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(54) Title: METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING MACULAR-DEGENERATION RELATED DISORDERS

(57) Abstract: The present invention provides methods for treating or preventing the development of macular degeneration-related disorders in a subject, including humans by administering to a subject therapeutically effective amount of a biologically active mixture of high purity, high molecular weight straight chain primary aliphatic alcohols (referred to collectively herein as policosanol).



WO 2006/014780 A2

METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING MACULAR-DEGENERATION RELATED DISORDERS

BACKGROUND OF THE INVENTION

1. Field of the Invention

[0001] The present invention relates to therapeutic compositions and methods for treating or preventing the development of macular degeneration-related disorders in a subject, including humans. More particularly the invention pertains to methods of treating or preventing the development of macular degeneration-related disorders by administering to a subject therapeutically effective amounts of a biologically active mixture of high purity, high molecular weight straight chain primary aliphatic alcohols (referred to collectively herein as policosanols).

2. Description of the State of Art

[0002] Age Related Macular Degeneration (AMD) is caused by the deterioration of the central portion of the retina known as the macula, i.e., the inside back layer of the eye that records images and sends them via the optic nerve from the eye to the brain. The macula is responsible for focusing central vision in the eye, and controls the ability to read, recognize faces or colors, and see objects in fine detail. AMD is grouped into two types, dry (nonexudative or non-neovascular) and wet (exudative or neovascular) macular degeneration. About 10 percent of people with AMD have the wet form. Wet AMD occurs when abnormal blood vessels behind the retina start to grow under the macula. These new blood vessels tend to be very fragile and often leak blood and fluid. The blood and fluid raise the macula from its normal place at the back of the eye, and damage to the macula occurs quickly. Wet AMD is considered to be advanced AMD, and is more severe than the dry form. AMD is a burden to the elderly population, and its consequences are increasing because treatment options, for example laser surgery or photodynamic therapy, are limited. Thus, prevention remains the best approach for decreasing the impact of this leading cause of blindness.

[0003] Seddon *et al.* (JAMA, vol. 291, No. 6, February 11, 2004) were prompted to investigate the inflammatory biomarkers in AMD based on the observation that many factors associated with AMD are also related to cardiovascular disease. One of these factors is C-reactive protein (CRP), a marker of systemic inflammation which

has been shown to be an independent indicator of risk for cardiovascular disease, stroke and peripheral arterial disease. The investigation was further based on the fact that inflammation is associated with angiogenesis, and neovascularization can occur in inflammatory eye diseases, similar to the most advanced form of AMD. Thus, it was postulated that AMD represents another chronic, age-related inflammatory disease that is manifested in the eye and other organs. After adjustment for age, sex and other variables, including smoking and body mass index, Seddon *et al.* noted that CRP levels were significantly higher among individuals with intermediate and advanced stages of AMD as compared with controls. Thus, while to date it has not been proven that CRP causes AMD, elevated blood levels of CRP are believed to increase the risk of AMD. These findings supported the theory that inflammation is associated with the pathogenesis of AMD, suggesting that anti-inflammatory agents might have a role in preventing AMD. Elevated CRP levels thus appear to reflect the presence of inflammation in blood vessels, specifically the coronary arteries.

[0004] In a related study, McGwin, *et al.* at the University of Alabama at Birmingham observed that subjects who take cholesterol-inhibiting drugs known as statins are less likely to develop symptoms of AMD. The findings suggest a possible association between AMD and cardiovascular disease. In a study reported in the September issue of the British Journal of Ophthalmology, McGwin *et al.* reported that individuals with a new diagnosis of AMD were 70 percent less likely to have filled a prescription for statins than a control group. According to McGwin, *et al.*, the overlap in risk factors for cardiovascular disease and AMD, such as smoking, high cholesterol and high blood pressure, is an indication that the two conditions have similar pathway. McGwin, *et al.* proposed that if AMD and cardiovascular disease share common mechanisms, it is possible that there exists a protective association between the use of cholesterol lowering drugs and AMD. Statins, a family of drugs used for reducing cholesterol levels, are have recently been shown to reduce blood levels of CRP in addition to having a significant anti-inflammatory action.

[0005] A mixture of high purity, high molecular weight straight chain aliphatic alcohols (collectively referred to herein as policosanols) has garnered much interest in recent years as a natural supplement for its cholesterol-lowering effects (Gouni-Berthold, *et al.*, *Am. Heart J.*, **143**(2):356-365 (2002)). The main constituents of

policosanols are tetracosanol, hexacosanol, octacosanol, and triacontanol, while eicosanol, docosanol, heptacosanol, nonacosanol, dotriacontanol, tetratriacontanol, and hexatriacontanol make up the remaining minor constituents of the straight chain aliphatic alcohols. There is a significant body of evidence demonstrating the benefits of policosanol with respect to cardiovascular disease. In the mid to late nineties, one research group proposed that policosanol was able to reduce endothelial damage by inhibiting the production of foam cells (Noa, *et al.*, *J. Pharm. Pharmacol.*, **48(3)**:306-309 (1996); Noa, *et al.*, *J. Pharm. Pharmacol.*, **49(10)**:999-1002 (1997)). Foam cells are macrophages that can migrate into the endothelium of the blood vessels and contribute to atherosclerotic plaque formation (Physicians' Desk Reference, 50 ed., Montvale, NJ: Medical Economics Company; 2002.). Other researchers believe policosanol has a modulating effect on HMG-CoA reductase, the rate-controlling enzyme in cholesterol biosynthesis, but the precise mechanism remains unclear (Menendez, *et al.*, *Biol. Res.*, **27(3-4)**:199-203 (1994); Menendez, *et al.*, *Biol. Res.*, **29(2)**:253-257 (1996); and Menendez, *et al.*, *Arch. Med. Res.*, **32(1)**:8-12 (2001)). Still other investigators believe policosanol may inhibit cholesterol synthesis in the liver at a step before mevalonate production, but total inhibition of the HMG-CoA reductase is doubtful (Gouni-Berthold, *et al.*, *Am. Heart J.*, **143(2)**:356-365 (2002)). More recent work suggests policosanol inhibits LDL cholesterol oxidation (Menendez, *et al.*, *Can. J. Physiol. Pharmacol.*, **80(1)**:13-21 (2002); Menendez, *et al.*, *Br. J. Clin. Pharmacol.*, **50(3)**:255-262 (2000)). This was revealed when markers of peroxidation, such as thiobarbituric acid reactive substances (TBARS), and malondialdehyde (MDA) were lower in the cultures treated with policosanol. Oxidation of LDL cholesterol has been linked to heart disease and was the recent cover story in Scientific American magazine (Physicians' Desk Reference, 50 ed., Montvale, NJ: Medical Economics Company; 2002).

[0006] New therapeutics for macular degeneration-related disorders are needed. For example, there is no therapy currently in use that significantly slows the degenerative progression of AMD for the majority of subjects. Current AMD treatment is limited, and while it may halt the progression of the disease, it does not reverse the dysfunction, repair the damage, or improve vision.

SUMMARY OF THE INVENTION

[0007] The present invention provides a method for treating or preventing the development of macular degeneration-related disorders in a subject by administering a therapeutically effective amount of a formulation of the present invention. The formulation of the present invention comprises a mixture of high purity, high molecular weight straight chain primary aliphatic alcohols, wherein the composition comprises from about 1% to about 90% by weight policosanols. The formulation may further comprise from 0% to about 65% by weight of pharmaceutically acceptable formulation aids including, but not limited to diluents, stabilizers, binders, buffers, lubricants, coating agents, preservatives, emulsifiers and/or suspension agents. In one embodiment of this invention, the policosanols comprise at least one high molecular weight straight chain primary aliphatic alcohol selected from 20 to 36 carbon atoms.

[0008] The daily dosage is preferably between 1 and 100 mg of policosanols (more preferably between about 3 and 20 mg) and is intended for administration in any type or form.

[0009] In another embodiment, the policosanols composition of this invention comprises 1-tetracosanol, 1-hexacosanol, 1-heptacosanol, 1-octacosanol, 1-triacontanol, 1-dotriacontanol and 1-tetratriacontanol.

[0010] In yet another embodiment, the composition of the present invention comprises policosanols having the following quantitative composition:

Components	Proportion in the mixture
1-eicosanol (C ₂₀)	0 – 5%
1-docosanol (C ₂₂)	0 – 5%
1-tetracosanol (C ₂₄)	0 – 30%
1-hexacosanol (C ₂₆)	5 – 30%
1-heptacosanol (C ₂₇)	0 – 5%
1-octacosanol (C ₂₈)	5 – 80%
1-nonacosanol (C ₂₉)	0 – 5%
1-triacontanol (C ₃₀)	5 – 40%
1-dotriacontanol (C ₃₂)	1 – 25%
1-tetratriacontanol (C ₃₄)	0 – 7%
1-hexatriacontanol (C ₃₆)	0 – 5%

[0011] The present invention further provides kits having one or more containers comprising the therapeutic composition of the present invention and a suitable

excipient as described herein and a set of instructions, generally written instructions although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use and dosage of the therapeutic composition of the present invention for the intended treatment. The instructions included with the kit generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers of the therapeutic composition of the present invention may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses.

[0012] Macular degeneration-related disorders that can be treated or prevented according to the methods of the present invention include age-related macular disorder (AMD), North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, dominant drusen, and malattia leventinese. Other diseases or disorders include retinal detachment, chorioretinal degenerations, retinal degenerations, photoreceptor degenerations, RPE degenerations, mucopolysaccharidoses, rod-cone dystrophies, cone-rod dystrophies, and cone degenerations.

[0013] Additional advantages and novel features of this invention shall be set forth in part in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following specification or may be learned by the practice of the invention. The advantages of the invention may be realized and attained by means of the instrumentalities, combinations, compositions, and methods particularly pointed out in the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The method of the present invention for treating or preventing the development of macular degeneration-related disorders comprises administering a therapeutically effective amount of a composition comprising a mixture of high purity, high molecular weight straight chain primary aliphatic alcohols (referred collectively herein to as policosanols) to a subject in need thereof.

[0015] The policosanols used in the present invention can be derived from any suitable source, each source being associated with a policanol of particular characteristics, usually in terms of the relative proportions of its primary aliphatic alcohol components. For example, policosanols can be extracted and purified from a wide array of starting materials, such as, but not limited to, pelu bug, natural waxes

such as but not limited to, beeswax, carnauba wax, and candellia wax; bee pollen; oils such as but not limited to, peanut oil, sesame oil, cod liver oil, rice bran oil, oat oil, and rosemary needles oil; and powders such as but not limited to rice bran, containing primarily natural esters of aliphatic alcohols with caboxylic acids. Consequently, the quantitative compositions of policosanols can vary depending on the extraction process and starting materials that are used in its production. In one embodiment, the policosanols has the quantitative composition set forth in Table 1.

Table I

Components	Proportion in the mixture
1-eicosanol (C ₂₀)	0 – 5%
1-docosanol (C ₂₂)	0 – 5%
1-tetracosanol (C ₂₄)	0 – 30%
1-hexacosanol (C ₂₆)	5 – 30%
1-heptacosanol (C ₂₇)	0 – 5%
1-octacosanol (C ₂₈)	5 – 80%
1-nonacosanol (C ₂₉)	0 – 5%
1-triacontanol (C ₃₀)	5 – 40%
1-dotriacontanol (C ₃₂)	1 – 25%
1-tetratriacontanol (C ₃₄)	0 – 7%
1-hexatriacontanol (C ₃₆)	0 – 5%

[0016] U.S. Patent Nos. 5,663,156; 5,856,316; 6,197,832; 6,225,354; and 6,596,776, all of which are incorporated herein by reference, disclose policosanols compositions that are specific to the starting material and extraction processes used. It should be noted that while any commercially available policosanols or any of the policosanols disclosed in the above-referenced patents are suitable for use in the present invention, for purposes of the remainder of this discussion the policosanols and methodologies disclosed in U.S. Patent No. 6,596,776 will be referenced. Specifically, in one embodiment the policosanols used in the present invention is obtained from beeswax and has the formulation set forth in Table II.

Table II

Components	Proportion in the mixture
1-eicosanol (C ₂₀)	0 – 5%
1-docosanol (C ₂₂)	0 – 5%
1-tetracosanol (C ₂₄)	13 – 28%
1-hexacosanol (C ₂₆)	5 – 30%
1-heptacosanol (C ₂₇)	0 – 5%
1-octacosanol (C ₂₈)	15 – 25%
1-triacontanol (C ₃₀)	25 – 40%
1-dotriacontanol (C ₃₂)	5 – 15%
1-tetratriacontanol (C ₃₄)	0 – 5%

[0017] The process used to isolate the policosanol composition described in Table II is incorporated herein by reference and is briefly described as follows. Beeswax is initially subjected to a homogenous phase saponification step, after which the saponified beeswax is dried and ground to a particle mesh size of 100-500 microns. Alternatively, unsaponified beeswax of varying purity may be used as the starting material and is initially dried and ground to a particle mesh size of 100-200 microns. The particles of saponified or unsaponified beeswax are placed into a conventional solid-liquid extractor and a hot organic solvent is introduced and contacted with the beeswax particles. The suspension is mixed and then hot-filtered to remove any solids.

[0018] The resulting extract is then maintained within the temperature range of 2°C to 10°C, causing the aliphatic alcohols to solidify and form a suspension. The suspension is filtered and the first solids are recovered and air dried. The dried solids are then sent to a purifier where they are contacted with and dissolved in a second hot solvent and hot-filtered. This solution is then cooled and the second solids are collected and dried under vacuum. The dried solids obtained from the second purification step are contacted with a third hot organic solvent, which dissolves the solids. This solution is hot-filtered and chilled, and the third solids are collected, dried, and powdered to provide the final product disclosed in Table II.

[0019] After the particles are dried, they can be formulated into a conventional pharmaceutical formulation for administration. The formulations of the present invention comprise a therapeutically effective amount policosanol in the range between about 0.5 and 99%.

[0020] Policosanol is extremely well tolerated. In animal toxicity studies, doses up to 500 mg/kg/day, a dose that is 1500 times the normal human dose of 20 mg/day, have shown no negative effects on carcinogenesis, reproduction, growth, or development. In one embodiment, a total dose of policosanol administered to a subject according to the present invention is in the range from about 1 mg to 100 mg per day. In another embodiment, a total dose of policosanol between about 5 mg to 40 mg per day is administered. In yet another embodiment, a total dose of policosanol between about 10 to 20 mg per day is administered.

[0021] As used herein, a "therapeutically effective amount" refers to an amount of the compositions of the present invention sufficient to provide the desired effect discussed herein. In vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. The precise dosage level should be determined by the attending physician or other health care provider and will depend upon well-known factors, including route of administration, and the age, body weight, sex and general health of the individual; the nature, severity and clinical stage of the macular degeneration-related disorder. The composition can be taken one or more times a day as needed to achieve the desired results, for example, to prevent or ameliorate a macular degeneration-related disorder.

[0022] The term "macular degeneration-related disorder" refers to any of a number of conditions in which the retinal macula degenerates or becomes dysfunctional, e.g., as a consequence of the abnormal growth of blood vessels behind the macula, decreased growth of cells of the macula, increased death or rearrangement of the cells of the macula (e.g., RPE cells), loss of normal biological function, or a combination of these events. Macular degeneration results in the loss of integrity of the histoarchitecture of the cells and/or extracellular matrix of the normal macula and/or the loss of function of the cells of the macula. Examples of macular degeneration-related disorder include Age Related Macular degeneration (AMD), North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, dominant drusen, and malattia leventinese (radial drusen). The term also encompasses extramacular changes that occur prior to, or following dysfunction and/or degeneration of the macula. Thus, the term "macular

degeneration-related disorder" also broadly includes any condition which alters or damages the integrity or function of the macula (e.g., damage to the RPE or Bruch's membrane). For example, the term encompasses retinal detachment, chorioretinal degenerations, retinal degenerations, photoreceptor degenerations, RPE degenerations, mucopolysaccharidoses, rod-cone dystrophies, cone-rod dystrophies and cone degenerations.

[0023] A "subject" includes both humans and other animals (particularly mammals) that receive either prophylactic or therapeutic treatment according to this invention.

[0024] The pharmaceutical formulations of the present invention can contain as an active ingredients from about 0.5 to about 95.0% wt of policosanol. This dosage is obtained by mixing the policosanol with one or more excipients, including, but not limited to agglutinants, disintegrators, lubricants, sliders or fillers. For example, specific excipients include, but are not limited to, lactose, corn starch, saccharose, magnesium stearate, microcrystalline cellulose, sodium croscarmellose gelatin, cellulose acetophthalate, titanium dioxide, special talc for tablets and polyethylene glycol. Other suitable excipients are well known in the art. The formulation may further comprise from 0% to about 65% by weight of pharmaceutically acceptable formulation aids, including but not limited to diluents, stabilizers, binders, buffers, lubricants, coating agents, preservatives, emulsifiers and/or suspension agents.

[0025] A composition of the present invention may be combined or used in combination with other methods known in the art for treating or preventing the development of macular degeneration-related disorders. For example, a method according to this invention can include administering policosanol and at least one additional agent for treating or preventing macular degeneration-related disorders, wherein said policosanol and said additional drug are administered as an admixture, separately and simultaneously, or separately in any order. Alternatively, policosanol can be administered before, during, or after conventional laser surgery or photodynamic therapy.

[0026] The amount of policosanol in the formulations of this invention that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will may contain, for example, from 1-30 g of policosanol compounded with

an appropriate and convenient amount of excipients which may vary from about 5 to about 95 percent by weight of the total composition. Dosage unit forms will generally contain about 1-30 g of policosanol. For further information on routes of administration and dosage regimes, see Chapter 25.3 in Volume 5 of *Comprehensive Medicinal Chemistry* (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990, which is specifically incorporated herein by reference.

[0027] In order to use the compositions of this invention for the therapeutic treatment (including prophylactic treatment) of a subject in need thereof according to the methods of this invention, policosanol is formulated in accordance with standard pharmaceutical practice as a pharmaceutical formulation as discussed above. According to this aspect of the invention there is provided a pharmaceutical composition comprising policosanol in association with a pharmaceutically acceptable diluent or carrier, wherein the policosanol is present in an amount for effectively treating or preventing macular degeneration-related disorders in an subject.

[0028] The formulations of the present invention can be administered to a subject by any available and effective delivery system including, but not limited to, parenteral, transdermal, intranasal, sublingual, transmucosal, intra-arterial, or intradermal modes of administration in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and in a vehicle as desired, such as a depot or a controlled release formulation.

[0029] For example, a pharmaceutically acceptable formulation of the composition of the present invention may be formulated for parenteral administration, e.g., for intravenous, subcutaneous, or intramuscular injection. For an injectable formulation, policosanol may be combined with a sterile aqueous solution which is preferably isotonic with the blood of the subject. Such a formulation may be prepared by dissolving a solid active ingredient in water containing physiologically-compatible substances such as sodium chloride, glycine, and the like, and having a buffered pH compatible with physiological conditions so as to produce an aqueous solution, and then rendering the solution sterile by methods known in the art. The formulations may be present in unit or multi-dose containers, such as sealed ampules or vials. The formulation may be delivered by any mode of injection, including, without limitation, epifascial, intracutaneous, intramuscular, intravascular, intravenous,

parenchymatous, subcutaneous, oral or nasal preparations (see, for example, U.S. Patent No. 5,958,877, which is specifically incorporated herein by reference).

[0030] Pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more appropriate dispersing or wetting agents and suspending agents. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

[0031] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, or intramuscular dosing or as a suppository for rectal dosing), or as vehicles such as a depot or other controlled release formulation.

[0032] Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

[0033] Compositions for oral use may be in the form of hard gelatin capsules in which policosanol is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

[0034] Aqueous suspensions generally contain policosanol in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl *p*-hydroxybenzoate, anti-oxidants (such as ascorbic acid), coloring agents, flavoring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

[0035] Oily suspensions may be formulated by suspending policosanol in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0036] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

[0037] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as

soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

[0038] Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

[0039] The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, wherein policosanol may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

[0040] Suppository formulations may be prepared by mixing policosanol with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

[0041] Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating policosanol with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

[0042] Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μm or much less, the powder itself comprising either policosanol alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50 mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

[0043] Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense policosanol either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used

and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

[0044] For further information on formulations, see Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990, which is specifically incorporated herein by reference.

[0045] Another aspect of this invention provides methods of treating or preventing macular disorders by delivering the composition of the present invention to a subject as a controlled release formulation. As used herein, the terms "controlled" "extended" "sustained" or "prolonged" release formulations and methods of the present invention will collectively be referred to as "controlled release" formulations and methods, and include continuous and discontinuous, linear and non-linear release of the composition of the present invention. There are many advantages for a controlled release formulation. Among these are to effectively treat the subject during a period when the subject would not be readily able or willing to periodically ingest the composition of the present invention. The single dose of composition of the present invention preferably is administered via ingestion of one or more controlled release unit dosage forms, so that effective policosanols levels are maintained.

[0046] 1. Tablets

[0047] A useful controlled release tablet is disclosed in U.S. Pat. No. 5,126,145 which is incorporated herein by reference. This tablet comprises, in admixture, about 5-30% high viscosity hydroxypropyl methyl cellulose, about 2-15% of a water-soluble pharmaceutical binder, about 2-20% of a hydrophobic component such as a waxy material, e.g., a fatty acid, and about 30-90% policosanols.

[0048] More specifically, one such useful controlled release tablet comprises: (a) about 5-20 percent by weight hydroxypropyl methylcellulose having a viscosity of about 10,000 CPS or greater, a substitution rate for the methoxyl group of about 7-30% and a substitution rate for the hydroxypropoxyl group of about 7-20%; (b) about 2-8 percent hydroxypropyl methylcellulose having a viscosity of less than about 100, CPS methyl cellulose, or polyvinyl pyrrolidone; (c) about 5-15 percent by weight hydrogenated vegetable oil or stearic acid; and (d) about 30-90% policosanols.

[0049] High viscosity water-soluble 2-hydroxypropyl methyl cellulose (HPMC) is particularly preferred for use in the present tablets and in the controlled-release

tablet coating, due to its sustaining properties with respect to policosanol release. A particularly preferred high viscosity HPMC has a nominal viscosity, two percent solution, of about 100,000 CPS, methoxyl content of about 19-24, a hydroxypropyl content of about 7-12 percent, and a particle size where at least 90% passes through a USS 100 mesh screen. (Methocel[®] K100MCR). Low viscosity HPMC is preferred as the binder component of the tablet. A particularly preferred low viscosity HPMC has a methoxyl content of about 20-30%, a hydroxypropyl content of about 7-12 percent, and a particle size where 100% will pass through a USS No. 30 mesh screen and 99% will pass through a USS 40 mesh screen (Methocel[®] E1S). In some cases, a portion of the high viscosity HPMC can be replaced by a medium viscosity HPMC, i.e., of about 2000-8,000 cps.

[0050] The viscosities reported herein are measured in centipoises (cps or cP), as measured in a 2% by weight aqueous solution of the cellulose either at 20°C using a rotational viscometer. A "high viscosity" cellulose ether possesses a viscosity of at least about 10,000 cps i.e., about 50,000-100,000 cps. A low-viscosity cellulose ether possesses a viscosity of less than about 100 cps, i.e., about 10-100 cps.

[0051] "Water soluble" for purposes of this application means that two grams of powdered cellulose ether can be dispersed by stirring into 100 grams of water at a temperature between 0°C and 100°C to provide a substantially clear, stable aqueous composition or dispersion (when the dispersion is brought to 20°C).

[0052] Useful hydrophobic components include natural and synthetic waxes such as beeswax, carnauba wax, paraffin, spermaceti, as well as synthetic waxes, hydrogenated vegetable oils, fatty acids, fatty alcohols and the like.

[0053] The controlled release policosanol tablets preferably can be formulated to contain 10 mg, 20 mg or 40 mg of policosanol, and are ingested orally. Preferably, these tablets will release about 10-35 wt % of the total policosanol within about 2 hours in an *in vitro* dissolution test, and about 40- 0 wt-% of the total policosanol in eight hours.

[0054] 2. Films

[0055] This invention further provides a prophylaxis for or method of treating macular disorders in a subject, comprising administering to a subject a biodegradable, biocompatible polymeric film comprising policosanol. The polymeric films are thin compared to their length and breadth. The films typically have a

uniform selected thickness between about 60 micrometers and about 5 mm. Films of between about 600 micrometers and 1 mm and between about 1 mm and about 5 mm thick, as well as films between about 60 micrometers and about 1000 micrometers; and between about 60 and about 300 micrometers are useful in the manufacture of therapeutic implants for insertion into a subject's body. The films can be administered to the subject in a manner similar to methods used in adhesion surgeries. For example, a policosanol film formulation can be sprayed or dropped onto a tissue site during surgery, or a formed film can be placed over the selected tissue site. In an alternative embodiment, the film can be used as controlled release coating on a medical device such as a stent.

[0056] Either biodegradable or nonbiodegradable polymers may be used to fabricate implants in which the policosanol is uniformly distributed throughout the polymer matrix. A number of suitable biodegradable polymers for use in making the biodegradable films of this invention are known to the art, including polyanhydrides and aliphatic polyesters, preferably polylactic acid (PLA), polyglycolic acid (PGA) and mixtures and copolymers thereof, more preferably 50:50 copolymers of PLA:PGA and most preferably 75:25 copolymers of PLA:PGA. Single enantiomers of PLA may also be used, preferably L-PLA, either alone or in combination with PGA. Polycarbonates, polyfumarates and caprolactones may also be used to make the implants of this invention.

[0057] A plasticizer may be incorporated in the biodegradable film to make it softer and more pliable for applications where direct contact with a contoured surface is desired.

[0058] The polymeric films of this invention can be formed and used as flat sheets, or can be formed into three-dimensional conformations or "shells" molded to fit the contours of the tissue site into which the film is inserted.

[0059] To make the polymeric films of this invention, a suitable polymeric material is selected, depending on the degradation time desired for the film. Selection of such polymeric materials is known to the art. A lower molecular weight, e.g., around 20,000 daltons, 50:50 or 55:45 PLA:PGA copolymer is used when a shorter degradation time is desired. To ensure a selected degradation time, the molecular weights and compositions may be varied as known to the art.

[0060] Polymeric films of this invention may be made by dissolving the selected polymeric material in a solvent known to the art, e.g., acetone, chloroform or methylene chloride, using about 20 mL solvent per gram of polymer. The solution is then degassed, preferably under gentle vacuum to remove dissolved air and poured onto a surface, preferably a flat non-stick surface such as BYTAC (Trademark of Norton Performance Plastics, Akron, OH) non-stick coated adhesive-backed aluminum foil, glass or TEFLON™ non-stick polymer. The solution is then dried, preferably air-dried, until it is no longer tacky and the liquid appears to be gone. The known density of the polymer may be used to back-calculate the volume of solution needed to produce a film of the desired thickness.

[0061] Films may also be made by heat pressing and melt forming/drawing methods known to the art. For example, thicker films can be pressed to form thinner films, and can be drawn out after heating and pulled over forms of the desired shapes, or pulled against a mold by vacuum pressure.

[0062] The amount of policosanol to be incorporated into the polymeric films of this invention is an amount effective to show a measurable effect in treating of a macular disorder. The composition of the present invention can be incorporated into the film by various techniques such as by solution methods, suspension methods, or melt pressing.

[0063] Solid implants comprising policosanol can also be made into various shapes other than films by injection molding or extrusion techniques. For example, the implant can comprise a core material such as ethylene/vinyl acetate copolymer, and a vinyl acetate content of 20% by weight or more and which functions as a matrix for the policosanol, in a quantity which is sufficient for a controlled release of policosanol, and a membrane which encases the core material and also consists of EVA material and an acetate content of less than 20% by weight. The implant can be obtained, for example, by means of a co-axial extrusion process, a method in which the two EVA polymers are extruded co-axially with the aid of a co-axial extrusion head. The co-axial extrusion process is well known in the art known and need not be described further.

[0064] 3. Transdermal Patch Device

[0065] Transdermal delivery involves delivery of a therapeutic agent through the skin for distribution within the body by circulation of the blood. Transdermal delivery can

be compared to continuous, controlled intravenous delivery of a drug using the skin as a port of entry instead of an intravenous needle. The therapeutic agent passes through the outer layers of the skin, diffuses into the capillaries or tiny blood vessels in the skin and then is transported into the main circulatory system.

[0066] Transdermal patch devices that can be used to provide a controlled, continuous administration of policosanol through the skin are well known in the art. Such devices, for example, are disclosed in U.S. Patent Nos. 4,627,429; 4,784,857; 5,662,925; 5,788,983; and 6,113,940, which are all incorporated herein by reference. Characteristically, these devices contain a drug-impermeable backing layer which defines the outer surface of the device and a permeable skin-attaching membrane, such as an adhesive layer, sealed to the barrier layer in such a way as to create a reservoir between them in which the therapeutic agent is placed. In one embodiment of the present invention, policosanol is introduced into the reservoir of a transdermal patch.

[0067] 4. Kits

[0068] The therapeutic composition of the present invention may be packaged in any convenient, appropriate packaging. The present invention therefore further provides kits having one or more containers comprising the therapeutic composition of the present invention and a suitable excipient as described herein and a set of instructions, generally written instructions although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use and dosage of the therapeutic composition of the present invention for the intended treatment. The instructions included with the kit generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers of the therapeutic composition of the present invention may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses.

[0069] The invention is further illustrated by the following non-limiting example. All scientific and technical terms have the meanings as understood by one with ordinary skill in the art. The specific examples which follow illustrate the methods in which the compositions of the present invention may be prepared and are not to be construed as limiting the invention in sphere or scope. The methods may be adapted to variation in order to produce compositions embraced by this invention but not

specifically disclosed. Further, variations of the methods to produce the same compositions in somewhat different fashion will be evident to one skilled in the art.

EXAMPLE 1

[0070] Tablets comprising a composition of the present invention are prepared as set out in Table III.

TABLE III

Ingredient	amt/cap	function
Policosanol	20 mg	active
Calcium phosphate	261.7 mg	base
Cellulose	49.4 mg	tablet coating agent
Stearic acid	23.8 mg	lubricant
Magnesium stearate	6.8 mg	lubricant
Silicon dioxide	9.4 mg	diluent

[0071] The foregoing description is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and process shown as described above. Accordingly, all suitable modifications and equivalents may be resorted to falling within the scope of the invention as defined by the claims that follow. The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for treating or preventing the development of macular degeneration-related disorders, comprising administering a therapeutically effective amount of a composition comprising policosanol to a subject in need thereof.

2. The method of claim 1 wherein said policosanol comprises at least one higher primary aliphatic alcohol selected from straight chain primary aliphatic alcohols having 20 to 36 carbon atoms.

3. The composition of claim 2 wherein said policosanol comprises 1-tetracosanol, 1-hexacosanol, 1-octacosanol, 1-triacontanol, 1-dotriacontanol and 1-tetratriacontanol.

4. The composition of claim 3, wherein said policosanol has the following quantitative composition:

1-docosanol (C-22)	0- 5 wt%
1-tetracosanol (C-24)	0-30 wt%
1-hexacosanol (C-26)	5-30 wt%
1-heptacosanol (C-27)	5-10 wt%
1-octacosanol (C-28)	10-20 wt%
1-nonacosanol (C-29)	0-5 wt%
1-triacontanol (C-30)	5-40 wt%
1-dotriacontanol (C-32)	1-25 wt%
1-tetratriacontanol (C-34)	0-7 wt%.

5. The method of claim 1, wherein said macular disorder is selected from the group consisting of Age Related Macular degeneration, North Carolina macular dystrophy, Sorsby's fundus dystrophy, Stargardt's disease, pattern dystrophy, Best disease, dominant drusen, malattia leventinese, retinal detachment, chorioretinal degenerations, retinal degenerations, photoreceptor degenerations, RPE degenerations, mucopolysaccharidoses, rod-cone dystrophies, cone-rod dystrophies and cone degenerations.

6. The method of claim 1, wherein said composition is administered by

parenteral, transdermal, intranasal, sublingual, transmucosal, intra-arterial, or intradermal administration.

7. The method of claim 1, wherein said composition is delivered to said subject as a controlled release composition.

8. The method of claim 7, wherein said controlled release composition comprises a flowable thermoplastic polymer composition comprising a biocompatible polymer, a biocompatible solvent, and policosanol, and is delivered to a bodily tissue or fluid in said subject, wherein the amounts of the polymer and the solvent are effective to form a biodegradable polymer matrix containing policosanol *in situ* when said composition contacts said bodily fluid tissue or fluid.

9. The method of claim 8, wherein said polymer is a poly(alkylene glycol) or a polysaccharide.

10. The method of claim 7, wherein the composition further comprises a controlled release additive.

11. The method of claim 8, wherein said biocompatible polymer is selected from the group consisting of polylactides, polyglycolides, polyanhydrides, polyorthoesters, polycaprolactones, polyamides, polyurethanes, polyesteramides, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyacrylates, polyalkylene succinates, poly(malic acid), poly(amino acids) and copolymers, terpolymers, cellulose diacetate, ethylene vinyl alcohol, and copolymers and combinations thereof.

12. The method of claim 8, wherein the polymer matrix releases said policosanol by diffusion, erosion, or a combination of diffusion or erosion as the polymer matrix biodegrades in said subject.

13. The method of claim 8, wherein said policosanol is added to said polymer composition prior to administration such that said solid polymer matrix further contains said policosanol.

14. The method of claim 7, wherein said controlled release composition is in film form.

15. The method of claim 14, wherein said film comprises polylactic acid, polyglycolic acid and mixtures and copolymers thereof.

16. The method of claim 7, wherein said controlled release composition is

in tablet form.

17. The method of claim 1, further comprising administering at least one additional agent for treating or preventing macular degeneration-related disorders, wherein said policosanol and said additional drug are administered as an admixture, separately and simultaneously, or separately in any order.

18. The method of claim 1, further comprising subjecting said subject to laser surgery or photodynamic therapy.

19. A kit comprising a first container comprising a controlled release formulation of policosanol, said formulation comprising an amount of policosanol effective to treat or reduce and/or prevent macular degeneration-related disorders.

20. The kit of claim 19, further comprising a puncture needle or catheter.