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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 12-117-299

**TÍTULO SOLICITADO: COMPOSICIONES OFTÁLMOLÓGICAS NO
IRRITABLES DE POVIDONA YODADA**

PUBLICACIÓN: Gaceta 658 de 12/12/2012, N° de publicación 1929

PRIORIDAD: US 61/286.697 de 15/12/2009

SOLICITANTE: FORESIGHT BIOTHERAPEUTICS. INC.

APODERADO: JESUS MARIA MENDEZ BERMUDEZ.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 11 de marzo de 2013, en los siguientes términos:

I. RATIFICACIÓN

Comendidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud

de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primer lugar, ante las reivindicaciones 12 a 15 que pretenden proteger usos o métodos de tratamiento, es menester recalcar que contravienen lo dispuesto en la Decisión 486 de 2000 en donde se refiere que no son patentables los métodos terapéuticos y dado que dichas reivindicaciones hacen referencia a la posibilidad de tratar o hacer profilaxis en un desorden ocular o en una infección y muestra los posibles desórdenes y patologías que serán parte de dichos tratamientos, no hacen parte por lo tanto, de las actividades industriales sino de las actividades médicas, de aquí que no hay nivel inventivo en ello toda vez que no cumplen con el estándar de aplicabilidad industrial, puesto que dichas modificaciones solo tienen efectos en los organismos específicos a nivel clínico más no son efectos técnicos.

- Teniendo en cuenta que la solicitud en cuestión reivindica la combinación farmacológica entre povidona yodada y una gran lista de fármacos antiinflamatorios no esteroideos, se puede considerar que todo efecto sinérgico o terapéutico entre fármacos no se refiere propiamente a una invención, sino que corresponde mejor a la categoría de un descubrimiento, dado que dicho efecto sinérgico o terapéutico conseguido mediante la combinación de fármacos ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos por los que todo fármaco o combinación de fármacos se deben evaluar. Así mismo es importante volver a enfatizar en que la combinación de fármacos para tratar ciertas patologías, hace parte de las actividades de la profesión médica, y no de las actividades industriales.

- Enfocándonos en el análisis de requerimientos de patentabilidad para la solicitud colombiana en trámite, encontramos que en la misma carece de novedad y para tal efecto, relacionamos varios documentos en los cuales se revelan con anterioridad las mismas preparaciones oftálmicas que comprenden povidona yodada con sus respectivos adyuvantes y analgésicos esteroideos y no esteroideos, veamos:

- La publicación americana **US 2009/02633455 “Otic compositions for the treatment of infections of the internal and external ear in mammals”**, revela composiciones con povidona útiles en infecciones virales y fúngicas agudas y crónicas en mamíferos y humanos.

En dicha publicación se revelan los elementos principales reivindicados de la solicitud en trámite, es decir, **povidona y lubricantes**, e incluso con las mismas concentraciones, de tal forma que la composición que se pretende proteger no es nueva ni sustenta nivel inventivo dado que también es sugerido explícitamente que tales composiciones pueden ser útiles como lágrimas artificiales, es decir, de forma oftálmica. Así mismo, encontramos que en dicha anterioridad se mencionan otros compuestos opcionales como **analgésicos, agentes de viscosidad, agentes de enfriamiento y bioadhesivos** tal como se sugiere en la solicitud en trámite.

De manera similar, se encontró en la misma publicación americana los posibles principios activos (esteroides y antiinflamatorios no esteroides) a combinar mencionados en las Rvs 1 a 5 de la composición reivindicada en la solicitud colombiana.

En consecuencia con dicha anterioridad y la composición sugerida allí, queda irrefutablemente demostrado que la solicitud colombiana en trámite no representa ningún aporte novedoso ni mucho menos nivel inventivo frente al arte anterior.

- La publicación americana **US 2007/0219170 “OPHTHALMIC COMPOSITIONS COMPRISION POVIDONE-IODINE”** demuestra que la solicitud colombiana en trámite carece de nivel inventivo ya que en dicho documento se sugieren preparaciones farmacéuticas oftalmológicas que comprenden **povidonas combinadas con esteroides y antiinflamatorios no esteroides** y que soluciona el mismo problema técnico propuesto por la solicitud en trámite al mencionar específicamente cómo las formulaciones con povidona combinadas con esteroides previenen la irritación ocular.

Esta anterioridad igualmente permite conocer cuáles son los esteroides y antiinflamatorios no esteroides que pueden utilizarse para combinar en este tipo

de formulación, se evidencia por tanto con un segundo documento que lo pretendido por la solicitud era ya conocido.

De aquí que, según lo previamente enseñado en el estado de la técnica, podemos evidenciar que la reivindicación independiente (1) y sus dependientes no cumplen con los requisitos de patentabilidad, ya que no son nuevas y por lo tanto tampoco son inventivas, más aún, cuando ya se sabía cómo resolver el mismo problema técnico propuesto por la solicitud colombiana CO 12-117-299.

II. COMPLEMENTO DE INFORMACIÓN.

Por si no fueren suficientes los argumentos dados en la oposición presentada oportunamente queremos someter a su consideración los siguientes:

- La publicación americana **US 2009/0214628** publicada el **27 de agosto de 2009**, titulada **“METHODS AND COMPOSITIONS FOR TREATMENT OF SKIN”** enseña cómo realizar composiciones que previenen, disminuyen o mejoran la apariencia de la piel y mucosas y a su vez evitan la irritación en el lugar de aplicación, aliviando síntomas y reacciones secundarias, de esta forma se logra solucionar **el mismo problema técnico** de la solicitud, dado que tales composiciones pueden ser incorporadas en diferentes formas farmacéuticas siendo una de ellas precisamente a nivel ocular ya que es utilizada para limpiar y desinfectar los lentes de contacto y que así puedan ser colocados impregnados de la composición en la superficie ocular, evitando así la irritación y mejorando los síntomas de molestia.

Contact Lens Cleaners

[0016] The present invention also relates to compositions that can be used for the effective cleaning and disinfection of contact lenses. Deposits such as protein derived from tears or lipid derived from discharge can adhere to the surfaces of contact lenses when the lenses are worn. These deposits must be removed from the lenses prior to subsequent use. The present invention addresses the need for novel contact lens cleaners.

BRIEF SUMMARY OF THE INVENTION

[0017] The present invention relates to methods and compositions for the treatment of human skin, particularly facial skin and the scalp. The invention also relates to compositions and methods for removing biofilms in the oral cavity and from contact lenses. Where the invention is used for the treatment of skin including the scalp, the compositions are useful for imparting a visual improvement in skin appearance, for alleviating the symptoms of cosmetic or dermatologic skin conditions, or for alleviating conditions of the scalp such as dandruff.

Por lo tanto, este es también un documento que combinado con otro de los anteriormente relacionados, le resta el nivel inventivo a la reivindicación 1 de la presente solicitud colombiana en trámite, que como habíamos resaltado anteriormente, se refiere a:

Una preparación oftálmica comprende::

(a) *Povidona yodada en una concentración entre 0.1% a 2.5% de dicha preparación oftálmica,*

(b) *Al menos un miembro seleccionado del grupo que consiste de un lubricante y un agente de enfriamiento, en una concentración que no irrita el ojo; y*

Opcionalmente:

uno o más miembros seleccionados del grupo que consiste en camfor, borneol, un lubricante, un emoliente, un compuesto esteroideal antiinflamatorio y un compuesto no esteroideal antiinflamatorio.

Esta anterioridad es un ejemplo más de que la solución al problema técnico propuesto por la solicitud en trámite estaba resuelto previamente en el estado de la técnica, habida cuenta de que los componentes en este tipo de formulación eran conocidos y estaba ampliamente establecida su finalidad en el arte, adicionalmente, se sugería la posibilidad de combinación con analgésicos de todo tipo y agentes antiinflamatorios, veamos:

[0099] Examples of suitable benefit agents include, but are not limited to, depigmentation agents; reflectants; detangling/wet combing agents; film forming polymers; humectants; amino acids and their derivatives; antimicrobial agents; allergy inhibitors; anti-acne agents; anti-aging agents; anti-wrinkling agents; antiseptics; analgesics; antitussives; antipruritics; local anesthetics; anti-hair loss agents; hair growth promoting agents; hair growth inhibitor agents, antihistamines such as *Mandragora Vernalis*, *Tanacetum Parthenium* and the like; antiinfectives such as *Acacia Catechu*, *Aloe*

Barbadensis, *Convallaria Majalis*, *Echinacea*, *Eucalyptus*, *Mentha Piperita*, *Rosa Canina*, *Sassafras Albidum*, and the like; inflammation inhibitors; anti-emetics; anticholinergics; vasoconstrictors; vasodilators; wound healing promoters; peptides, polypeptides and proteins; deodorants and anti-perspirants; medicament agents; skin emollients and skin moisturizers; skin firming agents, hair conditioners; hair softeners; hair moisturizers; vitamins; tanning agents; skin lightening agents; antifungals such as *Centaurea Cyanus*, *Kalmia Latifolia* and antifungals for foot preparations; depilating agents; shaving preparations, external analgesics; perfumes; counter-irritants; hemorrhoidals; insecticides, poison ivy products; poison oak products; burn products; anti-diaper rash agents; prickly heat agents; make-up preparations; vitamins; amino acids and their derivatives; herbal extracts; retinoids; flavonoids; sensates; anti-oxidants; skin conditioners; hair lighteners; chelating agents; cell turnover enhancers; coloring agents; pigments; sunscreens, those active ingredients disclosed in U.S. Pat. No. 6,063,397, which is incorporated herein by reference, anti-edema agents, collagen enhancers, and mixtures thereof.

En el siguiente párrafo puede observarse que ya había sido sugerido el **camfor** reivindicado como opcional en el literal c) de la reivindicación independiente en la solicitud colombiana en trámite:

[0127] Examples of suitable external analgesics and local anesthetics nonexclusively include benzocaine, dibucaine, benzyl alcohol, camphor, capsaicin, *capsicum*, *capsicum* oleoresin, juniper tar, menthol, methyl nicotinate, methyl salicylate, phenol, resorcinol, turpentine oil, and mixtures thereof.

[0128] Examples of suitable antiperspirants and deodorants nonexclusively include aluminium chlorohydrates, aluminium zirconium chlorohydrates, and mixtures thereof.

[0129] Examples of suitable counterirritants nonexclusively include camphor, menthol, methyl salicylate, peppermint and clove oils, ichtammol, and mixtures thereof.

A continuación, adjuntamos los párrafos de la publicación americana donde pueden evidenciarse los mismos componentes específicos tal y como se pretende proteger en las reivindicaciones 6 a 11 de la solicitud colombiana en trámite, es así que se infiere que la funcionalidad de los siguientes excipientes ya era conocida

para resolver el problema técnico que nos ocupa y se sabía además que podían ser utilizado para varias formas farmacéuticas incluidas las de uso oftálmico, tales excipientes consisten en: **polivinil alcohol, metil celulosa, hidroxipropilmetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, propilenglicol, polietilenglicol, hidroxipropil metilcelulosa, carbopol, ácido poliacrílico, lecitina de soya, goma xantan, gelatina, polivinilalcohol, goma gelan, tragacanto, y acacia:**

[0132] Most preferred benefit agents nonexclusively include DMAE, soy and derivatives thereof, colloidal oatmeal, sulfonated shale oil, olive leaf, elubiol, 6-(1-piperidinyl)2,4-pyrimidinediamine-3-oxide, finasteride, ketoconazole, salicylic acid, zinc pyrithione, coal tar, benzoyl peroxide, selenium sulfide, hydrocortisone, sulfur, menthol, pramoxine hydrochloride, tricetylmmonium chloride, polyquaternium 10, panthenol, panthenol triacetate, vitamin A and derivatives thereof, vitamin B and derivatives thereof, vitamin C and derivatives thereof, vitamin D and derivatives thereof, vitamin E and derivatives thereof, vitamin K and derivatives thereof, keratin, lysine, arginine, hydrolyzed wheat proteins, hydrolyzed silk proteins, octyl methoxycinnamate, oxybenzone, minoxidil, titanium dioxide, zinc dioxide, retinol, erythromycin, tretinoin, and mixtures thereof. (...)

[0173] Yet another type of product that may be formulated from a solution is an ointment. An ointment may comprise a simple base of animal or vegetable oils or semi-solid hydrocarbons. An ointment may comprise from about 2% to about 10% of an emollient(s) plus from about 0.1% to about 2% of a thickening agent(s). Examples of thickening agents include cellulose derivatives (methyl cellulose and hydroxyl propylmethylcellulose), synthetic high molecular weight polymers (e.g., carboxyvinyl polymer and polyvinyl alcohol), plant hydrocolloids (e.g., karaya gum and tragacanth gum), clay thickeners (e.g., colloidal magnesium aluminum silicate and bentonite), and carboxyvinyl polymers (CARBOPOLS; sold by B.F. Goodrich Company, (such polymers are described in Brown, U.S. Pat. No. 2,798,053), carboxylic acid polymers, crosslinked polyacrylates, polyacrylamides, xanthan gum and mixtures thereof. See also Sagarin, Cosmetics, Science and Technology, 2nd Ed. Vol. 1 or INCI Handbook pp. 1693-1697. for a more complete disclosure of thickening agents or viscosity increasing agents useful herein. (...)

gelling agent(s)). Suitable gelling agents for aqueous gels include, but are not limited to, natural gums, acrylic acid and acrylate polymers and copolymers, and cellulose derivatives (e.g. hydroxymethyl cellulose and hydroxypropyl cellulose). Suitable gelling agents for oils (such as mineral oil) include, but are not limited to, hydrogenated butylene/ethylene/styrene copolymer and hydrogenated ethylene/propylene/styrene copolymer. Such gels typically comprise between about 0.1% and 5%, by weight, of such gelling agents. (...)

[0178] Compositions can include at least one cosmetically acceptable vehicle other than water. Vehicles other than water include solids or liquids such as emollients, solvents, humectants, thickeners and powders. Suitable liquid vehicles include mineral oil, silicone oil, lipids (such as lecithin, vegetable oil, vitamin E, and derivatives of lanolin), low-molecular weight glycols such as PEG-4, PEG-6, propylene glycol, glycerine, and their lower alkyl conjugates, and ketones, such as acetone. Solvents containing unconjugated hydroxyls may undergo slow exchange with the ester groups of the polyhydroxy acids; this may affect the bulk consistency of the preparation, but would still result in slow release of the hydroxy acid monomers. Solvents include ethyl alcohol, isopropanol, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, and acetone. (...)

[0195] Thickening agents that may be used with the present invention include cellulose and derivatives such as cellulose, carboxymethyl hydroxyethylcellulose, cellulose acetate propionate carboxylate, hydroxyethylcellulose, hydroxyethyl ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, methyl hydroxyethylcellulose, microcrystalline cellulose, sodium cellulose sulfate, and mixtures thereof. Also useful herein are the alkyl substituted celluloses. Examples of alkyl groups useful herein include those selected from the group consisting of stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl (i.e. alkyl groups derived from the alcohols of coconut oil), palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, behenyl, and mixtures thereof. The material sold under the tradename Natrosol™, CS Plus from Aqualon Corporation may be used.

[0196] Other useful thickeners include acacia, agar, algin, alginic acid, ammonium alginate, amylopectin, calcium alginate, calcium carrageenan, carnitine, carrageenan, dextrin, gelatin, gellan gum, guar gum, guar hydroxypropyltrimonium chloride, hectorite, hyaluronic acid, hydrated silica, (...)

hydroxypropyl chitosan, hydroxypropyl guar, karaya gum, kelp, locust bean gum, natto gum, potassium alginate, potassium carrageenan, propylene glycol alginate, sclerotium gum, sodium carboxymethyl dextran, sodium carrageenan, tragacanth gum, xanthan gum, and mixtures thereof. Also useful are acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers sold by the B.F. Goodrich Company under the trade mark of Carbopol resins. Suitable Carbopol resins are described in WO98/22085. (...)

[0208] Humectants are generally substances that can attract water, usually out of the air. Humectants are generally considered to be moisturizers. Suitable humectants that can be used with the present invention include but are not limited to glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and poly(alkylene oxide)s, such as polyethylene glycol. Sodium carbonate is used in the art as a humectant. (...)

De otro lado, las posibles combinaciones de principios activos tal y como pretende protegerse en las reivindicaciones 4 y 5 de la presente solicitud colombiana en trámite, también había sido tenido en cuenta en la publicación americana en mención, veamos:

[0248] Anti-inflammatory agents useful herein include steroids such as hydrocortisone; panthenol and ether and ester derivatives thereof e.g. panthenol ethyl ether, panthenyl triacetate; pantothenic acid and salt and ester derivatives thereof, such as calcium pantothenate; aloe vera, bisabolol, allantoin and compounds of the liquorice (the plant genus/species *Glycyrrhiza glabra*) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof e.g. salts such as ammonium glycyrrhizinate and esters such as stearyl glycyrrhetinate. Suitable levels may be from about 0.1 to about 5%, or from about 0.5 to about 3%. Additional anti-inflammatory agents include, but are not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone alphamethyl dexamethasone, dexamethasone-phosphate, beclomethasone

dipropionate, clobetasol valerate, desonide, desoxymethasone, deoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fluadrenolone, fluclarolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene)acetate, flurandre-nolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide, medrysone, am-ciafel, amcinafide, betamethasone, chlorprednisone, chlorprednisone acetate, clocortolone, clescinalone, dichlorisone, difluprednate, fluclothinide, flunisolide, fluorometholone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, betamethasone dipropionate, and triamcinolone, and combinations thereof.

Si tenemos en cuenta lo descrito en la nueva reivindicación 1 independiente y sus dependientes, y conociendo lo enseñado por todas las publicaciones hasta ahora mencionadas US 2009/0263345, US 2007/0219170 y US 2009/0214628, la presente solicitud **no es nueva de acuerdo a US 2009/0263345 y varios documentos evidencian que tampoco es inventiva**, ya que todos los elementos característicos habían sido divulgados previamente en el estado de la técnica, es decir, las preparaciones con **povidona** conocidas por medio del documento US 2009/0263345 para preparaciones óticas y oftálmicas, y allí se sugiere su uso **como lágrimas artificiales** mediante gotero por su capacidad humectante que a su vez mejora la irritación ocular y adicional a dicho documento, hasta ahora se evidencian dos documentos más, dentro de los cuales presentamos el **US 2009/0214628** que enseña como una composición de este tipo puede ser utilizada para la limpieza y humectación de los lentes de contacto que irán en contacto permanente con el ojo mejorando síntomas de molestia e irritación al colocárselos nuevamente sin tener necesidad de frotarlos con los dedos posterior a la limpieza

con tal composición refiriéndonos por lo tanto a composiciones ampliamente usadas y aptas a nivel oftalmológico.

De ésta forma demostramos que la existencia y el conocimiento práctico de todos los componentes reivindicados ya había sido establecida previamente en el estado del arte y avalada para uso oftalmológico.

[0356] To clean, disinfect and store contact lenses using the liquid formulation for contact lenses of the present invention, the contact lenses taken off from eyes are soaked in the liquid formulation without cleaning by digital rubbing and left as they are for about 5 minutes to about 24 hours, or about 30 minutes to about 8 hours. Thereafter, the thus treated contact lenses can be worn in eyes without being rinsed with the liquid formulation. Although cleaning by digital rubbing which is generally necessary when MPS is used is not neces-

68. A method of cleaning a contact lens, which comprises contacting the contact lens with an effective amount of the ophthalmic solution of any of claim 61-68.

Por lo tanto la formulación reivindicada puede considerarse tan solo como una alternativa a lo ya conocido dado que según las enseñanzas de los anteriores tres (3) documentos, todos los posibles componentes (**povidona y demás preservativos, viscosantes, lubricantes, agentes de enfriamiento y bioadhesivos**) y además las posibles combinaciones con analgésicos, con las cuales puede formularse una composición para aliviar la irritación, humectar y mejorar síntomas en tejidos y mucosas de los pacientes, ya eran conocidos y por tanto resultarían obvios para una persona medianamente versada en la materia.

- Por si fuera poco, la publicación **US 2008/0172032** del 17 de julio de 2008 y titulada **“METHOD FOR PREVENTING TISSUE DAMAGE ASSOCIATED WITH IRRIGATION OF TISSUE WITH AN ANTIMICROBIAL SOLUTION”** revela:

SUMMARY

[0005] In light of the present need for a method preventing tissue damage associated with irrigation of biological tissue with povidone-iodine solutions, a brief summary of various exemplary embodiments is presented. Some simplifications and omission may be made in the following summary, which is intended to highlight and introduce some aspects of the various exemplary embodiments, but not to limit the scope of the methods. Detailed descriptions of various exemplary embodiments adequate to allow those of ordinary skill in the art to make and use the methods follow in later sections.

Como puede apreciarse, nos encontramos ante un documento que enseña los posibles usos de la povidona y sus bondades, mostrando explícitamente sus ventajas contra el daño tisular y en el alivio de la irritación pre y post quirúrgica en oftalmología, y para el efecto se sugiere un método que estandariza la composición al pH adecuado y la concentración oftalmológicamente correcta que conducirá a solucionar el problema técnico del posible daño tisular que causa la yodopovidona, de tal forma que sin perjuicio de la evidente carencia de novedad de la reivindicación independiente comprobada mediante el primer documento mostrado en la oposición, US 2009/0263345, cuando la solicitud colombiana elige *"al menos un miembro seleccionado del grupo que consiste de un lubricante y un agente de enfriamiento"*, la presente publicación internacional US 2008/0172032 bien podría unirse al documento previamente detallado, US 2009/0214628 y de esta forma demostrar la carencia de nivel inventivo de la solicitud colombiana en trámite.

[0007] In various exemplary embodiments, the biological tissue is irrigated in preparation for surgery or following surgery. Exemplary embodiments of tissues to be irrigated include, but are not limited to, the following: ophthalmic tissue, mucosal tissue, intestinal tissue, otic tissue, nasal tissue, oral tissue, esophageal tissue, musculoskeletal tissue and/or gynecological tissue. Some exemplary embodiments include methods for treating ocular conjunctivitis caused by bacterial, fungal and/or viral infection.

[0008] Two particular types of methods for preventing tissue damage, especially tissue damage associated with irrigation of ophthalmic tissue include methods of preventing endothelial toxicity and methods for preventing tear deficiency syndrome.

[0019] During an exemplary survey of surgical patients from a clinical practice, use of conventional povidone-iodine solutions resulted in an over 40% incidence of tear deficiency syndrome in post-operative cataract patients. Using the method for preventing tissue damage by pre-and/or post-operative irrigation with a povidone-iodine characterized by a pH of about 6.8-8.0 eliminated the incidence of post-operative tear deficiency syndrome in all cataract patients.

Adicionalmente, el documento en mención **enseña las concentraciones útiles** y el pH adecuado para el uso de la povidona a nivel oftalmológico tal y como se pretende proteger en las reivindicaciones 2 y 3, no obstante, tales reivindicaciones por si mismas no poseen nivel inventivo ya que el hecho de seleccionar cantidades o porcentajes, es una actividad rutinaria propia de las etapas de preformulación.

In various exemplary embodiments, the concentration of povidone-iodine solution ranges from about 0.5% to about 5% povidone-iodine.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- La publicación americana **US 2009/0214628** publicada el 27 de agosto de 2009 y titulada "METHODS AND COMPOSITIONS FOR TREATMENT OF SKIN" pág 2 – 23.
- La publicación americana **US 2008/0172032** publicada el 17 de julio de 2008 y titulada "METHOD FOR PREVENTING TISSUE DAMAGE ASSOCIATED WITH IRRIGATION OF TISSUE WITH AN ANTIMICROBIAL SOLUTION" abstract, pág 1 - 3.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.



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(54) **METHODS AND COMPOSITIONS FOR
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(76) **Inventor: Jan de Rijk, Vcendendall (NL)**

Correspondence Address:
FROST BROWN TODD, LLC
2200 PNC CENTER, 201 E. FIFTH STREET
CINCINNATI, OH 45202 (US)

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(63) **Continuation of application No. 10/596,095, filed on
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on Sep. 27, 2005.**

(60) **Provisional application No. 60/612,919, filed on Sep.
27, 2004.**

(51) **Int. Cl.**

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424/49; 510/127; 510/112**

(57) **ABSTRACT**

The present invention relates to compositions and their use for the treatment of human skin, particularly facial skin, to alleviate the symptoms of cosmetic or dermatologic skin conditions. The invention relates to compositions for treating and ameliorating skin conditions including acne, rosacea and wrinkling caused by photodamage or conditions related to aging, hormonal imbalances, hyper-pigmentation, melasma, keratosis or the like. The invention can also be used to treat conditions of the scalp such as dandruff. The present invention also relates to compositions that can be used to remove biofilms from contact lenses. More particularly, this invention relates to a composition comprising (a) one or more metasilicate; (b) one or more carbonate; (c) one or more glyconate; and (d) one or more sulfate. The composition may also contain (e) salts, e.g., sea salts and other additives or active agents.

brownish spots, keratoses, melasma, lentigines, age spots, liver spots, pigmented spots, wrinkles, skin lines, fine lines, oily skin, warts, eczema, pruritic skin, psoriasis, inflammatory dermatoses, or disturbed keratinization.

[0013] While there are many compounds described in the art useful for improving the appearance and condition of skin, there is still a need for compositions with improved efficacy without undesirable side effects. The present invention relates to cosmetic methods of improving skin appearance and/or condition by topical application of the subject compositions. The present invention also relates to a composition that may be used in hair color and bleaching products, shampoos, conditioners, lotions, bath oils and salts, bar soaps, facial cleansers, and foot treatments.

Toothpastes

[0014] The present invention relates to oral care compositions, including therapeutic rinses, especially mouthrinses and methods of use to provide significantly enhanced antimicrobial activity, thereby reducing oral bacteria and promoting overall oral health. Microbial populations such as *Streptococcus sanguis*, *Streptococcus mutans*, and *Streptococcus sobrinus* are pioneer species, the first microbial to absorb, multiply and form micro-colonies; and reduction of these species are correlated to disruption of plaque biofilm. (P. Marsh & M. Martin, Oral Microbiology, 3rd Edition, London, Chapman & Hall Publishers, 1996). The compositions described herein can be used to treat conditions in the oral cavity.

[0015] The present invention provides topical oral care compositions, including therapeutic rinses, especially mouth rinses, toothpastes, tooth gels, tooth powders, subgingival gels, chewing gums, mouth sprays, and lozenges (including breath mints), comprising an effective amount of the present composition for treating or preventing conditions of the oral cavity. In particular, the present invention addresses the need to remove bacteria and biofilm accumulation in the oral cavity.

Contact Lens Cleaners

[0016] The present invention also relates to compositions that can be used for the effective cleaning and disinfection of contact lenses. Deposits such as protein derived from tears or lipid derived from discharge can adhere to the surfaces of contact lenses when the lenses are worn. These deposits must be removed from the lenses prior to subsequent use. The present invention addresses the need for novel contact lens cleaners.

BRIEF SUMMARY OF THE INVENTION

[0017] The present invention relates to methods and compositions for the treatment of human skin, particularly facial skin and the scalp. The invention also relates to compositions and methods for removing biofilms in the oral cavity and from contact lenses. Where the invention is used for the treatment of skin including the scalp, the compositions are useful for imparting a visual improvement in skin appearance, for alleviating the symptoms of cosmetic or dermatologic skin conditions, or for alleviating conditions of the scalp such as dandruff.

[0018] The present invention is directed to a composition comprising (a) one or more metasilicate; (b) one or more carbonate; (c) one or more glyconate; and (d) one or more

sulfate, in a topical carrier. The composition may also contain (e) salts, e.g., sea salts and/or other additives.

[0019] In a first embodiment, a composition and method for improving the appearance or condition of skin is provided wherein an effective amount of the composition described herein in a pharmaceutically or cosmetically-acceptable topical carrier is applied to the surface of the skin or to the scalp using a hair care product. The present invention is directed to a composition comprising (a) one or more metasilicate; (b) one or more carbonate; (c) one or more glyconate; and (d) one or more sulfate, in a topical carrier. The composition may also contain (e) salts, e.g., sea salts and/or other additives.

[0020] In a second embodiment, a composition and method for improving the appearance or condition of teeth or the oral cavity is provided wherein an effective amount of the composition described herein in an acceptable carrier is applied to the oral cavity. Similar to the composition described above, such the composition comprises (a) one or more metasilicate; (b) one or more carbonate; (c) one or more glyconate; and (d) one or more sulfate, in a carrier that can be delivered orally.

[0021] In a third embodiment, a composition and method for disinfecting and cleaning contact lenses is provided. The composition and method employs a composition comprising (a) one or more metasilicate; (b) one or more carbonate; (c) one or more glyconate; and (d) one or more sulfate, in a carrier that can be delivered orally.

[0022] In a further embodiment of the above-described compositions, the one or more metasilicate is an alkali metal silicate selected from the group consisting of sodium or potassium metasilicate, sodium or potassium orthosilicate and mixtures thereof.

[0023] In yet a further embodiment of the above-described compositions, the one or more carbonate is selected from the group consisting of sodium carbonate, sodium sesquicarbonate, sodium sulfate, sodium bicarbonate and mixtures thereof.

[0024] In another embodiment of the above-described compositions, the glyconate is selected from the group consisting of ammonium glyconate, lithium glyconate, sodium glyconate, sodium starch glyconate, potassium glyconate, ammonium acid glyconate, sodium acid glyconate, lithium acid glyconate, potassium acid glyconate, ammonium D-glyconate, lithium D-glyconate, sodium D-glyconate, potassium D-glyconate, glyconic acid, glyconic D acid, glyconic L acid, ammonium L-glyconate, lithium L-glyconate, sodium L-glyconate, potassium L-glyconate, magnesium glyconate, magnesium acid glyconate, magnesium D-glyconate, magnesium L-glyconate, calcium glyconate, calcium acid glyconate, calcium D-glyconate, calcium L-glyconate and mixtures thereof.

[0025] In another embodiment of the above-described compositions, the one or more sulfate is selected from the group consisting of potassium aluminum sulfate, sulfuric acid, sodium sulfate, potassium sulfate, lithium sulfate, ammonium sulfate, magnesium sulfate, strontium sulfate, aluminum sulfate, and mixtures thereof. Topical carriers include powders, lotions, gels, sprays, sticks, creams, ointments, liquids, emulsions, foams and aerosols. The compositions may also be used in combination with a fragrance, an anti-microbial such as a bactericide or fungicide, acne medications, wart remover such as salicylic acid with or without other hydroxyl acids, a reductant to bleach skin spots such as hydroxyquinone, a nutrient such as vitamin A or other vitamins and sunscreens. The composition may also be incorporated into a cosmetic, night cream, or skin ointment. Further,

wherein the composition comprises from about 0.1% to about 40% by weight of the conditioning composition, from about 0.005% to about 20% by weight of a salt, and from about 40% to about 99% by weight of a suitable carrier.

[0091] In one embodiment, the present invention is directed to a cosmetic composition and corresponding methods of applying the composition directly to the skin or scalp, wherein the composition comprises from about 0.1% to about 20% by weight of the conditioning composition, from about 0.005% to about 20% by weight of a benefit agent, and from about 60% to about 99% by weight of a suitable carrier.

[0092] In another embodiment, the composition is a leave-on cosmetic composition and corresponding methods of applying the composition directly to the scalp, wherein the composition comprises from about 0.1% to about 20% by weight of the conditioning composition, from about 0.005% to about 20% by weight of a moisturizing agent or carrier, and from about 40% to about 99% by weight of a volatile liquid.

[0093] In another embodiment, the composition further comprises a thickening polymer in an amount of 0.01 to 20 wt % based on the weight of the conditioning composition.

[0094] In another embodiment, the composition further comprises one or more of at least one amphoteric surfactant; at least one nonionic surfactant or at least one phospholipid; and at least one wax; wherein the ingredients are present in a combined amount sufficient to allow the conditioning composition to be incorporated into an aqueous solution.

[0095] In another embodiment, the composition further comprises a fatty alcohol present in an amount of from about 2.5% to about 4% by weight of the composition.

[0096] In another embodiment, the composition further comprises water present in an amount of from about 60% to about 96% by weight of the composition.

[0097] In another embodiment, the composition further comprises at least one of the following additives: a thickener, a dye, a fragrance, and/or a preservative.

Benefit Agents

[0098] The compositions of the present invention may be used as a skin conditioning system. The skin conditioning system may further contain one or more benefit agents or pharmaceutically-acceptable salts thereof. The benefit agents useful herein may be categorized by their therapeutic benefit or their postulated mode of action. However, it is to be understood that the benefit agents useful herein may, in some circumstances, provide more than one therapeutic benefit or operate via greater than one mode of action. Therefore, the particular classifications provided herein are made for the sake of convenience and are not intended to limit the benefit agents to the particular application(s) listed. In addition, the compounds, which are identified below as being suitable for use as benefit agents, may be used in an amount over and above the amount that they may be used for other purposes in the conditioning system.

[0099] Examples of suitable benefit agents include, but are not limited to, depigmentation agents; reflectants; detangling/wet combing agents; film forming polymers; humectants; amino acids and their derivatives; antimicrobial agents; allergy inhibitors; anti-acne agents; anti-aging agents; anti-wrinkling agents; antiseptics; analgesics; antitussives; antipruritics; local anesthetics; anti-hair loss agents; hair growth promoting agents; hair growth inhibitor agents, antihistamines such as *Mandragora Vernalis*, *Tanacetum Parthenium* and the like; antiinfectives such as *Acacia Catechu*, *Aloe*

Barbadensis, *Convallaria Majalis*, *Echinacea*, *Eucalyptus*, *Mentha Piperita*, *Rosa Canina*, *Sassafras Albidum*, and the like; inflammation inhibitors; anti-emetics; anticholinergics; vasoconstrictors; vasodilators; wound healing promoters; peptides, polypeptides and proteins; deodorants and anti-perspirants; medicament agents; skin emollients and skin moisturizers; skin firming agents; hair conditioners; hair softeners; hair moisturizers; vitamins; tanning agents; skin lightening agents; antifungals such as *Centaurea Cyanus*, *Kalmia Latifolia* and antifungals for foot preparations; depilating agents; shaving preparations; external analgesics; perfumes; counter-irritants; hemorrhoidals; insecticides; poison ivy products; poison oak products; burn products; anti-diaper rash agents; prickly heat agents; make-up preparations; vitamins; amino acids and their derivatives; herbal extracts; retinoids; flavonoids; sensates; anti-oxidants; skin conditioners; hair lighteners; chelating agents; cell turnover enhancers; coloring agents; pigments; sunscreens, those active ingredients disclosed in U.S. Pat. No. 6,063,397, which is incorporated herein by reference, anti-edema agents, collagen enhancers, and mixtures thereof.

[0100] Examples of suitable anti-edema agents nonexclusively include bisabolol natural, synthetic bisabolol, and mixtures thereof.

[0101] Examples of suitable vasoconstrictors nonexclusively include horse chestnut extract, prickly ash, and mixtures thereof.

[0102] Examples of suitable anti-inflammatory agents nonexclusively include benoxaprofen, centella asiatica, bisabolol, feverfew (whole), feverfew (parthenolide free), green tea extract, green tea concentrate, hydrogen peroxide, lycopene, oat oil, chamomile, and mixtures thereof.

[0103] Examples of collagen enhancers nonexclusively include vitamin A, vitamin C, and mixtures thereof.

[0104] Examples of suitable skin firming agent nonexclusively include dimethylaminoethanol ("DMAE").

[0105] Examples of suitable antipruritics and skin protectants nonexclusively include oatmeal, betaglucon, feverfew, soy and derivatives thereof, bicarbonate of soda, colloidal oatmeal, surfactant based colloidal oatmeal cleanser, *Anagallis Arvensis*, *Oenothera Biennis*, *Verbena Officinalis*, and the like. These antipruritics may be used in an amount, based upon the total weight of the skin conditioning composition, from about 0.01 percent to about 40 percent, and preferably from about 1 percent to about 5 percent.

[0106] As used herein, colloidal oatmeal means the powder resulting from the grinding and further processing of whole oat grain meeting United States Standards for Number 1 or Number 2 oats. The colloidal oatmeal has a particle size distribution as follows: not more than 3 percent of the total particles exceed 150 micrometers in size and not more than 20 percent of the total particles exceed 75 micrometers in size.

[0107] Examples of suitable reflectants nonexclusively include mica, alumina, calcium silicate, glycol dioleate, glycol distearate, silica, sodium magnesium fluorosilicate, and mixtures thereof.

[0108] Suitable detangling/wet combing agents nonexclusively include polyquaternium-10, hydroxypropyltrimonium guar, dioleoylamidoethyl hydroxyethylmonium methosulfate, di-(soyoyl)hydroxyethylmonium methosulfate, hydroxyethyl behenamidopropyl dimonium chloride, olealkonium chloride, polyquaternium-47, stearylmonium chloride, tricetylmonium chloride, and mixtures thereof.

[0109] Suitable film forming polymers include those that, upon drying, produce a substantially continuous coating or film on the hair, skin, or nails. Nonexclusive examples of suitable film forming polymers include acrylamidopropyl trimonium chloride/acrylamide copolymer; corn starch/acrylamide/sodium acrylate copolymer; polyquaternium-10; polyquaternium-47; polyvinylmethylether/maleic anhydride copolymer; styrene/acrylates copolymers; and mixtures thereof.

[0110] Commercially available humectants which are capable of providing moisturization and conditioning properties to the skin conditioning composition are suitable for use in the present invention. The humectant is preferably present in an amount of from about 0 percent to about 10 percent, more preferably from about 0.5 percent to about 5 percent, and most preferably from about 0.5 percent to about 3 percent, based on the overall weight of the composition. Examples of suitable humectants nonexclusively include: 1) water soluble liquid polyols selected from the group comprising glycerine, propylene glycol, hexylene glycol, butylene glycol, pentyleneglycol, dipropylene glycol, and mixtures thereof; 2) polyalkylene glycol of the formula I: $\text{HO}-(\text{R}''\text{O})_n-\text{H}$ I, wherein R'' is an alkylene group having from about 2 to about 4 carbon atoms and n is an integer of from about 1 to about 10, such as PEG 4; 3) polyethylene glycol ether of methyl glucose of formula II: $\text{CH}_3-\text{C}_6\text{H}_{10}\text{O}_5-(\text{OCH}_2\text{CH}_2)_c-\text{OH}$ II, wherein c is an integer from about 5 to about 25; 4) urea; 5) fructose; 6) glucose; 7) honey; 8) lactic acid; 9) maltose; 10) sodium glucuronate; and 11) mixtures thereof, with glycerine being the preferred humectant.

[0111] Suitable amino acid agents include amino acids derived from the hydrolysis of various proteins as well as the salts, esters, and acyl derivatives thereof. Examples of such amino acid agents nonexclusively include amphoteric amino acids such as alkylamido alkylamines, i.e. stearyl acetyl glutamate, capryloyl silk amino acid, capryloyl collagen amino acids; capryloyl keratin amino acids; capryloyl pea amino acids; cocodimonium hydroxypropyl silk amino acids; corn gluten amino acids; cysteine; glutamic acid; glycine; hair keratin amino acids; amino acids such as aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, cystine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, cysteic acid, lysine, histidine, arginine, cysteine, tryptophan, citrulline; lysine; silk amino acids, wheat amino acids; and mixtures thereof.

[0112] Suitable proteins include those polymers that have a long chain, i.e. at least about 10 carbon atoms, and a high molecular weight, i.e. at least about 1000, and are formed by self-condensation of amino acids. Nonexclusive examples of such proteins include collagen, deoxyribonuclease, iodized corn protein; milk protein; protease; serum protein; silk; sweet almond protein; wheat germ protein; wheat protein; alpha and beta helix of keratin proteins; hair proteins, such as intermediate filament proteins, high-sulfur proteins, ultra-high-sulfur proteins, intermediate filament-associated proteins, high-tyrosine proteins, high-glycine tyrosine proteins, trichohyalin, and mixtures thereof.

[0113] In one embodiment, the composition further comprises a nutrient. What is meant by a nutrient is an organic substance occurring in foods that is not synthesized by the body and is necessary in trace amounts for the normal metabolic functioning of the body, such as vitamins, essential amino acids, and essential fatty acids.

[0114] Examples of suitable vitamins nonexclusively include vitamin B complex; including thiamine, nicotinic acid, biotin, pantothenic acid, choline, riboflavin, vitamin B6, vitamin B12, pyridoxine, inositol, camitine; vitamins A, C, D, E, K and their derivatives such as vitamin A palmitate and pro-vitamins, e.g. (i.e. panthenol (pro vitamin B5) and panthenol triacetate) and mixtures thereof.

[0115] Examples of such essential amino acids include, but are not limited to, arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Examples of essential fatty acids include, but are not limited to, linoleate and linolenate.

[0116] Examples of suitable antibacterial agents nonexclusively include bacitracin, erythromycin, neomycin, tetracycline, chlortetracycline, benzethonium chloride, phenol, and mixtures thereof.

[0117] Examples of suitable skin emollients and skin moisturizers nonexclusively include mineral oil, lanolin, vegetable oils, isostearyl isostearate, glyceryl laurate, methyl gluceth-10, methyl gluceth-20 chitosan, and mixtures thereof.

[0118] Examples of suitable hair conditioners nonexclusively include quaternized compounds such as behenamidopropyl PG-dimonium chloride, tricetylmonium chloride, dihydrogenated tallowamidoethyl hydroxyethylmonium methosulfate, and mixtures thereof as well as lipophilic compounds like cetyl alcohol, stearyl alcohol, hydrogenated polydecene, and mixtures thereof.

[0119] An example of a suitable hair softener nonexclusively includes silicone compounds, such as those that are either non-volatile or volatile and those that are water soluble or water insoluble. Examples of suitable silicones include organo-substituted polysiloxanes, which are either linear or cyclic polymers of monomeric silicone/oxygen monomers and which nonexclusively include cetyl dimethicone; cetyl triethylammonium dimethicone copolyol phthalate; cyclomethicone; dimethicone copolyol; dimethicone copolyol lactate; hydrolyzed soy protein/dimethicone copolyol acetate; silicone quaternium 13; stearylquaternium dimethicone copolyol phthalate; stearamidopropyl dimethicone; and mixtures thereof.

[0120] Examples of suitable hair moisturizers nonexclusively include panthenyl ethyl ether, phytantriol, and mixtures thereof.

[0121] Examples of sunscreen agents nonexclusively include benzophenones, bornelone, butyl paba, cinnamidopropyl trimethyl ammonium chloride, disodium distyrylbiphenyl disulfonate, paba, potassium methoxycinnamate, butyl methoxydibenzoylmethane, octyl methoxycinnamate, oxybenzone, octocrylene, octyl salicylate, phenylbenzimidazole sulfonic acid, ethyl hydroxypropyl aminobenzoate, menthyl anthranilate, aminobenzoic acid, cinoxate, diethanolamine methoxycinnamate, glyceryl aminobenzoate, titanium dioxide, zinc oxide, oxybenzone, Padimate O, red petrolatum, and mixtures thereof.

[0122] An example of a suitable tanning agent nonexclusively includes dihydroxyacetone.

[0123] Examples of skin lightening agents nonexclusively include hydroquinone, catechol and its derivatives, ascorbic acid and its derivatives, and mixtures thereof.

[0124] Examples of suitable insecticides (including insect repellents, anti-scabies and anti-lice treatments) nonexclusively include permethrin, pyrethrin, piperonyl butoxide, imidacloprid, N,N-diethyl toluamide, which refers to the mate-

rial containing predominantly the meta isomer, i.e., N,N-diethyl-m-toluamide, which is also known as DEET; compounds of the formula III. ##STR00001## wherein R₅ is a branched or unbranched alkyl group having about 1 to about 6 carbon atoms; R₆ is H, methyl or ethyl; R₇ is a branched or unbranched alkyl or alkoxy group having from about 1 to about 8 carbon atoms; and K is a—CN or a—COOR₆ group, wherein R₆ is a branched or unbranched alkyl group having from about 1 to about 6 carbon atoms, natural or synthetic pyrethroids, whereby the natural pyrethroids are contained in pyrethrum, the extract of the ground flowers of *Chrysanthemum cinerariaefolium* or *C. coccineum*; and mixtures thereof. Within the structure of Formula III are ethyl 3-(N-butylacetamido)propionate, wherein R₇ is a CH₃ group, R₅ is an n-butyl group, R₆ is H, K is COOR₆ and R₈ is ethyl, which is available commercially from Merck KGaA of Darmstadt, Germany under the name, "Insect Repellent 3535."

[0125] An example of an anti fungal for foot preparations nonexclusively includes tolnaftate.

[0126] Examples of suitable depilating agents nonexclusively include calcium thioglycolate, magnesium thioglycolate, potassium thioglycolate, strontium thioglycolate, and mixtures thereof.

[0127] Examples of suitable external analgesics and local anesthetics nonexclusively include benzocaine, dibucaine, benzyl alcohol, camphor, capsaicin, *capsicum*, *capsicum* oleoresin, juniper tar, menthol, methyl nicotinate, methyl salicylate, phenol, resorcinol, turpentine oil, and mixtures thereof.

[0128] Examples of suitable antiperspirants and deodorants nonexclusively include aluminium chlorohydrates, aluminium zirconium chlorohydrates, and mixtures thereof.

[0129] Examples of suitable counterirritants nonexclusively include camphor, menthol, methyl salicylate, peppermint and clove oils, ichthammol, and mixtures thereof.

[0130] An example of a suitable inflammation inhibitor nonexclusively includes hydrocortisone, *Fragaria Vesca*, *Matricaria Chamomilla*, and *Salvia Officinalis*.

[0131] Examples of suitable hemorrhoidal products nonexclusively include the anesthetics such as benzocaine, pramoxine hydrochloride, and mixtures thereof; antiseptics such as benzethonium chloride; astringents such as zinc oxide, bismuth subgallate, balsam Peru, and mixtures thereof; skin protectants such as cod liver oil, vegetable oil, and mixtures thereof.

[0132] Most preferred benefit agents nonexclusively include DMAE, soy and derivatives thereof, colloidal oatmeal, sulfonated shale oil, olive leaf, clubiol, 6-(1-piperidinyl)2,4-pyrimidinediamine-3-oxide, finasteride, ketoconazole, salicylic acid, zinc pyrithione, coal tar, benzoyl peroxide, selenium sulfide, hydrocortisone, sulfur, menthol, pramoxine hydrochloride, tricetylmmonium chloride, polyquaternium 10, panthenol, panthenol triacetate, vitamin A and derivatives thereof, vitamin B and derivatives thereof, vitamin C and derivatives thereof, vitamin D and derivatives thereof, vitamin E and derivatives thereof, vitamin K and derivatives thereof, keratin, lysine, arginine, hydrolyzed wheat proteins, hydrolyzed silk proteins, octyl methoxycinnamate, oxybenzone, minoxidil, titanium dioxide, zinc dioxide, retinol, erythromycin, tretinoin, and mixtures thereof.

[0133] One preferred type of benefit agent includes those therapeutic components that are effective in the treatment of dandruff, seborrheic dermatitis, and psoriasis as well as the symptoms associated therewith. Examples of such suitable

benefits agents nonexclusively include zinc pyrithione, anthralin, shale oil and derivatives thereof such as sulfonated shale oil, selenium sulfide, sulfur, salicylic acid; coal tar; povidone-iodine, imidazoles such as ketoconazole, dichlorophenyl imidazolodioxalan, which is commercially available from Janssen Pharmaceutica, N.V., under the tradename, "Elubiol", clotrimazole, itraconazole, miconazole, climbazole, tioconazole, sulconazole, butoconazole, fluconazole, miconazole nitrate and any possible stereo isomers and derivatives thereof; piroctone olamine (Octopirox); selenium sulfide; ciclopirox olamine; anti-psoriasis agents such as vitamin D analogs, e.g. calcipotriol, calcitriol, and tacalcitol; vitamin A analogs such as esters of vitamin A, e.g. vitamin A palmitate, retinoids, retinols, and retinoic acid; corticosteroids such as hydrocortisone, clobetasone, butyrate, clobetasol propionate and mixtures thereof.

[0134] The amount of benefit agent to be combined with the skin conditioning composition or the emulsion may vary depending upon, for example, the ability of the benefit agent to penetrate through the skin, hair or nail, the specific benefit agent chosen, the particular benefit desired, the sensitivity of the user to the benefit agent, the health condition, age, and skin, hair, and/or nail condition of the user, and the like. In sum, the benefit agent is used in a "safe and effective amount," which is an amount that is high enough to deliver a desired skin, hair or nail benefit or to modify a certain condition to be treated, but is low enough to avoid serious side effects, at a reasonable risk to benefit ratio within the scope of sound medical judgment. Unless otherwise expressed herein, typically the benefit agent is present in the skin conditioning system in an amount, based upon the total weight of the system, from about 0.01 percent to about 20.0 percent, and preferably from about 0.01 percent to about 5.0 percent, and more preferably from about 0.01 percent to about 2.0 percent.

[0135] Optionally, commercially available detergent thickeners that are capable of imparting the appropriate viscosity to conditioning shampoo compositions are suitable for use in this invention. If used, the detergent thickeners should be present in the shampoo compositions in an amount sufficient to raise the Brookfield viscosity of the composition to a value of between about 500 to about 10,000 centipoise. Examples of suitable detergent thickeners nonexclusively include: mono or diesters of polyethylene glycol of formula IV. HO—(CH₂CH₂O)_zH IV. wherein z is an integer from about 3 to about 200; fatty acids containing from about 16 to about 22 carbon atoms; fatty acid esters of ethoxylated polyols; ethoxylated derivatives of mono and diesters of fatty acids and glycerine; hydroxyalkyl cellulose; alkyl cellulose; hydroxyalkyl alkyl cellulose; and mixtures thereof. More specifically, suitable detergent thickeners nonexclusively include behenalkonium chloride; cetyl alcohol, quaternium-46, hydroxyethyl cellulose, cocodimonium chloride, polyquaternium-6, polyquaternium-7, quaternium-18, PEG-18 glycerol oleate/cocotate, a mixture of acrylates/steareth-50 acrylate copolymer, laureth-3 and propylene glycol, which is commercially available from Goldschmidt under the tradename "Antil 208," a mixture of cocamidopropylbetaine and glyceryl laurate which is commercially available from Goldschmidt under the tradename, "Antil HS60," a mixture of propylene glycol, PEG 55, and propylene glycol oleate, which is commercially available from Goldschmidt under the tradename, "Anti 414 liquid," and mixtures thereof. Preferred detergent thickeners include polyethylene glycol ester, and more preferably PEG-150 distearate which is available from

the Stepan Company of Northfield, Ill. or from Comiel, S.p.A. of Bologna, Italy under the tradename, "PEG 6000 DS".

[0136] In another embodiment, the compositions of the present invention are useful as a cleansing system and cleansing composition

[0137] In one embodiment, the cleansing system and cleansing composition may also optionally contain a foaming surfactant. The foaming surfactant may be non-ionic, cationic, amphoteric, or anionic; nonionic surfactants are preferred. By "foaming," it is meant that the surfactant, when used with the composition of the present invention, has a column height of foam greater than about 20 mm as determined by the Ross-Miles Test. As used herein, the term "amphoteric" shall mean: 1) molecules that contain both acidic and basic sites such as, for example, an amino acid containing both amino (basic) and acid (e.g., carboxylic acid, acidic) functional groups; or 2) zwitterionic molecules which possess both positive and negative charges within the same molecule. The charges of the latter may be either dependent on or independent of the pH of the composition.

[0138] The above described skin conditioning composition and cleaning system may be prepared by combining the desired components in a suitable container and mixing them under ambient conditions in any conventional mixing means well known in the art, such as a mechanically stirred propeller, paddle, and the like.

[0139] Another embodiment of the present invention is directed to a method for depositing a benefit agent onto the skin, hair and/or nails comprised of applying either the above-described skin conditioning system or cleansing composition with an effective amount of a benefit agent to a desired location on a human or animal. While the frequency and amount of the benefit agent-containing cleaning system to be applied will depend upon, for example, the type and amount of benefit agent available, the intended usage of the final composition, i.e. therapeutic versus maintenance regimen, the amount and type of detergent present, and the sensitivity of the individual user to the composition/emulsion, typically the benefit agent-containing cleaning system of the present invention should be topically applied to affected body parts at regular intervals, and preferably from about 2 to about 14 times per week. More preferably, the composition/emulsion is applied more frequently during the initial stages of treatment, e.g. from about 5 to about 7 times per week until the desired effect is achieved, then less frequently when maintenance is desired, e.g. from about 2 to about 5 times per week.

[0140] The above-described skin conditioning composition and cleansing system are capable of efficiently mediating the deposition and permeation of various benefit agents, such as antidandruff agents, onto and into the skin following topical administration thereto.

[0141] An alternative preferred embodiment of the present invention is directed to a method for treating hair loss, such as hair loss resulting from alopecia, comprising topically applying the above-described cleaning system and the hair loss benefit agent to a desired location on an animal or human, wherein the benefit agent is comprised of an effective amount of a hair loss treatment agent such as minoxidil or mixture thereof. As used herein, "hair loss treatment agents" shall include agents capable of growing hair and/or agents capable of preventing the loss of hair. By "effective amount," it is meant an amount effective for treating hair loss and preferably may range from, based upon the total weight of the skin

conditioning system, from about 0.001 percent to about 20 percent, and preferably from about 1 percent to about 5 percent.

[0142] Examples of benefit agents suitable for treating hair loss include, but are not limited to potassium channel openers or peripheral vasodilators such as minoxidil, diazoxide, and compounds such as N*-cyano-N-(tert-pentyl)-N'-3pyridinyl-guanidine ("P-1075") as disclosed in U.S. Pat. No. 5,244,664, which is incorporated herein by reference; vitamins, such as vitamin E and vitamin C, and derivatives thereof such as vitamin E acetate and vitamin C palmitate; hormones, such as erythropoietin, prostaglandins, such as prostaglandin E1 and prostaglandin F2-alpha; fatty acids, such as oleic acid; diuretics such as spironolactone; heat shock proteins ("HSP"), such as HSP 27 and HSP 72; calcium channel blockers, such as verapamil HCL, nifedipine, and diltiazemamiloride; immunosuppressant drugs, such as cyclosporin and FK-506; 5 alpha-reductase inhibitors such as finasteride; growth factors such as, EGF, IGF and FGF; transforming growth factor beta; tumor necrosis factor; non-steroidal anti-inflammatory agents such as benoxaprofen; retinoids such as tretinoin; cytokines, such as IL-6, IL-1 alpha, and IL-1 beta; cell adhesion molecules such as ICAM; glucocorticoids such as betamethasone; botanical extracts such as aloe, clove, ginseng, *rehmannia*, *swertia*, sweet orange, *zanthoxylum*, *Serenoa repens* (saw palmetto), *Hypoxis rooperi*, stinging nettle, pumpkin seeds, and rye pollen; other botanical extracts including sandlewood, red beet root, chrysanthemum, rosemary, burdock root and other hair growth promoter activators which are disclosed in DE 4330597 which is incorporated by reference in its entirety herein; homeopathic agents such as Kalium Phosphoricum D2, *Azadirachta indica* D2, and Joborandi D1; genes for cytokines, growth factors, and male-patterned baldness; antifungals such as ketoconazole and elubiol; antibiotics such as streptomycin; proteins inhibitors such as cycloheximide; acetazolamide; benoxaprofen; cortisone; diltiazem; hexachlorobenzene; hydantoin; nifedipine; penicillamine; phenothiazines; pinacidil; psoralens, verapamil; zidovudine; alpha-glycosylated rutin having at least one of the following rutins: quercetin, isoquercitrin, hespeddin, naringin, and methylhesperidin, and flavonoids and transglycosidated derivatives thereof which are all disclosed in JP 7002677, which is incorporated by reference in its entirety herein; and mixtures thereof.

[0143] Preferred hair loss treatment agents include minoxidil, 6-(1-piperidinyl)-2,4-pyrimidinediamine-3-oxide, N'-cyano-N-(tert-pentyl)-N'-3-pyridinyl-guanidine, finasteride, retinoids and derivatives thereof, ketoconazole, elubiol or mixtures thereof.

[0144] Another embodiment of the present invention is directed to a method for inhibiting hair growth comprising topically applying the above-described composition/system combined with a benefit agent to a desired area on an animal or human for inhibiting hair growth, wherein the benefit agent is comprised of an effective amount of a hair growth inhibiting agent. In a preferred embodiment, the cleaning system contains, based upon the total weight of the cleaning system, from about 0.001 percent to about 20 percent, and preferably from about 0.01 percent to about 5 percent hair growth inhibiting agent.

[0145] Examples of benefit agents suitable for use in inhibiting hair growth include: serine proteases such as trypsin; vitamins such as alpha-tocopherol (vitamin E) and derivatives thereof such as tocopherol acetate and tocopherol

palmitate; antineoplastic agents, such as doxorubicin, cyclophosphamide, chlormethine, methotrexate, fluorouracil, vincristine, daunorubicin, bleomycin and hydroxycarbamide; anticoagulants, such as heparin, heparinoids, coumaerins, detran and indandiones; antithyroid drugs, such as iodine, thiouracils and carbimazole; lithium and lithium carbonate; interferons, such as interferon alpha, interferon alpha-2a and interferon alpha-2b; retinoids, such as retinol (vitamin A), isotretinoin; glucocorticoids such as betamethasone, and dexamethasone; antihyperlipidaemic drugs, such as triparanol and clofibrate; thallium; mercury; albendazole; allopurinol; amiodarone; amphetamines; androgens; bromocriptine; butyrophonones; carbamazepine; cholestyramine; cimetidine; clofibrate; danazol; desipramine; dixyrazine; ethambutol; etionamide; fluoxetine; gentamicin, gold salts; hydantoin; ibuprofen; imipramine; immunoglobulins; indandiones; indomethacin; intraconazole; levodopa; maprotiline; methysergide; metoprolol; metyrapone; nadolol; nicotinic acid; potassium thiocyanate; propranolol; pyridostigmine; salicylates; sulfasalazine; terfenadine; thiamphenicol; thiouracils; trimethadione; tropanolol; valproic acid; and mixtures thereof.

[0146] Preferred hair growth inhibitory agents include serine proteases, retinol, isotretinoin, betamethasone, alpha-tocopherol and derivatives thereof, or mixtures thereof.

[0147] Another preferred embodiment of the present invention is directed to a method for treating acne and for reducing the signs of aging, i.e. wrinkles, fine lines, and other manifestations of photodamage, comprising topically applying the above-described cleaning system and the relevant benefit agent to the skin of an animal or human at a desired area, wherein the benefit agent is comprised of an effective amount of an anti-acne agent or an anti-aging agent, respectively.

[0148] Examples of suitable anti-aging agents include, but are not limited to inorganic sunscreens such as titanium dioxide and zinc oxide; organic sunscreens such as octyl-methoxy cinnamates and derivatives thereof; retinoids; vitamins such as vitamin E, vitamin A, vitamin C, vitamin B, and derivatives thereof such as vitamin E acetate, vitamin C palmitate, and the like; antioxidants including beta carotene, alpha hydroxy acids such as glycolic acid, citric acid, lactic acid, malic acid, mandelic acid, ascorbic acid, alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, alpha-hydroxyisocaproic acid, atrolactic acid, alpha-hydroxyisovaleric acid, ethyl pyruvate, galacturonic acid, glucoheptonic acid, glucoheptono 1,4-lactone, gluconic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, isopropyl pyruvate, methyl pyruvate, mucic acid, pyruvic acid, saccharic acid, saccharic acid 1,4-lactone, tartaric acid, and tartronic acid; beta hydroxy acids such as beta-hydroxybutyric acid, beta-phenyl-lactic acid, beta-phenylpyruvic acid; botanical extracts such as green tea, soy, milk thistle, algae, aloe, angelica, bitter orange, coffee, goldthread, grapefruit, horehellen, honeysuckle, Job's tears, lithospermum, mulberry, peony, pueraria, nice, safflower, and mixtures thereof.

[0149] Preferred anti-aging agents include retinoids, antioxidants, alpha-hydroxy acids and beta-hydroxy acid with retinol and tretinoin being most preferred. Suitable amounts of anti-aging agents include, based upon the total weight of the described cleaning system, from about 0.01 percent to about 20 percent, and preferably from about 0.04 percent to about 5 percent.

[0150] Examples of suitable anti-acne agents include, but are not limited to topical retinoids (tretinoin, isotretinoin,

motretinide, adapalene, tazarotene, azelaic acid, retinol); salicylic acid; benzoyl peroxide; resorcinol; antibiotics such as tetracycline and isomers thereof, erythromycin, and the anti-inflammatory agents such as ibuprofen, naproxen, hetprofen; botanical extracts such as *alnus*, *arnica*, *artemisia capillaris*, *asiasarum* root, birch, *calendula*, chamomile, *cnidium*, comfrey, fennel, galla rhois, hawthorn, *houltuynia*, *hypericum*, jujube, kiwi, licorice, magnolia, olive, peppermint, philodendron, *salvia*, *sasa albo-marginata*; imidazoles such as ketoconazole and elubiol, and those described in Gollnick, H et al. 196(I) Dermatology Sebaceous Glands, Acne and Related Disorders, 119-157 (1998), which is incorporated by reference herein, and mixtures thereof.

[0151] Preferred anti-acne agents include benzoyl peroxide, retinol, elubiol, antibiotics, and salicylic acid, with retinol and tretinoin being most preferred.

[0152] Suitable amount of anti-acne agents include, based upon the total weight of the described cleaning system, from about 0.01 percent to about 10 percent, and preferably from about 0.04 percent to about 5 percent.

[0153] Another preferred embodiment of the present invention is directed to a method for depigmenting the skin, comprising topically applying to skin at a desired area the above-described cleaning system and an effective amount of the depigmentation benefit agent. Suitable effective amounts of depigmentation agents include, based upon the total weight of the described cleaning system, from about 0.01 percent to about 10 percent, and preferably from about 0.04 percent to about 5 percent.

[0154] Examples of suitable depigmentation agents include, but are not limited to soy and derivatives thereof, retinoids such as retinol; Kojic acid and its derivatives such as, for example, kojic dipalmitate; hydroquinone and its derivatives such as arbutin; tranexamic acid; vitamins such as niacin, vitamin C and its derivatives; azelaic acid; placertia; licorice; extracts such as chamomile and green tea, and mixtures thereof, with retinol, Kojic acid, and hydroquinone, being preferred.

[0155] An alternative preferred embodiment of the present invention is directed to a method for treating the symptoms and/or the diseases of dandruff, seborrheic dermatitis and/or psoriasis, comprising topically applying the above-described cleaning system and the relevant benefit agent to a location desired wherein the benefit agent is comprised of an effective amount of a dandruff treatment agent, a seborrheic dermatitis treatment agent, or a psoriasis treatment agent, respectively. As used herein, "dandruff treatment agent," "seborrheic dermatitis treatment agent," or a "psoriasis treatment agent," respectively, shall include agents capable of treating the symptoms and/or the diseases of dandruff, seborrheic dermatitis, and psoriasis, respectively. By "effective amount," it is meant an amount effective for treating the disease and/or the symptoms associated therewith and preferably may range from, based upon the total weight of the cleaning system, from about 0.001 percent to about 10 percent, and preferably from about 0.01 percent to about 5 percent.

[0156] Examples of benefit agents suitable for treating the symptoms and/or the diseases of dandruff, seborrheic dermatitis and/or psoriasis, respectively, nonexclusively include those set forth above with shale oil and derivatives thereof, elubiol, ketoconazole, coal tar, salicylic acid, zinc pyrithione, selenium sulfide, hydrocortisone, sulfur, menthol, pramoxine hydrochloride, and mixtures thereof being particularly preferred.

[0157] The compositions of the present invention may be directed applied to the skin or may be applied onto other delivery implements such as wipes, sponges, brushes, and the like. The compositions may be used in products designed to be left on the skin, wiped from the skin, or rinsed off of the skin.

[0158] The invention illustratively disclosed herein suitably may be practiced in the absence of any component, ingredient, or step which is not specifically disclosed herein. Several examples are set forth below to further illustrate the nature of the invention and the manner of carrying it out. However, the invention should not be considered as being limited to the details thereof.

Vehicles/Carriers

[0159] In embodiments of the present invention related to skin and hair care compositions, the compositions of the present invention comprise a safe and effective amount of a dermatologically-acceptable carrier, suitable for topical application to the skin within which the essential materials and optional other materials are incorporated to enable the essential materials and optional components to be delivered to the skin at an appropriate concentration. The carrier can thus act as a diluent, dispersant, solvent, or the like for the active ingredients of the composition. The carrier ensures that the active ingredients of the composition can be applied to and distributed evenly over the selected target at an appropriate concentration.

[0160] The carrier can be solid, semi-solid or liquid. The carriers may be liquid or semi-solid, such as creams, lotions and gels. The carrier can itself be inert or it can possess dermatological benefits of its own. The carrier should also be physically and, chemically compatible with the essential components described herein, and should not unduly impair stability, efficacy or other use benefits associated with the compositions of the present invention.

[0161] The type of carrier utilized in the present invention depends on the type of product form desired for the composition. The topical compositions useful in the subject invention may be made into a wide variety of product forms such as are known in the art. These include, but are not limited to, lotions, creams, gels, sticks, sprays, ointments, pastes, and mousses. These product forms may comprise several types of carriers including, but not limited to, solutions, aerosols, emulsions, gels, solids, and liposomes. The compounds which are active in the compositions and methods of this invention may be delivered topically by any means known to those of skill in the art. If the delivery parameters of the topically active pharmaceutical or cosmetic agent so require, the topically active composition may be further composed of a pharmaceutically or cosmetically acceptable vehicle capable of functioning as a delivery system to enable the penetration of the topically active agent into the skin.

[0162] The composition described herein can be prepared in the form of a cosmetic composition. The composition can be prepared in the form of basic cosmetic compositions (facial cleansers, such as toilet water, cream, essence, cleansing foam and cleansing water, pack and body oil), color cosmetic compositions (foundation, lipstick, mascara, and make-up base), hair product compositions (shampoo, rinse, hair conditioner and hair gel) and soap etc., which comprise the composition described herein as an active ingredient, together with a dermatologically acceptable carrier. The cosmetic composition can be easily prepared in any method known in

the art, using the composition described herein together with at least one carrier and additives, which are commonly used in the field of preparing cosmetic compositions. Examples of cosmetic agents include emollients, humectants, colorants, pigments, fragrances, moisturizers, viscosity modifiers and any other cosmetic forming agent. One or more cosmetic agents can be included in the cosmetic composition. The form of the cosmetic composition can be a powder, lotion, gel, spray, stick cream, ointment, liquid, emulsion, foam or aerosol. In another embodiment, additional active ingredients as known in the art and described herein may also be used. Examples of the carriers may include, but are not limited to, a skin softener, a skin permeation enhancer, a colorant, an aromatic, an emulsifier, a thickener, and a solvent. Also, the cosmetic composition may further comprise a perfumery, a pigment, a bactericidal agent, an antioxidant, a preservative and a moisturizer, and also a thickener, inorganic salts and synthetic polymer substances, for the purpose of improving physical properties. Lists of such materials, and formulations for the creation of particular types of lotions, creams, sunscreens, lipsticks and other such forms are widely available in the patent literature and in commercial handbooks and can be used by those skilled in the preparation of such formulations to incorporate the composition described herein.

[0163] In one example, the facial cleanser and soap, which comprise the composition described herein, can be easily prepared by adding composition to the facial cleanser base and soap base. The cream can be prepared by adding the composition to a general oil-in-water (O/W) cream base. The cleanser, soap and cream may further comprise a perfumery, a chelating agent, a pigment, an antioxidant and a preservative, and also synthetic or natural materials, proteins, minerals and vitamins, for the purpose of improving physical properties. Detailed descriptions of methods by which the composition may be delivered are described below. However, it should be understood that these are not limited descriptions, but merely used to illustrate possible embodiments of the invention.

Topical Delivery Via Liposomes

[0164] One acceptable vehicle for topical delivery of some of the compositions of this invention, particularly those which include proteins, may contain liposomes. The liposomes may be present in an amount, based upon the total volume of the composition, from about 10 mg/mL to about 100 mg/mL, or from about 20 mg/mL to about 50 mg/mL. The liposome may have a ratio of about 37.5:12.5:33.3:16.7. Suitable liposomes may be prepared in accordance with the protocol set forth in application U.S. Ser. No. 09/110,409, though other methods commonly used in the art are also acceptable. The above described composition may be prepared by combining the desired components in a suitable container and mixing them under ambient conditions in any conventional high shear mixing means well known in the art for non-ionic liposomes preparations, such as those disclosed in Niemiec et al., "Influence of Nonionic Liposomal Composition On Topical Delivery of Peptide Drugs Into Pilosebaceous Units: An In Vivo Study Using the Hamster Ear Model," 12 Pharm. Res. 1184-88 (1995) ("Niemiec"), which is incorporated by reference herein in its entirety. We have found that the presence of these liposomes in the compositions of this invention may enhance the therapeutic capabilities of some of the compositions of this invention.

Topical Delivery Via a Solution

[0165] The topical compositions useful in the present invention can be formulated as solutions. Solutions typically

include an aqueous solvent (e.g., from about 50% to about 99.99% or from about 90% to about 99% of a cosmetically acceptable aqueous solvent).

Topical Delivery Via Lotions, Creams, Emollients, or Ointments

[0166] The composition may also be delivered topically via a lotion. Lotions typically comprise from about 1% to about 20% (e.g., from about 5% to about 10%) of an emollient(s) and from about 50% to about 90% (e.g., from about 60% to about 80%) of water. Another type of product that may be formulated from a solution is a cream. A cream typically comprises from about 5% to about 50% (e.g., from about 10% to about 20%) of an emollient(s) and from about 45% to about 85% (e.g., from about 50% to about 75%) of water. Single emulsion skin care preparations, such as lotions and creams, of the oil-in-water type and water-in-oil type are well-known in the cosmetic art and are useful in the subject invention. Multiphase emulsion compositions, such as the water-in-oil-in-water type are also useful in the subject invention. In general, such single or multiphase emulsions contain water, emollients, and emulsifiers as essential ingredients.

[0167] Creams can be made with a support that is a soap-based or fatty alcohol-based formula in the presence of an emulsifier. The soaps can be any known in the cosmetic formulation art, and include natural fatty or synthetic acids having from 12 to 20 carbon atoms (such as lauric acid, myristic acid, palmitic acid, oleic acid, stearic acid and their mixtures) in concentrations of from 10 to 30% neutralized with cosmetically acceptable salts including sodium, potassium, ammonia, monoethanolamine, triethanolamine and their mixtures.

[0168] Topical compositions useful in the subject invention may be formulated as a solution comprising an emollient. Such compositions may contain from about 2% to about 50% of an emollient(s). As used herein, "emollients" refer to materials used for the prevention or relief of dryness, as well as for the protection of the skin. When the conditioning agent is an emollient it may be selected from hydrocarbons, fatty acids, fatty alcohols and esters. Isononyl isononanoate is a hydrocarbon type of emollient conditioning agent. Other hydrocarbons that may be employed include mineral oil, polyolefins such as polydecene, and paraffins such as isohexadecane (e.g. Permethil 99® and Permethil 101®). Other examples of such materials are described in WO 96/16636, incorporated by reference herein. One material that may be used is known by the INCI name sucrose polycottonseedate.

[0169] Organopolysiloxane oils: The organopolysiloxane oil may be volatile, non-volatile, or a mixture of volatile and non-volatile silicones. The term "non-volatile" as used in this context refers to those silicones that are liquid under ambient conditions and have a flash point (under one atmospheric pressure) of or greater than about 100° C. The term "volatile" as used in this context refers to all other silicone oils. Suitable organopolysiloxanes can be selected from a wide variety of silicones spanning a broad range of volatilities and viscosities. Non-volatile polysiloxanes are preferred. Suitable silicones are disclosed in U.S. Pat. No. 5,069,897, issued Dec. 3, 1991, which is incorporated by reference herein in its entirety. Organopolysiloxanes selected from the group consisting of polyalkylsiloxanes, alkyl substituted dimethicones, dimethiconols, polyalkylaryl siloxanes, and mixtures thereof may be used. Polyalkylsiloxanes, dimethicones and cyclomethicones may be used.

[0170] Vegetable oils and hydrogenated vegetable oils: Examples of vegetable oils and hydrogenated vegetable oils include safflower oil, castor oil, coconut oil, cottonseed oil, menhaden oil, palm kernel oil, palm oil, peanut oil, soybean oil, rapeseed oil, linseed oil, rice bran oil, pine oil, sesame oil, sunflower seed oil, partially and fully hydrogenated oils from the foregoing sources, and mixtures thereof. Animal fats and oils, e.g. cod liver oil, lanolin and derivatives thereof such as acetylated lanolin and isopropyl lanolate may be used. Also useful are C₄-C₂₀ alkyl ethers of polypropylene glycols, C₁-C₂₀ carboxylic acid esters of polypropylene glycols, and di-C₈-C₃₀ alkyl ethers, examples of which include PPG-14 butyl ether, PPG-15 stearyl ether, dioctyl ether, dodecyl octyl ether, and mixtures thereof. The compositions of the present invention may be substantially free of semi-solid hydrocarbons such as petrolatum, lanolin and lanolin derivatives, sterols (e.g., ethoxylated soya sterols), high molecular weight polybutenes and cocoa butter. By "substantially free," as used herein, means that the concentration of the semi-solid hydrocarbons are less than 10%, or less than 5% or less than 2% or 0.

[0171] C₁-C₃₀ mono- and poly-esters of sugars and related materials: These esters are derived from a sugar or polyol moiety and one or more carboxylic acid moieties. Depending on the constituent acid and sugar, these esters can be in either liquid or solid form at room temperature. Examples of liquid esters include: glucose tetraoleate, the glucose tetraesters of soybean oil fatty acids (unsaturated), the mannose tetraesters of mixed soybean oil fatty acids, the galactose tetraesters of oleic acid, the arabinose tetraesters of linoleic acid, xylose tetralinoleate, galactose pentaoleate, sorbitol tetraoleate, the sorbitol hexaesters of unsaturated soybean oil fatty acids, xylitol pentaoleate, sucrose tetraoleate, sucrose pentaoleate, sucrose hexaoleate, sucrose heptaoleate, sucrose octaoleate, and mixtures thereof. Examples of solid esters include: sorbitol hexaester in which the carboxylic acid ester moieties are palmitoleate and arachidate in a 1:2 molar ratio; the octaester of raffinose in which the carboxylic acid ester moieties are linoleate and behenate in a 1:3 molar ratio; the heptaester of maltose wherein the esterifying carboxylic acid moieties are sunflower seed oil fatty acids and lignocerate in a 3:4 molar ratio; the octaester of sucrose wherein the esterifying carboxylic acid moieties are oleate and behenate in a 1:3 molar ratio; and the octaester of sucrose wherein the esterifying carboxylic acid moieties are laurate, linoleate and behenate in a 1:3:4 molar ratio. A solid material that may be used is sucrose polyester in which the degree of esterification is 7-8, and in which the fatty acid moieties are C18 mono- and/or di-unsaturated and behenic, in a molar ratio of unsaturates: behenic of 1:7 to 3:5. A solid sugar polyester that may be used is the octaester of sucrose in which there are about 7 behenic fatty acid moieties and about 1 oleic acid moiety in the molecule. Other materials include cottonseed oil or soybean oil fatty acid esters of sucrose. The ester materials are further described in, U.S. Pat. No. 2,831,854, U.S. Pat. No. 4,005,196, to Jandacek, issued Jan. 25, 1977; U.S. Pat. No. 4,005,195, to Jandacek, issued Jan. 25, 1977, U.S. Pat. No. 5,306,516, to Letton et al., issued Apr. 26, 1994; U.S. Pat. No. 5,306,515, to Letton et al., issued Apr. 26, 1994; U.S. Pat. No. 5,305,514, to Letton et al., issued Apr. 26, 1994; U.S. Pat. No. 4,797,300, to Jandacek et al., issued Jan. 10, 1989; U.S. Pat. No. 3,963,699, to Rizzi et al, issued Jun. 15, 1976; U.S. Pat. No. 4,518,772, to Volpenhein, issued May 21, 1985; and U.S. Pat. No. 4,517,360, to Volpenhein, issued May 21, 1985.

[0172] The topical compositions of the subject invention generally comprise from about 1% to about 50%, or about 3% to about 15% of a dermatologically acceptable emollient. Emollients tend to lubricate the skin, increase the smoothness and suppleness of the skin, prevent or relieve dryness of the skin, and/or protect the skin. Emollients are typically water-immiscible, oily or waxy materials. A wide variety of suitable emollients are known and may be used herein. Sagarin, *Cosmetics, Science and Technology*, 2nd Edition, Vol. 1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of materials suitable as an emollient; See also *International Cosmetic Ingredient Dictionary and Handbook*, eds. Wenninger and McEwen, pp. 1656-61, 1626, and 1654-55 (The Cosmetic, Toilet, and Fragrance Assoc., Washington, D.C., 7 (th) Edition, 1997) (hereinafter "INCI Handbook") contains numerous examples of suitable materials. Emollients include stearyl alcohol, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, polydimethylsiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate.

[0173] Yet another type of product that may be formulated from a solution is an ointment. An ointment may comprise a simple base of animal or vegetable oils or semi-solid hydrocarbons. An ointment may comprise from about 2% to about 10% of an emollient(s) plus from about 0.1% to about 2% of a thickening agent(s). Examples of thickening agents include cellulose derivatives (methyl cellulose and hydroxyl propyl-methylcellulose), synthetic high molecular weight polymers (e.g., carboxyvinyl polymer and polyvinyl alcohol), plant hydrocolloids (e.g., karaya gum and tragacanth gum), clay thickeners (e.g., colloidal magnesium aluminum silicate and bentonite), and carboxyvinyl polymers (CARBOPOIS; sold by B.F. Goodrich Company, (such polymers are described in Brown, U.S. Pat. No. 2,798,053), carboxylic acid polymers, crosslinked polyacrylates, polyacrylamides, xanthan gum and mixtures thereof. See also Sagarin, *Cosmetics, Science and Technology*, 2nd Ed. Vol. 1 or INCI Handbook pp. 1693-1697, for a more complete disclosure of thickening agents or viscosity increasing agents useful herein.

Topical Delivery Via an Emulsion

[0174] The topical compositions useful in the present invention may be formulated as emulsions. If the carrier is an emulsion, from about 1% to about 10% (e.g., from about 2% to about 5%) of the carrier comprises an emulsifier(s). Emulsifiers may be nonionic, anionic or cationic. Suitable emulsifiers are disclosed in, for example, INCI Handbook, pp. 1673-1686. Lotions and creams can be formulated as emulsions. Typically such lotions comprise from 0.5% to about 5% of an emulsifier(s). Such creams would typically comprise from about 1% to about 20% (e.g., from about 5% to about 10%) of an emollient(s); from about 20% to about 80% (e.g., from 30% to about 70%) of water; and from about 1% to about 10% (e.g., from about 2% to about 5%) of an emulsifier(s).

Topical Delivery Via a Gel

[0175] The topical compositions of this invention can also be formulated as a gel (e.g., an aqueous gel using a suitable

gelling agent(s)). Suitable gelling agents for aqueous gels include, but are not limited to, natural gums, acrylic acid and acrylate polymers and copolymers, and cellulose derivatives (e.g. hydroxymethyl cellulose and hydroxypropyl cellulose). Suitable gelling agents for oils (such as mineral oil) include, but are not limited to, hydrogenated butylene/ethylene/styrene copolymer and hydrogenated ethylene/propylene/styrene copolymer. Such gels typically comprise between about 0.1% and 5%, by weight, of such gelling agents.

Topical Delivery Via a Solid Formulation

[0176] The topical compositions of the present invention can also be formulated into a solid formulation (e.g., a wax-based stick, soap bar composition, powder, or a wipe containing liquid or powder).

[0177] The topical compositions useful in the subject invention may contain, in addition to the aforementioned components, a wide variety of additional oil-soluble materials and/or water-soluble materials conventionally used in compositions for use on skin, hair, and nails at their art-established levels.

Liquid Vehicles

[0178] Compositions can include at least one cosmetically acceptable vehicle other than water. Vehicles other than water include solids or liquids such as emollients, solvents, humectants, thickeners and powders. Suitable liquid vehicles include mineral oil, silicone oil, lipids (such as lecithin, vegetable oil, vitamin E, and derivatives of lanolin), low-molecular weight glycols such as PEG-4, PEG-6, propylene glycol, glycerine, and their lower alkyl conjugates, and ketones, such as acetone. Solvents containing unconjugated hydroxyls may undergo slow exchange with the ester groups of the polyhydroxy acids; this may affect the bulk consistency of the preparation, but would still result in slow release of the hydroxy acid monomers. Solvents include ethyl alcohol, isopropanol, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, and acetone.

Additional Components

[0179] Nonlimiting examples of these additional ingredients include additional skin care actives such as peptides (e.g., Matrixyl [pentapeptide derivative]), farnesol, bisabolol, phytantriol, glycerol, urea, guanidine (e.g., amino guanidine); vitamins and derivatives thereof such as ascorbic acid, vitamin A (e.g., retinoid derivatives such as retinyl palmitate or retinyl propionate), vitamin E (e.g., tocopherol acetate), vitamin B₃ (e.g., niacinamide) and vitamin B₅ (e.g., panthenol) and the like and mixtures thereof; sunscreens; anti-acne medicaments (resorcinol, salicylic acid, and the like; antioxidants (e.g., phytosterols, lipoic acid); flavonoids (e.g., isoflavones, phytoestrogens); skin soothing and healing agents such as aloe vera extract, allantoin and the like; chelators and sequestrants; and agents suitable for aesthetic purposes such as essential oils, fragrances, skin sensates, opacifiers, aromatic compounds (e.g., clove oil, menthol, camphor, eucalyptus oil, and eugenol). Nonlimiting examples of suitable carboxylic copolymers, emulsifiers, emollients, and other additional ingredients are disclosed in U.S. Pat. No. 5,011,681, to Ciotti et al., issued Apr. 30, 1991 and U.S. Pat. No. 5,939,082, to Oblong et al., issued Aug. 17, 1999, both of which are herein incorporated by reference. The above-mentioned vitamin B₃ compounds can be incorporated as re-

crystallized crystals that remain in crystallized form in the composition or as partially solubilize crystals (i.e., some of the crystals are dissolved and some remain in crystalline form in the composition.).

[0180] Various other agents may be incorporated into the composition depending on therapeutic need, desired results or for purposes of shelf-life and stability.

Pigments/Colorants

[0181] Pigments are frequently added to cosmetic formulations to achieve a desired color for application to the skin. Such pigments are known and the concentrations required to achieve a desired coloring are readily determinable. Pigments may be inorganic or organic. Inorganic pigments include iron oxides (red, black, brown colors), manganese violet, ultramarines (green, blue, pink, red, or violet aluminum silicates), aquamarines, copper powder, mica, clays, silica, and titanium dioxide. Organic dyes that have been certified by the US FDA for cosmetic use generally have the prefix "D&C" and a suffix of a color and a number (for example, D&C Green #3). There are at least 27 D&C dyes, each of which may be present as a "lake", i.e., a salt of the dye with aluminum, zirconium, strontium, barium, calcium, potassium or other metallic cations, to produce increased adherence to a substrate. In Europe, many of the same colorants, and additional colorants not approved in the U.S., are listed as "CI" dyes; for example, CI 61570 is chemically the same as D&C Green #5. Each of these pigments may further have several different trade names, or be present in mixed compositions.

[0182] Certain embodiments of the present invention contain from about 0% to about 30%, or about 1% to about 20%, or from about 2% to about 15% or from about 5% to about 15%, of a colorant, on an anhydrous pigment weight basis. These are usually aluminum, barium or calcium salts or lakes. Dyes may be present at a concentration of from about 0% to about 3% and pearling agents and the like from 0% to about 10%.

[0183] Colorants useful herein are all inorganic and organic colors/pigments suitable for use in cosmetic compositions. When used, pigments are typically dispersed in emollients for the good dispersion of the pigments when incorporated into lip compositions of the present invention, thus providing an even distribution of color. Lakes are either a pigment that is extended or reduced with a solid diluent or an organic pigment that is prepared by the precipitation of a water-soluble dye on an adsorptive surface, which usually is aluminum hydrate. There is uncertainty in some instances as to whether the soluble dye precipitates on the surface of the aluminum hydrate to yield a dyed inorganic pigment or whether it merely precipitates in the presence of the substrate. A lake also forms from precipitation of an insoluble salt from an acid or basic dye. Calcium and barium lakes are also used herein.

[0184] Lakes suitable for use in the present invention include Red 3 Aluminum Lake, Red 21 Aluminum Lake, Red 27 Aluminum Lake, Red 28 Aluminum Lake, Red 33 Aluminum Lake, Yellow 5 Aluminum Lake, Yellow 6 Aluminum Lake, Yellow 10 Aluminum Lake, Orange 5 Aluminum Lake and Blue 1 Aluminum Lake, Red 6 Barium Lake, Red 7 Calcium Lake.

[0185] Other colors can also be included in the lipsticks, such as dyes. Suitable examples include Red 6, Red 21, Brown, Russet and Sienna dyes and mixtures thereof.

[0186] There are no specific limitations as to the pigment, colorant or filler powders used in the composition. Each may

be a body pigment, inorganic white pigment, inorganic colored pigment, pearling agent, and the like. Specific examples are talc, mica, magnesium carbonate, calcium carbonate, magnesium silicate, aluminum magnesium silicate, silica, titanium dioxide, zinc oxide, red iron oxide, yellow iron oxide, black iron oxide, ultramarine, polyethylene powder, methacrylate powder, polystyrene powder, silk powder, crystalline cellulose, starch, titanated mica, iron oxide titanated mica, bismuth oxychloride, and the like.

[0187] Additional pigment/powder fillers include, but are not limited to, inorganic powders such as gums, chalk, Fuller's earth, kaolin, sericite, muscovite, phlogopite, synthetic mica, lepidolite, biotite, lithia mica, vermiculite, aluminum silicate, starch, smectite clays, alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminum silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed aluminum starch octenyl succinate barium silicate, calcium silicate, magnesium silicate, strontium silicate, metal tungstate, magnesium, silica alumina, zeolite, barium sulfate, calcined calcium sulfate (calcined gypsum), calcium phosphate, fluorine apatite, hydroxyapatite, ceramic powder, metallic soap (zinc stearate, magnesium stearate, zinc myristate, calcium palmitate, and aluminum stearate), colloidal silicone dioxide, and boron nitride; organic powder such as polyamide resin powder (nylon powder), cyclodextrin, methyl polymethacrylate powder, copolymer powder of styrene and acrylic acid, benzoguanamine resin powder, poly(ethylene tetrafluoride) powder, and carboxyvinyl polymer, cellulose powder such as hydroxyethyl cellulose and sodium carboxymethyl cellulose, ethylene glycol monostearate; inorganic white pigments such as magnesium oxide. Other useful powders are disclosed in U.S. Pat. No. 5,688,831, to El-Nokaly et al., issued Nov. 18, 1997, herein incorporated by reference in its entirety. These pigments and powders can be used independently or in combination.

[0188] Also useful herein are pigment and/or dye encapsulates such nanocolorants from BASF and multi-layer interference pigments such as Sicopearls from BASF.

[0189] The pigments/powders may be surface treated to provide added stability of color and ease of formulation. Hydrophobically-treated pigments may be more easily dispersed in the solvent/oil phase. In addition, it may be useful to treat the pigments with a material that is compatible with a silicone phase. Particularly useful hydrophobic pigment treatments for use in water-in-silicone emulsions include polysiloxane treatments such as those disclosed in U.S. Pat. No. 5,143,722, incorporated herein by reference in its entirety. Pigment/powders having a primary average particle size of from about 10 nm to about 100,000 nm, or about 50 nm to about 5,000 nm, or about 100 nm to about 1000 nm may be used. Mixtures of the same or different pigment/powder having different particle sizes are also useful herein (e.g., incorporating a TiO₂ having a primary particle size of from about 100 nm to about 400 nm with a TiO₂ having a primary particle size of from about 10 nm to about 50 nm).

[0190] Dispersants may also be used in conjunction with the colors and pigments of the present invention. Examples of suitable dispersants include, but are not limited to, those described in U.S. Pat. No. 5,688,493, herein incorporated by reference in its entirety.

Film-Forming Agents

[0191] Film forming agents may be optionally included in the compositions of the present invention to aid film substan-

tivity and adhesion to the skin. Improving the long wear and non-transfer performance of the present compositions is quite desirable. Water-soluble, water insoluble, and water dispersible film forming agents can be used in the internal and external phases of the present compositions to give the desired end benefit.

[0192] The compositions may comprise from about 0% to about 20%, or from about 0.1% to about 10%, or from about 0.1% to about 5%, by weight of the composition, of the film-forming agent.

[0193] Film forming agents that may be used with the present invention include: 1) organic silicone resins, fluorinated silicone resins, copolymers of organic silicone resins, e.g., trimethylsiloxysilicate from GE (SR1000), GE's copolymers of silicone resins, e.g., SF1318 (silicone resin and an organic ester of isostearic acid copolymer) and CF1301 (silicone resin and alpha methyl styrene copolymer), Dow Corning's pressure sensitive adhesives—copolymers of silicone resins and various PDMS's (BIO-PSA series); and 2) acrylic and methacrylic polymers and resins, silicone-acrylate type copolymers and fluorinated versions of, including—silicones plus polymer SA70 from 3M, KP545 from Shin-Etsu, alkyl-acrylate copolymers, e.g., KP 561 and 562 from Shin-Etsu; 3) decene/butene copolymer from Collaborative Labs; 4) polyvinyl based materials, e.g., PVP, PVP/VA, including Antaron/Ganex from ISP (PVP/Triacontene copolymer), Luviskol materials from BASF; 5) polyurethanes, e.g., the Polyderm series from Alzo including but not limited to Polyderm PE/PA, Polyderm PPI-SI-WS, Polyderm PPI-GH, Luviset P.U.R. from BASF; 6) polyquaternium materials, e.g., Luvi-quat series from BASF; 7) acrylates copolymers and acrylates/acrylamide copolymers, e.g., Luvimer and Ultrahold series, both available from BASF; 8) styrene-based materials; and 9) chitosan and chitosan-based materials including cellulose and cellulose-based materials. Such film formers are disclosed for example in the International Cosmetic Ingredient Dictionary and Handbook, Seventh Edition, Vol 2, 1636-1638.

Thickening Agents

[0194] The compositions of the present invention may optionally also comprise a thickening agent from about 0.1% to about 5%, or from about 0.1% to about 3%, or from about 0.25% to about 2%, of a thickening agent.

[0195] Thickening agents that may be used with the present invention include cellulose and derivatives such as cellulose, carboxymethyl hydroxyethylcellulose, cellulose acetate propionate carboxylate, hydroxyethylcellulose, hydroxyethyl ethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, methyl hydroxyethylcellulose, microcrystalline cellulose, sodium cellulose sulfate, and mixtures thereof. Also useful herein are the alkyl substituted celluloses. Examples of alkyl groups useful herein include those selected from the group consisting of stearyl, isostearyl, lauryl, myristyl, cetyl, isocetyl, cocoyl (i.e. alkyl groups derived from the alcohols of coconut oil), palmityl, oleyl, linoleyl, linolenyl, ricinoleyl, behenyl, and mixtures thereof. The material sold under the tradename Natrosol™, CS Plus from Aqualon Corporation may be used.

[0196] Other useful thickeners include acacia, agar, algin, alginic acid, ammonium alginate, amylopectin, calcium alginate, calcium carrageenan, carnitine, carrageenan, dextrin, gelatin, gellan gum, guar gum, guar hydroxypropyltrimonium chloride, hectorite, hyaluronic acid, hydrated silica,

hydroxypropyl chitosan, hydroxypropyl guar, karaya gum, kelp, locust bean gum, natto gum, potassium alginate, potassium carrageenan, propylene glycol alginate, sclerotium gum, sodium carboxymethyl dextran, sodium carrageenan, tragacanth gum, xanthan gum, and mixtures thereof. Also useful are acrylic acid/ethyl acrylate copolymers and the carboxyvinyl polymers sold by the B.F. Goodrich Company under the trade mark of Carbopol resins. Suitable Carbopol resins are described in WO98/22085.

Shine-Control Agents

[0197] Cosmetic products that improve and/or regulate the condition of the shiny appearance of skin are increasingly popular with consumers and are referred to herein as "shine-control agents." Shine control agents may be included in the compositions of the present invention.

[0198] A frequent, undesirable condition is "oily skin", which results from the excessive amount of sebum and sweat that is excreted onto the skin. Sebum is an oily mixture, composed principally of squalene, triglycerides, fatty acids and wax esters. Sebum is produced in the sebaceous glands of the skin. Oily skin is associated with a shiny, undesirable appearance and disagreeable tactile sensation. Sweat is predominantly water with trace quantities of dissolved inorganic salts such as sodium chloride and potassium chloride.

[0199] Typically, shine-control agents are porous in nature. These agents, when applied to the skin provide a reservoir to absorb excess moisture into the pores, hence reducing the visible quantity of moisture on the skin.

[0200] Absorber and non-absorbing spherical particles may be combined to provide optimum shine control as well as providing a product with the best tactile sensory performance.

[0201] Suitable shine-control agents include, but are not limited to, silicas, magnesium aluminum silicates, talc, sericite and various organic copolymers. Particularly effective shine control agents include silicates or carbonates that are formed by reaction of a carbonate or silicate with the alkali (IA) metals, alkaline earth (IIA) metals, or transition metals, and silicas (silicon dioxide). Shine control agents that may be used include calcium silicates, amorphous silicas, calcium carbonates, magnesium carbonates, zinc carbonates, and combinations thereof. Some specific examples of the silicates and carbonates useful in this present invention are more fully explained in Van Nostrand Reinhold's Encyclopedia of Chemistry, 4th Ed. pp 155, 169, 556, and 849 (1984).

[0202] Synthetic versions of the shine-control agents, particularly silicates, may be used. Suitable synthetic carbonates are commercially available from Mallinckrodt or Whittaker, Clarke & Daniels. Examples of synthetic silicates useful in the present invention are Hubersorb 250™, or Hubersorb 600™, available from J. M. Huber.

[0203] Shine-control agents that primarily comprise silicas may be used instead of those materials comprising mainly silicates and/or carbonates when used for moisture and shine control. Silicas may also be in the form of microspheres and/or ellipsoids, as they have been found to contribute good skin feel characteristics in addition to efficient moisture absorption. Silica ellipsoids useful in the present invention are available from DuPont as ZELEC Sil and Kobo as Silica Shells. Silica microspheres are available from Kobo as MSS-500, MSS500/3, MSS-500H, MSS500/3N, MSS-500N and MSS 500/3N; Presperse as Spheron L1500, Spheron P1500. Fumed versions of silica can also be used with Aerosil from Degussa and Cab-O—Sil from Cabot both being useful.

[0204] Amongst the silicate series, magnesium aluminum silicates such as Sebumase, available from Miyoshi Kasei are useful.

[0205] When silicas, such as silica ellipsoids and silica microspheres are intended to be the main means for moisture absorption, the absorbent powder may comprise from about 1% to about 40%; or about 1% to about 25%, or about 2% to about 10%, by weight of the composition, of silicas.

[0206] Starch-based materials may also be used as shine control agents. Examples include Natrosorb W and Natrosorb HFW, DryFlo plus and DryFlo AF pure from National Starch and Chemical Company.

Skin-Conditioning Agents

[0207] Optionally, the compositions of the present invention may further comprise a skin-conditioning agent. These agents may be selected from humectants, exfoliants or emollients. Amounts of the skin-conditioning agent may range from about 0% to about 30%, or from about 1% to about 20%, or from about 1% to about 10% by weight.

Humectants

[0208] Humectants are generally substances that can attract water, usually out of the air. Humectants are generally considered to be moisturizers. Suitable humectants that can be used with the present invention include but are not limited to glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and poly(alkylene oxide)s, such as polyethylene glycol. Sodium carbonate is used in the art as a humectant.

Desquamation Agents/Exfoliants

[0209] A safe and effective amount of a desquamation agent may be added to the compositions of the subject invention, or from about 0.1% to about 10%, or from about 0.2% to about 5%, or from about 0.5% to about 4% of the composition. Desquamation agents enhance the skin appearance benefits of the present invention. For example, the desquamation agents tend to improve the texture of the skin (e.g., smoothness). A variety of desquamation agents are known in the art and are suitable for use herein, including organic hydroxy acids such as salicylic acid, glycolic acid, lactic acid, 5-octanoyl salicylic acid, hydroxyoctanoic acid, hydroxycaproic acid, and lanolin fatty acids. One desquamation system that may be used comprises sulphhydryl compounds and zwitterionic surfactants and is described in WO 96/01101, incorporated herein by reference. Another desquamation system that may be used comprises salicylic acid and zwitterionic surfactants and is described in WO 95/13048, incorporated herein by reference.

[0210] Exfoliants that may be used with the present invention include but are not limited to C2-C30 alpha-hydroxycarboxylic acids, beta-hydroxycarboxylic acids and salts of these acids. Glycolic, lactic and salicylic acids and their ammonium salts may be used. Amounts of the exfoliants may range from about 1 to about 15%, or from 2 to 10% by weight.

[0211] A wide variety of C2-C30 alpha-hydroxycarboxylic acids may be employed. Suitable examples of which include: alpha-hydroxyethanoic acid, alpha-hydroxypropanoic acid, alpha-hydroxyhexanoic acid, alpha-hydroxyoctanoic acid, alpha-hydroxydecanoic acid, alpha-hydroxydodecanoic acid, alpha-hydroxytetradecanoic acid, alpha-hydroxyhexadecanoic acid, alpha-hydroxyoctadecanoic acid, alpha-hy-

droxycosanoic acid, alpha-hydroxydocosanoic acid, alpha-hydroxyhexacosanoic acid, and alpha-hydroxyoctacosanoic acid.

Powders

[0212] Powders useful alone in dry compositions or as fillers in liquid compositions include chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl and/or trialkyl aryl ammonium silicate, organically modified montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, and sodium carboxymethyl cellulose.

Gels

[0213] Cosmetic gels may contain thickening or gelling agents such as sodium alginate or arabic gum or cellulose derivatives optionally in the presence of a solvent. The thickening agent concentration may range from about 0.5 to about 30 weight percent or from about 0.5 to about 15 weight percent. Solvents used can be aliphatic lower alcohols, glycols and their ethers with the concentration of the solvents ranging from about 2 to about 20%.

Solidifying Agents

[0214] The cosmetic compositions of this invention may also contain one or more materials, herein singly or collectively referred to as a "solidifying agent," that are effective to solidify the particular liquid base materials to be used in a cosmetic composition. (As used herein, the term "solidify" refers to the physical and/or chemical alteration of the liquid base material so as to form a solid or semi-solid at ambient conditions, i.e., to form a final composition that has a stable physical structure and is deposited on the skin during normal use conditions.) As is appreciated by those skilled in the art, the selection of the particular solidifying agent for use in the cosmetic compositions will depend upon the particular type of composition desired, i.e., gel or wax-based, the desired rheology, the liquid base material used and the other materials to be used in the composition. The solidifying agent may be present at a concentration of from about 0 to about 90%, or from about 1 to about 50%, or from about 5% to about 40%, or from about 1% to about 15%.

[0215] Suitable solidifying agents may include waxy materials such as candelilla, carnauba, beeswax, spermaceti, carnauba, baysberry, montan, ozokerite, ceresin, paraffin, synthetic waxes such as Fisher-Tropsch waxes, silicone waxes (e.g., DC 2503 from Dow Corning), microcrystalline waxes and the like; soaps, such as the sodium and potassium salts of higher fatty acids, i.e., acids having from 12 to 22 carbon atoms; amides of higher fatty acids; higher fatty acid amides of alkylolamines; dibenzaldehyde-monosorbitol acetals; alkali metal and alkaline earth metal salts of the acetates, propionates and lactates; and mixtures thereof. Also useful are polymeric materials such as, locust bean gum, sodium alginate, sodium caseinate, egg albumin, gelatin agar, carrageenin gum sodium alginate, xanthan gum, quince seed extract, tragacanth gum, starch, chemically modified starches and the like, semi-synthetic polymeric materials such as cellulose ethers (e.g. hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, hydroxypropylmethyl cellulose), polyvinylpyrrolidone, polyvinylalcohol, guar gum, hydroxypropyl guar gum, soluble starch, cationic celluloses, cationic guar and the like and synthetic

polymeric materials such as carboxyvinyl polymers, polyvinylpyrrolidone, polyvinyl alcohol polyacrylic acid polymers, polymethacrylic acid polymers, polyvinyl acetate polymers, polyvinyl chloride polymers, polyvinylidene chloride polymers and the like. Inorganic thickeners may also be used such as aluminum silicates, such as, for example, bentonites, or a mixture of polyethylene glycol and polyethylene glycol stearate or distearate. Naturally occurring polymers or biopolymers and their use are further described in European Application No. 522624, to Dunphy et al. Additional examples of naturally occurring polymers or biopolymers can be found in the Cosmetic Bench Reference, pp. 1.40-1.42, herein incorporated by reference.

Spray Propellants

[0216] Spray compositions may require propellants, including propane, butane, isobutane, carbon dioxide, and nitrous oxide.

Fragrances

[0217] The composition can also include a perfume in an amount sufficient to make the composition acceptable to the consumer and pleasant to use. Usually, the perfume will form from about 0.01% to about 10% by weight of the composition.

Surfactants

[0218] Compositions herein may contain an emulsifier and/or surfactant, generally to help disperse and suspend the discontinuous phase within the continuous phase. A surfactant may also be useful if the product is intended for skin cleansing. For convenience hereinafter emulsifiers will be referred to under the term "surfactants", thus "surfactant(s)" will be used to refer to surface active agents whether used as emulsifiers or for other surfactant purposes such as skin cleansing. Known or conventional surfactants can be used in the composition, provided that the selected agent is chemically and physically compatible with essential components of the composition, and provides the desired characteristics. Suitable surfactants include silicone materials, non-silicone materials, and mixtures thereof.

[0219] The compositions of the present invention may comprise from about 0.05% to about 15% of a surfactant or mixture of surfactants. The exact surfactant or surfactant mixture chosen will depend upon the pH of the composition and the other components present. Surface active agents (detergents) useful in cosmetic compositions include anionic surface active agents, such as salts of fatty acids (for example, sodium laurate and triethanolamine oleate), alkyl benzene sulfonates (such as triethanolamine dodecyl benzene sulfonate), alkyl sulfates such as sodium lauryl sulfate, alkyl ether sulfates, monoglyceride sulfates, isethionates, methyl taurides, acylsarcosinates, acyl peptides, acyl lactylates, polyalkoxylated ether glycolates, for example trideceth-7 carboxylic acid, and phosphates such as sodium dilauryl phosphate. Amphoteric surface active agents include imidazole compounds, N-alkyl amino acids, (such as sodium cocamino propionate and asparagine derivatives), and betaines. Nonionic surface active agents, such as fatty acid alkanolamides, for example, oleic ethanolamide; esters of polyalcohols, for example Span; polyglycerol esters; polyalkoxylated derivatives, for example TRITON X-100™, polyoxyethylene lauryl ether, and TWEEN™; and amine

oxides, such as dodecyl dimethyl amine oxides. Cationic surfactants may be of use in the composition. Mixtures of two or more of the above surface active agents can be employed in the composition. As noted above, many surfactants may also be used for their functionality as emollients, humectants or vehicles.

[0220] Other useful nonionic surfactants include the condensation products of alkylene oxides with fatty acids (i.e. alkylene oxide esters of fatty acids). These materials have the general formula $\text{RCO(X)}_n\text{OH}$ wherein R is a C_{10-30} alkyl group, X is $-\text{OCH}_2\text{CH}_2-$ (i.e. derived from ethylene glycol or oxide) or $-\text{OCH}_2\text{CHCH}_3-$ (i.e. derived from propylene glycol or oxide), and n is an integer from about 6 to about 200. Other nonionic surfactants are the condensation products of alkylene oxides with 2 moles of fatty acids (i.e. alkylene oxide diesters of fatty acids). These materials have the general formula $\text{RCO(X)}_n\text{OOCR}$ wherein R is a C_{10-30} alkyl group, X is $-\text{OCH}_2\text{CH}_2-$ (i.e. derived from ethylene glycol or oxide) or $-\text{OCH}_2\text{CHCH}_3-$ (i.e. derived from propylene glycol or oxide), and n is an integer from about 6 to about 100. Other nonionic surfactants are the condensation products of alkylene oxides with fatty alcohols (i.e. alkylene oxide ethers of fatty alcohols). These materials have the general formula $\text{R(X)}_n\text{OR}'$ wherein R is a C_{10-30} alkyl group, X is $-\text{OCH}_2\text{CH}_2-$ (i.e. derived from ethylene glycol or oxide) or $-\text{OCH}_2\text{CHCH}_3-$ (i.e. derived from propylene glycol or oxide), and n is an integer from about 6 to about 100 and R' is H or a C_{10-30} alkyl group. Still other nonionic surfactants are the condensation products of alkylene oxides with both fatty acids and fatty alcohols [i.e. wherein the polyalkylene oxide portion is esterified on one end with a fatty acid and etherified (i.e. connected via an ether linkage) on the other end with a fatty alcohol]. These materials have the general formula $\text{RCO(X)}_n\text{OR}'$ wherein R and R' are C_{10-30} alkyl groups, X is $-\text{OCH}_2\text{CH}_2-$ (i.e. derived from ethylene glycol or oxide) or $-\text{OCH}_2\text{CHCH}_3-$ (derived from propylene glycol or oxide), and n is an integer from about 6 to about 100, examples of which include ceteth-6, ceteth-10, ceteth-12, cetareth-6, cetareth-10, cetareth-12, steareth-6, steareth-10, steareth-12, PEG-6 stearate, PEG-10 stearate, PEG-100 stearate, PEG-12 stearate, PEG-20 glyceryl stearate, PI-80 glyceryl tallowate, PEG-10 glyceryl stearate, PEG-30 glyceryl cocoate, PEG-80 glyceryl cocoate, PEG-200 glyceryl tallowate, PEG-8 dilaurate, PEG-10 distearate, and mixtures thereof.

[0221] Still other useful nonionic surfactants include polyhydroxy fatty acid amide surfactants, which are described in more detail in WO 98/04241.

[0222] Other nonionic surfactants suitable for use herein include sugar esters and polyesters, alkoxyated sugar esters and polyesters, $\text{C}_1\text{-C}_{30}$ fatty acid esters of $\text{C}_1\text{-C}_{30}$ fatty alcohols, alkoxyated derivatives of $\text{C}_1\text{-C}_{30}$ fatty acid esters of $\text{C}_1\text{-C}_{30}$ fatty alcohols, alkoxyated ethers of $\text{C}_1\text{-C}_{30}$ fatty alcohols, polyglyceryl esters of $\text{C}_1\text{-C}_{30}$ fatty acids, $\text{C}_1\text{-C}_{30}$ esters of polyols, $\text{C}_1\text{-C}_{30}$ ethers of polyols, alkyl phosphates, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates, and mixtures thereof. Examples of these non-silicon-containing surfactants include: polysorbate 20, polyethylene glycol 5 soya sterol, steareth-20, cetareth-20, PPG-2 methyl glucose ether distearate, ceteth-10, polysorbate 80, polysorbate 60, glyceryl stearate, sorbitan monolaurate, polyoxyethylene 4 lauryl ether sodium stearate, polyglyceryl-4

isostearate, hexyl laurate, PPG-2 methyl glucose ether distearate, PEG-100 stearate, and mixtures thereof.

Sunscreen

[0223] The composition may include an effective amount of a sunscreen agent to provide protection from the harmful effects of excessive exposure to sunlight. This can be particularly important when the skin is partially debrided by the application of a hydroxy acid. Examples of suitable organic sunscreens, when required, include Benzophenone-3, DEA Methoxycinnamate, Ethyl dihydroxypropyl PABA, Glyceryl PABA, Octyl methoxycinnamate, Octyl salicylate, 2-phenylbenzimidazole-5-sulfonic acid, and Butyl methoxy dibenzoylmethane. An inorganic sunscreen, such as titanium dioxide or zinc oxide, can also be used. The sunscreen ingredients may be present free in the formulation. The organic sunscreens may also be coupled to the conjugate block copolymer, as described above.

Anti-Oxidants

[0224] Anti-oxidants/radical scavengers such as ascorbic acid (vitamin C) and its salts, ascorbyl esters of fatty acids, ascorbic acid derivatives (e.g., magnesium ascorbyl phosphate), beta-carotene, tocopherol (vitamin E), tocopherol sorbate, tocopherol acetate, other esters of tocopherol, butylated hydroxy benzoic acids and their salts, gallic acid and its alkyl esters, such as propyl gallate, uric acid and its salts and alkyl esters, sorbic acid and its salts, amines (e.g., N,N-diethylhydroxylamine, amino-guanidine), sulfhydryl compounds (e.g., glutathione), dihydroxy fumaric acid and its salts, bioflavonoids, lysine, methionine, proline, superoxide dismutase, silymarin, tea extracts, grape skin/seed extracts, melanin, and rosemary extracts may be used. Anti-oxidants/radical scavengers that may be used include tocopherol acetate, tocopherol sorbate and other esters of tocopherol.

[0225] The tocopherol (vitamin E group) used as an additive or as an antioxidant for retinol, or a derivative, when present in the composition may include alpha-tocopherol, beta-tocopherol, gamma-tocopherol, and delta-tocopherol. The amount of tocopherol, when present in the composition, may be from about 0.0001 to about 50%, or from about 0.001 to about 10% by weight of the composition.

Chelators

[0226] The composition may also further comprises bio-film dislodging enhancer agents such as chaotropic agents or calcium chelators.

[0227] The inclusion of a chelating agent is useful for providing protection against UV radiation which can contribute to excessive scaling or skin texture changes and against other environmental agents which can cause skin damage. A suitable amount is from about 0.01% to about 1%, or from about 0.05% to about 0.5%, of the composition. Exemplary chelators that are useful herein are disclosed in U.S. Pat. No. 5,487,884, incorporated herein by reference. Chelators that may be useful in compositions of the subject invention are ethylenediamine tetraacetic acid (EDTA), furildioxime and derivatives thereof.

[0228] A calcium chelator such as EDTA, may also be in a salt form, in a concentration of at least about 0.25%, or any

calcium chelator having a chelating potency substantially equivalent thereto may be added.

Skin-Lightening Agents

[0229] The compositions of the present invention can also comprise a skin lightening agent. When used, the compositions may comprise from about 0.1% to about 10%, or from about 0.2% to about 5%, or from about 0.5% to about 2%, of a skin lightening agent. Suitable skin lightening agents include those known in the art, including kojic acid, arbutin, ascorbic acid and derivatives thereof, e.g., magnesium ascorbyl phosphate. Further skin lightening agents suitable for use herein also include those described in WO 95/34280 and WO 95/23780; each incorporated herein by reference.

Anti-Aging Additives

[0230] The composition can also include an additional anti-aging active such as retinol (Vitamin A) and/or derivative thereof, to enhance repair of photodamage to skin following exposure to ultra-violet light. In addition to retinol itself, examples of derivatives of retinol include: Retinyl acetate, Retinyl butyrate, Retinyl propionate, Retinyl octanoate, Retinyl laurate, Retinyl palmitate, Retinyl oleate, and Retinyl linoleate. The amount of retinol, or a cosmetically acceptable derivative thereof, when present in the composition is from about 0.01 to about 10% or from about 0.1 to about 5% by weight of the composition. The retinols or derivatives may be coupled to the conjugate. Estradiol, estriol, hyaluronic acid, and green tea extract may be incorporated into anti-wrinkle skin cleaning or moisturizing compositions. These formulations may also have ascorbic acid, date palm extract or combinations thereof.

Particulate Material

[0231] Particulate materials, including both organic and inorganic particles, have been included in skin care compositions. See, for example, "Quantification of the Soft-Focus Effect," *Cosmetics & Toiletries*, Vol. 111, July 1996, pp. 57-61, which discloses that one can physically fill in skin lines with a reflective substance such as TiO₂. Compositions within the scope of the present invention may include particulate materials according to methods and materials described in U.S. Pat. No. 4,892,726, issued to Toshiba Silicone Co. Ltd. Compositions including particulate materials such as polymethylsilsequioxane powders in makeup and cosmetic compositions are smooth upon application and impart natural colour. An example of such a particle is Tospearl®, available from Toshiba Silicone Co. Ltd. U.S. Pat. No. 5,223,559 describes the use of a variety of particulate fillers of particle size from 0.5 to 50 µm, particularly from 1 to 15 µm, for blurring skin defects.

[0232] Particulate materials may have a neat primary particle size of from about 2 to about 15 µm, or from about 2 to about 10 µm, or from about 3 to about 7.5 µm. Median particle size can be determined by any suitable method known in the art, such as by using coulter-counter equipment or the ASTM Designation E20-85 "Standard Practice for Particle Size Analysis of Particulate Substances in the Range of 0.2 to 75 Micrometers by Optical Microscopy," ASTM Volume 14.02, 1993, incorporated herein by reference.

[0233] The particulate materials can be inorganic or organic, such as organosilicone, or organosilicone polymers. Particles may be free-flowing, solid, materials. By "solid" is

meant that the particles are not hollow. The void at the centre of hollow particles can have an adverse effect on refractive index and therefore the visual effects of the particles on either skin or the composition.

[0234] A representative commercially available example of a particulate material is Tospearl®145 which has a median particle size of about 4.5 µm. A further representative commercially available example is Orgasol®2002 D NAT COS available from Elf Atochem SA, Paris, France, which is an example of a polyamide organic particulate material. A representative commercially available example of the second particulate material is EA-209® from Kobo which is an ethylene/acrylic acid copolymer having a median particle size of about 10 µm. Other particulate materials that may be used are those made of polymethylsilsesquioxane, referenced above, polyamide, polythene, polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polystyrene, polytetrafluoroethylene (PTFE) and poly(vinylidene chloride). Copolymers derived from monomers of the aforementioned materials can also be used. Inorganic materials include silica and boron nitride.

[0235] The compositions of the present invention may comprise one or more particulate materials in a concentration of from about 0.5% to about 25%, or from about 1% to about 20%, or from about 2% to about 12%.

Other Additives

[0236] The composition can also contain adjuncts conventionally used in skin-treating compositions other than those already mentioned, depending on the form of the intended product. It is, for example, possible to include antiseptics, preservatives, and coloring agents, which can improve the stability and consumer appeal of the composition. Examples of other materials include anti-microbials including bactericides and fungicides, acne medication, and wart removers including salicylic acid. Agents known in the art for treatments of conditions such as blisters, insect bites, diaper rash and canker sores may be included; these may include local anesthetics, emollients, and other known materials.

pH-Adjusting Agents

[0237] The use of one or more pH-adjusting agents, including minor amounts of mineral acids, basic compositions, and organic acids may be used. An exemplary composition includes citric acid, such as is available in an anhydrous salt form of an alkali metal citric acid. The addition of an effective amount of such a pH-adjusting agent is useful in establishing a targeted pH range for compositions according to the invention. The addition of an effective amount of a pH buffering composition so as to maintain the pH of the inventive compositions may also be added. The pH of the final composition is about 4 to about 8, or about 5 to about 7.

[0238] Examples of such useful pH buffer compounds and/or pH buffering systems or compositions are alkali metal phosphates, polyphosphates, pyrophosphates, triphosphates, tetraphosphates, silicates, metasilicates, polysilicates, carbonates, hydroxides, and mixtures of the same. Certain salts, such as the alkaline earth phosphates, carbonates, hydroxides, can also function as buffers. It may also be suitable to use as buffers such materials as aluminosilicates (zeolites), borates, aluminates and certain organic materials such as gluconates, succinates, malates, citrates, and their alkali metal salts. Such buffers keep the pH ranges of the compositions of the present invention within acceptable limits. Others, not particularly elucidated here may also be used. Citric acid, such as is available in an anhydrous salt form of an alkali

metal citric acid may be added as it is readily commercially available, and effective. The addition of such a buffering agent is desirable in certain cases wherein long term, i.e., prolonged storage, is to be anticipated for a composition, as well as insuring the safe handling of the aqueous composition.

Preservatives

[0239] Suitable traditional preservatives for compositions of this invention are alkyl esters of parahydroxybenzoic acid. Other preservatives that have more recently come into use include hydantoin derivatives such as 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin, propionate salts, and a variety of quaternary ammonium compounds such as benzalkonium chloride, quaternium 15 (Dowicil 200), benzethonium chloride, and methylbenzethonium chloride. Cosmetic chemists are familiar with appropriate preservatives and routinely choose them to satisfy the preservative challenge test and to provide product stability. Disodium EDTA, phenoxyethanol, methyl paraben, propyl paraben, imidazolidinyl urea (commercially available as Germall 1157), sodium dehydroacetate or benzyl alcohol may be used with the present invention. The preservatives should be selected having regard for the use of the composition and possible incompatibilities between the preservatives and other ingredients in the emulsion. Preservatives are employed in amounts ranging from about 0% to about 5%, or from about 0.01% to about 2.5%, or from about 0.01% to about 1%, by weight of the composition.

Water

[0240] Where necessary, the compositions further include water sufficient to provide the remaining weight of the composition. Deionized or distilled water may be employed.

Additional Active Agents that May be Used with the Present Invention

Ingredients that Alleviate Psoriasis

[0241] The present invention may also include active agents that alleviate psoriasis. Such agents should be those that are acceptable for topical application. These agents are known to those of skill in the art. Examples of antipsoriatic agents include, but are not limited to, corticosteroids (e.g., betamethasone dipropionate, betamethasone valerate, clobetasol propionate, diflorasone diacetate, halobetasol propionate, triamcinonide, dexamethasone, fluocinonide, fluocinolone acetonide, halcinonide, triamcinolone acetate, hydrocortisone, hydrocortisone verlate, hydrocortisone butyrate, aclometasone dipropionate, flurandrenolide, mometasone furoate, and methylprednisolone acetate), methotrexate, cyclosporine, calcipotriene, anthralin, shale oil, elubiol, ketoconazole, coal tar, salicylic acid, zinc pyrithione, selenium sulfide, hydrocortisone, sulfur, menthol, and pramoxine hydrochloride, and combinations thereof. In one embodiment, the compositions of the present invention include an anti-viral agent. Examples of anti-viral agents include, but are not limited to, imiquimod, podofilox, podophyllin, interferon alpha, acyclovir, famcyclovir, valacyclovir, reticulos and cidofovir.

Antimicrobial Agents

[0242] In one embodiment, the compositions of the present invention include an antimicrobial agent. "Antimicrobial agent" as used herein is a compound that kills microorganisms or prevents or inhibits their growth or reproduction.

Examples of antimicrobial agents include, but are not limited to ethanol, propanol, betains, benzalkonium chloride, benzethonium chloride, lauric arginate, sugarquat, methyl benzethonium chloride, cetylpyridinium chloride, 2,4,4'-trichloro-2-hydroxydiphenyl ether (Triclosan), parachlorometa xlenol (PCMX), iodopropynyl butylcarbamate, diazolidinyl urea, chlorhexidine digluconate, chlorhexidine acetate, chlorhexidine isethionate, chlorhexidine hydrochloride, hexetidine, Quaternium 15, triclocarban, polyhexamethylene biguanide, cetylpyridium chloride, imidazolidinyl urea, diazolidinyl urea, 3-iodo-2-propynyl-N-butylcarbamate, 2-methyl-4-isothiazolin-3-one, dimethyl dimethyl hydantoin(5-chloro-2-(2,4-dichlorophenoxy)phenol, monolaurin glyceryl laurate, *camellia sinensis*, *candida bombi-cola*/glucose/methyl rapeseedate ferment, hydrogen peroxide, phenol, poloxamer 188, PVP-iodine, thiourea, natural antimicrobial agents, such as cinnamon oil, cinnamaldehyde, lemongrass oil, clove oil, saw palmetto extract, thyme oil white, thyme oil red, thymol, tea tree oil, *pinus pinaster* bark extract, rosemary leaf extract, grape seed extract, and betel oil, silver containing compounds, such as silver nitrate, silver lactate, silver citrate, and silver zeolite, antimicrobial fatty acid ester of a polyhydric alcohol, a fatty ether of a polyhydric alcohol and alkoxylated derivatives thereof, and combinations thereof.

[0243] Bactericidal agents used in the present invention may include enzymatic enzymes. These may include any member from the class of oxido-reductases, EC 1 that generate active oxygen; Monosaccharide oxidases, Peroxidases, Lactoperoxidases, Salivary peroxidases, Myeloperoxidases, Phenol oxidase, Cytochrome oxidase, Dioxygenases, Monooxygenases. The enzymes also include bacterial cell lytic enzymes, e.g., Lysozyme, Lactoferrin. Other agents include antimicrobials e.g., chlorhexidine, amine fluoride compounds, fluoride ions, hypochlorite, quaternary ammonium compounds e.g. cetylpyridinium chloride, hydrogen peroxide, monochloramine, povidone iodine, any recognized sanitizing agent or oxidative agent and biocides.

[0244] Compositions of the present invention may also include antibiotics including, but not limited to the following classes and members within a class: Aminoglycosides: Gentamicin, Tobramycin, Netilmicin, Amikacin, Kanamycin, Streptomycin, Neomycin; Quinolones/Fluoroquinolones: Nalidixic Acid, Cinoxacin, Norfloxacin, Ciprofloxacin, Perfloracin, Ofloxacin, Enoxacin, Fleroxacin, Levofloxacin; Antipseudomonal: Carbenicillin, Carbenicillin Indanyl, Ticarcillin, Azlocillin, Mezlocillin, Piperacillin; Cephalosporins: Cephalothin, Cephaprin, Cephalexin, Cephadrine, Cefadroxil, Cefazolin, Cefamandole, Cefoxitin, Cefaclor, Cefuroxime, Cefotetan, Ceforanide, Cefuroxime Axetil, Cefonicid, Cefotaxime, Moxalactam, Cefizoxime, Ceftriaxone, Cefoperazone, Cftazidime, Cephaloridine, Cefsulodin; Other beta-Lactam Antibiotics: Imipenem, Aztreonam; beta-Lactamase Inhibitors: Clavulanic Acid, Augmentin, Sulbactam; Sulfonamides: Sulfanilamide, Sulfamethoxazole, Sulfacetamide, Sulfadiazine, Sulfisoxazole, Sulfacytine, Sulfadoxine, Mafenide, p-Aminobenzoic Acid, Trimethoprim-Sulfamethoxazole; Urinary Tract Antiseptics Methenamine, Nitrofurantoin, Phenazopyridine and other naphthyridines; Penicillins: Penicillin G and Penicillin V; Penicillinase Resistant: Methicillin, Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin; Penicillins for Gram-Negative/Amino Penicillins: Ampicillin (Polymycin), Amoxicillin, Cyclacillin, Bacampicillin; Tetracyclines: Tetracycline,

Chlortetracycline, Demeclocycline, Methacycline, Doxycycline, Minocycline; Other Antibiotics Chloramphenicol (Chlormycetin), Erythromycin, Lincomycin, Clindamycin, Spectinomycin, Polymyxin B (Colistin), Vancomycin, Bacitracin; Tuberculosis Drugs: Isoniazid, Rifampin, Ethambutol, Pyrazinamide, Ethionamide, Aminosalicic Acid, Cycloserine; Anti-Fungal Agents: Amphoterin B, Cyclosporine, Flucytosine; Imidazoles and Triazoles: Ketoconazole, Miconazole, Itraconazole, Fluconazole, Griseofulvin; Topical Anti Fungal Agents: Clotrimazole, Econazole, Miconazole, Terconazole, Butoconazole, Oxiconazole, Sulconazole, Ciclopirox Olamine, Haloprogin, Tolnaftate, Naftifine, Polyene, Amphoterin B, Natamycin

[0245] In one embodiment, the amount of antimicrobial agent in the compositions is from about 0.001% to about 10%, such as from about 0.01% to about 5%, such as from about 0.05% to about 2% by weight, based on the total weight of the composition.

[0246] In one embodiment the antimicrobial agent is an anti-fungal agent such as an azole. Examples include, but are not limited to, miconazole, ketoconazole, econazole, itraconazole, sertaconazole, fluconazole, voriconazole, clioquinol, bifoconazole, terconazole, butoconazole, tioconazole, oxiconazole, sulconazole, saperconazole, clotrimazole, undecylenic acid, haloprogin, butenafine, tolnaftate, nystatin, ciclopirox olamine, terbinafine, amorolfine, naftifine, clubiol, griseofulvin, their cosmetically acceptable salts, and combinations thereof. In one embodiment the antimicrobial agent is an antibiotic or an antiseptic. Examples include, but are not limited to, mupirocin, neomycin sulfate bacitracin, polymyxin B, 1-ofloxacin, tetracyclines such as chlortetracycline hydrochloride, oxytetracycline-10 hydrochloride and tetracycline hydrochloride, clindamycin phosphate, gentamicin sulfate, metronidazole, hexylresorcinol, methylbenzethonium chloride, phenol, quaternary ammonium compounds, tea tree oil, and combinations thereof.

Anti-Inflammatory Agents

[0247] In another embodiment, the compositions of the present invention may include an anti-inflammatory agent. A safe and effective amount of an anti-inflammatory agent may be added to the compositions of the subject invention, from about 0.1% to about 5%, or from about 0.1% to about 2%, of the composition. The anti-inflammatory agent enhances the skin appearance benefits of the present invention, e.g., such agents contribute to a more uniform and acceptable skin tone or colour. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

[0248] Anti-inflammatory agents useful herein include steroids such as hydrocortisone; panthenol and ether and ester derivatives thereof e.g. panthenol ethyl ether, panthenyl triacetate; pantothenic acid and salt and ester derivatives thereof, such as calcium pantothenate; aloe vera, bisabolol, allantoin and compounds of the liquorice (the plant genus/species *Glycyrrhiza glabra*) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof e.g. salts such as ammonium glycyrrhizinate and esters such as stearyl glycyrrhetinate. Suitable levels may be from about 0.1 to about 5%, or from about 0.5 to about 3%. Additional anti-inflammatory agents include, but are not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone alphas methyl dexamethasone, dexamethasone-phosphate, beclomethasone

dipropionate, clobetasol valerate, desonide, desoxymethasone, deoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, diflucortolone valerate, fludrenolone, flucarlone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylester, fluocortolone, fluprednidene (fluprednylidene)acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenalone acetonide, medrysone, am-ciafel, amcinafide, betamethasone, chlorprednisone, chlorprednisone acetate, clocortolone, clescinolone, dichlorisone, difluprednate, fluclozinide, flunisolide, fluorometholone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, betamethasone dipropionate, and triamcinolone, and combinations thereof.

[0249] Other active agents that may be incorporated into embodiments of the present invention include, but are not limited to, wound healing enhancing agents such as calcium alginate, collagen, recombinant human platelet-derived growth factor (PDGF) and other growth factors, ketanserin, iloprost, prostaglandin E1 and hyaluronic acid; scar reducing agents such as mannose-6-phosphate; analgesic agents; debriding agents such as papain, and enzymatic debriding agents; and anesthetics such as lidocaine and benzocaine. In one embodiment, the composition comprises one or more of menthol, camphor, an antihistamine, or a local anesthetic such as tetracaine, lidocaine, prilocaine, benzocaine, bupivacaine, mepivacaine, dibucaine, etidocaine, butacaine, cyclomethycaine, hexylcaine, proparacaine, and lopivacaine, capsaicin, or oatmeal.

[0250] In one embodiment, the amount of anti-inflammatory agent, anti-viral agent, anti-psoriatic agent and/or other active agent in the compositions is from about 0.001% to about 10%, such as from about 0.01% to about 5% such as from about 0.05% to about 2% by weight, based on the total weight of the composition.

Preparation of Compositions

[0251] The compositions of the present invention are generally prepared by conventional methods such as are known in the art of making topical compositions. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like.

Methods for Regulating Skin Condition

[0252] The compositions of the present invention are useful for regulating mammalian skin condition, for example human skin, including the face, scalp, and hands or other non-facial parts of the body, including regulating visible and/or tactile discontinuities in skin, e.g., visible and/or tactile discontinuities in skin texture, such as discontinuities associated with skin ageing. Regulating skin condition involves topically applying to the skin a safe and effective amount of a composition of the present invention. The amount of the composition which is applied, the frequency of application and the

period of use will vary widely depending upon the active levels of a given composition and the level of regulation desired, e.g., in light of the level of skin ageing present in the subject and the rate of further skin ageing.

[0253] A wide range of quantities of the compositions of the present invention can be employed to provide a skin appearance and/or feel benefit. Quantities of the present compositions which are typically applied per application are, in mg composition/cm² skin, from about 0.1 mg/cm² to about 10 mg/cm². A particularly useful application amount is about 2 mg/cm². Typically applications would be on the order of about once per day, however application rates can vary from about once per week up to about three times per day or more.

[0254] The compositions of this invention provide a visible improvement in skin condition essentially immediately following application of the composition to the skin. Such immediate improvement involves coverage or masking of skin imperfections such as textural discontinuities (including those associated with skin ageing, such as enlarged pores), and/or providing a more even skin tone or color.

[0255] The compositions of the invention also provide visible improvements in skin condition following chronic topical application of the composition. "Chronic topical application" and the like involves continued topical application of the composition over an extended period during the subject's lifetime, for a period of at least about one week, or for a period of at least about one month, or for at least about three months, or for at least about six months, or for at least about one year. Chronic regulation of skin condition involves improvement of skin condition following multiple topical applications of the composition to the skin. Typically applications would be on the order of about once per day over such extended periods, however application rates can vary from about once per week up to about three times per day or more.

[0256] Regulating skin condition may be practiced by applying a composition in the form of a skin lotion, cream, cosmetic, or the like which is intended to be left on the skin for an extended period for some aesthetic, prophylactic, therapeutic or other benefit (i.e., a "leave-on" composition). As used herein, "leave-on" compositions exclude rinse-off skin cleansing products. After applying the composition to the skin, the leave-on composition is may be left on the skin for a period of at least about 15 minutes, or at least about 30 minutes, or at least about 1 hour, or for at least several hours, e.g., up to about 12 hours.

EXAMPLES

[0257] The compositions of the present invention are generally prepared by conventional methods such as are known in the art of making topical compositions. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum and the like.

[0258] The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention.



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(54) **METHOD FOR PREVENTING TISSUE
DAMAGE ASSOCIATED WITH IRRIGATION
OF TISSUE WITH AN ANTIMICROBIAL
SOLUTION**

(76) **Inventors:** James Pitzer Gills, Palm Harbor,
FL (US); James Pitzer Gills,
Clearwater Beach, FL (US)

Correspondence Address:
KRAMER & AMADO, P.C.
1725 DUKE STREET, SUITE 240
ALEXANDRIA, VA 22314

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(57) **ABSTRACT**

Methods for preventing tissue damage associated with irrigation of biological tissue with a povidone-iodine solution by irrigating the tissue to be treated with povidone-iodine solutions characterized by a pH of about 6.8 to about 8.0.

METHOD FOR PREVENTING TISSUE DAMAGE ASSOCIATED WITH IRRIGATION OF TISSUE WITH AN ANTIMICROBIAL SOLUTION

BACKGROUND

[0001] Povidone-iodine solutions are used in the medical arts as non-antibiotic antiseptics. The solutions are used both as topical antiseptics and as irrigating antiseptics to be applied prior to and/or following surgery. The surgical applications of povidone-iodine solutions are recommended throughout a diverse range of surgical procedures due to the antiseptic properties of the solutions against a wide spectrum of microbial fauna and the low allergic risk associated with their use. However, povidone-iodine solutions have been linked with tissue damage to the irrigated tissue as well as decreased wound healing. It has been hypothesized that the use of iodine as an antiseptic agent attacks the enzymes of mammalian cells followed by an attack on the cell membranes.

[0002] Various studies have documented the possible tissue damage caused by the application of povidone-iodine solutions. When applied to rabbit knee articular and periaricular connective tissue, povidone-iodine scrub solution was associated with severe gross and histologic damage to articular cartilage, synovia and muscle. In contrast, povidone-iodine prep solution injected directly into the rabbit knee caused minimal gross and histological damage. Other studies have shown that tissue damage caused by povidone-iodine solutions may be concentration specific, where lower concentrations of povidone-iodine solutions have a decreased risk of tissue damage. When applied to rabbit eyes, povidone-iodine solutions induced significant endothelial damage at concentrations of 0.1%. At concentrations of 1%, povidone-iodine solutions caused corneal edema and endothelial cell loss as demonstrated by pachymetry, histopathology, and elevated intraocular pressure.

[0003] Despite the possible tissue damage caused by povidone-iodine solutions, the antiseptic benefits of such solutions promotes their continued use. In particular, povidone-iodine solutions have made a significant contribution to pre- and post-operative ocular surgical prophylaxis, ophthalmia neonatorum prophylaxis and treatment of bacterial conjunctivitis. Varying concentrations of povidone-iodine solutions have been used in the aforementioned methods including 5% solution for before ocular surgery, 1.25% solution after ocular surgery, 2.5% solution at birth and 1.25% solution for some forms of conjunctivitis.

[0004] Of particular importance is the use of povidone-iodine solutions in pre- and post-operative surgical prophylaxis. However, the use of such solutions for pre- and post-operative prophylactic irrigation has resulted in damage to the sensitive tissues of the eye. The tissue damage may present as extreme eye dryness and painful irritation, often arising after surgery. A specific condition characterized by eye dryness is known as Tear Deficiency Syndrome. The diagnosis of a Tear Deficiency Syndrome is made formally by the Schirmer Test. A standard filter strip is hinged in the lateral conjunctival cul-de-sac and the extent of wetting of the strip is measured after five minutes. Less than 3 mm of wetting is considered diagnostic of tear deficiency. Post-operative Tear Deficiency Syndrome is currently treated using temporary therapies such

as artificial tears. However, there is no current preventative method for the long term elimination of post-operative Tear Deficiency Syndrome.

SUMMARY

[0005] In light of the present need for a method preventing tissue damage associated with irrigation of biological tissue with povidone-iodine solutions, a brief summary of various exemplary embodiments is presented. Some simplifications and omission may be made in the following summary, which is intended to highlight and introduce some aspects of the various exemplary embodiments, but not to limit the scope of the methods. Detailed descriptions of various exemplary embodiments adequate to allow those of ordinary skill in the art to make and use the methods follow in later sections.

[0006] Various exemplary embodiments relate to a method for preventing tissue damage associated with irrigation of biological tissue with an antimicrobial solution by irrigating biological tissue with a povidone-iodine solution characterized by a pH of about 6.8-8.0.

[0007] In various exemplary embodiments, the biological tissue is irrigated in preparation for surgery or following surgery. Exemplary embodiments of tissues to be irrigated include, but are not limited to, the following: ophthalmic tissue, mucosal tissue, intestinal tissue, otic tissue, nasal tissue, oral tissue, esophageal tissue, musculoskeletal tissue and/or gynecological tissue. Some exemplary embodiments include methods for treating ocular conjunctivitis caused by bacterial, fungal and/or viral infection.

[0008] Two particular types of methods for preventing tissue damage, especially tissue damage associated with irrigation of ophthalmic tissue include methods of preventing endothelial toxicity and methods for preventing tear deficiency syndrome.

DETAILED DESCRIPTION

[0009] For simplicity and illustrative purposes, the principles are shown by way of examples of compositions and methods described. In the following description, numerous specific details are set forth in order to provide a thorough understanding of the examples. It will be apparent however, to one of ordinary skill in the art, that the examples may be practiced without limitation to these specific details. In other instances, well known methods and compositions are not described in detail so as not to unnecessarily obscure understanding of the examples.

[0010] In various exemplary embodiments, povidone-iodine solutions are used as antiseptic solutions in pre- and post-operative procedures. The terms pre- and post-operative encompass procedures taking place prior to or following an operation or surgery. The povidone-solutions are directly applied to the biological tissue on which the operation or surgery is performed. Particular of the types of biological tissue to be treated include mammalian tissue. In various exemplary embodiments, the mammalian tissue to be treated includes, but is not limited to ophthalmic tissue, endothelial tissue, mucosal tissue, intestinal tissue, otic tissue, nasal tissue, oral tissue, esophageal tissue, muscular tissue, connective tissue, skeletal tissue, epidermal tissue and/or gynecological tissue. Muscular, connective and skeletal tissue may be grouped together under the term musculoskeletal tissue. The term gynecological tissue defines a wide range of tissues

or organs associated with the female reproductive system, including but not limited to vaginal and/or uterine tissue.

[0011] Some exemplary methods for preventing tissue damage associated with application of antimicrobial solutions include treating ocular conjunctivitis with povidone-iodine solutions. The ocular conjunctivitis may be caused by bacterial, fungal and/or viral infection.

[0012] In various exemplary embodiments, the povidone-iodine solutions are neutralized prior to, being applied to the biological tissue. The pH of such solutions is preferably neutralized to having a pH between 6.8 and 8.5. In various exemplary embodiments, the povidone-iodine solutions have a pH of in the range of about 7.0 and 8.0. The term about, as used consistently throughout the specification, means a variation of plus or minus 10%. The method of applying neutralized povidone-iodine solutions is useful for preventing tissue damage when used in all biological tissue types which are able to withstand conventional povidone-iodine solutions without tissue damage.

[0013] The method may further include the use of diluted povidone-iodine solutions. In various embodiments, the povidone-iodine solutions may be diluted from about 1:2 to about 1:1000. Particular exemplary embodiments include dilutions from about 1:10 to 1:500. The particular dilutions when used in the methods for preventing tissue damage may vary according to the type of biological tissue to be treated and the operation or surgical procedure that accompanies the irrigation with antiseptic solutions. In various exemplary embodiments, a higher dilution (i.e. lower concentration) is used for prophylaxis, whereas a lower dilution (i.e. higher concentration) or even an undiluted solution is used for a frank infection or where asepsis is of particular concern.

[0014] Conventional povidone-iodine solutions are commercially available for use in antiseptic irrigations. Such conventional solutions are not neutralized. A brand name of convention povidone-iodine solutions is the brand BETA-DINE® available from Purdue Pharma. BETADINE® Solution is described as 10% povidone-iodine in an aqueous solution having 1% available iodine. The methods for preventing tissue damage associated with irrigation of biological tissue include neutralizing commercially available povidone-iodine solutions.

[0015] In various exemplary embodiments, neutralized povidone-iodine solutions are neutralized with one or more physiologically-tolerated, non-toxic alkaline compounds. Various examples of such compounds include, but are not limited to, sodium hydroxide, potassium hydroxide, sodium bicarbonate, disodium phosphonate and mixtures thereof. In various embodiments the neutralized solutions are mixed with aqueous salt solutions. Commercially available salt solutions include BSS®, available from Alcon Laboratories, Inc. BSS® Sterile Irrigating Solution is a sterile physiological balanced salt solution, each mL, containing Sodium Chloride (NaCl) 0.64%, Potassium Chloride (KCl) 0.075%, Calcium Chloride Dihydrate ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$) 0.048%, Magnesium Chloride Hexahydrate ($\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$) 0.03%, Sodium Acetate Trihydrate ($\text{C}_2\text{H}_3\text{NaO}_2 \cdot 3\text{H}_2\text{O}$) 0.39%, Sodium Citrate Dihydrate ($\text{C}_6\text{H}_5\text{Na}_3\text{O}_7 \cdot 2\text{H}_2\text{O}$) 0.17%, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH), and Water.

[0016] An exemplary embodiment of a neutralized povidone-iodine solution includes 10 cc povidone-iodine (10% in aqueous solution); 7 cc sodium bicarbonate and 3 cc BSS®.

In various exemplary embodiments, the concentration of povidone-iodine solution ranges from about 0.5% to about 5% povidone-iodine.

[0017] In various exemplary embodiments, a method for preventing tissue damage associated with the irrigation of biological tissue with an antimicrobial solution includes irrigating ophthalmic tissue with a povidone-iodine solution characterized by a pH of about 6.8-8.0. The ophthalmic tissue is irrigated with the neutralized povidone-iodine solution prior to or following ophthalmic surgery.

[0018] The term ophthalmic surgery includes, but is not limited, to any surgery on or around the eye, including, but not limited to cataract surgery, glaucoma surgery, retina surgery, and corrective vision surgery, ICL, CLEAR, and LASIK. In various exemplary embodiments, the purpose of the irrigation is to provide asepsis prior to intraocular or extraocular procedures. In various exemplary embodiments, the method of irrigating ophthalmic tissue with neutralized povidone-iodine solutions prevents tissue damage, particularly toxicity. In various embodiments, the method of irrigating ophthalmic tissue with neutralized povidone-iodine solutions prevents tissue damage which presents as tear deficiency syndrome.

[0019] During an exemplary survey of surgical patients from a clinical practice, use of conventional povidone-iodine solutions resulted in an over 40% incidence of tear deficiency syndrome in post-operative cataract patients. Using the method for preventing tissue damage by pre-and/or post-operative irrigation with a povidone-iodine characterized by a pH of about 6.8-8.0 eliminated the incidence of post-operative tear deficiency syndrome in all cataract patients.

What is claimed is:

1. A method for preventing tissue damage associated with irrigation of biological tissue with an antimicrobial solution, comprising:

irrigating biological tissue to be irrigated with an antimicrobial irrigation solution;

wherein the antimicrobial irrigation solution comprises a povidone-iodine solution; and

wherein the povidone-iodine solution is characterized by a pH of about 6.8-8.0.

2. The method of claim 1 wherein the biological tissue is irrigated in preparation for surgery.

3. The method of claim 1, wherein the biological tissue is irrigated after surgery.

4. The method of claim 1, wherein the biological tissue to be irrigated is ophthalmic tissue.

5. The method of claim 4, wherein the ophthalmic tissue is irrigated before or after ophthalmic surgery is performed on the tissue.

6. The method of claim 5, further comprising preventing endothelial toxicity.

7. The method of claim 5, further comprising preventing Tear Deficiency Syndrome.

8. The method of claim 1, wherein the biological tissue is mucosal tissue.

9. The method of claim 1, wherein the biological tissue is intestinal tissue.

10. The method of claim 1, wherein the biological tissue is otic tissue.

11. The method of claim 1, wherein the biological tissue is nasal tissue.

12. The method of claim 1, wherein the biological tissue is oral tissue.

13. The method of claim 1, wherein the biological tissue is esophageal tissue.

14. The method of claim 1, wherein the biological tissue is musculoskeletal tissue.

15. The method of claim 1, wherein the biological tissue is gynecological tissue.

16. A method for preventing endothelial toxicity associated with irrigation of biological tissue with an antimicrobial solution, comprising:

irrigating endothelial tissue to be irrigated with an antimicrobial irrigation solution;

wherein the antimicrobial irrigation solution comprises a povidone-iodine solution; and

wherein the povidone-iodine solution is characterized by a pH of about 6.8-8.0.

17. The method of claim 16, wherein the endothelial tissue is irrigated prior to surgery.

18. The method of claim 17, wherein the endothelial tissue is ophthalmic tissue.

19. A method for preventing post-operative Tear Deficiency Syndrome, comprising:

irrigating ophthalmic tissue to be irrigated with an antimicrobial irrigation solution prior to or following ophthalmic surgery on a patient;

wherein the antimicrobial irrigation solution comprises a povidone-iodine solution;

wherein the povidone-iodine solution is characterized by a pH of about 6.8-8.0; and

wherein the patient does not suffer from Tear Deficiency Syndrome following the ophthalmic surgery.

20. The method of claim 19, wherein the ophthalmic surgery is cataract surgery.

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