, the composition is sterile, endotoxin-free or essentially endotoxin-free, ophthalmic, and/or ophthalmically compatible.

[0057] Kalayoglu (PCT/US2012/021692; WO2012/099942) teaches certain formulations for systemic (transdermal) delivery of a PFPPRA to the bloodstream. These include two emulsions (Lipoderm or pluronic lecithin organogel). Emulsions are challenging to manufacture and susceptible to phase separation; e.g., for example, pluronic lecithin organogel is prone to phase separation at temperatures of about 5°C or below. Thus, in some embodiments, the composition is a non-emulsion, i.e., is not an emulsion. In some embodiments, the composition is a non-emulsion comprising latanoprost, fatty acid ester (isopropyl myristate), and an ointment base. In some embodiments, the composition is a non-emulsion comprising latanoprost, fatty acid ester (isopropyl myristate), an organic alcohol, and an ointment base.

[0058] The PFPPRA compound is latanoprost, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, polymorph, tautomer, or isotopically enriched derivative thereof.

[0059] The PFPPRA compound is latanoprost; in some embodiments, the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 0.1 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive.

[0060] The final concentration of the fatty acid ester (isopropyl myristate) is between 1 percent to 20 percent by weight, inclusive. In some embodiments, the final concentration is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, inclusive. In certain embodiments, the final concentration of the fatty acid ester (isopropyl myristate) is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 percent by weight. These percentages are expressed

by weight of the total weight of the composition.

[0061] The PFPRA compound is latanoprost; in some embodiments, the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, about 0.05 and about 5 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive. These percentages are expressed by weight of the total weight of the composition.

[0062] In some embodiments, the composition comprises an ointment base, e.g., a hydrocarbon base. In some embodiments, the hydrocarbon base is selected from the group consisting of white wax, yellow wax, hard paraffin wax, petroleum jelly, and cetyl esters wax. In some embodiments, the final concentration of ointment base is between about 50 percent and about 99 percent by weight. In some embodiments, the final concentration of ointment base is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. In some embodiments, the ointment base is petroleum jelly, and the final concentration of petroleum jelly is between about 50 percent and about 99 percent by weight, inclusive. In some embodiments, the final concentration of petroleum jelly is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive.

[0063] The PFPRA compound is latanoprost; in some embodiments, the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; the final concentration of fatty acid ester (isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; and the final concentration of the ointment base (e.g., petroleum jelly) is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[0064] In some embodiments, the composition further comprises an organic alcohol (e.g., propylene glycol). In some embodiments, the final concentration of propylene glycol is between about 5 percent and about 50 percent by weight, inclusive. In some embodiments, the final concentration of the organic alcohol (e.g., propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent, about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive.

[0065] The PFPRA compound is latanoprost; in some embodiments, the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 5 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (e.g., isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about

10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; and the final concentration of the organic alcohol (e.g., propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[0066] The PFPPRA compound is latanoprost; in some embodiments, the final concentration of latanoprost is between about 0.001 percent and about 1 percent, 0.001 and about 0.003 percent, about 0.001 and about 0.01 percent, about 0.003 and about 0.01 percent, about 0.01 and about 0.03 percent, about 0.01 and about 0.1 percent, about 0.05 and about 0.3 percent, about 0.03 and about 0.1 percent, about 0.1 and about 0.3 percent, about 0.1 and about 1 percent, or about 0.3 and about 1 percent (by weight), inclusive; and the final concentration of fatty acid ester (isopropyl myristate) is between about 5 and about 15 percent, about 1 and about 10 percent, about 1 and about 2 percent, about 1 and about 3 percent, about 2 and about 4 percent, about 3 and about 5 percent, about 3 and about 7 percent, about 4 and about 6 percent, about 5 and about 7 percent, about 6 and about 8 percent, about 7 and about 10 percent, about 10 and about 20 percent, about 10 and about 15 percent, or about 15 and about 20 percent, by weight, inclusive; the final concentration of the organic alcohol (e.g., propylene glycol) is between about 5 percent and 10 percent, about 5 percent and about 15 percent, about 5 percent and about 20 percent, about 10 percent and about 15 percent, about 10 percent and about 20 percent, about 15 percent and about 20 percent, about 15 percent and about 25 percent, about 20 percent and about 25 percent, about 20 percent and 30 percent about 25 percent and about 30 percent, about 25 percent and about 35 percent, about 30 percent and about 35 percent, about 30 percent and about 40 percent, about 35 percent and about 40 percent, about 35 percent and about 45 percent, about 40 percent and about 50 percent, about 40 percent and about 45 percent, or about 45 percent and about 50 percent, inclusive; and the final concentration of the ointment base (e.g., petroleum jelly) is between about 50 percent and 60 percent, 50 percent and about 70 percent, about 60 percent and about 70 percent, about 60 percent and about 80 percent, about 70 percent and about 80 percent, about 70 percent and about 90 percent, about 70 percent and about 99 percent, about 80 percent and about 90 percent, about 85 percent and about 95 percent, about 90 percent and about 95 percent, about 90 percent and about 99 percent, and about 95 percent and about 99 percent, inclusive. These percentages are expressed by weight of the total weight of the composition.

[0067] In certain embodiments, the composition may further comprise other pharmaceutically acceptable excipients including, but not limited to, solvents, diluents or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, lubricants and the like. General considerations in the formulation and/or manufacture of topical compositions can be found, for example, *in* Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and Remington: The Science and Practice of Pharmacy, 21st Edition (Lippincott Williams & Wilkins, 2005).

[0068] In some embodiments, the composition is sterile. Generally, methods of manufacturing a sterile composition include gamma irradiation, heat (e.g., autoclave or dry heat), and microfiltration (e.g., with a 0.2 micron filter); however, some of these methods can be unsuitable for certain compositions. For example, gamma irradiation or heat can cause degradation of the PFPPRA compound; oleaginous bases such as petroleum jelly are not amenable to autoclave sterilization; and some excipients may be incompatible or poorly compatible with a 0.2 micron filter.

[0069] Compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the composition comprising a predetermined amount of the PFPPRA compound. The amount of the PFPPRA compound is generally equal to the dosage of the PFPPRA compound which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0070] Relative amounts of the PFPPRA compound, the pharmaceutically acceptable excipient, and/or any additional ingredients in a composition will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered.

Other Features of Compositions

[0071] Pharmaceutically acceptable excipients used in the manufacture of provided compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as coloring agents, coating agents, perfuming agents, and sunscreens may also be present in the composition.

[0072] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge,

cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and combinations thereof.

[0073] Exemplary surface active agents and/or emulsifiers include lipids/natural emulsifiers (*e.g.* acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.* bentonite [aluminum silicate] and Veegum [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (*e.g.* stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.* carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.* carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.* polyoxyethylene sorbitan monooleate [Tween 20], polyoxyethylene sorbitan [Tween 60], polyoxyethylene sorbitan monooleate [Tween 80], sorbitan monopalmitate [Span 40], sorbitan monostearate [Span 60], sorbitan tristearate [Span 65], glyceryl monooleate, sorbitan monooleate [Span 80]), polyoxyethylene esters (*e.g.* polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.* Cremophor), polyoxyethylene ethers, (*e.g.* polyoxyethylene lauryl ether [Brij 30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F 68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, *etc.* and/or combinations thereof.

[0074] Exemplary binding agents include starch (*e.g.* cornstarch and starch paste), gelatin, sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, *etc.*, and/or combinations thereof.

[0075] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[0076] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[0077] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal. Chlorobutanol, for example, can be used as a preservative in an ointment formulation at a concentration of 0.001 % to 1 % by weight (such as 0.5 % per weight) of the total weight of the final composition.

[0078] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[0079] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol.

[0080] Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[0081] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

[0082] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium

acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and combinations thereof.

[0083] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, *etc.*, and combinations thereof.

[0084] Exemplary oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mint, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and combinations thereof.

[0085] A composition of the invention can be combined with, incorporated into, and/or delivered by means of a patch or dressing, which often have the added advantage of providing controlled delivery of the PFPRA compound to the body. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the PFPRA compound in a polymer matrix and/or gel.

[0086] The composition may further comprise one or more of the additional ingredients described herein. In some embodiments, the additional ingredient is a sunscreen, moisturizer, colorant, antibiotic, antifungal, antiviral, antifibrotic, anti-inflammatory, anesthetic, analgesic, vasoconstrictor, vasodilator, vitamin or mineral, or antioxidant.

[0087] Although the descriptions of compositions provided herein are principally directed to compositions that are suitable for topical administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation. General considerations in the formulation and/or manufacture of compositions can be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005.

[0088] Also described herein are kits comprising a composition of the invention as described herein and instructions for use. Kits provided may comprise a provided composition and a container (*e.g.*, a tube, vial, ampoule, bottle, syringe, and/or dispenser package, or other suitable container).

Use

[0089] As generally described herein, the compositions described herein are contemplated useful in the reduction of subcutaneous fat in a subject in need thereof. Methods of use include cosmetic methods, as described herein. For example, in one aspect, provided is a method of reducing body fat in a subject, comprising topically administering a composition as described herein to a subject in need thereof. In another aspect, provided is a composition of the present invention for use in method of reducing body fat in a subject. In another aspect, provided use of a composition of the present invention in the manufacture of a medicament for reducing body fat in a subject. In certain embodiments, the method is a cosmetic method.

[0090] Fat reduction can include reducing fat as measured by at least one of volume, size, mass, bulk, density, amount, and/or quantity. The present invention is expected to reduce fat by greater than or equal to 75%, greater than or equal to 70%, greater than or equal to 60%, greater than or equal to 50%, greater than or equal to 40%, greater than or equal to 30%, greater than or equal to 25%, greater than or equal to 20%, greater than or equal to 15%, greater than or equal to 10%, or greater than or equal to 5%. For example, fat reduction can also include reducing fat cell amount (for example, fat cell number), reducing fat cell volume, reducing fat cell maturation, and/or dedifferentiating a fat cell.

[0091] In certain embodiments, the body fat is local, *e.g.*, concentrated on the face, chin, neck, arms, abdomen, chest, breast, buttocks, hips, thighs, legs, and/or knees.

[0092] In certain embodiments, the subject suffers from or is likely to suffer from obesity, excess fat on the breast, excess fat on the chin, gynecomastia, drug-induced obesity, hypothyroidism, pseudohypoparathyroidism, hypothalamic obesity, polycystic ovarian disease, depression, binge eating, postpartum obesity, obesity associated with smoking cessation, Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, Down syndrome, Turner syndrome, growth hormone deficiency, growth hormone resistance, leptin deficiency or resistance, Cushing syndrome, pseudo-Cushing syndrome, hypertrophy of dorsocervical fat/dorsocervical fat hypertrophy ("buffalo hump"), moon facies, HIV lipodystro-

phy, orbital fat prolapse, age-related descent of abnormal fat, other acquired lipodystrophy, familial lipodystrophy, lipoma, lipomatosis, or Madelung disease. In certain embodiments, the subject suffers from or is likely to suffer from obesity, gynecomastia, HIV lipodystrophy, lipoma, steatoblepharon, excess eyelid fat, excess periorbital fat, or excess fat on the chin. In certain embodiments, the subject has a cosmetic condition.

[0093] In certain embodiments, the subject suffers from or is likely to suffer from excess submental fat. Thus, in one aspect, provided is a composition for use in for reducing fat in a subject suffering from excess submental fat. In another aspect, provided is a composition as described herein for use in treating excess submental fat in a subject.

[0094] In certain embodiments, the subject suffers from or is likely to suffer from steatoblepharon. Thus, in one aspect, provided is a composition for use in for reducing fat in a subject suffering from steatoblepharon. In another aspect, provided is a composition as described herein for use in treating steatoblepharon in a subject. In another aspect, provided is use a composition as described herein in the manufacture of a medicament for treating steatoblepharon in a subject.

[0095] As described herein, the route of administering is topical. In certain embodiments, the administering is to a body part selected from the group consisting of the face, chin, submental region, jowls, cheeks, periorbital skin, neck, arms, abdomen, chest, breast, buttocks, hips, thighs, legs, and knees.

[0096] In certain embodiments, the subject has excess body fat as a side effect of medication (e.g., for example, cortisol and analogs, corticosteroids, megace, sulfonylureas, anti-retrovirals, antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, oral contraceptives, insulin or a form of insulin, risperidone, clozapine, and thiazolidinediones).

[0097] In certain embodiments, the subject has excess body fat due to changes in hormonal status (e.g., as a result of physiologic changes such as pregnancy or menopause).

[0098] In certain embodiments, the subject with excess body fat is undergoing or has recently undergone smoking cessation.

[0099] In certain embodiments, the subject has body fat of cosmetic significance, for example, due to age-related orbital fat prolapse, excess submental fat, or descent of the malar fat pads.

[0100] This aspect of invention may also be useful as an adjunct to any of various kinds of surgery and/or non-invasive therapy, whether used in the pre-operative, peri-operative, or post-operative period. The invention further contemplates uses preceding abdominal, thoracic, oncologic, endocrine, neurologic, transplant, and dermatologic surgery, whereby surgical exposure may be improved; preceding or following orthopedic procedures, whereby surgical exposure as well as post-operative recovery may be improved; and preceding cosmetic procedures using lasers, another type of radiation, thermal therapy, cryotherapy, ultrasound, electrolysis, chemical treatment and the like, e.g., skin tightening, skin resurfacing, collagen remodeling, and the like.

Process for manufacturing a sterile ointment

[0101] For ophthalmic use, e.g., application on the eyelid for reduction of steatoblepharon, a sterile composition is preferred. Certain of the inventive formulations (e.g., a composition comprising latanoprost, isopropyl myristate, and petrolatum) are not compatible with all forms of sterilization. For example, the inventors found that gamma irradiation caused degradation of latanoprost (Example 14). Petroleum jelly is incompatible with autoclave sterilization and poorly suited for microfiltration.

[0102] The inventors sought a practicable alternative. Having discovered that latanoprost is exceptionally soluble in isopropyl myristate (Example 3), the inventors developed a manufacturing process (cf. Example 4) comprising the steps of: (1) dissolving the PFPPRA (latanoprost) and optionally other components (e.g., chlorobutanol) in the fatty acid ester (isopropyl myristate) to make a solution; (2) microfiltration of the solution (e.g., under aseptic conditions) to make a sterile filtrate; and (3) addition of the filtrate to sterile petroleum jelly, which is optionally liquefied, e.g., by heating (e.g., from about 40° C to about 70° C, e.g., about 50 to about 60° C); and (4) mixing to obtain a uniform mixture. Upon reading the Examples, the skilled artisan can appreciate several advantages to combining the latanoprost and PFPPRA compound prior to microfiltration, as opposed to filtering these components separately: latanoprost is very viscous and poorly suited to microfiltration; the volume of latanoprost is generally small and therefore prone to measurement error (i.e., imprecision) and losses in the so-called "dead space" of the microfilter; and diluting the latanoprost in the isopropyl myristate promotes uniformity of the latanoprost in the final composition. However, the skilled artisan will also appreciate that the strategy of dissolving the latanoprost in the isopropyl myristate would not be practicable, except for the fortuitously good solubility found by the inventors (Example 3). Furthermore, a surprising and advantageous property of mixing the isopropyl myristate in the petroleum jelly is that it substantially reduces the viscosity of the mixture, as compared to that of the pure petroleum jelly. This not only facilitates mixing (thereby promoting uniformity of the mixture) but also renders the composition more flowable and spreadable on the skin, i.e., the pharmaceutical composition is easier to dispense from a container and apply to the skin.

[0103] Thus, in another aspect, provided is a process for manufacturing one or more of the inventive compositions in a sterile fashion, whereby the composition is sterile, endotoxin-free, and ophthalmically compatible, and therefore suitable

for use on the eyelid or near the eye. For example, in one embodiment, provided is a process for manufacturing a sterile ointment, comprising dissolving a PFPPRA compound (latanoprost) in a fatty acid ester (isopropyl myristate) to make a solution; microfiltration of the solution to make a filtrate; and combining the filtrate with an ointment base (e.g., a hydrocarbon base such as petroleum jelly). In certain embodiments, the method further comprises dissolving a preservative (e.g., chlorobutanol) in the fatty acid ester (isopropyl myristate).

Examples

[0104] Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that these compositions may also consist essentially of, or consist of, the recited components. Further, it should be understood that the order of steps or order for performing certain actions are immaterial so long as the invention remains operable. Moreover, two or more steps or actions may be conducted simultaneously. In light of the foregoing description, the specific examples presented below are for illustrative purposes and not intended to limit the scope of the invention in any way.

Example 1

[0105] A composition for local reduction of subcutaneous fat was prepared as follows:

Table 1.	
Ingredients	Amount
Latanoprost	100 mg
Isopropyl myristate	5 g
Propylene glycol	15 g
White petroleum jelly	79.9 g

[0106] Neat latanoprost was added to a mixture of propylene glycol and isopropyl myristate. To the resulting mixture was added melted petroleum jelly. The mixture was stirred thoroughly and allowed to cool, yielding about 100 grams of an ointment with a final latanoprost concentration of 0.1% (w/w). It was noted that the compared to pure petrolatum, the mixture was more flowable, more spreadable, more easily mixed (*i.e.*, requiring less force to mix), and more easily dispensed from a container, *e.g.*, ajar or compressible tube (*i.e.*, requiring less force and flowing in a more controlled manner).

Example 2

[0107] A composition for local reduction of subcutaneous fat was prepared as follows:

Table 2.	
Ingredients	Amount per 100 g of composition
Latanoprost	0.3 g
Chlorobutanol, anhydrous	0.5 g
Isopropyl myristate	5 g
White petroleum jelly	94.2 g

[0108] Chlorobutanol was dissolved in isopropyl myristate, and to the resulting solution neat latanoprost was added and dissolved. To the resulting solution was added melted petroleum jelly. The mixture was stirred thoroughly and allowed to cool, yielding about 100 grams of an ointment with a final latanoprost concentration of 0.3% (w/w). Compositions were prepared according to the above formula at various scales ranging from about 50 to about 1000 g. Furthermore, comparable formulations comprising 0.1%, 0.15%, and 0.5% (w/w) were likewise prepared, with the difference in latanoprost content balanced by the amount of petroleum jelly. On HPLC analysis, these compositions were found to be uniform and to have the correct potency.

Example 3

[0109] The solubility of latanoprost in a 10:1 solution of isopropyl myristate and chlorobutanol was assessed by a standard (USP) protocol at 25° C. The upper limit of solubility at this temperature was found to be about 60 to about 85 mg/g. This high degree of solubility was surprising, because latanoprost is insoluble or poorly soluble in most solvents. Furthermore, this high degree of solubility was crucial for practicing the aseptic process described in the next example.

Example 4

[0110] A sterile, ophthalmically compatible composition for local reduction of fat was prepared as follows:

Table 3.	
Ingredients	Amount
Latanoprost	100 mg
Chlorobutanol, anhydrous	0.5 g
Isopropyl myristate	5 g
White petroleum jelly	94.4 g

[0111] The process was carried out aseptically. Chlorobutanol (CB) was dissolved in isopropyl myristate (IM). To this solution latanoprost was added and readily dissolved. The resulting solution was filtered through a 0.2 micron filter to yield a filtrate, which was placed in a sterile vessel. To the vessel was added sterile, melted petroleum jelly. The mixture was stirred thoroughly, yielding about 100 grams of a uniform ointment with a final latanoprost concentration of 0.1% (w/w). On laboratory analysis, the ointment was sterile and free of endotoxins. A comparable ointment comprising 0.3% (w/w) was prepared, with the additional latanoprost replacing a like amount of petroleum jelly. The skilled artisan will appreciate that the above process requires latanoprost solubility in the IM:CB solution of at least 18 or 55 mg/g for the 0.1% and 0.3% products, respectively.

Example 5

[0112] Compositions were prepared according to Example 2 and stored in a tight-sealed container at room temperature. The latanoprost concentration, uniformity, and lack of impurities were verified by High Performance Liquid Chromatography (HPLC). The composition was stored and reanalyzed and tested on HPLC at regular intervals for 2 months. At each interval, organoleptic inspection showed physical stability of the composition, and HPLC shows a stable latanoprost concentration and a lack of known degradants (e.g., latanoprost free acid, 15-keto latanoprost). Thus, it was concluded that the composition demonstrates excellent physical and chemical stability.

Example 6

[0113] Skin permeation studies were conducted with various formulations of latanoprost, *ex vivo*, on fresh human skin. Fresh human skin was obtained from live donors undergoing abdominoplasty and mounted on a standard (Franz-type) diffusion cell apparatus. All formulations contained 0.8% of latanoprost, expressed as weight of latanoprost per total weight of the composition. Each test article (8 mg) was uniformly applied to a skin surface of 0.8 cm². All formulations were tested on skin from at least two different donors. Treated skin was left open to the atmosphere to simulate clinical conditions. Receptor fluid flowed continuously over 24 hours and was collected in fractions. The amount of drug (latanoprost free acid) in these fractions was determined by High-Performance Liquid Chromatography (HPLC) with ultraviolet detection. The following amounts of drug were recovered from receptor fluid over 24 hours:

Table 4.	
Vehicle Formulation	Drug mass (ng, mean)
PG 15%, IM 5%, WPJ 80%	10,808
PG 15%, PS 5%, WPJ 80%	3795
PG 7.5%, LL 7.5%, PS 5%, WPJ 80%	3635

(continued)

Table 4.

Vehicle Formulation	Drug mass (ng, mean)
PG 7.5%, PS 5%, WPJ 87.5%	2082
PG 15%, PS 15%, WPJ 70%,	1127
Ethanol 70%, PG 30%	3930
Ethanol 75%, DGME 25%	1260
Ethanol 75%, LL 25%	890
Ethanol 50%, LL 25%, DGME 25%	840
DMSO 99% Gel	5850
DGME = diethylene glycol monomethyl ether, DMSO = dimethylsulfoxide, IM = isopropyl myristate, LL = lauryl lactate, PG = propylene glycol, PS = polysorbate 80, WPJ = white petroleum jelly.	

[0114] Thus, a formulation of latanoprost comprising isopropyl myristate in a hydrocarbon base provided substantially more dermal drug penetration compared to similar formulations lacking isopropyl myristate. The formulation comprising isopropyl myristate also provided superior drug penetration to a positive control, which is DMSO 99% Gel, and compared to a range of other formulations comprising enhancers such as lauryl lactate, polysorbate 80, and diethylene glycol monoethyl ether.

Example 7

[0115] Skin permeation studies were conducted with various formulations of latanoprost, *ex vivo*, on fresh pig skin, according to methods as described in the foregoing example. All formulations contained 0.25% of latanoprost, expressed as weight of latanoprost per total weight of the composition. The following flux values for LFA were observed over 24 hours:

Table 5.

Vehicle Formulation	LFA flux (ng/cm ² /h)
MO 15%, IM 5%, WPJ 80%	8
IM 5%, WPJ 95%	18
MO 15%, WPJ 85%	6
IM 5%, MO 95%	2
IM = isopropyl myristate, MO = mineral oil, WPJ = white petroleum jelly.	

[0116] Thus, a formulation of latanoprost comprising petroleum jelly and isopropyl myristate, but lacking mineral oil, provided superior delivery of LFA to formulations of latanoprost comprising mineral oil with isopropyl myristate, petroleum jelly, or both.

Example 8

[0117] Compositions as described in Example 2, comprising latanoprost at a final concentration of 0.1% or 0.5%, were tested in Gottingen minipigs (3 animals per dose concentration). All animals were treated once daily for 10 days, over 10% of body surface area on the dorsal skin. Animals were monitored for skin condition, body weight, and safety. Serial plasma samples were taken to assess pharmacokinetics. Twenty-four hours after the last dose, animals were sacrificed. Skin and fat were dissected from the treatment area. Tissues were examined histologically. Tissue was also used to measure drug (LFA) concentrations in subcutaneous fat (mid-depth of tissue) by liquid chromatography / tandem mass spectrometry (LC/MS/MS). The product was well tolerated, with no adverse effects in any animal. LFA concentrations in subcutaneous fat and plasma on Day 10 are shown in Table 6.

Table 6.

Formulation	Duration	LFA in mid-depth fat ($\mu\text{g/g}$) (trough level)
0.10% latanoprost 5% IM, 0.5% CB, 94.4% petroleum jelly	10 days	0.2
0.50% latanoprost, 5% IM, 0.5% CB, 94% petroleum jelly	10 days	1
CB = chlorobutanol; IM = isopropyl myristate		

[0118] Thus, the compositions were well tolerated and, following application to a thick-skinned mammal, delivered LFA locally to subcutaneous fat.

Example 9

[0119] Compositions as described in Example 2, comprising latanoprost at a final concentration of 0.1% or 0.5%, were tested on the periocular skin of Gottingen minipigs (3 animals per dose concentration). All animals were treated once daily for 10 days. Animals were monitored for skin condition, body weight, and safety. Twenty-four hours after the last dose, animals were sacrificed. Skin and fat were dissected from the treatment area. Some of this tissue was examined histologically. The product was well tolerated, with no adverse effects in any animal.

Example 10

[0120] Formulations consisting of latanoprost (0.1% or 0.5%), chlorobutanol 0.5%, isopropyl myristate 5%, and white petroleum jelly q.s. (all w/w) were tested in a standard rabbit ocular irritation test. The formulations did not cause any adverse effects.

Reference example 9a

[0121] A composition comprising isopropyl myristate 5%, propylene glycol 15%, and white petroleum jelly 80% (without active ingredient) was applied to skin on the volar forearms on healthy adult men and women ($n=4$). The application area was 5 cm x 5 cm. Application was once daily for 7 consecutive days. Skin condition and participant experience were noted daily, with results as follows:

Table 4.		
Participant	Skin Condition	Participant Experience
1	Normal (100%)	Well-tolerated, aesthetically pleasing
2	Normal (100%)	Well-tolerated, aesthetically pleasing
3	Normal (100%)	Well-tolerated, aesthetically pleasing
4	Normal (100%)	Well-tolerated, aesthetically pleasing

[0122] Thus, the above formulations were non-irritating and aesthetically pleasing when applied to human skin.

Example 10a

[0123] Different compositions, comprising latanoprost, e.g., 0.1% w/w, are tested on obese mice. Mice approximately six weeks old, all with similar baseline body mass, are randomized and prospectively treated as follows ($n=5$ animals per group):

Table 5.		
Group	Compound	Formulation (w/w)
A	Vehicle only	White petroleum jelly 100%
B	Vehicle only	IM 5%, CB 0.5%, white petroleum jelly q.s.

(continued)

Table 5.		
Group	Compound	Formulation (w/w)
C	Latanoprost	White petroleum jelly q.s.
D	Latanoprost	IM 5% CB 0.5%, white petroleum jelly q.s.

[0124] The dose is 0.1 cc to the right flank, daily. Mice are fed *ad libitum* and weighed daily for about 28 days. On or about day 28, mice are sacrificed and samples of skin with subcutaneous fat are collected for histologic examination. It is predicted that after about 28 days, mice in Group D will show relatively less weight gain (or more weight loss) and relatively less adiposity compared to mice in any of Groups A, B, or C. Thus, it is predicted that in a mouse model of obesity, the foregoing results show superior reduction of adiposity with a latanoprost formulation comprising petroleum jelly, chlorobutanol, and isopropyl myristate, as compared to a equimolar latanoprost formulation with a vehicle consisting essentially of petroleum jelly.

Example 11

[0125] A composition consisting essentially of latanoprost 0.5%, isopropyl myristate 5%, chlorobutanol 0.5%, and white petroleum jelly 94% (all w/w) was administered to the dorsal skin (10% of body surface area) of six Gottingen minipigs, once daily for 13 weeks. An equal number of animals are treated with a placebo composition, consisting essentially of isopropyl myristate 5%, chlorobutanol 0.5%, and white petroleum jelly 94.5%. (all w/w). Animals were observed for safety and tolerability. The compositions were well tolerated in all animals. After 13 weeks, animals were sacrificed and dorsal skin, fat, and muscle were dissected *en bloc* from a standardized portion of the treatment area. As compared to animals treated with the placebo composition, there was gross atrophy, *i.e.*, a thickness reduction of 30% to 70%, of subcutaneous fat in animals treated with the latanoprost 0.5% article.

Example 12

[0126] From the study described in Example 11, a portion of the tissue is fixed in formalin, stained with hematoxylin and eosin, and examined histopathologically. Subcutaneous fat thickness is measured systematically, for example by measuring the thickness of fat from the dermis to the panniculus carnosus using image analysis software such as ImageJ (National Institutes of Health). From another portion of the tissue, subcutaneous fat is dissected, washed, pulverized, and homogenized, with the homogenate submitted for quantification of latanoprost free acid concentration using liquid chromatography with tandem mass spectrometry (a method known in the art). It is predicted that the composition containing latanoprost will be associated with reduced subcutaneous fat thickness, as compared to control. It is further predicted that the latanoprost composition will be associated with amounts of latanoprost free acid in subcutaneous fat that are considered therapeutically effective, with reference to other *in vivo* experiments and *in vitro* assays. It is further predicted that the latanoprost composition of this example will be associated with higher tissue concentrations of latanoprost free acid and/or higher degrees of subcutaneous fat reduction compared to other formulations hitherto disclosed.

Example 13

[0127] The following experiment describes a randomized, placebo-controlled, double-blind trial in human subjects to test whether the safety and efficacy of a PFPPRA compound composition for reduction of submental fat. The composition can be, for example, as described in Example 2, wherein the PFPPRA compound is latanoprost.

[0128] Eligible subjects (for example, n = 60) with excess submental fat are entered into a randomized double-blind study. Subjects are randomized in 1:1 fashion to receive either the active composition (for example, comprising latanoprost 0.3%), or the corresponding inactive vehicle. Subjects are instructed to apply, once a day, a dose of 0.5 ml in a thin film the chin. Serial clinical assessments, photographs, and magnetic resonance imaging (MRI) scans are performed prior to the first dose and then at 13 weeks. Treatment continues for a total of 13 weeks. It is contemplated that over time, for example after 13 weeks of treatment, the composition comprising latanoprost will be associated with more reduction in the depth and/or volume of submental fat, as measured by clinical assessment and/or MRI, as compared to vehicle alone.

Example 14

[0129] The following experiment describes a randomized, placebo-controlled, double-blind trial in human subjects to test whether the safety and efficacy of a PFPPRA compound composition for reduction of periorbital fat. The composition can be, for example, a sterile composition as described in Example 4, wherein the PFPPRA compound is latanoprost.

[0130] Eligible subjects (for example, n = 60) with excess periorbital fat are entered into a randomized double-blind study. Subjects are randomized in 1:1 fashion to receive either the active composition (for example, comprising latanoprost 0.1%), or the corresponding inactive vehicle. Subjects are instructed to apply, once a day, a dose of 0.1 ml in a thin film the periorbital skin. Serial clinical assessments and photographs are performed prior to the first dose and then at 6 and 12 weeks. Treatment continues for a total of 12 weeks. It is contemplated that over time, for example after 12 weeks of treatment, the composition comprising latanoprost will be associated with more reduction in the volume of periorbital fat, as measured by clinical assessment, as compared to vehicle alone.

Example 15

[0131] A latanoprost ointment was prepared according to Example 2 and subjected to various doses of gamma radiation, as are commonly used for sterilization. A validated HPLC method was used to evaluate the ointment for latanoprost content and degradants. Significant degradation of latanoprost was observed at all gamma radiation doses. Thus, it was found that gamma irradiation is not suitable for sterilizing compositions comprising latanoprost.

Other Embodiments

[0132] In the claims articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. It is also noted that the terms "comprising" and "containing" are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included.

[0133] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

Claims

1. A composition comprising latanoprost and isopropyl myristate wherein the composition comprises between 1 percent and 20 percent of isopropyl myristate, by weight of the total weight of the composition.
2. The composition of claim 1, wherein the latanoprost concentration is between 0.01 percent and 0.5 percent of the final composition, by weight of the total weight of the composition.
3. The composition of claim 1 wherein the composition comprises between 1 percent and 10 percent isopropyl myristate, by weight of the total weight of the composition.
4. The composition of any one of claims 1-3, further comprising an ointment base.
5. The composition of claim 4, wherein the ointment base is petroleum jelly.
6. The composition of claim 4, wherein the composition comprises between 70 percent and 99 percent petroleum jelly, by weight of the total weight of the composition.
7. The composition of claim 1, further comprising propylene glycol.
8. The composition of claim 7, wherein the composition comprises between 5 percent and 20 percent propylene glycol, by weight of the total weight of the composition.

9. The composition of any one of claims 1-8, further comprising a preservative.

10. The composition of claim 1, wherein the composition is sterile.

5 11. A composition of any one of claims 1-10 for use in a method for reducing body fat in a subject.

12. The composition for use of claim 11, wherein the subject suffers from steatoblepharon.

10 13. A composition of any one of claims 1-10 for use in reducing eyelid fat.

14. A process for manufacturing a sterile ointment, comprising:

15 dissolving latanoprost in isopropyl myristate to make a solution;
 microfiltration of the solution to make a filtrate; and
 combining the filtrate with petroleum jelly.

15. The process of claim 14, further comprising dissolving a preservative in the isopropyl myristate.

20 16. The process of any one of claims 14-15, wherein the microfiltration of the solution is performed under aseptic conditions.

Patentansprüche

25 1. Zusammensetzung, umfassend Latanoprost und Isopropylmyristat, wobei die Zusammensetzung zwischen 1 Gew.-% und 20 Gew.-% vom Gesamtgewicht der Zusammensetzung an Isopropylmyristat umfasst.

30 2. Zusammensetzung nach Anspruch 1, wobei die Latanoprostkonzentration zwischen 0,01 Gew.-% und 0,5 Gew.-% vom Gesamtgewicht der Zusammensetzung an der fertigen Zusammensetzung beträgt.

3. Zusammensetzung nach Anspruch 1, wobei die Zusammensetzung zwischen 1 Gew.-% und 10 Gew.-% vom Gesamtgewicht der Zusammensetzung an Isopropylmyristat umfasst.

35 4. Zusammensetzung nach einem der Ansprüche 1-3, welche weiterhin eine Salbengrundlage umfasst.

5. Zusammensetzung nach Anspruch 4, wobei es sich bei der Salbengrundlage um Vaseline handelt.

40 6. Zusammensetzung nach Anspruch 4, wobei die Zusammensetzung zwischen 70 Gew.-% und 99 Gew.-% vom Gesamtgewicht der Zusammensetzung an Vaseline umfasst.

7. Zusammensetzung nach Anspruch 1, welche weiterhin Propylenglykol umfasst.

45 8. Zusammensetzung nach Anspruch 7, wobei die Zusammensetzung zwischen 5 Gew.-% und 20 Gew.-% vom Gesamtgewicht der Zusammensetzung an Propylenglykol umfasst.

9. Zusammensetzung nach einem der Ansprüche 1-8, welche weiterhin einen Konservierungsstoff umfasst.

10. Zusammensetzung nach Anspruch 1, wobei die Zusammensetzung steril ist.

50 11. Zusammensetzung nach einem der Ansprüche 1-10 zur Verwendung in einem Verfahren zur Verringerung des Körperfetts bei einem Patienten.

12. Zusammensetzung zur Verwendung nach Anspruch 11, wobei der Patient an Steatoblepharon leidet.

55 13. Zusammensetzung nach einem der Ansprüche 1-10 zur Verwendung bei der Verringerung von Augenlidfett.

14. Verfahren zur Herstellung einer sterilen Salbe, bei dem man:

Latanoprost unter Bildung einer Lösung in Isopropylmyristat löst,
die Lösung zur Herstellung eines Filtrats einer Mikrofiltration unterzieht und
das Filtrat mit Vaseline vereinigt.

- 5 15. Verfahren nach Anspruch 14, bei dem man weiterhin einen Konservierungsstoff im Isopropylmyristat löst.
16. Verfahren nach einem der Ansprüche 14-15, wobei das Mikrofiltrieren der Lösung unter aseptischen Bedingungen durchgeführt wird.

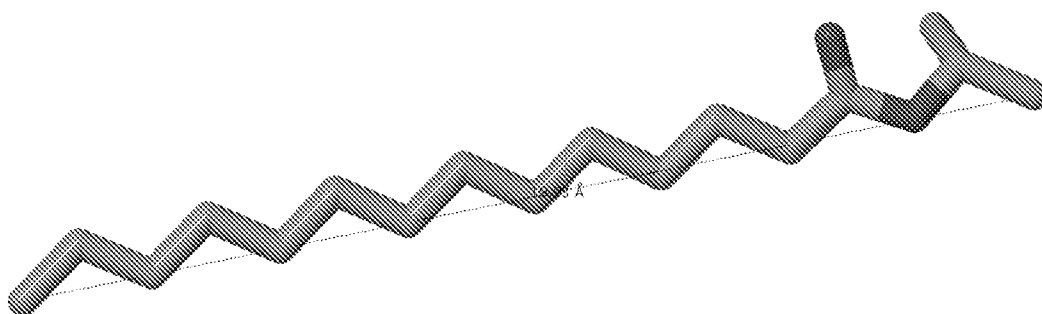
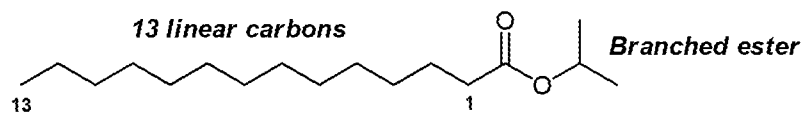
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Revendications

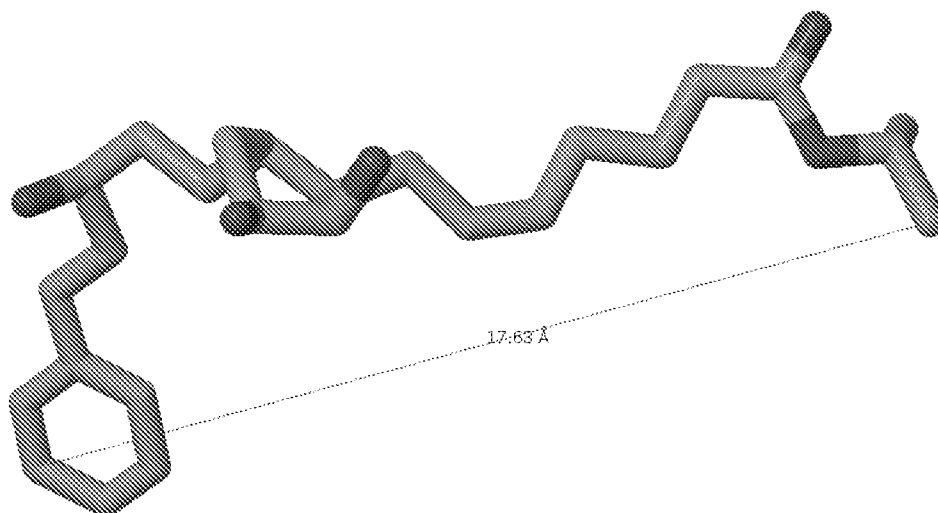
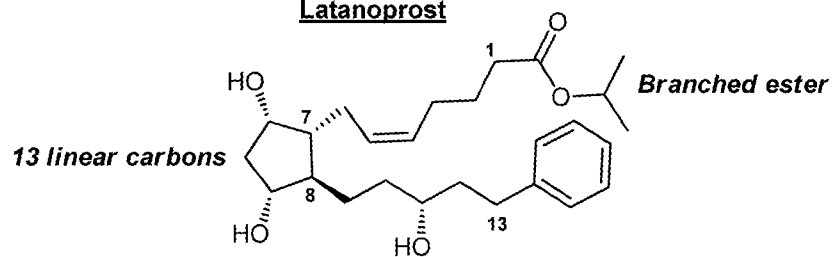
- 15 1. Composition comprenant du latanoprost et du myristate d'isopropyle, où la composition comprend entre 1 pour cent et 20 pour cent de myristate d'isopropyle, en masse par rapport à la masse totale de la composition.
- 20 2. Composition selon la revendication 1, où la concentration en latanoprost est comprise entre 0,01 pour cent et 0,5 pour cent de la composition finale, en masse par rapport à la masse totale de la composition.
3. Composition selon la revendication 1, où la composition comprend entre 1 pour cent et 10 pour cent de myristate d'isopropyle, en masse par rapport à la masse totale de la composition.
- 25 4. Composition selon l'une quelconque des revendications 1 à 3, comprenant en outre une base d'onguent.
5. Composition selon la revendication 4, où la base d'onguent est de la vaseline.
6. Composition selon la revendication 4, où la composition comprend entre 70 pour cent et 99 pour cent de vaseline, en masse par rapport à la masse totale de la composition.
- 30 7. Composition selon la revendication 1, comprenant en outre du propylène glycol.
8. Composition selon la revendication 7, où la composition comprend entre 5 pour cent et 20 pour cent de propylène glycol, en masse par rapport à la masse totale de la composition.
- 35 9. Composition selon l'une quelconque des revendications 1 à 8, comprenant en outre un conservateur.
10. Composition selon la revendication 1, où la composition est stérile.
- 40 11. Composition selon l'une quelconque des revendications 1 à 10 pour utilisation dans une méthode de réduction de la graisse corporelle chez un sujet.
12. Composition pour utilisation selon la revendication 11, où le sujet souffre d'oedème palpébral.
- 45 13. Composition selon l'une quelconque des revendications 1 à 10, pour utilisation dans la réduction de la matière grasse des paupières.
14. Procédé de fabrication d'un onguent stérile, comprenant :
- 50 la dissolution du latanoprost dans le myristate d'isopropyle pour fabriquer une solution ;
 la microfiltration de la solution pour fabriquer un filtrat ; et
 la combinaison de filtrat avec de la vaseline.
15. Procédé selon la revendication 14, comprenant en outre la dissolution d'un conservateur dans le myristate d'isopropyle.
- 55 16. Procédé selon l'une quelconque des revendications 14 à 15, où la microfiltration de la solution est mise en oeuvre en conditions aseptiques.

Figure 1

isopropyl myristate



Latanoprost



REFERENCES CITED IN THE DESCRIPTION

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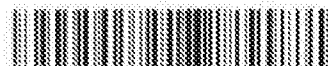
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Szabadalmi igénypontok

1. Készítmény, amely tartalmaz latanoprosztot és izopropil-mirisztátot, ahol a készítmény izopropil-mirisztátot 1 tömeg% és 20 tömeg% között tartalmaz a készítmény teljes tömegére vonatkoztatva.
2. Az 1. igénypont szerinti készítmény, ahol a latanoproszt koncentráció a végső készítményben 0,01 tömeg% és 0,5 tömeg% közötti, a készítmény teljes tömegére vonatkoztatva.
3. Az 1. igénypont szerinti készítmény, ahol a készítmény izopropil-mirisztátot 1 tömeg% és 10 tömeg% között tartalmaz a készítmény teljes tömegére vonatkoztatva.
4. Az 1-3. igénypontok bármelyike szerinti készítmény, amely tartalmaz továbbá egy kenőcs bázist.
5. A 4. igénypont szerinti készítmény, ahol a kenőcs bázis vazelin.
6. A 4. igénypont szerinti készítmény, ahol a készítmény vazelint 70 tömeg% és 99 tömeg% között tartalmaz a készítmény teljes tömegére vonatkoztatva.
7. Az 1. igénypont szerinti készítmény, amely tartalmaz továbbá propilén-glikolt.
8. A 7. igénypont szerinti készítmény, ahol a készítmény propilén-glikolt 5 tömeg% és 20 tömeg% között tartalmaz a készítmény teljes tömegére vonatkoztatva.
9. Az 1-8. igénypontok bármelyike szerinti készítmény, amely tartalmaz továbbá tartósítószer.
10. Az 1. igénypont szerinti készítmény, ahol a készítmény steril.
11. Az 1-10. igénypontok bármelyike szerinti készítmény betegben a testzsír csökkentésének eljárásában történő alkalmazásra.
12. Készítmény alkalmazásra a 11. igénypont szerinti, ahol a beteg szemhéj zsírdaganattól (steatoblepharon) szenved.
13. Az 1-10. igénypontok bármelyike szerinti készítmény szemhéjzsír csökkentésében történő alkalmazásra.
14. Eljárás steril kenőcs előállítására, amely eljárás tartalmazza:
latanoproszt feloldását izopropil-mirisztátban, és így oldatot készítünk;
az oldat mikroszűrését, és így szűrletet készítünk; és
a szűrlet elegyítését vazelinnel.
15. A 14. igénypont szerinti eljárás, amely továbbá tartalmazza tartósítószer feloldását az izopropil-mirisztátban.
16. A 14. vagy 15. igénypont szerinti eljárás, ahol az oldat mikroszűrését aszeptikus körülmények között végezzük.



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