Title: STERoidal COMPOSITIONS CONTAINING HYDROxycarboxylic ACIDS AND METHODS OF USING THE SAME

Abstract: Pharmaceutical compositions suitable for topical administration comprising two active ingredients, a hydroxycarboxylic acid and prednicarbate, and a pyrrolidone carboxylate salt moisturizing agent. In a particular aspect, the two active ingredients in the present inventive compositions have a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the active ingredients. These compositions are used for topical medical applications, particularly to treat steroid responsive dermatoses.
STEROIDAL COMPOSITIONS CONTAINING HYDROXYCARBOXYLIC ACIDS
AND METHODS OF USING THE SAME

FIELD OF THE INVENTION

The present inventive subject matter relates to pharmaceutical compositions suitable for topical administration comprising two active ingredients, a hydroxycarboxylic acid and prednicarbate, and a pyrrolidone carboxylate salt moisturizing agent. In a particular aspect, the two active ingredients in the present inventive compositions have a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the active ingredients. These compositions are used for topical medical applications, particularly to treat steroid responsive dermatoses.

BACKGROUND OF THE INVENTION

Topical medications that include corticosteroids are known in the art as useful for treating skin conditions such as atopic dermatitis, psoriasis and other pathologies of the skin. Current steroid-containing products are available mainly as gels, lotions or ointments that are supplied in tubes or bottles and applied to an affected area of the skin by hand.
However, the results of using corticosteroids in topical treatment of, for example, psoriasis have been variable and unpredictable. In some cases topical corticosteroids seemed to improve and eradicate the psoriatic lesions, but in other cases corticosteroids appeared to be ineffective on topical administration. Drug resistance and rebound worsening are also common features when corticosteroids alone are used in the treatment of psoriasis. Accordingly, it is often required to use corticosteroids in combination with another ingredient that stabilizes and enhances the activity of the corticosteroid.

U.S. Patent No. 3,879,537 describes the use of certain α-hydroxy acids, α-keto acids, and related compounds for topical treatment of fish-scale like ichthyotic conditions in humans.

Similarly, U.S. Patent No. 3,920,835 describes the use of these certain α-hydroxy acids, α-keto acids, and their derivatives for topical treatment of dandruff, acne, and palmar and plantar hyperkeratosis. α-hydroxy acids and α-keto acids, then, were also well known in the art as having dermatological effects.

In view of these prior teachings, U.S. Patent No. 4,246,261 discloses that hydroxy acids and related compounds greatly enhance the therapeutic efficacy of corticosteroids in the topical treatment of such
dermatological disorders as psoriasis, eczema, seborrheic dermatitis, and other inflammatory skin conditions.

A number of products have entered the marketplace taking advantage of this hydroxy acid-corticosteroid combination. For example, the Lacticare-HC Lotion product (Stiefel Laboratories, Inc., Coral Gables, FL) contains a combination of hydrocortisone and lactic acid. This product has been well known for use in the treatment of, for example, pruritis.

Numerous other similar products have entered the marketplace containing a combination of hydroxy acids such as lactic acid and a corticosteroid such as hydrocortisone. The majority of these products, however, contain hydrocortisone as the steroidal active ingredient.

Excessive use of hydrocortisone is well-known to exhibit a variety of undesired side effects, including blurred vision, halos around lights, an irregular heartbeat, insomnia, mood changes, weight gain, fatigue, redness, blistering, burning, itching, peeling, thinning of the skin, and stretch marks. Additionally, it is well known that children are especially sensitive to the unwanted side effects of topically administered hydrocortisone. Accordingly, there remains a need in the art for topical corticosteroid products containing a steroid other than hydrocortisone, especially for the
treatment of children.

Several such topical products containing a steroid other than hydrocortisone have been sold. However, none of these teach or suggest the use of a moisturizing agent which may aid in the therapeutic effects and patient compliance with these compositions. As shown by U.S. Patent No. 5,874,974 it is desirable to include an agent having a moisturizing or emollient effect with a composition containing a steroid to supplement the curative action of the steroid and to enhance the effect of the steroid on the skin.

One deficiency of the prior art topical steroid compositions is the lack of recognition for maintaining a high purity level of the active drugs with a low amount of degradates. This deficiency is overcome with the present formulations which not only contain three essential components but also require a high drug purity and low drug degradates, which increases the effectiveness and shelf-life of the topical composition.

Accordingly, there remains a need in the art for topical steroidal compositions useful in treating a variety of dermatological disorders that contain a steroid other than hydrocortisone, a second ingredient, such as a hydroxy acid, to stabilize and enhance the activity of the steroid, and a moisturizing agent to supplement the curative activity of the steroid. There
further remains a need for such topical compositions that 
maintain a high purity level of the active drug(s) and a 
low level of degradates thereof. The present inventive 
subject matter addresses these needs.

**SUMMARY OF THE INVENTION**

The present inventive subject matter relates to a 
pharmaceutical composition suitable for topical 
administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid 
or a pharmaceutically acceptable salt thereof having a 
purity of at least 90% and a concentration of degradation 
product(s) less than about 10% of the starting 
concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate 
or a pharmaceutically acceptable salt thereof having a 
purity of at least 90% and a concentration of degradation 
product(s) less than about 10% of the starting 
concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone 
carboxylate salt.

In a preferred embodiment, the present inventive 
subject matter relates to a method of treating a steroid 
responsive dermatosis in a mammal, comprising topically 
administering to a mammal in need thereof a 
therapeutically effective amount of a pharmaceutical
composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

In another preferred embodiment, the present inventive subject matter relates to a method of treating diseased tissue in a mammal, comprising topically administering to said diseased tissue a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate
or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

5 about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

In yet another preferred embodiment, the present inventive subject matter relates to use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt

for treating a steroid responsive dermatosis in a

25 patient.

In still another preferred embodiment, the present
inventive subject matter relates to use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt

for treating diseases tissue in a patient.

In a further preferred embodiment, the present inventive subject matter relates to pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two
emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

In still yet another preferred embodiment, the present inventive subject matter relates to a method of treating a steroid responsive dermatosis in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid
derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an \( \alpha \)-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said \( \alpha \)-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

In yet another preferred embodiment, the present inventive subject matter relates to a method of treating diseased tissue in a mammal, comprising topically administering to said diseases tissue a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected
from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbamate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbamate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

In yet another further preferred embodiment, the present inventive subject matter relates to use of an α-hydroxy acid or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising an emulsion comprising:

an oil phase comprising an oily material selected
from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0

for treating a steroid responsive dermatosis in a patient.

In another preferred embodiment, the present inventive subject matter further relates to use of an α-hydroxy acid or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical
composition comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0

for treating diseased tissue in a patient.

In yet another particularly preferred embodiment,

the present inventive subject matter relates to a process for preparing a pharmaceutical composition suitable for
topical administration comprising an emulsion, said process comprising:

1) preparing an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

2) preparing an aqueous phase comprising an \( \alpha \)-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said \( \alpha \)-hydroxy acid and a pyrrolidone carboxylate salt;

3) adjusting the pH of said aqueous phase to a range of about 3.0 to about 6.0.

4) adding said oil phase to said aqueous phase while mixing at a temperature of about 55 to about 85 \( ^{\circ} \)C to obtain a homogenous emulsion;

5) cooling said emulsion to a temperature of about 25 to about 45 \( ^{\circ} \)C;

6) solubilizing prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate in a lower
alkyl alcohol and dispersing said prednicarbate throughout said emulsion; and
7) recovering a topical emulsion pharmaceutical composition.

5 In still another preferred embodiment, the present inventive subject matter relates to pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of lactic acid or a pharmaceutically acceptable salt thereof;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof; and

about 0.5 to about 10% by weight of sodium pyrrolidone carboxylate.

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DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, “degradation products” refers to the product(s) produced by decomposition of one or more of the active ingredients of the present inventive compositions.

As used herein, an “extended period of time” refers to the shelf life of a composition of the present inventive subject matter, including time spent on the shelf at a pharmacy as well as the entire time period after sale of the composition during which the
composition remains effective for the indicated use.

As used herein, "lactones" refers to derivatives of the subject compound(s), modified so that a hydroxyl group and a carboxylic acid group combine to form a cyclic ester, that possess the same pharmacological activity as the subject compound(s) and which are neither biologically nor otherwise undesirable. Non-limiting examples of suitable lactones include gluconolactone, galactonolactone, glucuronolactone, galacturonolactone, gulanolactone, ribonolactone, saccharic acid lactone, pantoyllactone, glucoheptonolactone, mannolactone, and galactoheptonolactone.

As used herein, "pharmaceutically acceptable salts" refers to salts of the active compound(s) which possess the same pharmacological activity as the active compound(s) and which are neither biologically nor otherwise undesirable. A salt can be formed with, for example, organic or inorganic acids. Non-limiting examples of suitable acids include acetic acid, acetylsalicylic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, bisulfic acid, boric acid, butyric acid, camphoric acid, camphorsulfonic acid, carbonic acid, citric acid, cyclopentane propionic acid, digluconic acid, dodecylsulfic acid, ethanesulfonic acid, formic acid, fumaric acid, glyc eric acid, glycerophosphoric acid,
glycine, glucoheptanoic acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hemisulfic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthylanesulfonic acid, naphthyl acid, nicotinic acid, nitrous acid, oxalic acid, pelargonic, phosphoric acid, propionic acid, saccharin, salicylic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, thioglycolic acid, thiosulfuric acid, tosyl acid, undecylenic acid, ethanolamine, naturally and synthetically derived amino acids. Non-limiting examples of base salts include ammonium salts; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; salts with organic bases, such as dicyclohexylamine salts; methyl-D-glucamine; and salts with amino acids, such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl, and diamyl sulfates; long chain halides, such as decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides; asthma halides, such as benzyl and phenethyl
bromides; and others. Water or oil-soluble or dispersible products are thereby obtained.

Other terms as used herein are meant to be defined by their well-known meanings in the art.

**Topical Pharmaceutical Compositions**

The present inventive subject matter pertains to a pharmaceutical composition suitable for topical administration comprising:

- about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;
- about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and
- about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

The present inventive pharmaceutical compositions suitable for topical administration contain two active ingredients: an α-hydroxy acid and prednicarbate. The presence of these two different active ingredients conveys a synergistic, or a greater than additive, effect upon application of the present inventive compositions to
the skin. That is, the present inventive compositions containing both of these active ingredients produce a greater medical effect than would be exhibited by adding the medical effects of an α-hydroxy acid and prednicarbate applied to the same skin separately.

Additionally, the present inventive pharmaceutical compositions contain a moisturizing agent, preferably a pyrrolidone carboxylate salt moisturizing agent. This moisturizing agent acts to further enhance the effects and curative action of the prednicarbate on the skin. Further, the moisturizing agent moisturizes the skin, avoiding normal side effects of corticosteroid use such as drying, redness, blistering, burning, itching, and peeling of the skin. Accordingly, the addition of the moisturizing agent to the present compositions will improve patient compliance with a prescribed treatment regimen.

The present inventive compositions are preferably formed as an oil-in-water emulsion, i.e. an emulsion having an oil phase and an aqueous phase. Preferably, the oil phase of the emulsion comprises an oily material and an emulsifier to aid in formation of the emulsion. More preferably, the oil phase contains at least two emulsifiers.

The first active ingredient, α-hydroxy acid or pharmaceutically acceptable salt thereof, is preferably
contained in the aqueous phase of the emulsion. The aqueous phase additionally preferably contains the moisturizing agent of the present inventive compositions, i.e. the pyrrolidone carboxylate salt. The pH of this aqueous phase, if required, is adjusted to a range of about 3.0 to about 6.0 before it is combined with the oil phase to form the emulsion. In a particularly preferred embodiment, the pH of the aqueous phase is adjusted to a pH range of about 4.0 to about 5.0.

Once the oil phase and the aqueous phase are combined to form the emulsion, the second active ingredient, prednicarbate or a pharmaceutically acceptable salt thereof, is solubilized in a suitable solvent and dispersed throughout the emulsion.

Since the emulsion is an oil-in-water emulsion having water as the major component, the final composition will have a pH mirroring that of the aqueous phase. Accordingly, the pH of the final composition preferably ranges from about 3.0 to about 6.0. In a particularly preferred embodiment, the pH of the final composition ranges from about 4.0 to about 5.0.

These particular emulsion and pH characteristics convey to the present compositions the unique advantages of being able to maintain a high purity level and a low concentration of degradation products of the active ingredients. The high purity level and low concentration
of degradation products permits the present inventive compositions to have a longer shelf life and increased pharmaceutical effectiveness when compared with other corticosteroid products previously known in the art.

In this regard, the present inventive compositions maintain a purity level of at least 90%, preferably at least 92.5%, more preferably at least 95% of each of the active ingredients over an extended period of time.

Likewise, the present inventive compositions are able to maintain a low concentration of degradation product(s) of the active ingredients over an extended period of time. In this regard, the present compositions will maintain a concentration of degradation product(s) less than about 10%, preferably less than about 7.5%, more preferably less than about 5% of the starting concentration of each of the active ingredients. These advantageous properties were previously unknown in the prior art compositions.

**α-Hydroxy Acids**

The present inventive compositions preferably contain about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof as a first active ingredient. In a particularly preferred embodiment, the present inventive compositions contain about 1 to about 10% by weight of the α-hydroxy acid or a pharmaceutically acceptable salt thereof. In a most
preferred embodiment, the present inventive compositions contain about 3 to about 7% by weight of the \( \alpha \)-hydroxy acid or a pharmaceutically acceptable salt thereof.

It is an essential aspect for the present inventive compositions to maintain a purity level of at least 90%, preferably at least 92.5%, more preferably at least 95% of the \( \alpha \)-hydroxy acid over an extended period of time. Likewise, the present inventive compositions are able to maintain a low concentration of degradation product(s) of the \( \alpha \)-hydroxy acid, namely less than about 10%, preferably less than about 7.5%, more preferably less than about 5% of the starting concentration of the \( \alpha \)-hydroxy acid over an extended period of time.

The \( \alpha \)-hydroxy acids useful in the present inventive compositions are 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:

\[
(R_a)\,(R_b)\,\text{C(OH)COOH}
\]

where \( R_a \) and \( R_b \) each independently are an 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. In addition \( R_a \) and \( R_b \) may each carry one or more OH, CHO, COOH, or alkoxy groups having 1 to 9 carbon atoms. The \( \alpha \)-hydroxy acids may exist as stereoisomers as
D, L, and DL forms when Rₐ and Rₐ are not identical.

The α-hydroxy acid may be present in the inventive compositions as a free acid, in lactone form, or in a salt form with an organic base or an inorganic alkali. In a preferred embodiment, the α-hydroxy acid is present in the inventive compositions as a mixture of an acid and a salt.

Typical alkyl, aralkyl and aryl groups for Rₐ and Rₐ include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl, and phenyl, etc. These α-hydroxy acids may be divided into the following non-limiting exemplary groups: (1) alkyl α-hydroxy acids, (2) aralkyl and aryl α-hydroxy acids, (3) polyhydroxy α-hydroxy acids, and (4) polycarboxylic α-hydroxy acids.

The following are representative, non-limiting examples of α-hydroxy acids in each subgroup.

(1) Alkyl α-hydroxy acids

1. 2-Hydroxyethanoic acid (Glycolic acid, hydroxyacetic acid)

   \[(\text{H}) (\text{H}) \text{C(OH)} \text{COOH}\]

2. 2-Hydroxypropanoic acid (Lactic acid)

   \[(\text{CH}_3) (\text{H}) \text{C(OH)} \text{COOH}\]

3. 2-Methyl 2-hydroxypropanoic acid (Methyllactic acid)

   \[(\text{CH}_3) (\text{CH}_3) \text{C(OH)} \text{COOH}\]

4. 2-Hydroxybutanoic acid
(C₂H₅)(H)C(OH)COOH

5. 2-Hydroxypentanoic acid

(C₃H₇)(H)C(OH)COOH

6. 2-Hydroxyhexanoic acid

(C₄H₉)(H)C(OH)COOH

7. 2-Hydroxyheptanoic acid

(C₅H₁₁)(H)C(OH)COOH

8. 2-Hydroxyoctanoic acid

(C₆H₁₃)(H)C(OH)COOH

10. 2-Hydroxynonanoic acid

(C₇H₁₅)(H)C(OH)COOH

10. 2-Hydroxydecanoic acid

(C₈H₁₇)(H)C(OH)COOH

11. 2-Hydroxyundecanoic acid

(C₉H₁₉)(H)C(OH)COOH

12. 2-Hydroxydodecanoic acid (Alpha hydroxylauric acid)

(C₁₀H₂₁)(H)C(OH)COOH

13. 2-Hydroxytetradecanoic acid (Alpha hydroxymyristic acid)

(C₁₂H₂₅)(H)C(OH)COOH

14. 2-Hydroxyhexadecanoic acid (Alpha hydroxypalmitic acid)

(C₁₄H₂₉)(H)C(OH)COOH

15. 2-Hydroxyoctadecanoic acid (Alpha hydroxystearic acid)
(C_{16}H_{34}) (H)C(OH)COOH

16. 2-Hydroxyeicosanoic acid (Alpha hydroxyarachidonic acid)

(C_{18}H_{37}) (H)C(OH)COOH

5 (2) Aralkyl And Aryl α-hydroxy acids

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

(C_6H_5) (H)C(OH)COOH

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

(C_6H_5) (C_6H_5)C(OH)COOH

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

(C_6H_5CH_2) (H)C(OH)COOH

4. 2-Phenyl 2-methyl 2-hydroxyethanoic acid

(Atrolactic acid)

(C_6H_5) (CH_3)C(OH)COOH

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

(HO-C_6H_4) (H)C(OH)COOH

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

(Cl-C_6H_4) (H)C(OH)COOH

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

(HO-,CH_3O-C_6H_3) (H)C(OH)COOH

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

\[(\text{HO-}, \text{CH}_3\text{O-}\text{C}_6\text{H}_3) (\text{H}) \text{C(OH)COOH}\]

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

\[\text{HO-C}_6\text{H}_4\text{-CH}_2(\text{H}) \text{C(OH)COOH}\]

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

\[\text{HO-C}_6\text{H}_4\text{-CH}_2(\text{H}) \text{C(OH)COOH}\]

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

\[\text{HO-}, \text{HO-C}_6\text{H}_3(\text{H}) \text{C(OH)COOH}\]

(3) Polyhydroxy \(\alpha\)-hydroxy acids

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

\[(\text{HOCH}_2)(\text{H}) \text{C(OH)COOH}\]

15. 2,3,4-Trihydroxybutanoic acid (Isomers; erythronic acid, threonic acid)

\[\text{HOCH}_2(\text{HO})\text{CH}_2(\text{H}) \text{C(OH)COOH}\]

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

\[\text{HOCH}_2(\text{HO})\text{CH}_2(\text{HO})\text{CH}_2(\text{H}) \text{C(OH)COOH}\]

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)

\[\text{HOCH}_2(\text{HO})\text{CH}_2(\text{HO})\text{CH}_2(\text{HO})\text{CH}_2(\text{H}) \text{C(OH)COOH}\]
5. 2,3,4,5,6,7-Hexahydroxyheptanoic acid (Isomers; glucoheptonic acid, galactoheptonic acid etc.)

\[ \text{HOCH}_2(\text{HO})\text{CH}_2(\text{HO})\text{CH}_2(\text{HO})\text{CH}_2(\text{HO})\text{CH}_2(\text{H})\text{C(OH)}\text{COOH} \]

(4) Polycarboxylic α-hydroxy acids

5. 2-Hydroxypropane-1,3-dioic acid (Tartronic acid)

\[ \text{HOOC}(\text{H})\text{C(OH)}\text{COOH} \]

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

\[ \text{HOOCCH}_2(\text{H})\text{C(OH)}\text{COOH} \]

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

\[ \text{HOOC}(\text{HO})\text{CH}(\text{H})\text{C(OH)}\text{COOH} \]

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

\[ \text{HOOCCH}_2\text{C(OH)}(\text{COOH})\text{CH}_2\text{COOH} \]

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

\[ \text{HOOC}(\text{CHOH})_4\text{COOH} \]

Particularly preferred α-hydroxy acids useful in the present inventive compositions are those selected from the group consisting of atrolactic acid, benzilic acid, 4-chloromandelic acid, citric acid, 3,4-dihydroxymandelic acid, ethyl pyruvate, galacturonic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, 2-hydroxybutanoic acid, 2-hydroxypentanoic acid, 2-hydroxyhexanoic acid, 2-hydroxyheptanoic acid, 2-hydroxyoctanoic acid, 2-hydroxyxactanoic acid, 2-hydroxynonanoic acid, 2-
hydroxydecanoic acid, 2-hydroxyundecanoic acid, 4-
hydroxymandelic acid, 3-hydroxy-4-methoxymandelic acid,
4-hydroxy-3-methoxymandelic acid, \( \alpha \)-hydroxyarachidonic
acid, \( \alpha \)-hydroxybutyric acid, \( \alpha \)-hydroxyisobutyric acid, \( \alpha \) -
hydroxylauric acid, \( \alpha \)-hydroxymyristic acid, \( \alpha \) -
hydroxypalmitic acid, \( \alpha \)-hydroxystearic acid, 3-(2’-
hydroxyphenyl)lactic acid, 3-(4’-hydroxyphenyl)lactic
acid, lactic acid, malic acid, mandelic acid,
methyllactic acid, methylypyruvate, mucic acid, \( \alpha \) -
phenylactic acid, \( \alpha \)-phenylpyruvic acid, pyruvic acid,
saccharic acid, tartaric acid, tartronic acid, pharmaceutically acceptable salts thereof, and mixtures thereof.

In a most preferred embodiment, the \( \alpha \)-hydroxy acid
is lactic acid or a salt thereof.

**Prednicarbate**

The present inventive compositions further contain
about 0.05 to about 2.0% by weight of the steroid
prednicarbate or a pharmaceutically acceptable salt
thereof as a second active ingredient. In a particularly
preferred embodiment, the present inventive compositions
contain about 0.1 to about 1.0% by weight of the
prednicarbate or a pharmaceutically acceptable salt
thereof. In a most preferred embodiment, the present
inventive compositions contain about 0.15 to about 0.5%
by weight of the prednicarbate or a pharmaceutically
acceptable salt thereof.

It is an essential aspect for the present inventive compositions to maintain a purity level of at least 90%, preferably at least 92.5%, more preferably at least 95% of the prednicarbate over an extended period of time. Likewise, the present inventive compositions are able to maintain a low concentration of degradation product(s) of the prednicarbate, e.g. less than about 10%, preferably less than about 7.5%, more preferably less than about 5% of the starting concentration of the prednicarbate, over an extended period of time.

Prednicarbate is especially useful in the present inventive compositions since children and those having sensitive skin more easily tolerate it than other known steroids, such as hydrocortisone. Accordingly, by virtue of the presence of prednicarbate rather than hydrocortisone, the present inventive compositions permit a greater frequency of administration and a greater amount of drug to be delivered to children and those with sensitive skin.

However, it is further contemplated as within the scope of the presently claimed invention that another steroid may be used as a substitute for the prednicarbate so long as the other steroid maintains a purity level of at least 90% and a concentration of degradation product(s) less than about 10% over an extended period of
time. Additionally, the other steroid must be easier tolerated by children and those with sensitive skin than is hydrocortisone.

Non-limiting examples of such substitute steroids include desonide, triamcinolone acetonide, betamethasone valerate, betamethasone dipropionate, betamethasone benzoate, clobetasol propionate, halcinonide, desoximetasone, amcinonide, fluocinonide, fluandrenolide, alclometasone dipropionate, fluocinolone acetonide, diflorasone diacetate, mometasone furoate, fluorometholone, clocortolone pivalate, halcinonide, and the like.

**Moisturizing Agents**

The present inventive compositions further contain as an essential component a moisturizing agent, preferably about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt as a moisturizing agent. In a particularly preferred embodiment, the present inventive compositions contain about 1 to about 8% by weight of the pyrrolidone carboxylate salt. In a most preferred embodiment, the present inventive compositions contain about 3 to about 7% by weight of the pyrrolidone carboxylate salt.

Preferred non-limiting examples of pyrrolidone carboxylate salts useful in the present inventive compositions include sodium, potassium, chitosan,
magnesium, calcium, strontium, and lithium pyrrolidone carboxylate. A particularly preferred salt in this regard is sodium pyrrolidone carboxylate.

It is further contemplated as within the scope of the presently claimed invention that other moisturizing agents known to those of ordinary skill in the topical pharmaceutical arts may be used as a substitute for the pyrrolidone carboxylate salt. Non-limiting examples of such substitute moisturizing agents include C₃-C₆ diols and triols, glycerin, sorbitol, propylene glycol, dipropylene glycol, 1,3-butylene glycol, glucose, xylitol, maltitol, polyethylene glycol, hyaluronic acid, chondroitin sulfuric acid, polyoxyethylene methylglycoside, and polyoxypropylene methylglycoside.

The addition of the moisturizing agent to the present inventive pharmaceutical compositions enhances the effects and curative action of the prednicarbate on the skin. Further, the moisturizing agent moisturizes the skin, avoiding normal side effects of corticosteroid use such as drying, redness, blistering, burning, itching, and peeling of the skin. Accordingly, the addition of the moisturizing agent to the present compositions will improve patient compliance with a prescribed treatment regimen.

Additional Ingredients
The present inventive compositions are preferably
formed as an oil-in-water emulsion having an oil phase and an aqueous phase. In this regard, the oil phase of the emulsion comprises an oily material and at least one emulsifier to aid in formation of the emulsion.

Non-limiting exemplary oily materials include mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof.

At least one emulsifier is used in the present inventive compositions to form the emulsion. In a preferred embodiment, at least two emulsifiers are present in the oil phase to help form the emulsion. Preferred, non-limiting examples of emulsifiers used in the present inventive compositions include polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, propylene glycol stearate, glyceryl monostearate, polyethylene glycol, fatty alcohols, polymeric ethylene oxide-propylene oxide block polymers (Pluronics), derivatives thereof, pharmaceutically acceptable salts thereof, and mixtures thereof. In a preferred embodiment, the emulsifiers used in the present inventive compositions are either naturally or synthetically prepared.

Particularly preferred emulsifies useful in the present inventive compositions include but are not limited to stearyl alcohol and polyoxyethylene(20)
cetostearyl ether (Ceteareth-20), and glyceryl stearate and polyethyleneglycol-100 (PEG-100)/glyceryl stearate.

The aqueous phase forms the major portion of the present emulsion compositions. Accordingly, the present compositions preferably comprise about 50 to about 98% by weight water. In a particularly preferred embodiment, the present compositions comprise about 55 to about 85% by weight water.

The present inventive compositions may further comprise several additional excipients commonly known to those of ordinary skill in the art as useful in topical compositions. Several non-limiting examples of such additional excipients include antioxidants, chelates, preservatives, emollients, humectants, fluid alkyl alcohols, thickening agents, pH modifier, and mixtures thereof.

Non-limiting examples of specific antioxidants useful in the present inventive compositions include ascorbic acid, fumaric acid, malic acid, alpha tocopherol, ascorbic acid palmitate, butylated hydroxyanisole, propyl gallate, sodium ascorbate, sodium metabisulfite, and mixtures thereof.

Non-limiting examples of specific preservatives useful in the present inventive compositions include methylparaben, benzalkonium chloride, propylparaben, benzoic acid, EDTA, phenolic acid, sorbic acid, benzyl
alcohol, isopropyl alcohol, benzethonium chloride, bronopol, butylparaben, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, ethylparaben, glycerol, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, potassium sorbate, propylene glycol, sodium benzoate, sodium propionate, sorbic acid, thimerosal, and mixtures thereof. A particularly preferred preservative in this regard is methylparaben.

Non-limiting examples of specific emollients useful in the present inventive compositions include myristyl lactate, isopropyl palmitate, light liquid paraffin, cetearyl alcohol, lanolin, mineral oil, petrolatum, ceryl esters wax, cholesterol, glycerol, glycerol monostearate, isopropyl myristate, lecithin, and mixtures thereof. Particularly preferred emollients in this regard are myristyl lactate, isopropyl palmitate, and light liquid paraffin.

Non-limiting examples of specific humectants useful in the present inventive compositions include glycerin, propylene glycol, sorbitol, and triacetin.

Non-limiting examples of specific fluid alkyl alcohols useful in the present inventive compositions include ethanol, isopropyl alcohol, octodecyl alcohol, propyl alcohol, butanol, and pentanol. A particularly preferred fluid alkyl alcohol in this regard is ethanol.

Non-limiting examples of specific thickening agents
useful in the present inventive compositions include cetyl alcohol, Carbomers, acrylates/C10-30 alkyl acrylate
crosspolymers, hydroxystyrylcellulose, hydroxypropylcellulose, polyethylene oxide, and mixtures
thereof. Particularly preferred thickening agents in this regard are cetyl alcohol, Carbomer 940, and
acrylates/C10-30 alkyl acrylate crosspolymer.

The pH modifiers useful in the present inventive compositions include acids, bases, and mixtures thereof.

Preferred non-limiting examples of pH modifiers in this regard include acetic acid, acetylsalicylic acid,
ascorbic acid, boric acid, carbonic acid, citric acid, formic acid, ethanesulfonic acid, fumaric acid,
glycerophosphoric acid, hippuric acid, hydrochloric acid, maleic acid, methanesulfonic acid, nitrous acid, oxalic
acid, phosphoric acid, saccharin, sorbic acid, sulfuric acid, thiosulfuric acid, undecylenic acid, ethanolamine,
triethanolamine, sodium carbonate, sodium acetate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium
citrate, sodium bicarbonate, sodium hydroxide, and mixtures thereof.

In a particularly preferred embodiment, the pH modifier contains a hydroxyl group. A most preferred pH
modifier containing a hydroxyl group useful in the present inventive compositions is sodium hydroxide.
Methods of Treatment

The present inventive subject matter additionally pertains to a method of treating a steroid responsive dermatosis in a mammal, comprising topically administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

Several specific steroid responsive dermatoses may be treated according to the present inventive methods. Exemplary among these dermatoses are contact dermatitis, eczema, atopic dermatitis, ichthyosis, psoriasis, xeroderma, seborrheic dermatitis, nummular dermatitis, stasis dermatitis, lichen simplex chronicus,
dermatophytids, candidiasis, scabies, pityriasis rosea, lichen planus, pityriasis rubra pilaris, bullous pemphigoid, miliaria, acute and chronic eczema, lupus erythematosis, photoallergic reactions, pruritis, and combinations thereof. Other steroid responsive dermatoses known to those of ordinary skill in the art are further contemplated as within the scope of the present inventive subject matter.

The steroid responsive dermatosis treated according to the present inventive methods can have a variety of causes. Several non-limiting examples of such causes include hypersensitivity, IgE mediation, anti-membrane antibody, immune complex disease, cell mediated immunity, and combinations thereof.

The steroid responsive dermatosis may also be caused by an insult to a tissue of the mammal having the dermatosis. Several non-limiting examples of such insults include a physical insult, a chemical insult, an environmental insult, a topically mediated insult, an internally mediated insult, and combinations thereof.

Additionally, said steroid responsive dermatosis may be a secondary physiologic response to a primary disease. Several non-limiting examples of such primary diseases causative of the steroid responsive dermatosis include an infection, an allergic response, a hyperproliferative disorder, an immunologic disorder, a metabolic disorder,
a drug induced response, a disorder related to proper or improper organ function, and combinations thereof.

The steroid responsive dermatosis may cause a variety of symptoms in the mammal afflicted therewith. Non-limiting examples of possible symptoms include inflammation, redness, tissue disruption, tissue deformation, exudates, crusting, pain, pruritis, and mixtures thereof.

In addition to treating steroid responsive dermatosis, the present inventive methods also contemplate using the inventive compositions described herein for treating diseases tissue in a mammal.

**Methods of Production**

The present inventive subject matter further relates to a process for preparing a pharmaceutical composition suitable for topical administration comprising an emulsion, said process comprising:

1) preparing an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

2) preparing an aqueous phase comprising an \( \alpha \)-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a
concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and a pyrrolidone carboxylate salt;

3) adjusting the pH of said aqueous phase to a range of about 3.0 to about 6.0.

4) adding said oil phase to said aqueous phase while mixing at a temperature of about 55 to about 85 °C to obtain a homogenous emulsion;

5) cooling said emulsion to a temperature of about 25 to about 45 °C;

6) solubilizing prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate in a lower alkyl alcohol and dispersing said prednicarbate throughout said emulsion; and

7) recovering a topical emulsion pharmaceutical composition.

In a preferred embodiment of the present inventive subject matter, the oil phase is prepared by mixing an oily material and at least two emulsifiers at a temperature of about 55 to about 85 °C. In a particularly preferred embodiment, the oil phase is prepared by further mixing a thickening agent, an emollient, and a preservative with the oily material and
the at least two emulsifiers.

In another preferred embodiment of the present inventive subject matter, the aqueous phase is prepared by first mixing a preservative followed by a polymer thickening agent in purified water at a temperature of about 55 to about 85 °C before adding an α-hydroxy acid or a pharmaceutically acceptable salt thereof and a pyrrolidone carboxylate salt. Once these ingredients are mixed, a pH modifier is added to the aqueous phase to ensure a pH of about 3.0 to about 6.0, preferably about 4.0 to about 5.0. In a particularly preferred embodiment, the pH is adjusted by adding sodium hydroxide to the aqueous phase. This pH represents the final pH of the composition. It is necessary to adjust the pH of the aqueous phase before addition of the oil phase to ensure that the oil phase does not intermingle with the aqueous phase, destroying the emulsion, during addition of the pH modifier.

In a particularly key aspect of the present inventive process, the emulsion is cooled from a temperature of about 55 to about 85 °C to a temperature of about 25 to about 45 °C before the prednicarbate is dispersed therein. This cooling step is particularly important because a substantial amount of prednicarbate degradation products will form at temperatures above 63 °C. Accordingly, it is necessary to cool the emulsion
before adding the prednicarbate to maintain the high prednicarbate purity and low amount of prednicarbate degradation products essential to the present inventive compositions.

Further contemplated as within the scope of the present inventive subject matter are pharmaceutical compositions produced according to the above-described process, wherein the α-hydroxy acid and the prednicarbate in said compositions each maintain a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the α-hydroxy acid and the prednicarbate. If produced according to the present inventive process, these compositions exhibit chemical and physical stability suitable for topical administration.

The compositions produced according to these processes can further be used in a lotion, cream, ointment, shampoo, or other pharmaceutically acceptable topical dosage form. These compositions can be placed in a suitable containment vessel comprising a product contact surface composed of a material selected from the group consisting of glass, plastic, steel, stainless steel, aluminum, Teflon, polymeric structure, ceramic structure, alloys, and mixtures thereof. These containment vessels are used to facilitate manufacturing, handling, processing, packaging, storage, and
administration of said composition.

**Dosage**

Appropriate dosage levels for the active agents contemplated in the present inventive subject matter are well known to those of ordinary skill in the art. Dosage levels on the order of about 0.001 mg to about 5,000 mg per kilogram body weight of the active therapeutic compounds or compositions are known to be useful in the treatment of the diseases, disorders, and conditions contemplated in the present invention. Typically, this effective amount of the active therapeutic agents will generally comprise from about 0.1 mg to about 100 mg per kilogram of patient body weight per day. Moreover, it will be understood that this dosage of active therapeutic agents can be administered in a single or multiple dosage units to provide the desired therapeutic effect. If desired, other therapeutic agents can be employed in conjunction with those provided by the present inventive subject matter.

As previously discussed, excessive use of hydrocortisone is well-known to exhibit a variety of undesired side effects, including redness, blistering, peeling, thinning of the skin, and stretch marks. These hydrocortisone side effects are especially pronounced in children and those having sensitive skin. The present inventive compositions solve these art-recognized
problems since they contain the steroid prednicarbate, which is more easily tolerated by children and those having sensitive skin, rather than hydrocortisone. Accordingly, the present inventive compositions are especially formulated for pediatric use and for administration to sensitive skin. The present inventive compositions permit a greater frequency of administration and a greater amount of drug to be delivered to children and those with sensitive skin due to inclusion of the steroid prednicarbate rather than hydrocortisone.

The present inventive compositions may be given in a single or multiple doses daily. In a preferred embodiment, the present inventive compositions are given from one to three times daily. Starting with a low dose twice daily and slowly working up to higher doses if needed is a preferred strategy. The amount of active ingredients that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the nature of the disease, disorder, or condition, and the nature of the active ingredients.

It is understood, however, that a specific dose level for any particular patient will depend upon a variety of factors well known in the art, including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the
time of administration; the rate of excretion; drug combination; the severity of the particular disorder being treated; and the form of administration. One of ordinary skill in the art would appreciate the variability of such factors and would be able to establish specific dose levels using no more than routine experimentation.

The optimal pharmaceutical formulations will be determined by one skilled in the art depending upon considerations such as the particular drug or drug combination and the desired dosage. See, for example, "Remington's Pharmaceutical Sciences", 18th ed. (1990, Mack Publishing Co., Easton, PA 18042), pp. 1435-1712, the disclosure of which is hereby incorporated by reference. Such formulations may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the therapeutic agents.

EXAMPLES

The following examples are illustrative of the present inventive subject matter and are not intended to be limitations thereon. All polymer molecular weights are mean average molecular weights. All percentages are based on the percent by weight of the final delivery system or formulation prepared unless otherwise indicated and all totals equal 100% by weight.
**EXAMPLE 1**

The following example illustrates the preparation of a lotion of the present inventive subject matter:

<table>
<thead>
<tr>
<th>% W/W</th>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>64.467</td>
<td>Purified Water</td>
</tr>
<tr>
<td>0.590</td>
<td>Cetyl Alcohol</td>
</tr>
<tr>
<td>2.160</td>
<td>Stearyl Alcohol (and) Ceteareth-20</td>
</tr>
<tr>
<td>0.600</td>
<td>Carbomer 940</td>
</tr>
<tr>
<td>1.4200</td>
<td>Glyceryl Stearate</td>
</tr>
<tr>
<td>2.000</td>
<td>Sodium Hydroxide</td>
</tr>
<tr>
<td>0.800</td>
<td>Myristyl Lactate</td>
</tr>
<tr>
<td>0.050</td>
<td>Methyl paraben</td>
</tr>
<tr>
<td>3.920</td>
<td>Isopropyl Palmitate</td>
</tr>
<tr>
<td>5.200</td>
<td>Sodium pyrrolidone carboxylate</td>
</tr>
<tr>
<td>0.150</td>
<td>Propylparaben</td>
</tr>
<tr>
<td>9.520</td>
<td>Light liquid paraffin</td>
</tr>
<tr>
<td>5.573</td>
<td>Lactic acid</td>
</tr>
<tr>
<td>3.000</td>
<td>Anhydrous ethanol</td>
</tr>
<tr>
<td>0.300</td>
<td>Acrylates/C10-30 Alkyl Acrylate</td>
</tr>
<tr>
<td></td>
<td>Crosspolymer</td>
</tr>
<tr>
<td>0.250</td>
<td>Prednicarbate</td>
</tr>
</tbody>
</table>

100.0%

**Preparation of the composition:**

1. Combine the materials cetyl alcohol, myristyl
lactate, light liquid paraffin, isopropyl palmitate, propylparaben, stearyl alcohol (and) Ceteareth-20, and Glyceryl Stearate PEG-100/Glyceryl Stearate, mix and heat to 70 °C ± 1 °C to form an oil phase.

2. Heat purified water to 70 °C ± 1 °C, add methylparaben and mix until clear. Add Carbomer 940 and Acrylates/C10-30 Alkyl Acrylate Crosspolymer and mix. Add sodium pyrrolidone carboxylate and lactic acid and mix to form an aqueous phase. In a separate vessel dissolve sodium hydroxide in water and add to the aqueous phase.

3. Add the oil phase to the aqueous phase and mix, maintaining the temperature of 70 °C ± 1 °C to form an emulsion. Cool to 35 °C with mixing. Solubilize prednicarbate in anhydrous ethanol, add to the emulsion, and mix.

**EXAMPLE 2**

A patient is suffering from contact dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 3**

A patient is suffering from eczema. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient.
It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 4**

A patient is suffering from atopic dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 5**

A patient is suffering from ichthyosis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 6**

A patient is suffering from psoriasis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 7**

A patient is suffering from xeroderma. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.
EXAMPLE 8

A patient is suffering from seborrheic dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 9

A patient is suffering from nummular dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 10

A patient is suffering from stasis dermatitis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 11

A patient is suffering from lichen simplex chronicus. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 12

A patient is suffering from dermatophytids. A
pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 13**

A patient is suffering from candidiasis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 14**

A patient is suffering from scabies. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 15**

A patient is suffering from pityriasis rosea. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

**EXAMPLE 16**

A patient is suffering from lichen planus. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient.
It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 17

A patient is suffering from pityriasis rubra pilaris. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 18

A patient is suffering from bullous pemphigoid. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 19

A patient is suffering from miliaria. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 20

A patient is suffering from acute eczema. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.
EXAMPLE 21

A patient is suffering from chronic eczema. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 22

A patient is suffering from lupus erythematosis. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 23

A patient is suffering from photoallergic reactions. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

EXAMPLE 24

A patient is suffering from pruritus. A pharmaceutical composition of the present inventive subject matter is topically administered to the patient. It would be expected that the patient would improve his/her condition or recover.

The inventive subject matter being thus described, it will be apparent that the same may be modified or
varied in many ways. Such modifications and variations are not to be regarded as a departure from the spirit and scope of the inventive subject matter, and all such modifications and variations are intended to be included within the scope of the following claims.
WE CLAIM:

1. A pharmaceutical composition suitable for topical administration comprising:

   about 1 to about 30% by weight of an \( \alpha \)-hydroxy acid

or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said \( \alpha \)-hydroxy acid;

   about 0.05 to about 2.0% by weight of prednicarbate

or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

   about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

2. The pharmaceutical composition of claim 1, comprising about 1 to about 10% by weight of said \( \alpha \)-hydroxy acid, about 0.1 to about 1.0% by weight of said prednicarbate, and about 1 to about 8% by weight of said pyrrolidone carboxylate salt.

3. The pharmaceutical composition of claim 2, comprising about 3 to about 7% by weight of said \( \alpha \)-hydroxy acid, about 0.15 to about 0.5% by weight of said prednicarbate, and about 3 to about 7% by weight of said
pyrrolidone carboxylate salt.

4. The pharmaceutical composition of claim 1, wherein said \( \alpha \)-hydroxy acid is present in said composition as an acid or salt.

5. The pharmaceutical composition of claim 1, wherein said \( \alpha \)-hydroxy acid is present in said composition as mixture of an acid and a salt.

6. The pharmaceutical composition of claim 1, wherein said \( \alpha \)-hydroxy acid is selected from the group consisting of atrolactic acid, benzilic acid, 4-chloromandelic acid, citric acid, 3,4-dihydroxymandelic acid, ethyl pyruvate, galacturonic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic 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, 4-hydroxymandelic acid, 3-hydroxy-4-methoxymandelic acid, 4-hydroxy-3-methoxymandelic acid, \( \alpha \)-hydroxyarachidonic acid, \( \alpha \)-hydroxybutyric acid, \( \alpha \)-hydroxisobutyric acid, \( \alpha \)-hydroxylauric acid, \( \alpha \)-hydroxymyristic acid, \( \alpha \)-hydroxypalmitic acid, \( \alpha \)-hydroxystearic acid, 3-(2'-hydroxyphenyl)lactic acid, 3-(4'-hydroxyphenyl)lactic
acid, lactic acid, malic acid, mandelic acid, methyllactic acid, methylpyruvate, mucic acid, α-phenylactic acid, α-phenylpyruvic acid, pyruvic acid, saccharic acid, tartaric acid, tartronic acid, pharmaceutically acceptable salts thereof, and mixtures thereof.

7. The pharmaceutical composition of claim 6, wherein said α-hydroxy acid is lactic acid or a pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of claim 1, wherein said pyrrolidone carboxylate salt is sodium pyrrolidone carboxylate.

9. The pharmaceutical composition of claim 1, wherein said composition has a pH of about 3.0 to about 6.0.

10. The pharmaceutical composition of claim 9, wherein said composition has a pH of about 4.0 to about 5.0.

11. The pharmaceutical composition of claim 1, wherein said composition is an emulsion having an oil phase and an aqueous phase.
12. The pharmaceutical composition of claim 11, wherein said oil phase comprises an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof.

13. The pharmaceutical composition of claim 11, wherein said emulsion is formed using an emulsifier selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, propylene glycol stearate, glyceryl monostearate, polyethylene glycol, fatty alcohols, polymeric ethylene oxide-propylene oxide block polymers, derivatives thereof, pharmaceutically acceptable salts thereof, and mixtures thereof.

14. The pharmaceutical composition of claim 13, wherein said emulsifier is a combination of stearyl alcohol and polyoxyethylene(20) cetostearyl ether, and glyceryl stearate and polyethyleneglycol-100/glyceryl stearate.

15. The pharmaceutical composition of claim 13, wherein said emulsion is formed with an emulsifier that
is either naturally or synthetically prepared.

16. The pharmaceutical composition of claim 11, wherein said oil phase contains at least two emulsifiers.

17. The pharmaceutical composition of claim 1, wherein said α-hydroxy acid and said pyrrolidone carboxylate salt are present in said aqueous phase.

18. The pharmaceutical composition of claim 17, wherein said prednicarbate is dispersed in the emulsion.

19. The pharmaceutical composition of claim 1, wherein said composition further comprises about 50 to about 90% by weight of water.

20. The pharmaceutical composition of claim 1, further comprising an additional excipient selected from the group consisting of antioxidants, chelates, preservatives, emollients, humectants, fluid alkyl alcohols, thickening agents, pH modifier, and mixtures thereof.

21. The pharmaceutical composition of claim 20, wherein said pH modifier is selected from the group consisting of an acid, base, and mixtures thereof.
22. The pharmaceutical composition of claim 20, wherein said pH modifier has a hydroxyl group.

23. The pharmaceutical composition of claim 22, wherein said pH modifier is sodium hydroxide.

24. The pharmaceutical composition of claim 1, wherein said composition is in a lotion, cream, ointment, shampoo, or other pharmaceutically acceptable topical dosage form.

25. The pharmaceutical composition of claim 1, wherein said composition is placed in a suitable containment vessel comprising a product contact surface composed of a material selected from the group consisting of glass, plastic, steel, stainless steel, aluminum, Teflon, polymeric structure, ceramic structure, alloys, and mixtures thereof.

26. The pharmaceutical composition of claim 25, wherein said composition is placed in said suitable containment vessel to facilitate manufacturing, handling, processing, packaging, storage, and administration of said composition.
27. A method of treating a steroid responsive dermatosis in a mammal, comprising topically administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

28. The method of claim 27, wherein said steroid responsive dermatosis has a cause selected from the group consisting of hypersensitivity, IgE mediation, anti-membrane antibody, immune complex disease, cell mediated immunity, and combinations thereof.

29. The method of claim 27, wherein said steroid
responsive dermatosis is caused by an insult to a tissue of said mammal, wherein said insult is selected from the group consisting of a physical insult, a chemical insult, an environmental insult, and combinations thereof.

30. The method of claim 29, wherein said insult is a topical or internally mediated insult.

31. The method of claim 27, wherein said steroid responsive dermatosis is a secondary physiologic response to a primary disease.

32. The method of claim 31, wherein said primary disease is selected from the group consisting of an infection, an allergic response, a hyperproliferative disorder, an immunologic disorder, a metabolic disorder, a drug induced response, a disorder related to proper or improper organ function, and combinations thereof.

33. The method of claim 27, wherein said steroid responsive dermatosis produces a symptom in said mammal selected from the group consisting of inflammation, redness, tissue disruption, tissue deformation, exudates, crusting, pain, pruritis, and mixtures thereof.

34. The method of claim 27, wherein said steroid
responsive dermatosis is selected from the group consisting of contact dermatitis, eczema, atopic dermatitis, ichthyosis, psoriasis, xeroderma, seborrheic dermatitis, nummular dermatitis, stasis dermatitis, lichen simplex chronicus, dermatophytids, candidiasis, scabies, pityriasis rosea, lichen planus, pityriasis rubra pilaris, bullous pemphigoid, miliaria, acute and chronic eczema, lupus erythematosus, photoallergic reactions, pruritis, and combinations thereof.

35. The method of claim 27, wherein the composition is formulated for pediatric use.

36. The method of claim 27, wherein the composition is administered to sensitive skin.

37. A method of treating diseased tissue in a mammal, comprising topically administering to said diseased tissue a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising:

about 1 to about 30% by weight of an \( \alpha \)-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said \( \alpha \)-hydroxy acid;
about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt.

38. Use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising:

about 1 to about 30% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone carboxylate salt

for treating a steroid responsive dermatosis in a patient.
39. The use of claim 38, wherein said steroid responsive dermatosis has a cause selected from the group consisting of hypersensitivity, IgE mediation, anti-membrane antibody, immune complex disease, cell mediated immunity, and combinations thereof.

40. The use of claim 38, wherein said steroid responsive dermatosis is caused by an insult to a tissue of said patient, wherein said insult is selected from the group consisting of a physical insult, a chemical insult, an environmental insult, and combinations thereof.

41. The use of claim 40, wherein said insult is a topical or internally mediated insult.

42. The use of claim 38, wherein said steroid responsive dermatosis is a secondary physiologic response to a primary disease.

43. The use of claim 42, wherein said primary disease is selected from the group consisting of an infection, an allergic response, a hyperproliferative disorder, an immunologic disorder, a metabolic disorder, a drug induced response, a disorder related to proper or improper organ function, and combinations thereof.
44. The use of claim 38, wherein said steroid responsive dermatosis produces a symptom in said patient selected from the group consisting of inflammation, redness, tissue disruption, tissue deformation, exudates, crusting, pain, pruritis, and mixtures thereof.

45. The use of claim 38, wherein said steroid responsive dermatosis is selected from the group consisting of contact dermatitis, eczema, atopic dermatitis, ichthyosis, psoriasis, xeroderma, seborrheic dermatitis, nummular dermatitis, stasis dermatitis, lichen simplex chronicus, dermatophytids, candidiasis, scabies, pityriasis rosea, lichen planus, pityriasis rubra pilaris, bullous pemphigoid, miliaria, acute and chronic eczema, lupus erythematosus, photoallergic reactions, pruritis, and combinations thereof.

46. The use of claim 38, wherein said composition is formulated for pediatric use.

47. The use of claim 38, wherein said composition is formulated for administration to sensitive skin.

48. Use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising:
about 1 to about 30% by weight of an α-hydroxy acid
or a pharmaceutically acceptable salt thereof having a
purity of at least 90% and a concentration of degradation
product(s) less than about 10% of the starting
concentration of said α-hydroxy acid;

about 0.05 to about 2.0% by weight of prednicarbate
or a pharmaceutically acceptable salt thereof having a
purity of at least 90% and a concentration of degradation
product(s) less than about 10% of the starting
concentration of said prednicarbate; and

about 0.5 to about 10% by weight of a pyrrolidone
carboxylate salt

for treating diseases tissue in a patient.

49. A pharmaceutical composition suitable for
topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected
from the group consisting of mineral oil, petrolatum,
petroleum derivatives, fatty acids, fatty acid
derivatives, fatty alcohols, fatty alcohol derivatives,
paraffins, and mixtures thereof and at least two
emulsifiers;

an aqueous phase comprising about 1 to about 10% by
weight of an α-hydroxy acid or a pharmaceutically
acceptable salt thereof having a purity of at least 90%
and a concentration of degradation product(s) less than
about 10% of the starting concentration of said \( \alpha \)-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

50. The pharmaceutical composition of claim 49, wherein said \( \alpha \)-hydroxy acid is present in said composition as an acid or a salt.

51. The pharmaceutical composition of claim 49, wherein said \( \alpha \)-hydroxy acid is present in said composition as a mixture of an acid and a salt.

52. The pharmaceutical composition of claim 49, wherein said \( \alpha \)-hydroxy acid is selected from the group consisting of atralactic acid, benzilic acid, 4-chloromandelic acid, citric acid, 3,4-dihydroxymandelic acid, ethyl pyruvate, galacturonic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic 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, 4-
hydroxymandelic acid, 3-hydroxy-4-methoxymandelic acid,
4-hydroxy-3-methoxymandelic acid, \( \alpha \)-hydroxyarachidonic
acid, \( \alpha \)-hydroxybutyric acid, \( \alpha \)-hydroxyisobutyric acid, \( \alpha \)-
hydroxylauric acid, \( \alpha \)-hydroxymyristic acid, \( \alpha \)-
hydroxypalmitic acid, \( \alpha \)-hydroxystearic acid, 3-(2’-
hydroxyphenyl)lactic acid, 3-(4’-hydroxyphenyl)lactic
acid, lactic acid, malic acid, mandelic acid,
methyllactic acid, methylpyruvate, mucic acid, \( \alpha \)-
phenylactic acid, \( \alpha \)-phenylpyruvic acid, pyruvic acid,
saccharic acid, tartaric acid, tartronic acid,
pharmaceutically acceptable salts thereof, and mixtures
thereof.

53. The pharmaceutical composition of claim 52,
wherein said \( \alpha \)-hydroxy acid or salt thereof is lactic
acid or a pharmaceutically acceptable salt thereof.

54. The pharmaceutical composition of claim 49,
wherein said pyrrolidone carboxylate salt is sodium
pyrrolidone carboxylate.

55. The pharmaceutical composition of claim 49,
wherein said composition has a pH of about 4.0 to about 5.0.

56. The pharmaceutical composition of claim 49, wherein said at least two emulsifiers are selected from the group consisting of polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, propylene glycol stearate, glyceryl monostearate, polyethylene glycol, fatty alcohols, polymeric ethylene oxide-propylene oxide block polymers, derivatives thereof, pharmaceutically acceptable salts thereof, and mixtures thereof.

57. The pharmaceutical composition of claim 56, wherein said at least two emulsifiers are stearyl alcohol and polyoxyethylene(20) cetostearyl ether, and glyceryl stearate and polyethyleneglycol-100/glyceryl stearate.

58. The pharmaceutical composition of claim 49, wherein said composition comprises about 50 to about 98% by weight of water.

59. The pharmaceutical composition of claim 49, further comprising an additional excipient selected from the group consisting of antioxidants, chelates, preservatives, emollients, humectants, fluid alkyl alcohols, thickening agents, pH modifier, and mixtures
thereof.

60. The pharmaceutical composition of claim 59, wherein said pH modifier is selected from the group consisting of an acid, base, and mixtures thereof.

61. The pharmaceutical composition of claim 59, wherein said pH modifier has a hydroxyl group.

62. The pharmaceutical composition of claim 61, wherein said pH modifier is sodium hydroxide.

63. The pharmaceutical composition of claim 49, wherein said composition is in a lotion, cream, ointment, shampoo, or other pharmaceutically acceptable topical dosage form.

64. A method of treating a steroid responsive dermatosis in a mammal, comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives,
paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

65. A method of treating diseased tissue in a mammal, comprising topically administering to said diseases tissue a therapeutically effective amount of a pharmaceutical composition suitable for topical administration comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid
derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an $\alpha$-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said $\alpha$-hydroxy acid and about 1 to about 8% by weight of a pyrrolidine carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0.

66. Use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising an emulsion comprising:

an oil phase comprising an oily material selected from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid
derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

an aqueous phase comprising about 1 to about 10% by weight of an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and

about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,

wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0

for treating a steroid responsive dermatosis in a patient.

67. Use of prednicarbate or a pharmaceutically acceptable salt thereof for the preparation of a topical pharmaceutical composition comprising an emulsion comprising:

an oil phase comprising an oily material selected
from the group consisting of mineral oil, petrolatum, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two
emulsifiers;
an aqueous phase comprising about 1 to about 10% by weight of an \( \alpha \)-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said \( \alpha \)-hydroxy acid and about 1 to about 8% by weight of a pyrrolidone carboxylate salt; and
about 0.1 to about 1.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate dispersed throughout said emulsion,
wherein said pharmaceutical composition has a pH of from about 3.0 to about 6.0
for treating diseased tissue in a patient.

68. A process for preparing a pharmaceutical composition suitable for topical administration comprising an emulsion, said process comprising:

8) preparing an oil phase comprising an oily material
selected from the group consisting of mineral oil, petroleum derivatives, fatty acids, fatty acid derivatives, fatty alcohols, fatty alcohol derivatives, paraffins, and mixtures thereof and at least two emulsifiers;

9) preparing an aqueous phase comprising an α-hydroxy acid or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said α-hydroxy acid and a pyrrolidone carboxylate salt;

10) adjusting the pH of said aqueous phase to a range of about 3.0 to about 6.0.

11) adding said oil phase to said aqueous phase while mixing at a temperature of about 55 to about 85 °C to obtain a homogenous emulsion;

12) cooling said emulsion to a temperature of about 25 to about 45 °C;

13) solubilizing prednicarbate or a pharmaceutically acceptable salt thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said prednicarbate in a lower alkyl alcohol and dispersing said prednicarbate throughout said emulsion; and

14) recovering a topical emulsion pharmaceutical
composition.

69. The process of claim 68, wherein said oil phase is prepared by mixing said oily material and said at least two emulsifiers at a temperature of about 55 to about 85 °C.

70. The process of claim 69, wherein said oil phase is prepared by further mixing a thickening agent, an emollient, and a preservative with said oily material and said at least two emulsifiers.

71. The process of claim 70, wherein said aqueous phase is prepared by first mixing a preservative followed by a polymer thickening agent in purified water at a temperature of about 55 to about 85 °C before adding said α-hydroxy acid and said pyrrolidone carboxylate salt.

72. The process of claim 71, wherein said preservative is methylparaben and said polymer thickening agent is selected from the group consisting of carbomer 940, acrylates/C10-30 alkyl acrylate copolymer, and mixtures thereof.

73. The process of claim 68, wherein said α-hydroxy acid is lactic acid or a pharmaceutically acceptable salt.
thereof and said pyrrolidone carboxylate salt is sodium pyrrolidone carboxylate.

74. The process of claim 68, wherein said pH is adjusted by adding sodium hydroxide to said aqueous phase.

75. The process of claim 68, wherein said pH is adjusted to a range of from about 4.0 to about 5.0.

76. The process of claim 68, wherein said α-hydroxy acid is present as mixture of an acid and a salt.

77. A pharmaceutical composition produced according to the process of claim 68, wherein the α-hydroxy acid and the prednicarbate in said composition each maintain a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the α-hydroxy acid and the prednicarbate.

78. The pharmaceutical composition of claim 77, wherein said composition exhibits chemical and physical stability suitable for topical administration.

79. A pharmaceutical composition suitable for
topical administration comprising:

about 1 to about 30% by weight of lactic acid or a pharmaceutically acceptable salt thereof;

about 0.05 to about 2.0% by weight of prednicarbate or a pharmaceutically acceptable salt thereof; and

about 0.5 to about 10% by weight of sodium pyrrolidone carboxylate.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC(7) : A61K 9/10; 7/48
   US CL : 424/401, 78.05; 514/870
   According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
   Minimum documentation searched (classification system followed by classification symbols)
   U.S. : 424/401, 78.05; 514/870

   Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
   NONE

   Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
   Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

   Category * Citation of document, with indication, where appropriate, of the relevant passages
   Y US 6,479,058 A (MCCADDEN et al.) 12 November 2002, see columns 3-5 and column
   9, line 65.

   Relevant to claim No.
   1-79

* Further documents are listed in the continuation of Box C.  See patent family annex.

* "A" document defining the general state of the art which is not considered to be of particular relevance
* "B" earlier application or patent published on or after the international filing date
* "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
* "O" document referring to an oral disclosure, use, exhibition or other means
* "P" document published prior to the international filing date but later than the priority date claimed
* "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* "Y" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* "Z" document member of the same patent family

Date of the actual completion of the international search
08 December 2003 (08.12.2003)

Date of mailing of the international search report
10 MAY 2004

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
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Dwayne C Jones
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Form PCT/ISA/210 (second sheet) (July 1998)
Continuation of B. FIELDS SEARCHED Item 3:
REGISTRY, CAPLUS, USPATFULL, MEDLINE, BIOSIS search terms include: (###hydroxy(6a) acid/), prednicarbate, arolactic acid, benzilic acid, glycolic acid, galcturonic acid, hydroxyarachidonic acid, hydroxylauric acid, hydroxymyristic acid, lactic acid, pyruvic acid, tartaric acid