ADDITIVES ENHANCING TOPICAL APPLICATIONS OF THERAPEUTIC AGENTS

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ABSTRACT

Preventive as well as therapeutic treatment to alleviate cosmetic conditions and symptoms of dermatologic disorders with amphoteric compositions containing alpha hydroxyacids, alpha ketooicids, related compounds or polymeric forms of hydroxyacids is disclosed. The cosmetic conditions and the dermatologic disorders in which the amphoteric compositions and the polymeric compounds may be useful include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging, and skin requiring cleansers.
ADDITIVES ENHANCING TOPICAL APPLICATIONS OF THERAPEUTIC AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS


BACKGROUND OF THE INVENTION

0002 This invention relates generally to therapeutic treatment as well as to preventive measures for cosmetic conditions and dermatologic disorders by topical administration of amphoteric compositions or polymeric forms of alpha hydroxyacids, alpha ketoacids and related compounds. We initially discovered that alpha hydroxy or keto acids and their derivatives were effective in the topical treatment of disease conditions such as dry skin, ichthyosis, eczema, palmar and plantar hyperkeratoses, dandruff, acne, and warts.

0003 We have now discovered that amphoteric compositions and polymeric forms of alpha hydroxyacids, alpha ketoacids, and related compounds of topical administration are therapeutically effective for various cosmetic conditions and dermatologic disorders.

0004 In U.S. Pat. No. 3,879,537, entitled “Treatment of Ichthyosisiform Dermatoses,” we described and claimed the use of certain alpha hydroxyacids, alpha ketoacids, and related compounds for topical treatment of fish scale-like ichthyotic conditions in humans. In U.S. Pat. No. 3,920,835, entitled “Treatment of Disturbed Keratinization,” we described and claimed the use of these alpha hydroxyacids, alpha ketoacids, and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis.

0005 In U.S. Pat. No. 4,105,783, entitled “Treatment of Dry Skin,” we described and claimed the use of alpha hydroxyacids, alpha ketoacids, and their derivatives for topical treatment of dry skin. In U.S. Pat. No. 4,240,261, entitled “Additives Enhancing Topical Corticosteroid Action,” we disclosed that alpha hydroxyacids, alpha ketoacids and their derivatives could greatly enhance the therapeutic efficacy of corticosteroids in topical treatment of psoriasis, eczema, seborrheic dermatitis, and other inflammatory skin conditions.

0006 In U.S. Pat. No. 4,363,815, entitled “Alpha Hydroxyacids, Alpha Ketoacids and Their Use in Treating Skin Conditions,” we disclosed alpha hydroxyacids and alpha ketoacids related to or originating from amino acids, whether or not found in proteins, for effective in topical treatment of skin disorders associated with disturbed keratinization or inflammation. These skin disorders include dry skin, ichthyosis, palmar and plantar hyperkeratosis, dandruff, Darier’s disease, lichen simplex chronicus, keratoses, acne, psoriasis, eczema, pruritus, warts, and herpes.

BRIEF SUMMARY OF THE INVENTION

0007 There is no doubt that alpha hydroxyacids, alpha ketoacids, and related compounds are therapeutically effective for topical treatment of various cosmetic conditions and dermatologic disorders including dry skin, acne, dandruff, keratoses, age spots, wrinkles, and disturbed keratinization. However, the compositions containing these acids may irritate human skin after repeated topical applications, due to the lower pH levels of the formulations. The irritation may range from a sensation of tingling, itching, and burning to clinical signs of redness and peeling. Causes for such irritation may arise from the following:

0008 Upper layers of normal skin have a pH of 4.2 to 5.6, but the compositions containing most alpha hydroxyacids or alpha ketoacids have pH values of less than 3.0. For example, a topical formulation containing 7.6% (1 M) glycolic acid has a pH of 1.9, as does a composition containing 9% (1 M) lactic acid. These compositions of lower pH values, on repeated topical applications, can cause a drastic pH decrease in the stratum corneum of human skin, and provoke disturbances in intercorneocyte bondings, resulting in adverse skin reactions, especially in individuals with sensitive skin.

0009 Moreover, it remains difficult to formulate a lotion, cream, or an ointment emulsion which contains a free acid form of the alpha hydroxyacid, and which is a physically stable commercial product for cosmetic or pharmaceutical use.

0010 When a formulation containing an alpha hydroxy-acid or alpha ketoacid is reacted equimolarly or equimolarly with a metallic alkali, such as sodium hydroxide or potassium hydroxide, the composition becomes therapeutically ineffective. The reasons for such loss of therapeutic effects are believed to be as follows:

0011 The intact skin of humans is a very effective barrier to many natural and synthetic substances. Cosmetic and pharmaceutical agents may be pharmacologically effective by oral or other systematic administration, but many of them are much less or totally ineffective on topical application to the skin. Topical effectiveness of a pharmaceutical agent depends on two major factors: (a) bioavailability of the active ingredient in the topical preparation, and (b) percutaneous absorption, penetration, and distribution of the active ingredient to its target site in the skin. For example, a topical preparation containing 5% salicylic acid is therapeutically effective as a keratolytic, but one containing 5% sodium salicylate is not an effective product. The reason for
such difference is that salicylic acid is a bioavailable form and can penetrate the stratum corneum, but sodium salicylate is not, and therefore cannot penetrate the stratum corneum of the skin.

[0012] In the case of alpha hydroxyacids, a topical preparation containing 5% glycolic acid is therapeutically effective for dry skin, but one containing 5% sodium glycolate is not effective. The same is true in case of 5% lactic acid versus 5% sodium lactate. The reason for such difference is that both glycolic acid and lactic acid are bioavailable forms and can readily penetrate the stratum corneum, but sodium glycolate and sodium lactate are not, and therefore cannot penetrate the stratum corneum of the skin.

[0013] When a formulation containing an alpha hydroxyacid or alpha ketoacid is reacted equimolarly or equinormaly with ammonium hydroxide or an organic base, the composition still shows some therapeutic effects for certain cosmetic conditions, such as dry skin; however, the composition has lost most of its potency for other dermatologic disorders, such as wrinkles, keratoses, age spots, and skin changes associated with aging.

[0014] It has now been discovered that amphoteric compositions containing alpha hydroxyacids, alpha ketoacids, or related compounds, and also the compositions containing dimeric or polymeric forms of hydroxyacids, overcome the aforementioned shortcomings and retain therapeutic efficacies for cosmetic conditions and dermatologic disorders. The amphoteric composition contains, in combination, an amphoteric or pseudoamphoteric compound and at least one of the alpha hydroxyacids, alpha ketoacids, or related compounds. Such amphoteric system has a suitable pH, and can release the active form of an alpha hydroxyacid or alpha ketoacid into the skin. The dimeric and polymeric forms of alpha, beta, or other hydroxyacids in non-aqueous compositions have a more desired pH than that of the monomeric form of the hydroxyacids. The non-aqueous compositions can be formulated and induced to release the active form of hydroxyacids after the compositions have been topically applied to the skin. The cosmetic conditions and dermatologic disorders in humans and animals, in which the amphoteric compositions containing the dimeric or polymeric forms of hydroxyacids may be useful, include dry skin, dandruff, acne, keratoses, psoriasis, eczema, pruritus, age spots, lentigines, melasmas, wrinkles, warts, blemished skin, hyperpigmented skin, hyperkeratotic skin, inflammatory dermatoses, skin changes associated with aging and as skin cleansers.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Amphoteric substances by definition should behave either as an acid or a base, and can be an organic or an inorganic compound. The molecule of an organic amphoteric compound should consist of at least one basic and one acidic group. The basic groups include, for example, amino, imino, and guanido groups. The acidic groups include, for example, carboxylic, phosphoric, and sulfonic groups. Some examples of organic amphoteric compounds are amino acids, peptides, polypeptides, proteins, creatine, aminoalcoholic acids, aminouronic acids, lauryl aminopropylglycine, aminomalic acids, neuraminic acid, desulfated heparin, deacetylated hyaluronic acid, hyaloburonic acid, chondrosine, and deacetylated chondroitin.

[0016] Inorganic amphoteric compounds are certain metallic oxides, such as aluminum oxide and zinc oxide.

[0017] Pseudoamphoteric compounds are either structurally related to true amphoteric compounds or are capable of inducing the same function when they are incorporated into the compositions containing alpha hydroxyacids or ketoacids. Some examples of pseudoamphoteric compounds are creatinine, stearamidemethyl diethyamine, stearamidemethyl diethanolamine, stearamidomethyl dimethylamine, quaternary ammonium hydroxide, and quatemium hydroxide.

[0018] The amphoteric composition of the instant invention contains, in combination, an alpha hydroxyacid or alpha ketoacid and an amphoteric or pseudoamphoteric compound. There are two advantages of utilizing an amphoteric or the like compound in the therapeutic composition containing an alpha hydroxy or ketoacid. These are: (a) the overall pH of the composition is raised, so that the composition becomes less or non-irritating to the skin, and (b) some alpha hydroxy or ketoacid molecules react with the amphoteric compound to form a quadruple ionic complex which acts as buffering system to control the release of alpha hydroxy or ketoacid into the skin, therefore eliminating skin irritation while retaining therapeutic efficacies.

[0019] For example, 2-hydroxyethanoic acid (glycic acid) 1 M aqueous solution has a pH of 1.9. The pH of the composition changes to 3.0, 3.2 when arginine 0.5 M and creatinine 0.5H respectively are incorporated into the formulation. 2-Hydroxypropanoic acid (lactic acid) 1 M aqueous solution has a pH of 1.9. The pH of the composition changes to 3.1 and 6.9 when arginine 0.5 M and 1.0 M respectively are incorporated into the formulation. 2-Methyl 2-hydroxypropanoic acid (methylactic acid) 1 M aqueous solution has a pH of 1.9. The pH of the compositions change to 3.3, 3.4, and 3.2 when 0.5 M each of arginine, creatinine, and 4-amino butanolic acid, respectively, are incorporated into the formulation. 2-Hydroxybutane-1,4-dioic acid (malic acid) 1 M aqueous solution has pH 1.8, but the pH of the composition changes to 3.0 when creatine 0.5 M is incorporated into the formulation.

[0020] Ideally, an amphoteric compound should contain both anionic and cationic groups or functional groups capable of behaving both as an acid and a base. Although inorganic amphoteric compounds such as aluminum oxide, aluminum hydroxide, and zinc oxide may be utilized, organic amphoteric compounds have been found to be more efficient in formulating therapeutic compositions of the instant invention.

[0021] Organic amphoteric and pseudoamphoteric compounds may be classified into three groups, namely (a) amino acid-type, (b) imidazoline and lecithin amphoterics, and (C) pseudoamphoteric and miscellaneous amphoterics.

[0022] (a) Amino Acid-Type Amphoterics.

[0023] Amphoteric compounds of amino acid-type include all the amino acids, dipeptides, polypeptides, proteins, and the like, which contain at least one of the basic groups such as amino, imirio, guanido, imidazolino, and imidazolyl, and one of the acidic groups such as carboxylic, sulfonic, sulfinic, and sulfate.

[0024] Glycine is a simple amphoteric compound that contains only one amino group and one carboxylic group.
Lysine contains two amino groups and one carboxylic group. Aspartic acid contains one amino group and two carboxylic groups. Arginine contains one amino group, one guanidino group, and one carboxylic group. Histidine contains one amino group, one imidazolyl group, and one carboxylic group. Taurine contains one amino group and one sulfonic group. Cysteine sulfonic acid contains one amino group, one carboxylic group, and one sulfonic group. The amino group of an amphoteric compound may also be substituted, such as in betaine which is a glycine \( N,N,N \)-trimethyl inner salt.

[0025] Glycylglycine is a simple dipeptide that contains one free amino group and one free carboxylic group. Glycylhistidine is also a dipeptide that contains one free amino group, one imidazolyl group, and one free carboxylic group.

[0026] The representative amphoteric compounds of amino acid-type may be listed as follows: glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, asparagine, glutamic acid, glutamine, arginine, lysine, 5-hydroxylysine, histidine, phenylalanine, tyrosine, tryptophan, 3-hydroxyproline, 4-hydroxyproline, and proline.

[0027] The related amino acids include homocysteine; homoserine; ornithine; citrulline; creatine; 3-aminopropanoic acid; threonine; 2-aminobutanoic acid; 4-aminobutanoic acid; 2-aminooxypropanoic acid; 2-methyl-3-aminopropanoic acid; 2,6-diaminopimelic acid; 2-aminooxypropanoic acid; phenylglycine; canavanine; canalin; 4-hydroxyarginine; 4-hydroxyornithine; homoglutamine; 4-hydroxyhomoglutamine; \( \beta \)-lysine; 2,4-diaminobutanoic acid; 2,3-diaminopropanoic acid; 2-methylserine; 3-phenylserine; and betaine.

[0028] Sulfur-containing amino acids include taurine, cystinesulfonic acid, methionine sulfoxide, and methionine sulfone.

[0029] The halogen-containing amino acids include 3,5-diodotyrosine, tyrosine and monoiodotyrosine. The amino-type acids include piperocolic acid, 4-aminopirocolic acid and 4-methylproline.

[0030] The dipeptides include for example, glycylglycine, camosine, asparagine, homocarnosine, \( \beta \)-alanyllysin, \( \beta \)-alanylgarginine. The tripeptides include for example, glutathione, ophthalmic acid, and norophtalmic acid. Short chain polypeptides of animal, plant, and bacterial origin containing up to 100 amino acid residues include bradykinin and glucagon. The preferred proteins include for example protamines, histones and other lysine- and arginine-rich proteins.

[0031] (b) Imidazoline and Lecithin Amphoterics.

[0032] The amphoteric compounds of imidazoline derived type are commercially synthesized from 2-substituted-2-imidazolines obtained by reacting a fatty acid with an aminomethylthanolamine. These amphoterics include cocoamphoglycine, cocoamphopropionate, and cocoamphopropylsulfonate. The amphoteric compounds of lecithin and related type include, for example, phosphatidyl ethanolamine, phosphatidyl serine, and sphingomyelin.

[0033] (c) Pseudoamphoterics and Miscellaneous Amphoterics.

[0034] Many pseudoamphoterics compounds are chemically related or derived from true amphoterics. For example, creatinine is derived from creatine. Other pseudoamphoteric compounds may include fatty amide amines, such as stearamidoethyl diethlamine, stearamidoethyl diethanolamine, and stearamidopropyl dimethylamine. Other pseudoamphoteric related compounds include quaternary ammonium hydroxide and quaternium hydroxide.

[0035] In accordance with the present invention, the alpha hydroxyacid, the alpha ketocids, and the related compounds which are incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders may be classified into three groups.

[0036] The first group is organic carboxylic acids in which one hydroxyl group is attached to the alpha carbon of the acids. The generic structure of such alpha hydroxyacids may be represented as follows:

\[(R)_{\alpha}\text{CHOH}COOH\]

where \( R_1 \) and \( R_2 \) are H, F, Cl, Br, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition \( R_1 \) and \( R_2 \) may carry OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha hydroxyacids may be present as a free acid or lactone form, or in a salt form with an organic base or an inorganic alkali. The alpha hydroxyacids may exist as stereoisomers as D, L, and DL forms when \( R_1 \) and \( R_2 \) are not identical.

[0038] Typical alkyl, aralkyl and aryl groups for \( R_1 \) and \( R_2 \) include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl, phenyl, etc. The alpha hydroxyacids of the first group may be divided into (1) alkyl alpha hydroxyacids, (2) aralkyl and aryl alpha hydroxyacids, (3) polyhydroxy alpha hydroxyacids, and (4) poly-carboxylic alpha hydroxyacids. The following are representative alpha hydroxyacids in each subgroup.

[0039] (1) Alkyl Alpha Hydroxyacids

[0040] 1. 2-Hydroxyethanoic acid (Glycic acid, hydroxyacetic acid)

[0041] (H) (H) (OH) COOH

[0042] 2. 2-Hydroxypropanoic acid (Lactic acid)

[0043] (CH₃) (H) (OH) COOH

[0044] 3. 2-Methyl-2-hydroxypropanoic acid (Methyl-lactic acid)

[0045] (CH₃) (CH₂) (CH₂) (OH) COOH

[0046] 4. 2-Hydroxybutanoic acid

[0047] (C₂H₅) (H) (C) (OH) COOH

[0048] 5. 2-Hydroxypentanoic acid

[0049] (C₃H₇) (H) (C) (OH) COOH

[0050] 6. 2-Hydroxyhexanoic acid

[0051] (C₄H₉) (H) (C) (OH) COOH

[0052] 7. 2-Hydroxyheptanoic acid

[0053] (C₅H₁₁) (H) (C) (OH) COOH

[0054] 8. 2-Hydroxyoctanoic acid

[0055] (C₆H₁₃) (H) (C) (OH) COOH
9. 2-Hydroxynonanoic acid

10. 2-Hydroxydecanoic acid

11. 2-Hydroxyundecanoic acid

12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)

13. 2-Hydroxytetradecanoic acid (Alpha hydroxyoctadecanic acid)

14. 2-Hydroxyhexadecanoic acid (Alpha hydroxyhexadecanic acid)

15. 2-Hydroxyoctadecanoic acid (Alpha hydroxyoctadecanic acid)

16. 2-Hydroxyeicosanoic acid (Alpha hydroxyeicosadecanic acid)

(2) Aralkyl and Aryl Alpha Hydroxyacids

1. 2-Phenyl 2-hydroxyethanoic acid (Mandelic acid)

2. 2,2-Diphenyl 2-hydroxyethanoic acid (Benzillic acid)

3. 3-Phenyl 2-hydroxypropanoic acid (Phenylactic acid)

4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid (Athralactic acid)

5. 2- (4-Hydroxyphenyl) 2-hydroxyethanoic acid (4-Hydroxymandelic acid)

6. 2- (4-Chlorophenyl) 2-hydroxyethanoic acid (4-Chloromandelic acid)

7. 2-(3'-Hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid (3-Hydroxy-4-methoxy mandelic acid)

8. 2- (4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid (4-Hydroxy-3-methoxy mandelic acid)

9. 3-(2-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(2-Hydroxyphenyl) lactic acid]

HO—C₆H₅—CH₂(H) C (OH) COOH

10. 3-(4-Hydroxyphenyl) 2-hydroxypropanoic acid [3-(4-Hydroxyphenyl) lactic acid]

HO—C₆H₅—CH₂ (H) C (OH) COOH

11. 2-(3', 4'-Dihydroxyphenyl) 2-hydroxyethanoic acid (3,4-Dihydroxymandelic acid)

HO—, HO—C₆H₅ (H) C (OH) COOH

(3) Polyhydroxy Alpha Hydroxyacids

1. 2,3-Dihydroxypropanoic acid (Glyceric acid)

HOCH₂(H) C (OH) COOH

2. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid)

HOCH₂(H) CH₂ (H) C (OH) COOH

3. 2,3,4,5-Tetrahydroxypentanoic acid (Isomers; ribonic acid, arabinonic acid, xylonic acid, lyxonic acid)

HOCH₂ (H) CH₂ (HO) CH₂ (H) C (OH) COOH

4. 2,3,4,5,6-Penta hydroxyhexanoic acid (Isomers; allonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid)

HOCH₂ (HO) CH₂ (HO) CH₂ (HO) CH₂ (H) C (OH) COOH

5. 2,3,4,5,6,7-Heptahydroxyheptanoic acid (Isomers; glucotechotic acid, galactoheptonic acid etc.)

HOCH₂ (HO) CH₂ (HO) CH₂ (HO) CH₂ (HO) CH₂ (H) C (OH) COOH

(4) Polycarboxylic Alpha Hydroxyacids

1. 2-Hydroxypropane-1,3-dioic acid (Traticonic acid)

HOOC (H) C (OH) COOH

2. 2-Hydroxybutane-1,4-dioic acid (Malic acid)

HOOC CH₂ (H) C (OH) COOH

3. 2,3-Dihydroxybutane-1,4-dioic acid (Tartaric acid)

HOOC (HO) CH₂ (H) C (OH) COOH

4. 2-Hydroxy-2-carboxypentane-1,5-dioic acid (Citric acid)

HOOC CH₂ (H) C (OH) COOH

5. 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers; succharic acid, mucic acid etc.)

HOOC (CHOH)₄ COOH

(5) Lactate Forms

The typical lactone forms are gluconolactone, galactono lactone, glucuronic acid, galacturonolactone, gulonolactone, ribonolactone, saccharic acid lactone, pantoy lactone, glucoheptonolactone, mannonolactone, and galactoheptonolactone.
(R<sub>n</sub>CO COO(R<sub>n</sub>))

[0120] The second group of compounds which may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders, is organic carboxylic acids in which the alpha carbon of the acids is in keto form. The generic structure of such alpha ketoacids may be represented as follows:

\[ (\text{R}_n\text{CO COO(R}_n) \]

[0120] wherein \( R_n \) and \( R_n \) are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and in addition \( R_n \) may carry F, Cl, Br, I, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha ketoacids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for \( R_n \) and \( R_n \) include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.

[0121] In contrast to alpha hydroxyacids, the ester form of alpha ketoacids has been found to be therapeutically effective for cosmetic and dermatologic conditions and disorders. For example, while ethyl lactate has a minimal effect, ethyl pyruvate is therapeutically very effective. Although the mechanism for such difference is not known, we have speculated that the ester form of an alpha keto acid is chemically and/or biochemically very reactive, and a free keto acid form of the alpha keto acid is released in the skin after the topical application.

[0122] The representative alpha ketoacids and their esters which may be useful in amphoteric or pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders are listed below:

[0123] 1. 2-Ketothanoic acid (Glyoxylic acid)
[0124] (H) CO COOH
[0125] 2. Methyl 2-ketothanoate
[0126] (H) CO COOCH<sub>3</sub>
[0127] 3. 2-Ketopropanoic acid (Pyruvic acid)
[0128] CH<sub>3</sub> CO COOH
[0129] 4. Methyl 2-ketopropanoate (Methyl pyruvate)
[0130] CH<sub>3</sub> CO COOCH<sub>3</sub>
[0131] 5. Ethyl 2-ketopropanoate (Ethyl pyruvate)
[0132] CH<sub>3</sub> CH COOCH<sub>3</sub>
[0133] 6. Propyl 2-ketopropanoate (Propyl pyruvate)
[0134] CH<sub>3</sub> CH<sub>2</sub> COOCH<sub>3</sub>
[0135] 7. 2-Phenyl-2-ketothanoic acid (Benzoylformic acid)
[0136] C<sub>6</sub>H<sub>5</sub> CO COOH
[0137] 8. Methyl 2-phenyl-2-ketothanoate (Methyl benzoylformate)
[0138] C<sub>6</sub>H<sub>5</sub> CO COOCH<sub>3</sub>
[0140] C<sub>6</sub>H<sub>5</sub> CO COOC<sub>2</sub>H<sub>5</sub>
[0141] 10. 3-Phenyl-2-ketopropanoic acid (Phenylpyruvic acid)
[0142] C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub> CO COOH
[0143] 11. Methyl 3-phenyl-2-ketopropanoate (Methyl phenylpyruvate)
[0144] C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub> CO COOCH<sub>3</sub>
[0145] 12. Ethyl 3-phenyl-2-ketopropanoate (Ethyl phenylpyruvate)
[0146] C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub> CO COOC<sub>2</sub>H<sub>5</sub>
[0147] 13. 2-Ketobutanoic acid
[0148] C<sub>3</sub>H<sub>7</sub> CO COOH
[0149] 14. 2-Ketopentanoic acid
[0150] C<sub>3</sub>H<sub>7</sub> CO COOH
[0151] 15. 2-Ketohexanoic acid
[0152] C<sub>3</sub>H<sub>7</sub> CO COOCH<sub>3</sub>
[0153] 16. 2-Ketohexanoic acid
[0154] C<sub>3</sub>H<sub>7</sub> CO COOH
[0155] 17. 2-Ketoheptanoic acid
[0156] C<sub>3</sub>H<sub>13</sub> CO COOH
[0157] 18. 2-Ketodecanoic acid
[0158] C<sub>10</sub>H<sub>21</sub> CO COOH
[0159] 19. Methyl 2-ketoctanoate
[0160] C<sub>6</sub>H<sub>13</sub> CO COOCH<sub>3</sub>

[0161] The third group of compounds that may be incorporated into amphoteric or pseudoamphoteric compositions for cosmetic and dermatologic conditions and disorders, is chemically related to alpha hydroxyacids or alpha ketoacids. The third group of compounds include ascorbic acid, quinic acid, isocitric acid, tropic acid, trethocanic acid, 3-chlorolactic acid, cerebrosic acid, citramalic acid, agarcidic acid, 2-hydroxyervonic acid, auletric acid and pantoic acid.

[0162] II. Dimeric and Polymeric Forms of Hydroxyacids

[0163] When two or more molecules of hydroxycarboxylic acids, either identical or non-identical compounds, are reacted chemically to each other, dimeric or polymeric compounds will be formed. Such dimeric and polymeric compounds may be classified into three groups, namely (a) acyclic esters, (b) cyclic esters and (c) miscellaneous dimers and polymers.

[0164] (a) Acyclic esters. The acyclic ester of a hydroxy-carboxylic acid may be a dimer or a polymer. The dimer is formed from two molecules of a hydroxycarboxylic acid by reacting the carboxyl group of one molecule with the hydroxy group of a second molecule. For example, glycolyl glycollate is formed from two molecules of glycolic acid by eliminating one mole of water molecule. Likewise, lactic lactate is formed from two molecules of lactic acid. When two molecules of different hydroxycarboxylic acids are intermolecularly reacted, a different dimer is formed. For example, glycolyl lactate is formed by the reaction of the carboxyl group of lactic acid with the hydroxy group of glycolic acid. The polymer is formed in a similar manner but from more than two molecules of a hydroxycarboxylic acid.
For example, glycol glycol glycolate is formed from three molecules of glycolic acid. Copolymer is formed from two or more than two different kinds of hydroxycarboxylic acids. For example, glycolyl lactyl glycolate is formed from two molecules of glycolic acid and one molecule of lactic acid.

[0165] The acyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

\[ \text{H}(-\text{O}(-\text{R}(-\text{R}(-\text{R}(-\text{OH})\text{)}\text{)}\text{)}\text{)}\text{)} \]

[0166] wherein R₂ or R₃ is a hydrogen atom, alkyl, aralkyl aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or other integer up to 200. R₁ and R₄ in monomer unit 2, 3, 4 and so on may be the same or the different groups from that in monomer unit 1. For example, R₂ or R₃ is a hydrogen atom in monomer unit 1, and R₄ is CH₃ and R₅ is a hydrogen atom in monomer unit 2 when n=2 is a dimer called lactyl glycolate, because the first monomer is glycolate unit and the second monomer is lactic acid unit. The hydrogen atom in R₂ and R₃ may be substituted by a halogen atom or a radical such as a lower alkyl, aryl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms. The dimer and copolymer of a hydroxycarboxylic acid may be present as a free acid, ester or salt form with organic base or inorganic alkali.

[0167] The typical alkyl, aralkyl and aryl groups for R₁ and R₄ include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative acyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

[0168] 1. Glycol glycolate (Glycolic acid glycolate)
[0169] R₁, R₄=H in units 1 & 2, n=2
[0170] 2. Lactyl lactate (Lactic acid lactate)
[0171] R₁=CH₃ and R₄=H in units 1 & 2, n=2
[0172] 3. Mandel lactyl mandel lactate
[0173] R₅=CH₃ and R₆=H in units 1 & 2, n=2
[0174] 4. Atrolactyl atrolactate
[0175] R₅=CH₃ and R₆=CH₃ in units 1 & 2, n=2
[0176] 5. Phenyllactyl phenyllactate
[0177] R₅=CH₃ and R₆=H in units 1 & 2, n=2
[0179] R₅ and R₆=CH₃ in units 1 & 2, n=2
[0180] 7. Glycyl lactate
[0181] R₁=CH₃ in unit 1, R₄=H in unit 2, R₅=H in units 1 & 2, n=2
[0182] 8. Lactyl glycolate
[0183] R₅=H in unit 1, R₄=CH₃ in unit 2, R₅=H in units 1 & 2, n=2
[0184] 9. Glycolyl glycolyl glycolate
[0185] R₅, R₆=H in units 1, 2 & 3, n=3

[0186] 10. Lactyl lactyl lactate
[0187] R₅=CH₃, R₆=H in units 1, 2 & 3, n=3
[0188] 11. Lactyl glycolyl lactate
[0189] R₅=CH₃ in units 1 & 3, R₆=H in unit 2, R₅=H in units 1, 2 & 3, n=3
[0190] 12. Glycolyl glycolyl glycolyl lactate
[0191] R₅, R₆=H in units 1, 2, 3 & 4, n=4
[0192] 13. Lactyl lactyl lactyl lactate
[0193] R₅=CH₃ and R₆=H in units 1, 2, 3 & 4, n=4
[0194] 14. Glycolyl lactyl lactyl lactyl lactate
[0195] R₅=H in units 1, 3 & 5 and R₆=CH₃ in units 2 & 4,
[0196] 15. Polylactyl acid and polylactyl acid

[0198] (b) Cyclic ester. The cyclic ester of a hydroxycarboxylic acid may also be a dimer or polymer. The most common type, however, is a dimer form. The cyclic dimer may be formed from an identical monomer or from different monomers. For example, glycolide is formed from two molecules of glycolic acid by removing two molecules of water. Lactide is formed from two molecules of lactic acid in the same manner. The cyclic ester of dimeric and polymeric hydroxycarboxylic acids may be shown by the following chemical structure:

\[ \text{H}(-\text{O}(-\text{R}(-\text{R}(-\text{R}(-\text{OH})\text{)}\text{)}\text{)}\text{)}\text{)} \]

[0199] wherein R₁ and R₄=H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 25 carbon atoms, and n=1 or any integer, preferably 2. R₇ and R₈ in units 1, 2, 3, and so on may be the same or the different groups.

[0200] For example, in glycolide, R₇ and R₈ are hydrogen atoms in both units 1 & 2, but in lactoglycolide R₇ is H in unit 1, CH₃ in unit 2, and R₈ is a hydrogen atom in both units 1 & 2. The hydrogen atom in R₇ and/or R₈ may be substituted by a halogen atom or a radical such as a lower alkyl, aryl, aryl or alkoxy of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 9 carbon atoms.

[0201] The typical alkyl, aralkyl and aryl groups for R₇ and R₈ include methyl, ethyl, propyl, isopropyl, butyl, benzyl and phenyl. Representative cyclic esters of hydroxycarboxylic acids which may be useful for cosmetic conditions and dermatologic disorders are listed below:

[0202] 1. Glycolide
[0203] R₇ and R₈=H, n=2
[0204] 2. Lactide
[0205] R₇=CH₃ and R₈=H in units 1 & 2, n=2
[0206] 3. Mandelide
[0207] R₇=CH₃ and R₈=H in units 1 & 2, n=2
[0208] 4. Atrolactide
[0209] R₇=CH₃ and R₈=CH₃ in units 1 & 2, n=2
5. Phenylactide
6. Benzilide
7. Methylactide
8. Lactoglyceride
9. Glycolactide

(b) Miscellaneous dimers and polymers. This group includes all the dimeric and polymeric forms of hydroxy- carboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethacanic acid, and septic acid. When a hydroxyacrylic acid has more than one hydroxy or carboxy group in the molecule, a complex polymer may be formed. Such complex polymer may consist of acyclic, as well as cyclic, structures.

(c) Miscellaneous dimers and polymers. This group includes all the dimeric and polymeric forms of hydroxy-carboxylic acids, which can not be represented by any one of the above two generic structures, such as those formed from tropic acid, trethacanic acid, and septic acid. When a hydroxyacrylic acid has more than one hydroxy or carboxy group in the molecule, a complex polymer may be formed. Such complex polymer may consist of acyclic, as well as cyclic, structures.

The following hydroxyacrylic acids have more than one hydroxy group: glyceric acid, gluconic acid and gluconolactone, galactaric acid and galactarolactone, gluconic acid and gluconolactone, riboc acid and ribono- lactone, galactaric acid and galactarolactone, ascorbic acid, gulonic acid and gulonolactone, glucoseptonic acid and glucoseptonic lactone. These polyhydroxyacrylic acids can form complex polymers with themselves or with other simple monohydroxymonocarboxylic acids.

The following hydroxyacrylic acids have more than one carboxy group: malic acid, citric acid, citramalic acid, tartaric acid, garagic acid and isocitric acid. These monohydroxypolyacrylic acids can also form complex polymers with themselves or with other simple hydroxyacrylic acids.

The following hydroxyacrylic acids have more than one hydroxy group and more than one carboxy group: tartaric acid, mucic acid, and saccharic acid. These polyhydroxyxypolyacrylic acids can form even more complex polymers with themselves or with other hydroxyacrylic acids.

III. Combination Compositions

Any cosmetic and pharmaceutical agents may be incorporated into amphoteric or pseudoamphoteric compositions, or into compositions containing dimeric or polymeric forms of hydroxycids with or without amphoteric or pseudoamphoteric systems to enhance therapeutic effects of those cosmetic and pharmaceutical agents to improve cosmetic conditions or to alleviate the symptoms of dermatologic disorder. Cosmetic and pharmaceutical agents include those that improve or eradicate age spots, keratoses, and wrinkles; analgesics; antioxidants; antibiotic agents; antifungal agents; antiviral agents; antitumour agents; antidermatitis agents; antipruritic agents; antiemetics; antiinflammatory agents; antihyperkeratolytic agents; antidyshkin agents; antiperspirants; antisperiorotic agents; antiseborrheic agents; hair conditioners and hair treatment agents; antiaging and antiwrinkle agents; antiallergic agents and bronchodilators; sunscreen agents; antihistamine agents; skin lightening agents; depigmenting agents; vitamins; corticosteroids; tanning agents; hormones; retinoids; topical cardiovascular agents and other dermatological agents.

Some examples of cosmetic and pharmaceutical agents are clotrimazone, ketoconazole, miconazole, griseofulvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzonate, erythromycin, tetracycline, clindamycin, metacycloxine, hydroquine, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, renoic acid, 13-cis retinoic acid, hydrocortisone, hydrocortisone 21-acetate, hydrocortisone 17-valerate, hydrocortisone 17- butyrate, betamethasone valerate, betamethasone dipropionate, trimcinolone acetonide, fluocinolone, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate, and vitamin E acetate.

IV. Specific Compositions for Skin Disorders

We have discovered that topical formulations or compositions containing specific alpha hydroxyacids, alpha ketoacids, or related compounds are therapeutically effective for certain skin disorders without utilizing any amphoteric or pseudoamphoteric systems. The alpha hydroxyacids and the related compounds include 2-hydroxyethylenic acid, 2-hydroxypropanoic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethylenic acid, 2-phenyl 2-hydroxyethylenic acid, and 2-phenyl 3-hydroxypropanoic acid. The alpha ketoacids and their esters include 2-ketopropanoic acid, methyl 2-keto- topropanoate, and ethyl 2-ketopropanoate. The mentioned skin disorders include warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

In general, the concentration of the alpha hydroxyacid, the alpha ketoacid, or the related compound used in the composition is a full strength to an intermediate strength, therefore dispensing and the application of such compositions require special handling and procedures.

If the alpha hydroxyacid, the alpha ketoacid, or the related compound at full strength (usually 95-100%) is a liquid form at room temperature, such as 2-hydroxypropanoic acid, 2-ketopropanoic acid, methyl 2-ketopropanoate and ethyl 2-ketopropanoate, the liquid compound with or without a gelling agent may be directly dispensed as 0.5 to 1 ml aliquots in small vials.

If the alpha hydroxyacid, the alpha ketoacid or the related compound at full strength is a solid form at room temperature, such as 2-hydroxyethylenic acid, 2-methyl 2-hydroxypropanoic acid, 2-phenyl 2-hydroxyethylenic acid, 2,2-diphenyl 2-hydroxyethylenic acid, and 2-phenyl 3-hydroxypropanoic acid, the solid compound is first dissolved in a minimal amount of vehicle or vehicle system, such as water, ethanol and/or propylene glycol, with or without a gelling agent. For example, 2-hydroxyethylenic acid 70 g is dissolved in water 30 g, and the 70% strength solution thus obtained is dispensed as 0.5 to 1 ml aliquots in small vials. If a gelling agent is desired, 0.5 to 3% of, for example,
hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose, or carbomer may be incorporated into the above solution.

To prepare an intermediate strength (usually 20%-50%), the alpha hydroxyacid, alpha ketoacid, or related compound either a liquid or solid form at room temperature is first dissolved in a vehicle or vehicle system such as water, acetone, alcohol, propylene glycol and butane 1,3-diol. For example, 2-hydroxyethanoic acid or 2-ketopropanoic acid 30 g is dissolved in ethanol 56 g and propylene glycol 14 g, and the 30% strength solution thus obtained is dispensed as 7 to 14 ml aliquots in dropper bottles.

For topical treatment of warts, keratoses, age spots, acne, nail infections, wrinkles or aging related skin changes, patients are advised to apply a small drop of the medication with a toothpick or a fine brush, such as commonly-available artists’ camel hair brushes, to affected lesions only and not to surrounding skin. Prescribed applications have been 1 to 6 times daily for keratoses and ordinary warts of the hands, fingers, palms, and soles. For age spots, acne, nail infections, wrinkles and aging-related skin changes, topical applications have been 1 to 2 times daily.

Very often, frequency and duration of applications have been modified according to clinical responses and reactions of the lesions, and the patient or responsible family member is instructed accordingly. For example, some clinical manifestations other than pain have been used as a signal to interrupt application. These manifestations include distinct blanching of the lesions or distinct peripheral erythema.

Alternatively, an office procedure may be adapted when a full strength of 2-ketopropanoic acid or 70% 2-hydroxyethanoic acid is used for topical treatment of age spots, keratoses, acne, warts, or facial wrinkles.

We have found that the above mentioned alpha hydroxyacids, alpha ketoacids and related compounds are therapeutically effective for topical treatments of warts, keratoses, age spots, acne, nail infections, wrinkles and aging related skin changes.

Preparation of the Therapeutic Compositions

Amphoteric and pseudoamphoteric compositions of the instant invention may be formulated as solution, gel, lotion, cream, ointment, shampoo, spray, stick, powder, or other cosmetic and pharmaceutical preparations.

To prepare an amphoteric or pseudoamphoteric composition in solution form, at least one of the aforementioned amphoteric or pseudoamphoteric compounds and at least one of the hydroxyacids or the related compounds are dissolved in a solution which may consist of ethanol, water, propylene glycol, acetone, or other pharmaceutically acceptable vehicle. The concentration of the amphoteric or pseudoamphoteric compound may range from 0.01 to 10, the preferred concentration ranges from 0.1 to 3 M. The concentration of hydroxyacids or the related compounds may range from 0.02 to 12 M, the preferred concentration ranges from 0.2 to 5 M.

In the preparation of an amphoteric or pseudoamphoteric composition in lotion, cream or ointment form, at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds are initially dissolved in a solvent such as water, ethanol, and/or propylene glycol. The solution thus prepared is then mixed in a conventional manner with a commonly available cream or ointment base such as hydrophilic ointment or petrolatum. The concentrations of amphoteric or pseudoamphoteric compounds and hydroxyacids used in the compositions are the same as described above.

Amphoteric and pseudoamphoteric compositions of the instant invention may also be formulated in a gel form. A typical gel composition of the instant invention utilizes at least one of the amphoteric or pseudoamphoteric compounds and one of the hydroxyacids or the related compounds. The selected compounds are dissolved in a mixture of ethanol, water, and propylene glycol in a volume ratio of 40:40:20, respectively. A gelling agent such as methyl cellulose, ethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer, or ammoniated glycyrrhizinate is then added to the mixture with agitation. The preferred concentration of the gelling agent may range from 0.1 to 4 percent by weight of the total composition.

Since dimeric and polymeric forms of hydroxyacids are less stable in the presence of water or the like vehicle, cosmetic and pharmaceutical compositions should be prepared as anhydrous formulations. Typical vehicles suitable for such formulations include mineral oil, petrolatum, isopropyl myristate, isopropyl palmitate, diisopropyl adipate, octyl palmitate, acetone, squalene, squalane, silicone oils, vegetable oils, and the like. Therapeutic compositions containing dimeric or polymeric forms of hydroxyacids do not require any incorporation of an amphoteric or pseudoamphoteric compound. The concentration of the dimeric or polymeric form of a hydroxyacid used in the composition may range from 0.1 to 100%, the preferred concentration ranges from 1 to 40%. Therapeutic compositions may be formulated as an anhydrous solution, a lotion, an ointment, a spray, a powder or the like.

To prepare a combination composition in a pharmaceutically acceptable vehicle, a cosmetic or pharmaceutical agent is incorporated into any one of the above compositions by dissolving or mixing the agent into the formulation.

The following are illustrative examples of formulations and compositions according to this invention. Although the examples utilize only selected compounds and formulations, it should be understood that the following examples are illustrative and not limited, therefore, any of the aforementioned amphoteric or pseudoamphoteric compounds, hydroxyacids, dimeric or polymeric forms of hydroxyacids may be substituted according to the teachings of this invention in the following examples.

**EXAMPLE 1**

An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 L-arginine in solution form for dandruff or dry skin may be formulated as follows.

2-Hydroxyethanoic acid (glycolic acid) 7.6 g is dissolved in water 60 ml and propylene glycol 20 ml. L-arginine 8.7 g is added to the solution, with stirring, until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has pH 3.0. An amphoteric composition formulated from 1 M 2-hydroxyethanoic acid
and 1 L-arginine has pH 6.3. The solution has pH 1.9, if no amphoteric compound is incorporated.

EXAMPLE 2

[0249] An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

[0250] 2-Hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.3.

EXAMPLE 3

[0251] An amphoteric composition containing 12-hydroxyethanoic acid and 0.5H 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

[0252] 2-Hydroxyethanoic acid 7.6 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has a pH 3 of 1.

EXAMPLE 4

[0253] A pseudoamphoteric composition containing 12-hydroxyethanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

[0254] 2-Hydroxyethanoic acid 7.6 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has a pH of 3.2. The composition has a pH of 4.0 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 5

[0255] An amphoteric composition containing 1 M 2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

[0256] 2-Hydroxyethanoic acid 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.2.

EXAMPLE 6

[0257] An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M dippeptide of β-alamyl-L-histidine for cosmetic and dermatologic conditions may be formulated as follows.

[0258] 2-Hydroxyethanoic acid 3.8 g and L-camosine (β-alamyl-L-histidine) 11.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 4.5.

EXAMPLE 7

[0259] An amphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.5 M cyclocelucine for cosmetic and dermatologic conditions may be formulated as follows.

[0260] 2-Hydroxyethanoic acid 3.8 g and 1-aminocyclopentane-1-carboxylic acid (cycloelucine) 6.5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved a sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.2.

EXAMPLE 8

[0261] A pseudoamphoteric composition containing 0.5 M 2-hydroxyethanoic acid and 0.25 M 1,12-diaminododecane for cosmetic and dermatologic conditions may be formulated as follows.

[0262] 2-Hydroxyethanoic acid 3.8 g and 1,12-diaminododecane 5 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 9

[0263] An amphoteric composition containing 0.5H 2-hydroxyethanoic acid and 5% protamine for cosmetic and dermatologic conditions may be formulated as follows.

[0264] 2-Hydroxyethanoic acid 3.8 g and protamine 5 g, isolated and purified from salmon sperm, are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.2.

EXAMPLE 10

[0265] An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

[0266] 2-Hydroxypropanoic acid (DL-lactic acid) USP grade 9.0 g is dissolved in water 60 ml and propylene glycol 20 ml. L-arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.1. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-arginine has a pH of 6.9. The solution has a pH of 1.9 if no amphoteric compound is incorporated.

EXAMPLE 11

[0267] An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M L-lysine in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

[0268] 2-Hydroxypropanoic acid 9.0 g and L-lysine 7.3 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water
emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.6. An amphoteric composition formulated from 1 M 2-hydroxypropanoic acid and 1 M L-lysine has a pH of 8.4.

EXAMPLE 12

[0269] An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

[0270] 2-Hydroxypropanoic acid 9.0 g and 4-aminobutanoic acid 5.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has a pH of 3.0.

EXAMPLE 13

[0271] pseudoamphoteric composition containing 1 M 2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

[0272] 2-Hydroxypropanoic acid 9.0 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has a pH of 3.3. The composition has a pH of 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 14

[0273] An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

[0274] 2-Hydroxypropanoic acid 9.0 g and L-histidine 15.5 g are dissolved in 35 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated was a pH of 4.9.

EXAMPLE 15

[0275] An amphoteric composition containing 1 M 2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

[0276] 2-Hydroxypropanoic acid 9.0 g and glycyglycine 13.2 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved, a sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.0.

EXAMPLE 16

[0277] An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M L-arginine in solution form for dandruff or dry skin may be formulated as follows.

[0278] 2-Methyl-2-hydroxypropanoic acid (methylactic acid) 10.4 g is dissolved in water 60 ml and propylene glycol 20 ml. L-arginine 8.7 g is added to the solution with stirring until all the crystals are dissolved. Ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.3. An amphoteric composition formulated from 1 M 2-methyl-2-hydroxypropanoic acid and 1 M L-arginine has a pH of 6.5. The solution has a pH of 1.9 if no amphoteric compound is incorporated.

EXAMPLE 17

[0279] An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M 4-aminobutanoic acid in a cream form for dry skin and other dermatologic and cosmetic conditions may be formulated as follows.

[0280] 2-Methyl-2-hydroxypropanoic acid 10.4 g and 4-aminobutanoic acid 5.2 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.2.

EXAMPLE 18

[0281] An amphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 1 M dipeptide of Gly-Gly in lotion form for cosmetic and dermatologic conditions may be formulated as follows.

[0282] 2-Methyl-2-hydroxypropanoic acid 10.4 g and glycyglycine 13.2 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has a pH of 3.0.

EXAMPLE 19

[0283] A pseudoamphoteric composition containing 1 M 2-methyl-2-hydroxypropanoic acid and 0.5 M creatinine in solution form for cosmetic conditions and dermatologic disorders may be formulated as follows.

[0284] 2-Methyl-2-hydroxypropanoic acid 10.4 g is dissolved in water 70 ml and propylene glycol 10 ml. Creatinine 5.7 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has a pH of 3.4. The composition has a pH of 4.4 when 1 M instead of 0.5 M creatinine is incorporated into the formulation.

EXAMPLE 20

[0285] An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-histidine in a cream form for dermatologic and cosmetic conditions may be formulated as follows.

[0286] 2-Phenyl 2-hydroxyethanoic acid (mandelic acid) 7.6 g and L-histidine 7.8 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 5.0. The composition has a pH of 2.2 if no amphoteric compound is incorporated.
EXAMPLE 21

[0287] An amphoteric composition containing 0.5 M 2-phenyl-2-hydroxyethanoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

[0288] 2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-lysine 7.3 g are dissolved in 25 ml of water. The solution thus obtained is mixed with an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 4.6.

EXAMPLE 22

[0289] A pseudoamphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

[0290] 2-Phenyl 2-hydroxyethanoic acid 7.6 g and creatinine 5.7 g are dissolved in 30 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 4.6.

EXAMPLE 23

[0291] An amphoteric composition containing 0.5 M 2-phenyl 2-hydroxyethanoic acid and 0.5 M L-citriulline for cosmetic and dermatologic conditions may be formulated as follows.

[0292] 2-Phenyl 2-hydroxyethanoic acid 7.6 g and L-citriulline 8.8 g are dissolved in water 30 ml, and the solution is mixed with 50 g of an oil-in-water emulsion. The lotion thus obtained is made up to 100 ml in volume with more oil-in-water emulsion. The amphoteric composition thus formulated has a pH of 3.0.

EXAMPLE 24

[0293] An amphoteric composition containing 1 M citric acid and 1 M L-arginine for cosmetic conditions and dermatologic disorders may be formulated as follows.

[0294] Citric acid 19.2 g is dissolved in water 50 ml and propylene glycol 10 ml. L-Arginine 17.4 g is added to the solution with stirring until all the crystals are dissolved. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.0. The composition has a pH of 1.8 if no amphoteric compound is incorporated.

EXAMPLE 25

[0295] A pseudoamphoteric composition containing 1 M citric acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

[0296] Citric acid 19.2 g and creatinine 11.3 g are dissolved in 40 ml of water, and the solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.7.

EXAMPLE 26

[0297] An amphoteric composition containing 1 M malic acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

[0298] 2-Hydroxybutanedioic acid (DL-malic acid) 13.4 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.3. The composition has a pH of 1.8 if no amphoteric compound is incorporated.

EXAMPLE 27

[0299] A pseudoamphoteric composition containing 1 M malic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

[0300] DL-malic acid 13.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has a pH of 3.0. The composition has a pH of 3.8 when 1 M creatinine, instead of 0.5 M creatinine, is incorporated into the formulation.

EXAMPLE 28

[0301] An amphoteric composition containing 1 M tartaric acid and 1 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

[0302] 2,3-Dihydroxybutanedioic acid (DL-tartaric acid) 15.9 g and L-arginine 17.4 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved sufficient amount of water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.0. The composition has a pH of 1.7 if no amphoteric compound is incorporated.

EXAMPLE 29

[0303] A pseudoamphoteric composition containing 1 M tartaric acid and 1 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

[0304] DL-Tartaric acid 15.0 g and creatinine 11.3 g are dissolved in 35 ml of water. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 3.4.

EXAMPLE 30

[0305] An amphoteric composition containing 1 M gluconolactone and 0.5 M L-arginine for cosmetic and dermatologic conditions may be formulated as follows.

[0306] Gluconolactone 17.8 g and L-arginine 8.7 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.1. The composition has a pH of 5.9 when 1 M instead of 0.5 M L-arginine is incorporated into the formulation. If no amphoteric compound is incorporated, the pH of the composition is 1.8.

EXAMPLE 31

[0307] An amphoteric composition containing 1 M gluconolactone and 0.5 M 4-aminobutanoic acid for cosmetic and dermatologic conditions may be formulated as follows.
Gluconolactone 17.8 g and 4-aminobutanoic acid 5.2 g are dissolved in water 60 ml and propylene glycol 10 ml. After all the crystals have been dissolved sufficient water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.2.

EXAMPLE 32

An amphoteric composition containing 1 M gluconolactone and 1 M dipeptide of Gly-Gly for cosmetic and dermatologic conditions may be formulated as follows.

Gluconolactone 17.8 g and glycylglycine 13.2 g are dissolved in water 50 ml and propylene glycol 5 ml. More water is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 3.1.

EXAMPLE 33

A pseudoamphoteric composition containing 1 M gluconolactone and 0.5 M creatinine for cosmetic conditions and dermatologic disorders may be formulated as follows.

Gluconolactone 17.8 g and creatinine 5.7 g are dissolved in water 60 ml and propylene glycol 10 ml. More water is added to make a total volume of the solution to 100 ml. The pseudoamphoteric composition thus formulated has a pH of 3.2. The composition has a pH of 4.8 when 1 M creatinine, instead of 0.5 M creatinine, is incorporated into the formulation.

EXAMPLE 34

A pseudoamphoteric composition containing 1 M pyruvic acid and 1 M creatinine for dermatologic and cosmetic conditions may be formulated as follows.

2-Ketopropanoic acid (pyruvic acid) 8.8 g and creatinine 11.3 g are dissolved in water 25 ml. The solution thus obtained is mixed with sufficient amount of an oil-in-water emulsion to make a total volume of 100 ml. The amphoteric composition thus formulated has a pH of 3.4.

EXAMPLE 35

An amphoteric composition containing 0.5 M benzoic acid and 0.5 M L-lysine for cosmetic and dermatologic conditions may be formulated as follows.

2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid) 11.4 g and L-lysine 7.3 g are dissolved in water 40 ml and propylene glycol 20 ml. After all the crystals have been dissolved, a sufficient amount of ethanol is added to make a total volume of the solution to 100 ml. The amphoteric composition thus formulated has a pH of 4.9. The composition has a pH of 2.7 if no amphoteric compound is incorporated.

EXAMPLE 36

An amphoteric composition containing 0.5 M benzoic acid and 0.5 M L-histidine for cosmetic and dermatologic conditions may be formulated as follows.

Benzilic acid 11.4 g and L-histidine 7.8 g are dissolved in water 40 ml and propylene glycol 20 ml. Ethyl cellulose 2 g is added with stirring, and a sufficient amount of ethanol is added to make a total volume of the gel to 100 ml. The amphoteric gel composition thus formulated has a pH of 5.0.

EXAMPLE 37

A pseudoamphoteric composition containing 0.5 M benzilic acid and 0.5 M creatinine for cosmetic and dermatologic conditions may be formulated as follows.

Benzilic acid 11.4 g and creatinine 5.7 g are dissolved in water 40 ml and propylene glycol 20 ml. A sufficient amount of ethanol is added to make a total volume of the solution to 1100 ml. The amphoteric composition thus formulated has pH 4.9.

EXAMPLE 38

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05% betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 39

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 40

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.1% trimcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Trimcinolone acetonide 2% solution of aceton/ethanol (50:50), 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 41

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 0.2% 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.
2-Hydroxyethanoic acid 3.8 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol: water (95:5) 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.1.

EXAMPLE 42

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.05% betamethasone dipropionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of a oil-in-water emulsion. Betamethasone dipropionate 1% in ethanol solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.1.

EXAMPLE 43

A pseudoamphoteric composition containing in combination 0.5 M hydroxypropanoic acid and 0.05% clobetasol propionate in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Clobetasol propionate 1% in acetone solution 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.1.

EXAMPLE 44

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.1% triamcinolone acetonide in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. Triamcinolone acetonide 2% solution of acetone:ethanol (50:50) 5 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.1.

EXAMPLE 45

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 0.2% 5-fluorouracil in a cream form for dermatologic disorders may be formulated as follows.

2-Hydroxypropanoic acid 4.5 g and creatinine 5.7 g are dissolved in 20 ml of water, and the solution thus obtained is mixed with 50 g of an oil-in-water emulsion. 5-Fluorouracil 2% solution of propylene glycol:water (95:5), 10 ml is added to the above mixture. More oil-in-water emulsion is added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.1.

EXAMPLE 46

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% clotrimazole in a cream form for athletes’ foot and other fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in water 20 ml and propylene glycol 5 ml, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 47

A pseudoamphoteric composition 0.5 M 2-hydroxyethanoic acid and 2% erythromycin in solution form for acne may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, erythromycin 2 g, and creatinine 5.7 g are dissolved in water 25 ml, ethanol 40 ml, and propylene glycol 15 ml. More water is then added to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 48

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 1% ketoconazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, ketoconazole 1 g and creatinine 5.7 g are dissolved in water 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.2.

EXAMPLE 49

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxypropanoic acid and 2% clotrimazole in a cream form for fungal infections may be formulated as follows.

2-Hydroxypropanoic acid 3.8 g, clotrimazole 2 g and creatinine 5.7 g are dissolved in 25 ml of water, and the solution thus obtained is mixed with enough amount of an oil-in-water emulsion to make a total volume of 100 ml. The pseudoamphoteric composition thus formulated has a pH of 4.1.

EXAMPLE 50

A pseudoamphoteric composition containing in combination 0.5 M 2-hydroxyethanoic acid and 2% tetracycline in a gel form for dermatologic disorders may be formulated as follows.

2-Hydroxyethanoic acid 3.8 g, tetracycline 2 g, creatinine 5.7 g, xanthan gum 0.2 g, carbomer-941 1 g, propylene glycol 5 ml, ethanol 20 ml, and sufficient water
are homogenized to make a total volume of 100 mL. The pseudoamphoteric composition thus formulated for acne and oily skin has a pH of 4.2.

EXAMPLE 51

[0347] An amphoteric composition containing 0.2 M alamic acid and 0.1 M L-lysine in a solution form for cosmetic and dermatologic conditions may be formulated as follows.

[0348] Alamic acid 6.1 g and L-lysine 1.5 g are dissolved in sufficient amount of solution of ethanol:propylene glycol 50:50 to make a total volume of 100 mL. The amphoteric composition thus formulated has a pH of 6.4.

EXAMPLE 52

[0349] A typical composition containing a dimeric form of alpha hydroxyacid in solution for acne or dandruff, and for use as a skin cleanser may be formulated as follows.

[0350] Glycol powder 1.0 g is dissolved in ethanol 89 mL and propylene glycol 10 mL. The composition thus formulated has a pH of 4.0, and contains 1% active ingredient.

EXAMPLE 53

[0351] A typical composition containing a dimeric form of alpha hydroxyacid in ointment for dry skin, psoriasis, eczema, pruritis, wrinkles, and other skin changes associated with aging may be formulated as follows.

[0352] Glycol powder 2.0 g is mixed uniformly with petrolatum 66 g and mineral oil 32 g. The composition thus formulated contains 2% active ingredient.

EXAMPLE 54

[0353] A typical composition containing a full strength or a high concentration of an alpha hydroxyacid, alpha ketoacid, or closely related compound for topical treatments of warts, keratoses, acne, age spots, nail infections, wrinkles and aging-related skin changes may be prepared as follows.

[0354] If the alpha hydroxyacid, alpha ketoacid, or closely related compound at full strength is a liquid form at room temperature such as 2-hydroxypropionic acid, 2-ketopropionic acid, methyl 2-ketopropionate, and/or ethyl 2-keto-propanoate, the compound is directly dispensed as 0.5 to 1 mL aliquots in small vials. If the compound is a solid form at room temperature such as 2-hydroxyethanoic acid and 2-methyl 2-hydroxypropionic acid, it is first dissolved in minimal amount of an appropriate solvent or solvent system such as water or ethanol and propylene glycol with or without a gelling agent. For example, 2-hydroxyethanoic acid 70 g is dissolved in water 30 mL, and the 70% strength 2-hydroxyethanoic acid thus obtained is dispensed as 0.5 to 1 mL aliquots in small vials. If a gelling agent is desired, methyl cellulose or hydroxyethyl cellulose 1 g may be added to the above solution.

EXAMPLE 55

[0355] A typical composition containing an intermediate strength of an alpha hydroxyacid, alpha ketoacid, or closely related compound for topical treatment of warts, keratoses, acne, nail infections, age spots, wrinkles and aging related skin changes may be prepared as follows.

[0356] 2-Hydroxyethanoic acid or 2-ketopropanoic acid 40 g is dissolved in ethanol 54 g and propylene glycol 6 g, and the 40% strength solution thus obtained is dispensed as 5 to 10 mL aliquots in dropper bottles.

Test Results

[0357] In order to determine whether amphoteric and pseudoamphoteric compositions of the instant invention were therapeutically effective for various cosmetic conditions and dermatologic disorders, a total of more than ninety volunteers and patients participated in these studies. Some participating subjects were given two preparations: an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound, and a vehicle placebo. Others were given multiple preparations containing a known pharmaceutical agents such as a corticosteroid with or without incorporation of an amphoteric or pseudoamphoteric composition consisting of an alpha hydroxyacid or the related compound of the instant invention. The amphoteric and pseudoamphoteric compositions were formulated according to the Examples described in the previous section. The results of the tests conducted using these compositions are set forth below.


[0359] Human subjects having ordinary dry skin or with moderate degrees of dry skin as evidenced by dryness, flaking, and cracking of the skin were instructed to apply the preparation twice daily topical application of an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound in amphoteric or pseudoamphoteric composition, to the affected area of the skin. Topical application, two to three times daily, was continued for two to four weeks.

[0360] In all the twenty-eight subjects tested, the feeling of the skin dryness disappeared within a week of topical application. The rough and cracked skin became less pronounced and the skin appeared normal and felt smooth after several days of topical treatment. The alpha hydroxyacid and the related compounds which have been found to be therapeutically effective when incorporated into the amphoteric or pseudoamphoteric compositions for dry skin are as follows:

[0361] 2-hydroxyethanoic acid (glycolic acid), 2-hydroxypropionic acid (lactic acid), 2-methyl-2-hydroxypropanoic acid (methyl lactylactic acid), phenyl 2-hydroxyethanoic acid (mandelic acid), phenyl 2-methyl-2-hydroxyethanoic acid (atrolactic acid), 3-phenyl-2-hydroxypropanoic acid (phenyllactic acid), diphenyl 2-hydroxyethanoic acid (benzilie acid), glucoronolactone, tartaric acid, citric acid, saccharic acid, malic acid, terep acid, glucuronic acid, galacturonic acid, gluconic acid, 3-hydroxybutanoic acid, quinic acid, ribonolactone, glucuronolactone, pyruvic acid, methyl pyruvate, ethyl pyruvate, phenylpyruvic acid, benzoylformic acid, and methyl benzoylelformate.

[0362] The ordinary dry skin conditions, once restored to normal appearing skin, remained improved for some time until causes of dry skin, such as low humidity, cold weather, excessive contact pressure, detergents, soaps, solvents, chemicals, etc., again caused recurrence of the dry skin condition. On continued use it was also found that twice daily topical application of an amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the
related compound of the instant invention prevented the development of new dry skin lesions.

[0363] 2. Severe Dry Skin.

[0364] In severe dry skin, the skin lesions are different from the ordinary dry skin. A main cause of severe dry skin is inherited genetic defects of the skin. The involved skin is hyperplastic, fissured and has thick adherent scales. The degree of thickening is such that lesions are palpably and visually elevated. The thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These two attributes of thickness and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows:

<table>
<thead>
<tr>
<th>Degree of Improvement</th>
<th>None (0)</th>
<th>Mild (1+)</th>
<th>Moderate (2+)</th>
<th>Substantial (3+)</th>
<th>Complete (4+)</th>
</tr>
</thead>
</table>

Thickness
- Highly elevated
- Detectable reduction
- Readily apparent reduction
- Uneven but not rough
- Barely elevated thickness

Texture
- Visibly rough
- Palpably rough
- Slightly uneven
- Visibly and palpably smooth

[0365] By means of such parameters, degrees of change in lesions can be numerically recorded and comparisons made of one treated site to another.

[0366] In order to evaluate the amphoteric and pseudoamphoteric compositions of the instant invention, a total of six patients having severe dry skin conditions were treated with the compositions containing an alpha hydroxyacid or the related compound.

[0367] Tested areas were of a size convenient for topical applications, i.e., circles of 5 cm in diameter were demarcated with a plastic ring of that size inked on a stamp pad. The medicinal lotions or creams were topically applied by the patient in an amount sufficient to cover the treatment sites. Applications were made three times daily and without occlusive dressings. Applications were discontinued at any time when resolutions of the lesion on the treatment area was clinically judged to be complete.

[0368] The test results of amphoteric and pseudoamphoteric compositions containing the following alpha hydroxyacids or the related compounds on patients with severe dry skin are summarized as follows:

[0369] 4+ Effectiveness: glycolic acid, lactic acid, methyl- lactic acid, mandelic acid, tropic acid, atrolactic acid, and pyruvic acid.

[0370] 3+ Effectiveness: benzoic acid, gluconolactone, malic acid, tartaric acid, citric acid, saccharic acid, methyl pyruvate, ethyl pyruvate, phenylactic acid, phenylpyruvic acid, glucuronic acid, and 3-hydroxybutanoic acid.

[0371] 2+ Effectiveness: mucic acid, ribonolactone, 2-hydroxydodecanoic acid, quinic acid, benzoilformic acid, and methyl benzoyleformate.


[0373] The involved skin in psoriasis is hyperplastic (thickened), erythematous (red or inflamed), and has thick adherent scales. The degree of thickening is such that lesions are elevated up to 1 mm above the surface of adjacent normal skin; erythema is usually an intense red; the thickened adherent scales cause the surface of involved skin to be markedly rough and uneven. These three attributes of thickness, color, and texture can be quantified to allow objective measurement of degree of improvement from topically applied test materials as follows:

<table>
<thead>
<tr>
<th>Degree of Improvement</th>
<th>None (0)</th>
<th>Mild (1+)</th>
<th>Moderate (2+)</th>
<th>Substantial (3+)</th>
<th>Complete (4+)</th>
</tr>
</thead>
</table>

Thickness
- Highly elevated
- Detectable Reduction
- Readily apparent reduction
- Uneven but not rough
- Barely elevated thickness

Texture
- Visibly rough
- Palpably rough
- Slightly uneven
- Visibly and palpably smooth

Color
- Intense red
- Red
- Dark pink
- Light pink
- Normal skin color

[0374] By means of such parameters, degree of improvement in psoriatic lesions can be numerically recorded and comparisons made of one treated site to another.

[0375] Patients having psoriasis participated in this study. Amphoteric and pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and a corticosteroid were prepared according to the Examples. Compositions containing only a corticosteroid were also prepared and included in the comparison test. Test areas were kept to minimal size convenient for topical application, i.e., circles of approximately 4 cm in diameter. The medicinal compositions were topically applied by the patient in an amount sufficient to cover the test site [usually about 0.1 milliliter]. More applications were made two to three times daily and without occlusive dressings. Test periods usually lasted for two to four weeks. The test results on patients having psoriasis are summarized on the following table.

[0376] Topical Effects on Psoriasis of Antipsoriatic Compositions

<table>
<thead>
<tr>
<th>Compositions*</th>
<th>Therapeutic Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone 2.5% alone</td>
<td>1+</td>
</tr>
<tr>
<td>With lactic acid</td>
<td>2+</td>
</tr>
<tr>
<td>With glycolic acid</td>
<td>2+</td>
</tr>
<tr>
<td>With ethyl pyruvate</td>
<td>2+</td>
</tr>
<tr>
<td>With methyl pyruvate</td>
<td>2+</td>
</tr>
<tr>
<td>With benzoic acid</td>
<td>2+</td>
</tr>
<tr>
<td>With pyruvic acid</td>
<td>2+</td>
</tr>
<tr>
<td>With methylpyruvic acid</td>
<td>2+</td>
</tr>
<tr>
<td>Hydrocortisone 17-valerate 0.2% alone</td>
<td>2+</td>
</tr>
<tr>
<td>With lactic acid</td>
<td>3+</td>
</tr>
<tr>
<td>With glycolic acid</td>
<td>3+</td>
</tr>
<tr>
<td>With benzoic acid</td>
<td>3+</td>
</tr>
<tr>
<td>With ethyl pyruvate</td>
<td>3+</td>
</tr>
<tr>
<td>With methyl pyruvate</td>
<td>3+</td>
</tr>
<tr>
<td>With gluconolactone</td>
<td>3+</td>
</tr>
</tbody>
</table>
Except the “alone” preparations, all others were amphoteric or pseudoamphoteric compositions containing 0.2 to 2 M alpha hydroxycids or related compounds.

We have also found that an amphoteric or pseudoamphoteric composition containing an alpha hydroxycid or the related compound in combination with an antimetabolite agent such as 5-fluorouracil with or without additional incorporation of a corticosteroid is therapeutically effective for topical treatment of psoriasis.

Eczema.

In a topical treatment of eczema patients, hydrocortisone alone at 2.5% or hydrocortisone 17-valerate alone at 0.2% would achieve only 2+ improvement, and betamethasone dipropionate or clobetasol propionate alone at 0.05% would achieve only a 3+ improvement on all the eczema patients tested. Test results of amphoteric and pseudoamphoteric compositions containing both a corticosteroid and one of the following alpha 15 hydroxycids or the related compounds are shown as follows:

<table>
<thead>
<tr>
<th>Composition*</th>
<th>Therapeutic Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>With pyruvic acid</td>
<td>3+</td>
</tr>
<tr>
<td>Betamethasone dipropionate 0.05% alone</td>
<td>3+</td>
</tr>
<tr>
<td>With lactic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With glycolic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With ethyl pyruvate</td>
<td>4+</td>
</tr>
<tr>
<td>With methyl pyruvate</td>
<td>4+</td>
</tr>
<tr>
<td>With mandelic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With benzoic acid</td>
<td>4+</td>
</tr>
<tr>
<td>Clobetasol propionate 0.05% alone</td>
<td>3+</td>
</tr>
<tr>
<td>With lactic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With glycolic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With ethyl pyruvate</td>
<td>4+</td>
</tr>
<tr>
<td>With methyl pyruvate</td>
<td>4+</td>
</tr>
<tr>
<td>With methyllactic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With mandelic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With tropic acid</td>
<td>4+</td>
</tr>
<tr>
<td>With benzoic acid</td>
<td>4+</td>
</tr>
</tbody>
</table>

The degree of improvement of oily skin, as well as the rate of improvement of acne lesions, were clinically evaluated. Most participants reported that oiliness of skin disappeared within one to two weeks of topical administration, and the skin so treated became smooth and soft. Many participating subjects preferred gel preparations than the solution compositions. It was found that all the participants showed substantial improvements of oily skin and acne lesions by six weeks of topical administration of amphoteric or pseudoamphoteric compositions containing alpha hydroxycids or the related compounds of the instant invention.

Those alpha hydroxycids and the related compounds which have been found to be therapeutically effective for oily skin and as skin cleansers include: benzoic acid, glycolic acid, lactic acid, methylactic acid, mandelic acid, pyruvic acid, ethyl pyruvate, methyl pyruvate, tropic acid, malic acid, gluconolactone, 3-hydroxybutanoic acid, glycolide and polyglycolic acid. As a skin cleanser for oily skin or acne-prone skin, the amphoteric or pseudoamphoteric composition containing an alpha hydroxycid or the related compounds may also be incorporated with other dermatologic agents. For example, an amphoteric gel composition may consist of both an alpha hydroxycid and erythromycin or tetracycline.

6. Acne.

Amphoteric and pseudoamphoteric compositions containing alpha hydroxycids or the related compounds of the instant invention in a solution or gel form were provided to patients having comedogenic and/or papulopustular lesions of acne. Each participating patient was instructed to apply topically the composition on the involved areas of the skin such as forehead, face and chest. Three times daily administration was continued for six to twelve weeks.

The degree and rate of improvement on acne lesions were clinically evaluated. It was found that acne lesions consisting mainly of comedones improved substantially after six to eight weeks of topical administration with the amphoteric or the pseudoamphoteric composition containing an alpha hydroxycid or the related compound. The time for complete clearing of comedogenic acne treated with the amphoteric or pseudoamphoteric composition of the instant invention varied from six to twelve weeks.

As a topical treatment for papulopustular and/or pustular acne the amphoteric or pseudoamphoteric composition containing an alpha hydroxycid or the related compound may incorporate in addition an antiacne agent. The antiacne agents include antibiotics such as erythromycin, tetracycline, clindamycin, meclocycline, and minocycline, and retinoids such as retinoic acid. Such combination compositions have been found to be therapeutically more effective for topical treatment of severe acne.

Many small and large discolored lesions, commonly called “age spots” on the face and the back of the hands are benign keratoses, if they are not variants of actinic keratoses. Very few of such age spots are true lentigines, therefore alpha hydroxycids and the related compounds may be effective in eradicating most age spots without concurrent use of skin bleaching agents such as hydro-
quinone and monobenzone. However, additional beneficial effects have been found when a skin bleaching agent such as hydroquinone or monobenzone is also incorporated into the compositions of the instant invention for age spots involving pigmented lesions.

[0393] Amphoteric and pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds, with or without incorporation of hydroquinone were provided to volunteer subjects and patients having age spot keratoses, melasma, lentigines and/or other pigmented lesions. Each participating subject received two products, i.e., products with or without the addition of 2% hydroquinone to the amphoteric or pseudoamphoteric composition containing an alpha hydroxyacid or the related compound.

[0394] The volunteer subjects and patients were instructed to apply topically one medication on one side of the body such as left side of the face or on the back of the left hand, and the other medication on the other side of the body such as on right side of the face or on the back of the right hand. Specific instructions were given to the participating subjects that the medications were applied three times daily to the lesions of age spot keratoses, melasma, lentigines and/or other pigmented lesions. Clinical photos were taken of participating subjects before the initiation of the topical treatment and every four weeks during the course of treatment.

[0395] At the end of four to eight weeks, improvement of age spot keratoses was clinically discernible. After four to six months of topical treatment, substantial improvement of age spot keratoses occurred in the majority of subjects tested. Complete eradication of age spot keratoses occurred after six to nine months of topical administration with the amphoteric or pseudoamphoteric compositions of the instant inventions.

[0396] Amphoteric or pseudoamphoteric compositions containing both an alpha hydroxyacid or the related compound and hydroquinone were judged to be more effective in eradicating pigmented age spots, melasma, lentigines, and other pigmented lesions.

[0397] The alpha hydroxyacids and the related compounds which have been found to be therapeutically effective for age spots with or without combination with hydroquinone include glycolic acid, lactic acid, methylylactic acid, mandelic acid, pyruvic acid, methyl pyruvate, ethyl pyruvate, benzoic acid, gluconolactone, malic acid, tartaric acid, citric acid, and troagic acid. For flat or slightly elevated seborrheic keratoses on the face and/or the back of the body, amphoteric or pseudoamphoteric compositions containing higher concentrations of alpha hydroxyacids or the related compounds have been found to be effective in eradicating such lesions.

[0398] Actinic keratoses may be successfully treated with amphoteric or pseudoamphoteric compositions containing alpha hydroxyacids or the related compounds in combination with an antimitobolite agent such as 5-fluorouracil.

[0399] 8. Warts.

[0400] Eradication of common warts by topical application of amphoteric or pseudoamphoteric compositions requires higher than usual concentrations of alpha hydroxy-
zole, miconazole, ketoconazole, and griseofulvin. When both feet, but not toenails were involved in the infection, the patients were instructed to apply topically the compositions of the instant invention on the left foot, and a brand-name antifungal product on the right foot. Three times daily applications were continued for one to four weeks. The degree and rate of improvement on skin lesions were clinically evaluated, and comparison was made one side of the body against the other. It was found that the skin lesions improved much faster with the amphoteric or pseudoamphoteric compositions containing both the antifungal agent and the alpha hydroxyacid or the related compound. The alpha hydroxyacids or the related compounds seemed to enhance the efficacies of the antifungal agents, and also to eliminate the discomfort such as itching, tingling, burning and irritation due to fungal infections. When toenails were not involved, the infected skin generally healed within one to two weeks from topical application of the amphoteric or pseudoamphoteric composition containing both an antifungal agent and an alpha hydroxyacid or the related compound.

[0410] Fungal infections of the nails are very difficult to treat, because antifungal products to date are not therapeutically effective for topical treatment of nails. One of the reasons is that most antifungal drugs have not been formulated as bioavailable forms in the commercial products. When toenails were involved in the infections, patients were provided with amphoteric or pseudoamphoteric compositions containing in combination an antifungal agent and an alpha hydroxyacid or an alpha ketoacid at higher concentrations ranging from 20% to 99%, dispersed as 1 to 2 ml aliquots in small vials. The patients were instructed to topically apply the compositions discretely to the infected nail surface by means of a fine artists' paint brush. The technique was the same as for conventional application of nail polish, that is careful avoidance of contact with lateral nail folds or any periangual skin. Once or twice daily applications were continued for two to eight weeks.

[0411] As mentioned above, brand-name antifungal products are usually not effective against fungus infections within or underneath the nail; however, it was found that the amphoteric or pseudoamphoteric compositions containing an antifungal agent and an alpha hydroxyacid or alpha ketoacid were therapeutically effective in eradicating fungal infections of the nails. Such treatment may cause in some instances the treated nail plate to become loose and eventually fall off from the nail bed. This happened quite naturally without any feeling of pain or bleeding, and the skin lesion healed quickly with normal growth of a new nail.


[0413] Wrinkles of skin may be due to natural aging and/or sun damage. Most fine wrinkles on the face are due to natural or innate aging, while coarse wrinkles on the face are the consequence of actinic or sun damage. Although the real mechanism of wrinkles formation in the skin is still unknown, it has been shown that visible fine wrinkles are due to diminution in the number and diameter of elastic fibers in the papillary dermis, and also due to atrophy of dermis as well as reduction in subcutaneous adipose tissue. Histopathology and electron microscopy studies indicate that coarse wrinkles are due to excessive deposition of abnormal elastic materials in the upper dermis and thickening of the skin. At present there are no commercial products that have been found to be therapeutically effective for topical eradication of wrinkles, although retinoic acid (tretinoin) has been shown to be beneficial for sun damaged skin.

[0414] In order to determine whether the amphoteric or pseudoamphoteric composition containing the alpha hydroxyacids, alpha ketoacids or the related compounds are therapeutically effective for wrinkles, patients and volunteer subjects participated in this study. The participants were instructed to apply the formulations of the instant invention twice daily on areas of facial wrinkles for four to twelve months. All participants were told to avoid sun exposure, and to use sunscreen products if exposure to sunlight was unavoidable.

[0415] Photographs of each side of the face for each participant were taken at the beginning of the study and repeated at one to three-month intervals. The participants were asked not to wear any facial make-up at the time of each office visit. Standardized photographic conditions were used including the use of same lot of photographic film, the same light source at two feet from the face, aimed at a focus on the frontal aspect of each cheek. Each time photographs were taken with camera aimed perpendicular to the cheek. At the end of study twenty two participants had been entered into the study for at least four months. Clinical evaluations and review of photographs have revealed substantial reductions in facial wrinkles of the temporal region and check area on at least one side of the face in eighteen cases. Degree of improvement and reduction in wrinkles has been evaluated and determined to be mild to moderate in six participants but very substantial in twelve participants.

[0416] The alpha hydroxyacids, alpha ketoacids, and other related compounds including their lactone forms which may be incorporated into the amphoteric and pseudoamphoteric compositions for cosmetic conditions and dermatologic disorders such as dry skin, acne, age spots, keratoses, warts, and skin wrinkles or in combination with other dermatologic agents to enhance therapeutic effects include the following:

[0417] (1) Alkyl Alpha Hydroxyacids.

[0418] 2-Hydroxyethanoic acid (glycolic acid), 2-Hydroxypropanoic acid (lactic acid), 2-Methyl 2-hydroxypropanoic acid (methyl-lactic acid), 2-Hydroxybutanoic acid, 2-Hydroxypentanoic acid, 2-Hydroxyhexanoic acid, 2-Hydroxyheptanoic acid, 2-Hydroxyoctanoic acid, 2-Hydroxynonanoic acid, 2-Hydroxydecanoic acid, 2-Hydroxyundecanoic acid, 2-Hydroxydodecanoic acid (alpha hydroxylauric acid), 2-Hydroxytetradecanoic acid (alpha hydroxymyristic acid), 2-Hydroxyhexadecanoic acid (alpha hydroxypalmitic acid), 2-Hydroxyoctadecanoic acid (alpha hydroxystearic acid), 2-Hydroxyeicosanoic acid (alpha hydroxyarachidonic acid).

[0419] (2) Aralkyl and Aryl Alpha Hydroxyacids.

[0420] 2-Phenyl 2-hydroxyethanoic acid (mandelic acid), 2,2-Diphenyl 2-hydroxyethanoic acid (benzilic acid), 3-Phenyl 2-hydroxypropanoic acid (phenyllactic acid), 2-Phenyl 2-methyl 2-hydroxyethanoic acid (atrolactic acid), 2-(4'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Chlorophenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(4'-Hydroxy-3'-methoxyphenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxyphenyl) 2-hydroxyethanoic acid, 2-(3'-Hydroxyphenyl) 2-hydroxypropanoic acid.
Hydroxyphenyl) 2-hydroxypropanoic acid; 2-(3', 4'-Dihydroxyphenyl) 2-hydroxyethanoic acid.

[0421] (3) Polyhydroxy Alpha Hydroxyacids.

[0422] 2,3-Dihydroxypropanoic acid (glyceric acid); 2,3, 4-Trihydroxybutanoic acid (Isomers: erythronic acid, threonic acid); 2,3,4,5-Tetrahydroxypentanoic acid (Isomers: ribonic acid, arabinonic acid, xylonic acid, lyxonic acid); 2,3,4,5,6-Pentahydroxyhexanoic acid (Isomers: aldonic acid, altronic acid, gluconic acid, mannoic acid, gulonic acid, idonic acid, galactonic acid, talonic acid); 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers: glucoheptonic acid, galactoheptonic acid, etc.).

[0423] (4) Polycarboxylic Alpha Hydroxyacids.

[0424] 2-Hydroxypropane-1,3-dioic acid (tartronic acid); 2-Hydroxybutane-1,4-dioic acid (malic acid); 2,3-Dihydroxybutane-1,4-dioic acid (tartaric acid); 2-Hydroxy-2-carboxypentane-1,5-dioic acid (citric acid); 2,3,4,5-Tetrahydroxyhexane-1,6-dioic acid (Isomers: saccharic acid, mucoic acid, etc.)

[0425] (5) Alpha Hydroxyacid Related Compounds

[0426] Ascorbic acid, quinic acid, isocitric acid, tropic acid, 3-chloroacetic acid, tretinocanic acid, erucronic acid, citramalic acid, agaricic acid, 2-hydroxynervonic acid, and aleuritic acid.

[0427] (6) Alpha Ketoacids and Related Compounds.

[0428] 2-Ketoethanoic acid (glyoxylic acid); Methyl 2-ketoethanoate; 2-Ketopropanoic acid (pyruvic acid); Methyl 2-ketopropanoate (methyl pyruvate); Ethyl, 2-ketopropanoate (ethyl pyruvate); Propyl 2-ketopropanoate (propyl pyruvate); Phenyl-2-ketoacetic acid (benzoylformic acid); Methyl 2-phenyl-2-ketoethanoate (methyl benzyloformate); Ethyl 2-phenyl-2-ketoethanoate (ethyl benzyloformate); 3-Phenyl-2-ketopropanoic acid (phenylpyruvic acid); Methyl 3-phenyl-2-ketopropanoate (ethyl phenylpyruvate); 2-Ketobutanoic acid; 2-Ketopentanoic acid; 2-Ketohexanoic acid; 2-Ketothanoic acid; 2-Ketoctanonic acid; 2-Ketododecanonic acid; Methyl 2-ketoctanoate.

[0429] The amphoteric and pseudoamphoteric compounds that may be incorporated into the compositions of the instant invention for cosmetic and dermatologic conditions include amino acids, peptides, polypeptides, proteins, and like compounds such as creatinine and creatine.

[0430] The dimeric and polymeric forms of alpha hydroxyacids and the related compounds which may be incorporated into the compositions of the instant invention include acyclic esters and cyclic esters; for example, glycolyl glycollate, lactyl lactate, glycolide, lactide, polyglycolic acid, and polyactic acid.

[0431] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims and all changes which come within the meaning and equivalency of the claims are therefore intended to be embraced therein.

[0432] It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications within the spirit and scope of the present invention as defined by the appended claims.

We claim:

1. A topical skin treating composition comprising:

- a) an effective amount of at least one hydroxy-carboxylic acid, wherein the at least one hydroxy-carboxylic acid is present in the form of a free acid, lactone, or salt,
- b) at least one agent selected from the group consisting of retinoids, wherein the agent is present in stereoisomeric or non-isomeric form, and
- c) a cosmetically-acceptable vehicle.

2. The composition of claim 1 wherein the composition is present in a formulation selected from the group consisting of a solution, a cream, an ointment, and a lotion composition for topical treatment or management of aging-related skin changes.

3. The composition of claim 2 wherein the at least one hydroxy-carboxylic acid is selected from the group consisting of glycolic acid, lactic acid, citric acid, tartaric acid, malic acid, methylactic acid, mandelic acid, 4-hydroxymandelic acid, benzilic acid, ribonic acid, ribonolactone, gluconic acid, gluconolactone, galactonic acid, galactonolactone, glucoheptonic acid, glucoheptonolactone, glucuronic acid, glucuronolactone, galacturonic acid, glucaic acid, gliceralactone, galactaric acid, and galactarolactone.

4. The composition of claim 2 wherein the composition is present in a formulation selected from the group consisting of a solution, a cream, an ointment, and a lotion composition for topical treatment or management of aging-related skin changes.

5. The composition of claim 1 wherein the at least one agent is selected from the group consisting of retinol, retinal, retinoic acid, retinyl acetate, retinyl palmitate, methyl retinoate, ethyl retinoate, propyl retinoate and isopropyl retinoate.

6. The composition of claim 1 wherein the at least one hydroxy-carboxylic acid is selected from the group consisting of gluconolactone and glucarolactone, and the at least one agent is selected from the group consisting of retinol, retinyl acetate, retinyl palmitate, retinal and retinoic acid.