A composition and method are provided for alleviating the dermatological signs of intrinsic and extrinsic aging. A topical formulation containing a cosmeceutically active base, wherein the formulation has a pH in the range of about 7.5 to 13.0, is applied to the skin in order to prevent or treat aging-related skin conditions such as wrinkles, dry skin, age spots, sun damage (particularly UV radiation-induced oxidative stress), blemishes, hyperpigmented skin, age spots, increased skin thickness, loss of skin elasticity and collagen content, dry skin, lentigines and melasmas. The cosmeceutically active base is either a hydroxide-releasing agent, such as an inorganic hydroxide, an inorganic oxide, or a metal salt of a weak acid, or is an organic base, particularly a nitrogenous base.
METHOD AND TOPICAL FORMULATION FOR TREATING SKIN CONDITIONS ASSOCIATED WITH AGING

TECHNICAL FIELD

[0001] This application relates to compositions and methods for alleviating the dermatological signs of aging, including changes or damage to skin associated with intrinsic aging, as well as changes or damage caused by extrinsic factors such as sunlight, radiation, air pollution, wind, cold, heat, dampness, chemicals and cigarette smoking.

BACKGROUND

[0002] Human skin is a structurally complex, relatively thick membrane comprised of two principal components, the outer epidermis and the underlying dermis, which is situated above the subcutaneous adipose or fat tissues.

[0003] The epidermis consists of four distinct layers: stratum corneum, stratum granulosum, stratum spinosum and stratum basale; in the skin of palms and soles only, there is normally one additional zone called the stratum lucidum between the stratum corneum and the stratum granulosum.

[0004] The dermis is comprised mainly of collagen, elastic fibers, glycosaminoglycans and proteoglycans including hyaluronic acid, dermman sulfate and chondroitin sulfate formerly known as mucopolysaccharides. Fibroblasts, the predominant cells of the dermis, synthesize collagen, elastic fibers, proteoglycans and glycosaminoglycans. Collagen makes up approximately 77%, elastic fibers account for about 2%, and glycosaminoglycans constitute around 0.2% of the dry weight of the dermis. Collagen provides the tensile strength and of elastic fibers give resilience to the dermis. The glycosaminoglycans bind water to form a gelatinous mass between collagen and elastic fibers, which acts as a lubricant and shock absorber for the dermis during movement of the skin.

[0005] Cutaneous aging, while having epidermal concomitants, primarily involves dermal and subcutaneous changes, and is caused by (a) internal factors alone, as in intrinsic aging and (b) external factors, as in extrinsic aging. Intrinsic and extrinsic aging is also known as natural or chronologic aging, and extrinsic aging is often called photoaging. "Photodamage" implies skin damage caused by chronic sun exposure. These terms may be described as follows.

[0006] Intrinsic aging of skin, in sun-protected skin of the upper arm and abdomen, is an inherent degenerative process due to declining physiologic functions and capacities. Such aging process may include qualitative and quantitative skin changes and includes diminished or defective synthesis of collagen and elastic fibers, and proteoglycans and glycosaminoglycans in the dermis. Signs of intrinsic aging include progressive thinning of skin, deepening of skin lines and fine wrinkles, lustreless skin surface, and loss of skin elasticity and recollability. Although intrinsic aging of living creatures is neither reversible nor preventable, modification and improvement of skin signs associated with such aging process can be achieved through topical management.

[0007] Extrinsic aging of skin is a distinctive process caused by external factors, which include sunlight, radiation, air pollution, wind, cold, dampness, heat and chemicals.

[0008] Photouging of skin may be defined as destructive cutaneous changes caused by chronic exposure to sunlight. Signs of photoaging on the face and back of hands include coarse and deepened wrinkles due to changes and degeneration of collagen and elastic fibers; marked loss of elasticity and recollability; leathery skin surface and skin lesions with abnormal pigmentation and increased numbers of age spots, pigmented spots, blotsches and nodules. Histologically, the qualities and quantities of elastin and collagen tissues are changed. Normal elastin in tissues is replaced by abnormal elastin characterized as solar elastosis, and the normal collagen fibers are decreased.

[0009] Photodamage of skin, also called solar damage, may be defined as cutaneous damage caused by chronic exposure to solar radiation and is associated with development of neoplastic lesions. Skin disorders caused by photodamage include pre-malignant lesions, basal cell carcino

SUMMARY OF THE INVENTION

[0011] It is thus a primary object of the invention address the above-discussed needs in the art by providing a novel method of treating an aging-related skin condition.

[0012] It is another object of the invention to provide such a method wherein the aging-related skin condition is treated by topical application of a formulation containing a cosmeceutically active base, a surprisingly effective yet simple means for treating aging-related skin conditions. To the best of applicants' knowledge, the use of cosmeceutically active bases as disclosed herein has not been suggested in the art and represents a significant and unexpected advance in the art.

[0013] It is a further object of the invention to provide such a method wherein the cosmeceutically acceptable base is an organic base, particularly a nitrogenous base.
It is still a further object of the invention to provide a topical formulation for carrying out the aforementioned methods, the formulation containing a cosmeceutically active agent consisting essentially of a cosmeceutically acceptable base at a concentration sufficient to provide a formulation pH in the range of approximately 7.5 to 13.0, preferably about 8.0 to 11.5, most preferably about 8.5 to about 11.0.

It is an additional object of the invention to provide such a formulation, wherein the formulation further contains at least one cosmeceutically acceptable excipient and/or at least one cosmeceutically acceptable carrier.

Additional objects, advantages and novel features of the invention will be set forth in the description that follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions And Nomenclature:

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular drugs or drug delivery systems, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, “a cosmeceutically active base” refers not only to a single such base but also to a mixture of two or more cosmeceutically active bases, reference to “a vehicle” or “a carrier” includes a single vehicle or a single carrier as well as mixtures of two or more vehicles or carriers, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms “treating” and “treatment” as used herein refer to reduction in severity and/or elimination of skin related conditions resulting from intrinsic and/or extrinsic aging processes of the skin. The present method of “treating” a skin condition related to aging, as the term is used herein, refers to the prevention of aging-related skin conditions as well as the treatment of aging-related skin conditions in affected individuals.

The term “aging-related skin condition” relates to any skin condition or disorder associated with, caused by, or affected by, intrinsic aging and/or extrinsic aging. Aging-related skin conditions that may be treated using the present methods and formulations include, but are not limited to, wrinkles, age spots, sun damage (particularly UV radiation-induced oxidative stress), blemishes, hyperpigmented skin, age spots, increased skin thickness, loss of skin elasticity and collagen content, dry skin, lentigines and melasmas.

By “cosmeceutically effective” is meant a nontoxic agent that has medicinal or drug-like properties which, when applied to the surface of skin, beneficially affects the biological functioning of that skin.

The terms “cosmeceutically active agent” and “cosmeceutically active base” are used interchangeably herein to refer to a cosmeceutically effective basic compound or composition of matter which, when topically administered to a human patient, is effective to treat one or more aging-related skin conditions as defined above. Also included are derivatives and analogs of those compounds or classes of compounds specifically mentioned that also induce the desired effect, i.e., treatment of an aging-related skin condition.

By “cosmeceutically acceptable,” such as in the recitation of a “cosmeceutically acceptable carrier,” or a “cosmeceutically acceptable derivative,” is meant a compound that is not biologically or otherwise undesirable, i.e., the compound may be incorporated into a cosmeceutical formulation of the invention and topically administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the cosmeceutical formulation in which it is contained.

The term “hydroxide-releasing agent” as used herein is intended to mean an agent that releases free hydroxide ions in an aqueous environment. The agent may contain hydroxide ions and thus release the ions directly (e.g., an alkali metal hydroxide), or the agent may be one that is acted upon chemically in an aqueous environment to generate hydroxide ions (e.g., a metal carbonate).

The terms “drug” and “pharmacologically active agent” are used interchangeably herein to refer to a chemical material or compound that induces a desired pharmacological effect when administered topically, and include agents that are therapeutically effective, prophylactically effective, or cosmeceutically effective. Also included are derivatives and analogs of those compounds or classes of compounds specifically mentioned that also induce the desired pharmacological effect. Topical pharmacologically active agents are optionally incorporated into the present cosmeceutical formulations. By “therapeutically effective” amount is meant a nontoxic but sufficient amount of a pharmacologically active agent to provide the desired therapeutic effect.

The term “topical administration” is used in its conventional sense to mean topical application of a formulation to the skin.

“Carriers” or “vehicles” as used herein refer to carrier materials suitable for incorporation in a topically applied composition. Carriers and vehicles useful herein include any such materials known in the art, which are nontoxic and do not interact with other components of the formulation in which it is contained in a deleterious manner.

The term “aqueous” refers to a formulation that contains water or that becomes water-containing following application to the skin or mucosal tissue.

In describing molecular structures and formulae herein, the phrase “having the formula” or “having the structure” is not intended to be limiting and is used in the same way that the term “comprising” is commonly used.

The term “alkyl” as used herein refers to a branched or unbranched saturated hydrocarbon group typically although not necessarily containing 1 to about 24 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl,
n-butyl, isobutyl, t-butyl, octyl, decyl, and the like, as well as cycloalkyl groups such as cyclopropyl, cyclohexyl and the like. Generally, although again not necessarily, alkyl groups herein contain 1 to about 12 carbon atoms. The term "lower alkyl" intends an alkyl group of one to six carbon atoms, preferably one to four carbon atoms. "Substituted alkyl" refers to alkyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkyl" and "heteroalkyl" refer to alkyl in which at least one carbon atom is replaced with a heteroatom. If not otherwise indicated, the terms "alkyl" and "lower alkyl" include linear, branched, cyclic, unsubstituted, substituted, and/or heteroatom-containing alkyl or lower alkyl.

[0035] The term "alkenyl" as used herein refers to a branched or unbranched hydrocarbon group typically although not necessarily containing 2 to about 24 carbon atoms and at least one double bond, such as ethenyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, octenyl, decenyl, and the like. Generally, although again not necessarily, alkenyl groups herein contain 2 to about 12 carbon atoms. The term "lower alkenyl" intends an alkenyl group of two to six carbon atoms, preferably two to four carbon atoms. "Substituted alkenyl" refers to alkenyl substituted with one or more substituent groups, and the terms "heteroatom-containing alkenyl" and "heteroalkenyl" refer to alkenyl in which at least one carbon atom is replaced with a heteroatom.

[0036] The term "aryl" as used herein, and unless otherwise specified, refers to an aromatic substituent containing a single aromatic ring or multiple aromatic rings that are fused together, linked covalently, or linked to a common group such as a methylene or ethylene moiety. The common linking group may also be a carbonyl as in benzophenone, an oxygen atom as in diphenylether, or a nitrogen atom as in diphenylamine. Preferred aryl groups contain one aromatic ring and are referred to as "monocyclic aryl." "Substituted aryl" refers to an aryl moiety substituted with one or more substituent groups, and the terms "heteroatom-containing aryl" and "heteroaryl" refer to aryl in which at least one carbon atom is replaced with a heteroatom.

[0037] The term "heteroatom-containing" as in a "heteroatom-containing hydrocarbyl group" refers to a molecule or molecular fragment in which one or more carbon atoms is replaced with an atom other than carbon, e.g., nitrogen, oxygen, sulfur, phosphorus or silicon. Similarly, the term "heterocyclic" refers to an alkenyl substituent that is heteroatom-containing, the term "heterocyclic" refers to a cyclic substituent that is heteroatom-containing, the term "heteroaryl" refers to an aryl substituent that is heteroatom-containing, and the like. When the term "heteroatom-containing" appears prior to a list of possible heteroatom-containing groups, it is intended that the term apply to every member of that group. That is, the phrase "heteroatom-containing alkyl, alkenyl and alkynyl" is to be interpreted as "heteroatom-containing alkyl, heteroatom-containing alkenyl and heteroatom-containing alkynyl."

[0038] By "substituted" as in "substituted alkyl," "substituted alkenyl," "substituted aryl," and the like, as alluded to in some of the aforementioned definitions, is meant that in the alkyl, alkenyl, aryl, or other moiety, at least one hydrogen atom bound to a carbon atom is replaced with one or more substituents that are functional groups such as hydroxyl, alkoxy, thio, amino, halo, and the like.

[0039] The terms "alkyl," "alkenyl," "aryl," and the like are, unless otherwise indicated, intended to include unsubstituted, substituted, heteroatom-containing and substituted heteroatom-containing such substituents.

II. Topical Formulations:

[0041] Any cosmeceutically active base and carrier material may be used at a concentration sufficient to provide a formulation pH in the range of approximately 7.5 to 13.0, preferably about 8.0 to 11.5, most preferably about 8.5 to 11.0, to produce a cream, lotion, solution, spray, gel, ointment, paste or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres, for use in a method of treating an aging-related skin condition.

[0042] A. Cosmeceutically Active Bases:

[0043] In accordance with the invention described herein, the synthetic or naturally occurring suitable bases may be classified into two groups, namely (I) hydroxide-releasing agents and (II) nitrogenous organic bases.

[0044] "Hydroxide-releasing agents" are a chemical compounds that release free hydroxide ions in the presence of an aqueous fluid. The aqueous fluid may be natural moisture at the skin surface, or the composition used may contain added water. Similarly, any liquid or semisolid formulation that is used is preferably aqueous or used in conjunction with. For those formulations in which the pharmacologically active base is a hydroxide-releasing agent, it is preferred although not essential that water be present. Thus, such a formulation may be aqueous, i.e., contain water, or may be nonaqueous and optionally used in combination with an occlusive overlay so that moisture evaporating from the body surface is maintained within the formulation upon application to the body surface and thereafter.

[0045] Any hydroxide-releasing agent may be used provided that the compound releases free hydroxide ions in the presence of an aqueous fluid. Hydroxide-releasing agents herein that are suitable cosmeceutically active bases for use in conjunction with the method and formulation of the invention include, but are not limited to, inorganic hydroxides, inorganic oxides, and alkali metal or alkaline earth metal salts of weak acids. Inorganic hydroxides include, for example, ammonium hydroxide, alkali metal hydroxide and alkaline earth metal hydroxides, such as sodium hydroxide, calcium hydroxide, potassium hydroxide, magnesium hydroxide, and the like. Inorganic oxides include, for example, magnesium oxide, calcium oxide, and the like. Metal salts of weak acids include, for example, sodium acetate, sodium borate, sodium carbonate, sodium bicarbonate, sodium phosphate (tribasic), sodium phosphate (dibasic), potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, potassium phosphate (dibasic), potassium phosphate (tribasic), ammonium phosphate (dibasic), and the like. Preferred hydroxide-releasing agents are metal hydroxides such as sodium hydroxide and potassium hydroxide.

[0046] It is important that the amount of hydroxide-releasing agent is effective to provide a pH at the body surface in contact with a formulation of the invention (i.e., the interface between the body surface and the formulation) in the range of approximately 7.5 to 13.0, preferably 8.0 to 11.5, most preferably about 8.5 to 11.0. This will typically although not necessarily mean that the pH of the cosmeceutical formu-
lation per se will be in the range of approximately 7.5 to 13.0, preferably 8.0 to 11.5, most preferably about 8.5 to 11.0.

[0047] In general, the amount of a metal hydroxide in the formulation will be the total of (a) the amount required to neutralize any acidic species in the formulation plus (b) an amount equal to approximately 0.5 wt. % to 4.0 wt. %, preferably about 0.5 wt. % to 3.0 wt. %, more preferably about 0.75 wt. % to 2.0 wt. % and optimally about 1.0 wt. %, of the formulation. For other hydroxide-releasing agents such as inorganic oxides and metal salts of weak acids, the amount of hydroxide-releasing agent in the formulation or patch may be substantially higher, as high as 20 wt. %, in some cases as high as 25 wt. % or higher, but will generally be in the range of approximately 2 wt. % to 20 wt. %.

[0048] Still greater amounts of hydroxide-releasing agent may be used by controlling the rate and/or quantity of release of the hydroxide-releasing agent, preferably during the drug delivery period itself.

[0049] The cosmeceutically active base is not necessarily one that releases hydroxide ions in the presence of water. Other bases can also be used. Organic bases, particularly nitrogenous bases, represent another class of cosmeceutically active bases useful in the method and formulation of the invention. Such bases are generally selected from primary amines, secondary amines, tertiary amines, amidines, oximes, nitrogen-containing heterocycles, and urea.

[0050] Suitable nitrogenous bases may contain any one or a combination of the following:

[0051] primary amino (—NH—) groups;

[0052] mono-substituted (secondary) amino groups —NHR where R is hydrocarboxyl, generally either alkyl or aryl, e.g., lower alkyl or phenyl, and may be substituted with one or more nonhydrocarboxyl substituents, e.g., 1 to 3 halo, hydroxyl, thiol, or lower alkoxo groups (such —NHR groups include, for example, methylamino, ethylamino, isopropylamino, butylamino, cyclopropylamino, cyclohexylamino, N-hexylamino, phenylamino, benzylamino, chloroethylamino, hydroxyethylamino, etc.);

[0053] di-substituted (tertiary) amino groups —NR'R" where R' and R" may be the same or different and are as defined above for R (suitable —NR'R" include, for example, dimethylamino, diethylamino, disopropylamino, dibutylamino, methylpropylamino, methylhexylamino, methylcy clohexylamino, ethylecyclopropylamino, ethylchloroethylamino, methylbenzylamino, methylphenylamino, methyltoluylamino, methyl-p-chlorophenylamino, methylcyclohexylamino, etc.);

[0054] amides —(CO)—NR'R" where R' and R" may be the same or different and are either hydrogen or R, wherein R is as defined above (including, for example, amides wherein one of R' and R" is H and the other is methyl, butyl, benzyl, etc.);

[0055] cyano (—CN);

[0056] aromatic nitrogen-containing heterocycles, typically five- or six-membered monocyclic substituents, or bicyclic fused or linked five- or six-membered rings (such as pyrrolyl, pyrrolidinyl, pyridyl, quinolinyl, indolyl, pyrimidinyl, imidazolyl, 1,2,4-triazolyl, tetrazolyl, etc.); and

[0057] non-aromatic nitrogen-containing heterocycles, typically four- to six-membered rings, including lactams and imides, e.g., pyrrolidine, morpholine, piperazine, pipericidin, N-phenyl-beta-propiolactam, y-butylactam, e-caprolactam, acetimide, phthalamide, succinimide, etc.

[0058] Primary amines, secondary amines, and tertiary amines may be generally grouped as encompassed by the molecular structure NR'R"R" wherein R', R" and R" are selected from H, alkyl, hydroxalkyl, alkoxyalkyl, alkenyl, hydroxalkeny1, alkoxyalkenyl, cycloalkyl, cycloalkyl-substituted alky1, monocyclic aryl, and monocyclic aryl-substituted alkyl, with the proviso that at least one of R', R" and R" is other than H. Examples of such amines include, without limitation, diethanolamine, triethanolamine, isopropanolamine, triisopropanolamine, dibutanol amine, tributanol amine, N-dodecylanethanolamine, N-(2-methoxyethyl) dodecylamine, N-(2,2-dimethoxyethyl)dodecylamine, N-ethyl-N-(dodecyl)ethanolamine, N-ethyl-N-(2-methoxyethyl)dodecylamine, N-ethyl-N(2,2-dimethoxyethyl) dodecylamine, dimethyl(dodecylamine)N-oxide, monoaloxyl lysine, dipalmitoyl lysine, dodecylamine, stearylamine, phe nylethylamine, triethyamine, PEG-2 oleamine, PEG-5 ole amine, dodecyl-(N,N-dimethylaminopropionate), bis(2-hydroxyethyl)oleylamine, and combinations thereof.

[0059] Amides, as will be appreciated by those in the art, have the molecular structure R'-CO—NR'R" where R', R" and R' are generally selected from H, alkyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl. Examples of suitable amides herein include, without limitation, hexamethyleneacetamide, hexamethyleneacetoamide, hexamethylene lauramide, hexamethylene palmitamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N,N-dimethylolactamide, N,N-dimethylolecamide, toluidine, dimethyl-toluidine, diethyl-toluidine, and combinations thereof.

[0060] Nitrogen-containing heterocycles suitable as the pharmacologically active base herein include, by way of example, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 1-propeyl-3-dodecylpyrrolidine, 1-dodecylcycloheptan-2-one, ethylene thiourea, hydantoin, oxalurea, imidazolidyl urea, N-octadecyl morpholine, dodecylepyridine, N-dodecylpyrrolidine, N-dodecylpyrrolidinum, N-dodecylpyrrolidine, and combinations thereof.

[0061] For all cosmeceutically active bases herein, the optimum amount of any particular base will depend on the strength or weakness of the base, the molecular weight of the base, and other factors. One skilled in the art may readily determine the optimum amount of any particular base by ensuring that a formulation is effective to provide a pH at the skin surface, upon application of the formulation, in the range of about 7.5 to about 13.0, preferably about 8.0 to about 11.5, preferably in the range of about 8.5 to about 11.0. This in turn ensures that the degree of treatment is maximized while the possibility of damage to the body surface is eliminated or at least substantially minimized.
B. Formulation Types:

As noted above, the present topical formulations may take any of a wide variety of forms, and include, for example, creams, lotions, solutions, sprays, gels, ointments, pastes or the like, and/or may be prepared so as to contain liposomes, micelles, and/or microspheres.

Creams, as is well known in the art of pharmaceutical formulation, are viscous liquids or semisolid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an emulsifier and an aqueous phase. The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic or amphoteric surfactant.

Lotions, which are preferred for delivery of cosmetic agents, are preparations to be applied to the skin surface without friction, and are typically liquid or semiliquid preparations in which solid particles, including the active agent, are present in a water or alcohol base. Lotions are usually suspensions of solids, and preferably, for the present purpose, comprise a liquid oily emulsion of the oil-in-water type. Lotions are preferred formulations herein for treating large body areas, because of the ease of applying a more fluid composition. It is generally necessary that the insoluble matter in a lotion be finely divided. Lotions will typically contain suspending agents to produce better dispersions as well as compounds useful for localizing and holding the active agent in contact with the skin, e.g., methylcellulose, sodium carboxymethylcellulose, or the like.

Solutions are homogeneous mixtures prepared by dissolving one or more chemical substances (solutes) in a liquid such that the molecules of the dissolved substance are dispersed among those of the solvent. The solution may contain other pharmaceutically acceptable chemicals to buffer, stabilize or preserve the solute. Commonly used examples of solvents used in preparing solutions are ethanol, water, propylene glycol or any other pharmaceutically acceptable vehicles.

As will be appreciated by those working in the field of pharmaceutical formulation, gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the carrier liquid, which is typically aqueous, but also, preferably, contain an alcohol and optionally an oil. Preferred "organic macromolecules," i.e., gelling agents, are crosslinked acrylic acid polymers such as the "carbomer" family of polymers, e.g., carboxypolysylyklenes that may be obtained commercially under the Carbopol® trademark. Also preferred are hydrophilic polymers such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers and polyvinylalcohol; cellulose polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose pthlate, and methyl cellulose; gums such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or gelcine can be added, or the gelling agent can be dispersed by titration, mechanical mixing or stirring, or combinations thereof.

Ointments, as also well known in the art, are semisolid preparations that are typically based on petrolatum or other petroleum derivatives. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and preferably, will provide for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonnonsensitizing. As explained in Remington: The Science and Practice of Pharmacy, 19th Ed. (Easton, Pa.: Mack Publishing Co., 1995), at pages 1399-1404, ointment bases may be grouped in four classes: oelaginous bases; emulsifiable bases; emulsion bases; and water-soluble bases. Oelaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petrolatum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin and stearic acid. Preferred water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy for further information.

Pastes are semisolid dosage forms in which the active agent is suspended in a suitable base. Depending on the nature of the base, pastes are divided between fatty pastes or those made from single-phase gels. The base in a fatty paste is generally petrolatum or hydrophilic petrolatum or the like. The pastes made from single-phase aqueous gels generally incorporate carboxymethylcellulose or the like as a base.

Formulations may also be prepared with liposomes, micelles, and microspheres. Liposomes are microscopic vesicles having a lipid wall comprising a lipid bilayer, and can be used as drug delivery systems herein as well. Generally, liposome formulations are preferred for poorly soluble or insoluble pharmaceutical agents. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. Cationic liposomes are readily available. For example, N[1,2-dioleoyloxypropyl]-N,N-triethylammonium (DOTMA) liposomes are available under the tradename Lipofectin® (GIBCO BRL, Grand Island, N.Y.). Similarly, anionic and neutral liposomes are readily available as well, e.g., from Avanti Polar Lipids (Birmingham, Al.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoyl phosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with DOTMA in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

Micelles are known in the art as comprised of surfactant molecules arranged so that their polar headgroups form an outer spherical shell, while the hydrophobic, hydrocarbon chains are oriented towards the center of the sphere, forming a core. Micelles form in an aqueous solution containing surfactant at a high enough concentration so that micelles naturally result. Surfactants useful for forming...
micelles include, but are not limited to, potassium laurate, sodium octane sulfonate, sodium decane sulfonate, sodium docane sulfonate, sodium lauryl sulfate, docosate sodium, decyltrimethylammonium bromide, docetyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, tetradecyltrimethylammonium chloride, dodecylammonium chloride, polyoxy-8 dodecyl ether, polyoxy-12 dodecyl ether, nonoxynol 10 and nonoxynol 30. Micelle formulations can be used in conjunction with the present invention either by incorporation into the reservoir of a topical or transdermal delivery system, or into a formulation to be applied to the body surface.

[0072] Microspheres, similarly, may be incorporated into the present formulations and drug delivery systems. Like liposomes and micelles, microspheres essentially encapsulate a drug or drug-containing formulation. They are generally although not necessarily formed from lipids, preferably charged lipids such as phospholipids. Preparation of lipidic microspheres is well known in the art and described in the pertinent texts and literature.

[0073] C. Additives:

[0074] Various additives, known to those skilled in the art, may be included in the topical formulations. For example, solvents, including relatively small amounts of alcohol, may be used to solubilize certain formulation components. Although the pharmacologically active bases herein do penetrate into the skin and have in fact been described as skin permeation enhancers, it may be desirable, with weaker bases or particularly severe skin conditions, to include an added permeation enhancer in the formulation. Examples of suitable enhancers include, but are not limited to, ethers such as diethylene glycol monomethyl ether (available commercially as Transcutol®) and diethylene glycol monomethyl ether; surfactants such as sodium laurate, sodium lauryl sulfate, cetlytrimethylammonium bromide, benzalkonium chloride, Poloxamers® (231, 182, 184), Tween® (20, 40, 60, 80) and lecithin (U.S. Pat. No. 4,783,450); alcohols such as ethanol, propanol, octanol, benzyl alcohol, and the like; polyethylene glycol and esters thereof such as polyethylene glycol monolaurate (PEGML; see, e.g., U.S. Pat. No. 5,468,343); amidoxides and other nitrogen compounds such as urea, dimethylacetamide (DMA), dimethylformamide (DMF), 2-pyrollidone, 1-methyl-2-pyrrolidone, ethanolamine, diethanolamine and triethanolamine; terpenes; alkanones; and organic acids, particularly citric acid and succinic acid. Alcone® and sulfonates such as DMSO and C20-80MSO may also be used, but are less preferred.

[0075] Most preferred enhancers are those lipophilic co-enhancers typically referred to as “plasticizing” enhancers, i.e., enhancers that have a molecular weight in the range of about 150 to 1000, an aqueous solubility of less than about 1 wt. %, preferably less than about 0.5 wt. %, and most preferably less than about 0.2 wt. %. The Hildebrand solubility parameter $\delta$ of plasticizing enhancers is in the range of about 2.5 to about 10, preferably in the range of about 5 to about 10. Preferred lipophilic enhancers are fatty esters, fatty alcohols, and fatty ethers. Examples of specific and most preferred fatty acid esters include methyl laurate, ethyl oleate, propylene glycol monolaurate, propylene glycol dilaurate, glycerol monolaurate, glycerol monoleate, isopropyl $n$-decanoate, and octyldodecyl myristate. Fatty alcohols include, for example, stearyl alcohol and oleyl alcohol, while fatty ethers include compounds wherein a diol or triol, preferably a C12-C18 alkane diol or triol, are substituted with one or two fatty ether substituents.

[0076] Additional permeation enhancers will be known to those of ordinary skill in the art of topical drug delivery, and/or are described in the pertinent texts and literature. See, e.g., Percutaneous Penetration Enhancers, eds. Smith et al. (CRC Press, 1995).

[0077] Various other additives may be included in the compositions of the present invention in addition to those identified above. These include, but are not limited to, antioxidants, astringents, perfumes, preservatives, emollients, pigments, dyes, humectants, propellants, and sunscreen agents, as well as other classes of materials whose presence may be cosmetically, medicinally or otherwise desirable. Typical examples of optional additives for inclusion in the formulations of the invention are as follows: preservatives such as sorbate; solvents such as isopropanol and propylene glycol; astringents such as menthol and ethanol; emollients such as polyalkylene glycol; humectants such as glycerine; emulsifiers such as glycerol stearate, PEG-100 stearate, polyglyceryl-3 hydroxysterlyl ether and polysorbate 60; sorbitol and other polyhydroxy alcohols such as polyethylene glycol; sunscreen agents such as octyl methoxycinnamate (available commercially as Parsol MCM) and butyl methoxy dibenzoylmethane (available under the tradename Parsol 1789); antioxidants such as ascorbic acid (vitamin C), $\alpha$-tocopherol (Vitamin E), $\beta$-tocopherol, $\gamma$-tocopherol, $\delta$-tocopherol, $\chi$-tocopherol, $\zeta$-tocopherol, $\eta$-tocopherol, and retinol (vitamin A); essential oils, ceramides, essential fatty acids, mineral oils, vegetable oils (e.g., soya bean oil, palm oil, liquid fraction of shea butter, sunflower oil), animal oils (e.g., perhydrosqualene), synthetic silicas or waxes (e.g., cyclomethicone and dimethicone), fluorinated oils (generally perfluoropolymers), fatty alcohols (e.g., cetyl alcohol), and waxes (e.g., beeswax, carnauba wax and paraffin wax); skin-feel modifiers; and thickeners and structurants such as swelling clays and cross-linked carboxypolyacrylates that may be obtained commercially under the Carbopol® trademark.

[0078] Other additives include beneficial agents such as those materials that condition the skin (particularly, the upper layers of the skin in the stratum corneum) and keep it soft by retarding the decrease of its water content and/or protect the skin. Such conditioners and moisturizing agents include, by way of example, pyrollidine carboxylic acid and amino acids; organic antimicrobial agents such as 2,4,4'-trichloro-2-hydroxy diphenyl ether (triclosan) and benzoic acid; anti-inflammatory agents such as acetylsalicylic acid and glycyrrhetinic acid; anti-seborrhoeic agents such as retinoic acid; vasodilators such as nicotinic acid; inhibitors of melanogenesis such as kojic acid; and mixtures thereof.

[0079] Other embodiments may include a variety of non-carcinogenic, non-irritating healing materials that facilitate treatment with the formulations of the invention. Such healing materials may include nutrients, minerals, vitamins, electrolytes, enzymes, herb extracts, glandular or animal extracts, or safe therapeutic agents that may be added to the formulation to facilitate the healing of dermal disorders.
The amounts of these various additives are those conventionally used in the cosmetics field, and range, for example, from about 0.01% to about 20% of the total weight of the topical formulation.

The formulations of the invention may also include conventional additives such as opacifiers, fragrance, colorant, gelling agents, thickening agents, stabilizers, surfactants and the like. Other agents may also be added, such as antimicrobial agents, to prevent spoilage upon storage, i.e., to inhibit growth of microbes such as yeasts and molds. Suitable antimicrobial agents are typically selected from the group consisting of the methyl and propyl esters of p-hydroxybenzoic acid (i.e., methyl and propyl paraben), sodium benzoate, sorbic acid, imidurea, and combinations thereof.

The formulations may also contain irritation-mitigating additives to minimize or eliminate the possibility of skin irritation or skin damage resulting from the chemical entity to be administered, or other components of the composition. Suitable irritation-mitigating additives include, for example: α-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohol such as 2-phenyl-1-ethanol; glyc erin; salicylates; ascorbates; tonophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; capsaicin; and chloroquine. The irritation-mitigating additive, if present, may be incorporated into the present enhancer compositions at a concentration effective to mitigate irritation or skin damage, typically representing not more than about 20 wt. %, more typically not more than about 5 wt. %, of the formulation.

The formulations of the invention may also contain a therapeutically effective amount of a pharmaceutically active agent suitable for topical administration. Such agents include an asymmetrical lamellar aggregate consisting of phospholipids and oxygen-loaded fluorocarbon or a fluorocarbon compound mixture, which are capable of improving oxygen supply in skin tissue, as described, for example, in International Patent Publication Nos. WO 94/00098 and WO 94/00109.

Suitable pharmaceutically active agents that may be incorporated into the present formulations and thus topically applied along with the cosmeceutically active base include, but are not limited to, the following: agents that improve or eradicate pigmented or non-pigmented age spots, keratoses and wrinkles; antimicrobial agents; antibacterial agents; antipruritic and antidermatoglyphic agents; local anesthetics and analgesics; corticosteroids; retinoids; vitamins; hormones; and antimetabolites.

Some examples of topical pharmacologically active agents include acetylcholine, amphotericin, chlorhexidine, clotrimazole, ketoconazole, econazole, miconazole, metronidazole, minocycline, nystatin, neomycin, kanamycin, phenytoin, para-aminobenzoic acid esters, octyl methoxy cinnamate, octyl salicylate, oxybenzone, dioxybenzone, tocopherol, tocopherol acetate, selenium sulfide, zinc pyrithione, diphenhydramine, pramoxine, lidocaine, procaine, cetylpyridinium, tetracycline, clindamycin, cromatoni, hydroquinone and its monomethyl and benzyl ethers, naproxen, ibuprofen, cromolyn, retinol, retinyl palmitate, retinyl acetate, four ter, griseofulvin, estradiol, hydrocortison e, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, progesterone, betamethasone valerate, betamethasone dipropionate, triamcinolone acetonide, fluocinonide, clobetasol propionate, minoxidil, diprydiamole, diphenhydantoin, benzoyl peroxide, and 5-fluorouracil.

A pharmaceutically acceptable carrier may also be incorporated in the cosmeceutical formulation of the present invention and may be any carrier conventionally used in the art. Examples thereof include water, lower alcohols, higher alcohols, polyhydric alcohols, monosaccharides, disaccharides, polysaccharides, hydrocarbon oils, fats and oils, waxes, fatty acids, silicone oils, nonionic surfactants, ion surfactants, silicone surfactants, and water-based mixtures and emulsion-based mixtures of such carriers.

III. Administration:

The method of delivery of the active agent may vary, but necessarily involves application of a formulation of the invention to an area of body surface prone to or affected by an aging-related skin condition, e.g., any skin condition or disorder associated with, caused by, or affected by, intrinsic aging and/or extrinsic aging. The aging-related skin condition may, for example, involve wrinkles, age spots, sun damage (particularly UV radiation-induced oxidative stress), blemishes, hyperpigmented skin, age spots, increased skin thickening, loss of skin elasticity and collagen content, dry skin, lentigines and melasmas.

A cream, lotion, gel, ointment, paste or the like may be spread on the affected surface and gently rubbed in. A solution may be applied in the same way, but more typically will be applied with a dropper, swab, or the like, and carefully applied to the affected areas.

The application regimen will depend on a number of factors that may readily be determined, such as the severity of the condition and its responsiveness to initial treatment, but will normally involve one or more applications per day on an ongoing basis. One of ordinary skill may readily determine the optimum amount of the formulation to be administered, administration methodologies and repetition rates. In general, it is contemplated that the formulations of the invention will be applied in the range of once or twice weekly up to once or twice daily.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, the foregoing description is intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. Furthermore, the practice of the present invention will employ, unless otherwise indicated, conventional techniques of cosmeceutical formulation that are within the skill of the art. Such techniques are fully explained in the literature.

All patents, patent applications, and publications mentioned herein are hereby incorporated by reference in their entireties.

EXAMPLE 1

A cream composition containing 30% dodecylamino is formulated as follows. Dodecylamine (30 grams) is dissolved in propylene glycol (15 ml). The solution thus prepared is mixed with hydrophilic ointment (55 grams) until a consistent cream is obtained.
EXAMPLE 2

[0094] A cream composition containing 25% N,N-dimethylectam ide is formulated as follows. N,N-Dimethylectamide (25 grams) is dissolved in propylene glycol (15 ml). The solution thus prepared is mixed with hydrophilic ointment (55 grams) until a consistent cream is obtained.

EXAMPLE 3

[0095] A solution composition containing 5% stearylamine, in oil-in-water emulsion is prepared as follows. Stearyleamine, (5 grams) is dissolved in propylene glycol (10 ml). The solution is then mixed with hydrophilic ointment, USP grade (85 grams) and the mixing continued until a uniform consistency is obtained.

EXAMPLE 4

[0096] A cream composition containing 10% isopropanolamine in oil-in-water emulsion is prepared as follows. Isopropanolamine (10 grams) are dissolved in propylene glycol (20 ml). The solution is then mixed with hydrophilic ointment, USP grade (70 grams) and the mixing continued until a uniform consistency is obtained.

EXAMPLE 5

[0097] A cream composition containing 25% 1-ethyl-2-pyrroldione, is formulated as follows. 1-Ethyl-2-pyrroldione (25 grams) is dissolved in propylene glycol (5 ml). The solution thus prepared is mixed with hydrophilic ointment (70 grams) until a consistent cream is obtained.

EXAMPLE 6

[0098] A therapeutic composition containing 5% hydroquinone and 8% N-ethyl-N-(dodecyl)ethanolamine in solution form for age spots, melasmas, lentigines and other pigmented skin spots may be formulated as follows. N-Ethyl-N-(dodecyl)ethanolamine (8 grams), hydroquinone (5 grams) and sodium metabisulphite (0.5 grams) are dissolved in a mixture of ethanol (70 ml), water (15 ml) and propylene glycol (7 ml) with stirring until a clear solution is obtained.

EXAMPLE 7

[0099] A therapeutic composition containing 0.5% hydrocortisone and 10% N-ethyl-N-(dodecyl)ethanolamine in solution form for use as an anti-inflammatory agent may be formulated as follows. N-Ethyl-N-(dodecyl)ethanolamine (10 grams), hydrocortisone (0.5 grams) are dissolved in a mixture of ethanol (70 ml), water (10 ml) and propylene glycol (10 ml) with stirring until a clear solution is obtained.

EXAMPLE 8

[0100] A therapeutic composition containing 5% hydroquinone and 8% N,N-dimethyldecamide in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows. N,N-Dimethyldecamide (8 grams), hydroquinone (5 grams) and sodium metabisulphite (0.5 grams) are dissolved in a mixture of ethanol (75 ml), water (10 ml) and propylene glycol (7 ml) with stirring until a clear solution is obtained.

EXAMPLE 9

[0101] A therapeutic composition containing 1% hydrocortisone and 8% N,N-dimethyldecamide in solution form for use as an anti-inflammatory agent may be formulated as follows. N,N-Dimethyldecamide (8 grams) and hydrocortisone (1 gram) are dissolved in a mixture of ethanol (70 ml), water (15 ml) and propylene glycol (7 ml) with stirring until a clear solution is obtained.

EXAMPLE 10

[0102] A therapeutic composition containing 2% kojic acid and 10% N-ethyl-N-(dodecyl)ethanolamine in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows. N-Ethyl-N-(dodecyl)ethanolamine (10 grams), kojic acid (2 grams) and hydroquinone (8 grams) are dissolved in a mixture of ethanol (70 ml), water (10 ml) and propylene glycol (10 ml) with stirring until a clear solution is obtained.

EXAMPLE 11

[0103] A sunscreen composition containing 5% octyl dimethyl para-amino benzoate, 3% dioxybenzone and 2% hexamethylenecotamide may be formulated as follows. Octyl dimethyl para-amino benzoate (5 grams), dioxybenzone (3 grams) and hexamethylenecotamide (2 grams) are dissolved in a mixture of ethanol (75 ml), water (10 ml) and propylene glycol (15 ml) with stirring until a clear solution is obtained.

EXAMPLE 12

[0104] A therapeutic composition containing 5% mono lauroyl lysine to alleviate dry or flaky skin may be formulated as follows. Monolauroyl lysine (5 grams) is dissolved in ethanol (20 ml), and the solution thus obtained is mixed with hydrophilic ointment USP (75 grams) with stirring until a uniform consistency is obtained.

EXAMPLE 13

[0105] A therapeutic composition containing 0.5% hydrocortisone and 2% potassium phosphate (dicasic) in solution form for use as an anti-inflammatory agent may be formulated as follows. Potassium phosphate (dicasic) (2 grams) and hydrocortisone (0.5 grams) are dissolved in a mixture of ethanol (80 ml), water (15 ml) and propylene glycol (5 ml) with stirring until a clear solution is obtained.

EXAMPLE 14

[0106] A therapeutic composition containing 0.5% hydrocortisone and 2% sodium phosphate (dibasic) in solution form for use as an anti-inflammatory agent may be formulated as follows. Sodium phosphate (dibasic) (2 grams) and hydrocortisone (0.5 grams) are dissolved in a mixture of ethanol (80 ml), water (15 ml) and propylene glycol (5 ml) with stirring until a clear solution is obtained.

EXAMPLE 15

[0107] A therapeutic composition containing 3% hydroquinone and 5% potassium citrate in solution form for age spots, keratoses, melasmas, lentigines and other pigmented skin spots may be formulated as follows. Potassium citrate (5 grams), hydroquinone (3 grams) are dissolved in a mixture of ethanol (80 ml), water (10 ml) and propylene glycol (10 ml) with stirring until a clear solution is obtained.

EXAMPLE 16

[0108] A therapeutic composition containing 5% hydroquinone and 8% ammonium phosphate (dibasic) in solution
form may be formulated as follows. Ammonium phosphate (dibasic) (8 grams), hydroquinone (5 grams) are dissolved in a mixture of ethanol (80 ml), water (10 ml) and propylene glycol (10 ml) with stirring until a clear solution is obtained.

**EXAMPLE 17**

**[0109]** A cream composition containing 10% isopropanolamine and 1% hydrocortisone in oil-in-water emulsion is prepared as follows. Isopropanolamine (10 grams) and hydrocortisone (1 gram) are dissolved in propylene glycol (20 ml). The solution is then mixed with hydrophilic ointment, USP grade (70 grams) and the mixing continued until a uniform consistency is obtained.

**EXAMPLE 18**

**[0110]** A cream composition containing 15% N,N-dimethylamino and 2% hydroquinone is formulated as follows. N,N-Dimethylammonium (15 grams) and hydroquinone (2 grams) are dissolved in propylene glycol (5 ml). The solution is then mixed with hydrophilic ointment, USP grade (80 grams) and the mixing continued until a uniform consistency is obtained.

**EXAMPLE 19**

**[0111]** A solution composition containing 10% hexamethylene palmmitate, in oil-in-water emulsion is prepared as follows. Hexamethylene palmmitate, (10 grams) is dissolved in propylene glycol (10 ml). The solution is then mixed with hydrophilic ointment, USP grade (80 grams) and the mixing continued until a uniform consistency is obtained.

We claim:

1. A method of treating an aging-related skin condition comprising topically applying to the skin a formulation consisting essentially of a cosmeceutically acceptable base at a concentration sufficient to provide a formulation pH in the range of approximately 7.5 to 13.0, at least one cosmeceutically acceptable excipient, and at least one cosmeceutically acceptable carrier.

2. The method of claim 1, wherein the pH is in the range of approximately 8.0 to 11.5.

3. The method of claim 2, wherein the pH is in the range of approximately 8.5 to 11.

4. The method of claim 1, wherein the formulation is aqueous.

5. The method of claim 4, wherein the aqueous formulation is selected from the group consisting of a cream, a gel, a lotion, and a paste.

6. The method of claim 5, wherein the aqueous formulation is a cream.

7. The method of claim 5, wherein the aqueous formulation is a gel.

8. The method of claim 5, wherein the aqueous formulation is a lotion.

9. The method of claim 5, wherein the aqueous formulation is a paste.

10. The method of claim 1, wherein the cosmeceutically acceptable base is a hydroxide-releasing agent.

11. The method of claim 10, wherein the hydroxide-releasing agent is selected from the group consisting of inorganic hydroxides, inorganic oxides, metal salts of weak acids, and mixtures thereof.

12. The method of claim 11, wherein the hydroxide-releasing agent is an inorganic hydroxide.

13. The method of claim 12, wherein the inorganic hydroxide is selected from the group consisting of ammonium hydroxide, alkali metal hydroxides, alkaline earth metal hydroxides, and mixtures thereof.

14. The method of claim 13, wherein the inorganic hydroxide is selected from the group consisting of ammonium hydroxide, sodium hydroxide, calcium hydroxide, potassium hydroxide, magnesium hydroxide, and mixtures thereof.

15. The method of claim 14, wherein the inorganic hydroxide is sodium hydroxide.

16. The method of claim 11, wherein the hydroxide-releasing agent is an inorganic oxide.

17. The method of claim 11, wherein the hydroxide-releasing agent is a metal salt of a weak acid.

18. The method of claim 1, wherein the cosmeceutically acceptable base is a nitrogenous base.

19. The method of claim 1, wherein the cosmeceutically acceptable base is an organic base.

20. The method of claim 19, wherein the organic base is selected from primary amines, secondary amines, tertiary amines, amidines, oximes, nitrogen-containing heterocycles, and urea.

21. The method of claim 20, wherein the organic base is a primary amine, a secondary amine, or a tertiary amine.

22. The method of claim 21, wherein the organic base has the structure NR'R'R' wherein R1, R2 and R3 are selected from H, alkyl, hydroxyalkyl, alkoxylalkyl, alkyl, hydroxyalkyl, alkoxylalkyl, cycloalkyl, cycloalkylic-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl, with the proviso that at least one of R1, R2 and R3 is other than H.

23. The method of claim 21, wherein the organic base is selected from the group consisting of diethanolamine, triethanolamine, isopropanolamine, triisopropanolamine, dibutanol amine, tributanol amine, N-dodecylammonium, N-(2-methoxyethyl) dodecylamine, N-(2,3-dimethoxyethyl) dodecylamine, N-ethyl-N-(2-dimethoxyethyl) dodecylamine, N-ethyl-N-(2,2-dimethoxyethyl) dodecylamine, dimethyldodecylamine-N-oxide, monoalanylated cine, dipalmitylated cine, dodecylamine, stearylamine, phytanethyllamine, triethy- lamine, PEG-2 oleamine, PEG-8 oleamine, dodecyl 2-(N, N-dimethylenimino) propionate, bis(2-hydroxyethyl) dodecylamine, and combinations thereof.

24. The method of claim 20, wherein the organic base is an amide.

25. The method of claim 24, wherein the amide has the structure R' = (CO) — NR'R'R' wherein R1, R2 and R3 are independently selected from H, alkyl, cycloalkyl, cycloalkyl-substituted alkyl, monocyclic aryl, and monocyclic aryl-substituted alkyl.

26. The method of claim 25, wherein the amide is selected from the group consisting of hexamethyleneacetamide, hexamethyleneacetamide, hexamethylene laurate, hexamethylene palmitamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N,N-dimethylamamide, N,N-dimethylamide, toluidine, dimethyltoluidine, diethylm-toluidine, and combinations thereof.

27. The method of claim 20, wherein the organic base is a nitrogen-containing heterocycle.

28. The method of claim 27, wherein the nitrogen-containing heterocycle is selected from the group consisting of 2-pyrroolidine, 1-methyl-2-pyrroolidine, 5-methyl-2-pyrroli-
done, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone,
1-propyl-3-dodecylpyrrolidinone, 1-dodecylazacycloheptan-
one, ethylene thiourea, hydantoin, oxylultra, imidazolidin-
diy urea, N-octadecyl morpholine, dodecylpyridinium,
N-dodecylpyrrolidinone, N-dodecylpiperidine, N-dodecyl-
omopiperidine, and combinations thereof.
29. The method of claim 1, wherein the formulation is
applied periodically over an extended time period.
30. The method of claim 1, wherein the formulation is
applied approximately twice weekly.
31. The method of claim 1, wherein the formulation is
applied once daily.
32. The method of claim 1, wherein the formulation is
applied twice daily.
33. The method of claim 1, wherein the formulation is
applied on an as-needed basis.
34. The method of claim 29, wherein said extended time
period is at least three months.
35. The method of claim 34, wherein said extended time
period is at least four months.
36. The method of claim 1, wherein the formulation is
applied to reduce the presence of age spots.
37. The method of claim 36, wherein the age spots are
pigmented.
38. The method of claim 1, wherein the formulation is
applied to effect a substantial increase in skin thickness.
39. The method of claim 1, wherein the formulation is
applied to effect a detectable decrease in wrinkles.
40. The method of claim 1, wherein the formulation is
applied to effect a detectable decrease in skin lines.
41. The method of claim 1, wherein the formulation is
applied to photaged skin.
42. The method of claim 1, wherein the formulation is
applied to photodamaged skin.
43. The method of claim 1, wherein the formulation is
applied to intrinsically aged skin.
44. The method of claim 1, wherein the formulation is
applied to stimulate the formation of a dermal component
selected from the group consisting of glycosaminoglycans,
proteoglycans, collagen and elastic fibers.
45. A method of reducing the appearance of an irregularity
present within a region of an individual's skin surface,
comprising topically applying to the skin surface, at least
within said region, a formulation consisting essentially of a
cosmeceutically acceptable base at a concentration sufficient
to provide a formulation pH in the range of approximately
8.0 to 13.0, at least one cosmeceutically acceptable excipient,
and at least one cosmeceutically acceptable carrier.
46. A topical formulation for treating an aging-related
skin condition and/or reducing the appearance of a skin
irregularity, consisting essentially of a cosmeceutically
acceptable base at a concentration sufficient to provide a
formulation pH in the range of approximately 8.0 to 13.0, at
least one cosmeceutically acceptable excipient, and at least
one cosmeceutically acceptable carrier.
47. The formulation of claim 46, wherein the pH is in the
range of approximately 8.0 to 11.5.
48. The formulation of claim 47, wherein the pH is in the
range of approximately 8.5 to 11.
49. The formulation of claim 46, wherein at least one
carrier is aqueous.
50. The formulation of claim 49, selected from the group
consisting of a cream, a gel, a lotion, and a paste.
51. The formulation of claim 50, in the form of a cream.
52. The formulation of claim 50, in the form of a gel.
53. The formulation of claim 50, in the form of a lotion.
54. The formulation of claim 50, in the form of a paste.
55. The formulation of claim 46, wherein the cosmeceutically
acceptable base is a hydroxide-releasing agent.
56. The formulation of claim 55, wherein the hydroxide-
releasing agent is selected from the group consisting of
inorganic hydroxides, inorganic oxides, metal salts of weak
acids, and mixtures thereof.
57. The formulation of claim 56, wherein the hydroxide-
releasing agent is an inorganic hydroxide.
58. The formulation of claim 57, wherein the inorganic
hydroxide is selected from the group consisting of ammonium
hydroxide, alkali metal hydroxides, alkaline earth metal
hydroxides, and mixtures thereof.
59. The formulation of claim 58, wherein the inorganic
hydroxide is selected from the group consisting of ammonium
hydroxide, sodium hydroxide, calcium hydroxide, potassium
hydroxide, magnesium hydroxide, and mixtures thereof.
60. The formulation of claim 59, wherein the inorganic
hydroxide is sodium hydroxide.
61. The formulation of claim 56, wherein the hydroxide-
releasing agent is an inorganic oxide.
62. The formulation of claim 56, wherein the hydroxide-
releasing agent is a metal salt of a weak acid.
63. The formulation of claim 46, wherein the cosmeceutically
acceptable base is a nitrogenuous base.
64. The formulation of claim 46, wherein the cosmeceutically
acceptable base is an organic base.
65. The formulation of claim 64, wherein the organic base
is selected from primary amines, secondary amines, tertiary
amines, oximes, nitrogen-containing heterocycles, and urea.
66. The formulation of claim 65, wherein the organic base
is a primary amine, a secondary amine, or a tertiary amine.
67. The formulation of claim 66, wherein the organic base
has the structure NR2R3 where R1 = R2 = R3 are
selected from H, alkyl, hydroxyalkyl, alkoxyalkyl, alkenyl,
hydroxalkenyl, alkoxyalkenyl, cycloalkyl, cycloalkyl-substi-
tuted alkyl, monocylic ary1, and monocyclic aryl-substi-
tuted alkyl, with the proviso that at least one of R3, R2 and
R1 is other than H.
68. The formulation of claim 67, wherein the organic base
is selected from the group consisting of diethanolamine,
triethanolamine, isopropanolamine, trisopropanolamine,
dibutanol amine, tributanol amine, N-dodecylethanolamine,
N-(2-methoxyethyl) dodecylamine, N-(2,2-dimethoxyethyl)-
dodecylamine, N-ethy1-N-(dodecyl)ethanolamine, N-ethyl-
N-(2-methoxyethyl)dodecylamine, N-ethy1-N-(2,2-
dimethoxyethyl) dodecylamine, dimethy1dodecylamine-
N-oxide, monolauryl lysine, dipalmitoyl lysine,
dodecylamine, stearylamine, phenylethylamine, triethyl-
lamine, PEG-2 oleamine, PEG-5 oleamine, dodecyl 2(N,
N-dimethy1amin0)propionate, bis(2-hydroxyethyl)ole-
cylamine, and combinations thereof.
69. The formulation of claim 65, wherein the organic base
is an amide.
70. The formulation of claim 69, wherein the amide has
the structure R4—(CO)—NR2R3 where R1, R2 and R3 are
independently selected from H, alkyl, cycloalkyl,
cycloalkyl-substituted alkyl, monocylic aryl, and monocy-
clic aryl-substituted alkyl.
71. The formulation of claim 70, wherein the amide is selected from the group consisting of hexamethyleneacetamide, hexamethyleneoctamide, hexamethylene lauramide, hexamethylene palmitamide, N,N-dimethyl formamide, N,N-dimethyl acetamide, N,N-dimethyloctamide, N,N-dimethyldecamide, toluidine, dimethyl-m-toluidine, diethyl-m-toluamide, and combinations thereof.

72. The formulation of claim 65, wherein the organic base is a nitrogen-containing heterocycle.

73. The formulation of claim 72, wherein the nitrogen-containing heterocycle is selected from the group consisting of 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, 1-propyl-3-dodecylpyrrolidine, 1-dodecylazacycloheptan-2-one, ethylene thiourea, hydantoin, oxatylurea, imidazolidinyl urea, N-octadecyl morpholine, dodecylpyridinium, N-dodecylpyrrolidine, N-dodecylpiperidine, N-dodecylhomopiperidine, and combinations thereof.

74. A topical formulation for treating an aging-related skin condition and/or reducing the appearance of a skin irregularity, consisting essentially of:

- a cosmeceutically acceptable base at a concentration sufficient to provide a formulation pH in the range of approximately 8.0 to 13.0;
- at least one pharmaceutically active agent suitable for topical drug delivery and effective to treat the aging-related skin condition and/or reduce the appearance of a skin irregularity;
- at least one cosmeceutically acceptable excipient; and
- at least one cosmeceutically acceptable carrier.

75. A sunscreen formulation for treating an aging-related skin condition and/or reducing the appearance of a skin irregularity, consisting essentially of:

- a cosmeceutically acceptable base at a concentration sufficient to provide a formulation pH in the range of approximately 8.0 to 13.0;
- at least one sunblock; and
- at least one cosmeceutically acceptable carrier.

76. A self-tanning formulation for treating an aging-related skin condition and/or reducing the appearance of a skin irregularity, consisting essentially of:

- a cosmeceutically acceptable base at a concentration sufficient to provide a formulation pH in the range of approximately 8.0 to 13.0;
- at least one agent that promotes the appearance of tanned skin without exposure to the sun; and
- at least one cosmeceutically acceptable excipient; and
- at least one cosmeceutically acceptable carrier.

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