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(54) **TOPICAL COMPOSITIONS COMPRISING A
CORTICOSTEROID**

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ABSTRACT

Related U.S. Application Data

(60) Provisional application No. 61/951,188, filed on Mar.
11, 2014.

Topical compositions comprising a corticosteroid and at least
one penetration enhancing agent, wherein the composition is
substantially free of propylene glycol.

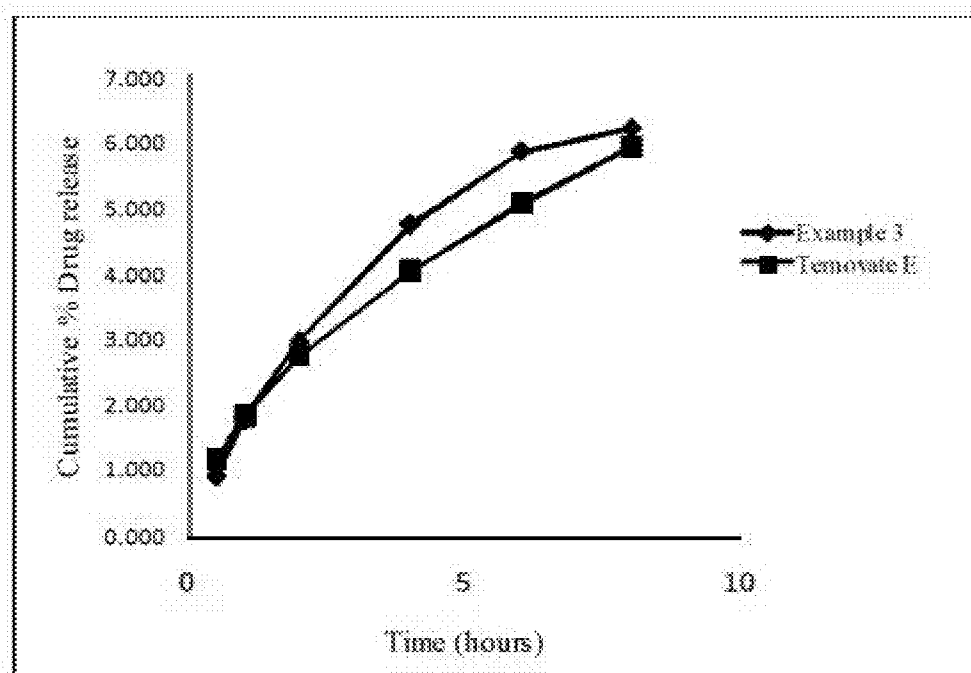


FIGURE 1

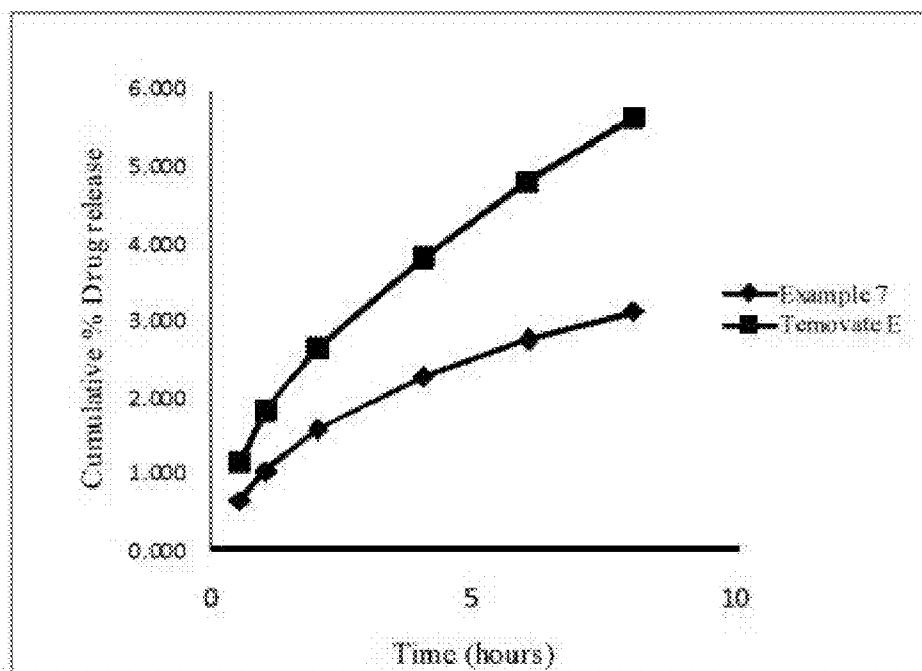


FIGURE 2

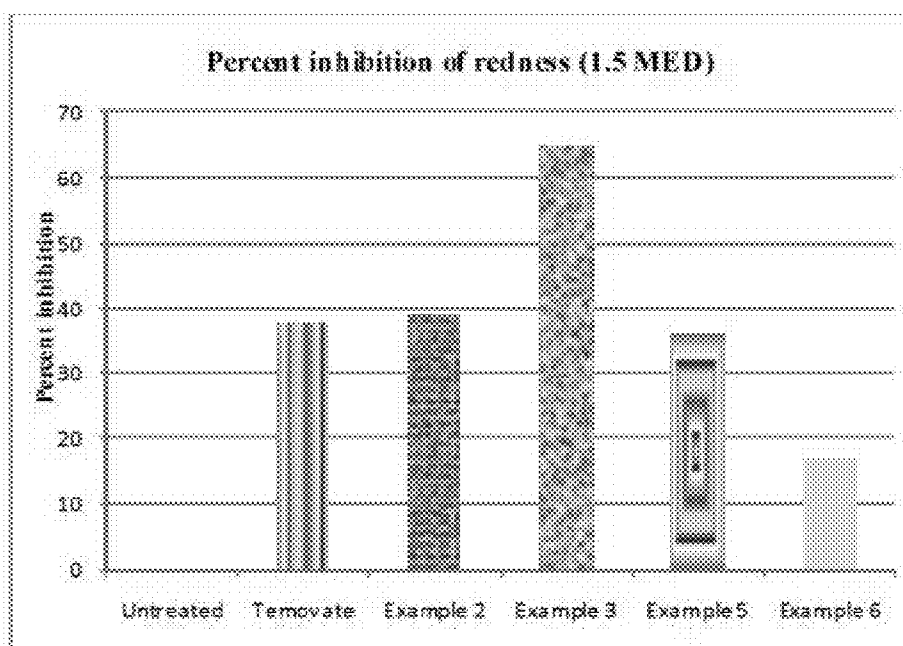


FIGURE 3

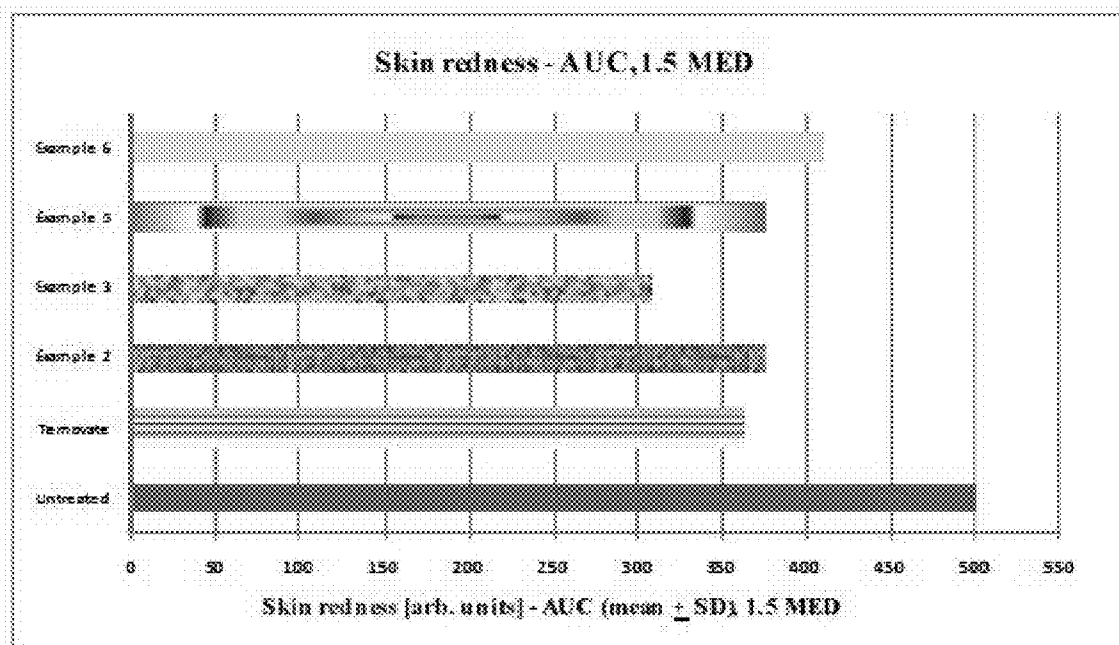


FIGURE 4

TOPICAL COMPOSITIONS COMPRISING A CORTICOSTEROID

RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Application Ser. No. 61/951,188 filed Mar. 11, 2014, the entire disclosure of which is incorporated herein by this reference.

TECHNICAL FIELD

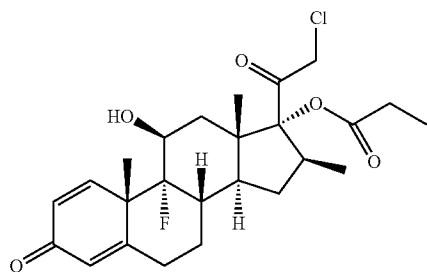
[0002] The present invention relates to a topical composition comprising a corticosteroid and at least one penetration enhancing agent, wherein the composition is substantially free of propylene glycol.

BACKGROUND

[0003] Topical corticosteroids are the most frequently prescribed drugs by dermatologists for treating psoriasis, relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses, and associated diseases or disorders. The corticosteroids are a class of compounds comprising steroids (lipids that contain a hydrogenated cyclopentoperhydrophenanthrene ring system) elaborated by the adrenal cortex (except sex hormones of adrenal origin) in response to the release of adrenocorticotrophin or adrenocorticotrophic hormone by the pituitary gland, or to any synthetic equivalent, or to angiotensin II. In pharmacologic doses, corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

[0004] Topical corticosteroids, such as clobetasol propionate, are effective in treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, antipruritic and vasoconstrictive actions. Clobetasol propionate is used to treat various other skin disorders including eczema and psoriasis. It is also highly effective for contact dermatitis caused by exposure to poison ivy/oak.

[0005] Clobetasol propionate is chemically known as [17-(2'-chloroacetyl)-9-fluoro-11-hydroxy-10,13,16-trimethyl-3-oxo-6,7,8,11,12,14,15,16-octahydrocyclopenta[a]phenanthren-17-yl] propanoate and is represented by structural Formula I:



Formula I

[0006] Clobetasol propionate is commercially available in compositions for topical application in the form of aerosol foam, cream, ointment, gel, solution, lotion, spray or shampoo, in a weight concentration of 0.05%. TEMOVATE Cream® is a commercially available product of clobetasol approved by U.S. Food and Drug Administration (FDA) on Dec. 27, 1985 and is currently being marketed by Fougere

Pharms. TEMOVATE Cream® contains Clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate and purified water. TEMOVATE® E is another approved product by U.S. Food and Drug Administration (FDA) containing Clobetasol propionate (0.05% w/w) in a cream base of cetostearyl alcohol, isopropyl myristate, propylene glycol, ceteth-20, dimethicone 350, citric acid monohydrate, sodium citrate, imidurea, and purified water.

[0007] U.S. Pat. No. 5,972,920 is related to a formulation characterized by a carrier compound formed of a combination of two components in a volume ratio of about 50/50, wherein a first carrier component is selected from the group consisting essentially of ethyl alcohol and isopropyl alcohol and a second carrier component is selected from the group consisting essentially of isopropyl myristate, isopropyl palmitate, octyl palmitate, octyl isononanoate, and isocetyl stearate. The formulation also comprises an anionic surfactant.

[0008] PCT Application WO 2006/115987 is related to a method for treating psoriasis by spraying a pharmaceutical composition containing an effective amount of clobetasol propionate onto the skin with psoriasis, using a daily treatment for at least 4 weeks. The preferred composition is a spray formulation of clobetasol propionate 0.05%, containing alcohol, isopropyl myristate, an anionic surfactant such as sodium lauryl sulfate, and optionally, an antimicrobial compound such as an antifungal compound, e.g., undecylenic acid.

[0009] U.S. Pat. Nos. 6,419,913 and 6,284,234 are related to topical delivery systems for active agents comprising micellar compositions.

[0010] U.S. Publication No. 2006/0099173 is related to a process of making a pharmaceutical composition for topical application, the composition being an emulsion comprising water and at least one active ingredient.

[0011] U.S. Publication No. 2007/0142343 is related to a composition comprising corticosteroids, penetration enhancers, solvents and emulsifiers. The vehicle of this composition utilizes at least two penetration enhancers, including diisopropyl adipate, dimethyl isosorbide, propylene glycol, 1,2,6-hexanetriol, and benzyl alcohol.

[0012] US publication No. 2009/0104131 is related to a topically applicable compositions in the form of oil-in-water (O/W) emulsions contain a pro-penetrating system including at least one glycol and at least one additional pro-penetrating agent, a suitable emulsifying system and at least one active agent of the family of steroidal anti-inflammatory agents. Propylene glycol is disclosed as pro-penetrating agent.

[0013] U.S. Pat. No. 6,579,512 is related to topical spray composition comprising clobetasol propionate, ethanol, propellant and isopropyl myristate.

[0014] U.S. Pat. Nos. 7,700,081 and 7,316,810 are related to clobetasol propionate (0.05 wt %) shampoo compositions used for washing and treating the ailments of scalp.

[0015] Dermatological corticosteroids, in particular clobetasol propionate topical preparations face multiple problems, such as delivery efficiency, stability, and tolerability, in particular with respect to excipients that would not cause irritation. In addition, corticosteroids can be absorbed through the skin and can cause systemic side effects, for example hypothalamic pituitary adrenal (HPA) axis suppression. Therefore, to avoid unwanted side effects, the corticosteroid is used at a concentration as low as possible. However, topical prepara-

tions containing low concentrations corticosteroids cannot ensure a sufficient therapeutic effect.

[0016] U.S. Publication No. 2010/0249060 is related to a low dose clobetasol propionate composition in aqueous vehicle based on propylene glycol and macrogol-glycerol hydroxystearate.

[0017] Although several of the above noted references disclose clobetasol propionate containing compositions, most of them are greasy, and hence are unpleasant to apply on large areas of the skin. In addition, some conventional cream and ointment bases containing propylene glycol are irritating to the skin, particularly over the long exposure that is frequently required for efficacy. The fluidity of lotions often makes their physical application difficult to control over a desired area. Further, formulations containing ethanol or propylene glycol may be associated with an elevated risk of sensitization and have a tendency to induce irritation, and thus, such formulations do not promote patient compliance. The currently available topical compositions comprising clobetasol appears to show adverse effect on endocrine system as described in TEMOVATE Cream® and TEMOVATE E Cream® labels (Hypothalamic-pituitary-adrenal axis suppression).

[0018] Accordingly, there is a long felt need to develop effective topical clobetasol composition with reduced concentration of active, but having an effect comparable to that obtainable with conventional topical clobetasol propionate compositions. Further it is desirable to have a clobetasol propionate composition with improved absorption without causing any skin irritation.

SUMMARY OF THE INVENTION

[0019] Accordingly, the present invention provides a topical pharmaceutical composition comprising at least one corticosteroid and at least one penetration enhancing agent. The composition of the present invention is substantially free of propylene glycol.

[0020] In one aspect, the present invention provides a topical pharmaceutical composition comprising a low dose of clobetasol; an oil phase comprising: at least one penetration enhancing agent and a non-polymeric thickening agent; an aqueous phase; and optionally at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of propylene glycol and substantially free of polymers; wherein the topical composition does not show significant adverse effects on endocrine system.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 shows drug release for a composition of the invention and a commercially available product.

[0022] FIG. 2 shows drug release for a composition of the invention and a commercially available product.

[0023] FIG. 3 shows percent of inhibition of redness for an untreated control, compositions of the invention, and a commercially available product.

[0024] FIG. 4 shows and AUC of skin redness for an untreated control, compositions of the invention, and a commercially available product.

DETAILED DESCRIPTION OF THE INVENTION

[0025] The details of one or more embodiments of the present invention are set forth in this document. Modifications to embodiments described in this document, and other embodiments, will be evident to those of ordinary skill in the

art after a study of the information provided in this document. The information provided in this document, and particularly the specific details of the described exemplary embodiments, is provided primarily for clearness of understanding and no unnecessary limitations are to be understood therefrom. In case of conflict, the specification of this document, including definitions, will control.

[0026] Definitions: The terms as used herein have the following meanings:

[0027] Clobetasol as used herein encompasses pharmaceutically acceptable, pharmacologically active derivatives of clobetasol, including clobetasol propionate, clobetasol base form, its ester form, its isomer form, both individual enantiomers of clobetasol (dextrogyral and levogyral enantiomers) in their substantially pure form and their pharmaceutically acceptable salts, mixtures (in any ratio) of clobetasol enantiomers and their pharmaceutically acceptable salts, and active metabolites of clobetasol and their pharmaceutically acceptable salts, unless otherwise noted. The solid state form of clobetasol used in the composition of the present invention is not critical. For example, clobetasol propionate can be amorphous or crystalline. As will be recognized by one of ordinary skill in the art upon study of this application, clobetasol(s) are corticosteroids. In some embodiment, the terms “active”, “active agent”, or “compound” herein refers to corticosteroids, including clobetasol, or to pharmaceutically acceptable forms thereof.

[0028] The phrase “low dose” as used herein, means an amount of corticosteroid, sufficient to induce a positive effect in the condition to be treated when provided in composition according to the present invention, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. In this regard, the “low dose” is a dose which is below the optimal dose for that corticosteroid when used in a single-compound treatment. The effective amount of the corticosteroid will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

[0029] The term “substantially free” as used herein indicates that the specified substance referred to is present in amounts not more than 10% by weight of the total composition.

[0030] The term “pharmaceutically-acceptable” as used herein, means that inert excipients are suitable for use in contact with the tissues of humans and lower animals without undue toxicity, incompatibility, instability, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

[0031] Terms such as “about,” “up to,” “generally,” “substantially” and the like are to be construed as modifying a term or value such that it is not an absolute. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technical error and instrumental error for a given experiment, technique or an instrument used to measure a value.

[0032] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as reaction condi-

tions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about”. Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the present invention.

[0033] As used herein, ranges can be expressed as from “about” one particular value, and/or to “about” another particular value. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as “about” that particular value in addition to the value itself. For example, if the value “10” is disclosed, then “about 10” is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0034] The present invention can comprise or consist essentially of the components of the present invention as well as other ingredients or elements described herein. As used herein, “comprising” means the elements recited, or their equivalent in structure or function, plus any other element or elements which are not recited. The terms “having,” “including,” and “comprised of” are also to be construed as open ended unless the context suggests otherwise. As used herein, “consisting essentially of” means that the invention may include ingredients in addition to those recited in the claim, but only if the additional ingredients do not materially alter the basic and novel characteristics of the claimed invention.

[0035] As used herein, “optional” or “optionally” means that the subsequently described event or circumstance does or does not occur or exist and that the description includes instances where said event or circumstance occurs or exists, and instances where it does not.

[0036] The term “improved efficacy” or “improving efficacy” or “improving therapeutic efficacy” as used herein refers to the therapeutically beneficial effects of the topical active with reduction of systemic adverse effects as described in the present invention.

[0037] The term “enhanced flux” as used herein refers to increase in the skin permeation of the active in skin layers of the subject up to dermis with less systemic exposure. i.e., enhanced flux allows to utilize lower dose of active to treat disease condition effectively.

[0038] The term “penetration enhancing agent(s)” as used herein means compounds that enhance the penetration rate of a corticosteroid through the skin or mucous membrane, such as by temporarily diminishing the impermeability of the skin or mucous membrane.

[0039] Generally, a penetration enhancing agent is a component used to enhance the penetration rate of steroid through the skin or mucous membrane, such as by temporarily diminishing the impermeability of the skin or membrane. Penetration enhancing agents are also been known as “accelerants” and “absorption promoters.”

[0040] Examples of suitable penetration enhancing agents include, but are not limited to, polyols, glycols (except propylene glycol), ethers, glycol ethers, esters, sulfoxides, fatty acids, fatty acid esters, fatty alcohols, essential oils, terpenes, terpenoids, PEGylated fatty acids, PEGylated fatty acid esters, PEGylated fatty alcohols and mixtures thereof, including polyethylene glycol, polyethylene glycol monolaurate, and butanediol; sulfoxides, including dimethylsulfoxide and decylmethylsulfoxide; ethers, including diethylene glycol monoethyl ether and diethylene glycol monomethyl ether;

fatty acids, including lauric acid, oleic acid, and valeric acid; fatty acid esters, including isopropyl myristate, isopropyl palmitate, methyl propionate, and ethyl oleate; nitrogenous compounds including urea, dimethyl acetamide, dimethylformamide 2-pyrrolidone, ethanolamine, methyl-2-pyrrolidone, diethanolamine, and triethanolamine; terpenes; terpenoids; alkanones; organic acids, including salicylic acid, citric acid, and succinic acid; and combinations comprising one or more of the foregoing materials. In an aspect, the penetration enhancing agent used in the pharmaceutical composition of the present invention is diethylene glycol monoethyl ether. The penetration enhancing agent(s) may interchangeably be used as solvent.

[0041] The term “localized region,” as used herein refers to a discrete location on the body surface of the subject, such as a location experiencing a symptom of condition being treated. As used herein, the term “subject” includes both human and animal subjects. Thus, veterinary therapeutic uses, as well as uses in connection with human subjects, are provided in accordance with the present invention.

[0042] As used herein, the terms “treatment” or “treating” relate to curing or substantially curing a condition, as well as ameliorating at least one symptom of the condition, and are inclusive of prophylactic treatment and therapeutic treatment. As would be recognized by one of ordinary skill in the art, treatment that is administered prior to clinical manifestation of a condition then the treatment is prophylactic (i.e., it protects the subject against developing the condition). If the treatment is administered after manifestation of the condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate, control, or maintain the existing condition and/or side effects associated with the condition). The terms relate to medical management of a subject with the intent to substantially cure, ameliorate, stabilize, or substantially prevent a condition, including but not limited to prophylactic treatment to preclude, avert, obviate, forestall, stop, or hinder something from happening, or reduce the severity of something happening, especially by advance action. As such, the terms treatment or treating include, but are not limited to: inhibiting the progression of a condition of interest; arresting or preventing the development of a condition of interest; reducing the severity of a condition of interest; ameliorating or relieving symptoms associated with a condition of interest; causing a regression of the condition of interest or one or more of the symptoms associated with the condition of interest; and preventing a condition of interest or the development of a condition of interest.

[0043] The present invention includes a topical composition including a corticosteroid. In one aspect, the present invention provides a topical pharmaceutical composition comprising at least one corticosteroid and at least one penetration enhancing agent. The composition of the present invention is substantially free of propylene glycol. In some embodiments, the composition includes not more than 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1% by weight of the total composition.

[0044] In a further aspect, the present invention provides a topical pharmaceutical composition comprising therapeutically effective amount of clobetasol propionate, at least one penetration enhancing agent and at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of propylene glycol. In another aspect, the present invention provides a method to provide an enhanced flux of clobetasol propionate through the localized region of the body surface to reach the dermis layer, comprising admin-

istering to an individual the effective amount of topical pharmaceutical composition comprising:

[0045] (a) low dose of clobetasol propionate,

[0046] (b) an oil phase comprising: at least one penetration enhancing agent and a non-polymeric thickening agent,

[0047] (c) an aqueous phase; and

[0048] (d) optionally, at least one pharmaceutically acceptable excipient; wherein the composition is substantially free of propylene glycol and substantially free of polymers.

[0049] In another aspect, the composition of the present application provides comparable or enhanced efficacy over the commercially available clobetasol propionate 0.05% w/w cream composition (TEMOVATE E® cream) and does not show significant adverse effect on endocrine system as described herein and as known to those of ordinary skill in the art.

[0050] Topical corticosteroids provide adverse effect on human endocrine system. High potent corticosteroids show high incidence of systemic side effects such as suppression of hypothalamus-pituitary-adrenal (HPA) axis this effect is reversible. Topical corticosteroids are absorbed systematically and show suppression of HPA axis. The HPA axis suppression is critical safety issue in topical corticosteroid therapy. The HPA axis suppression is generally evaluated by certain parameters such as levels of cortisol and levels of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) in a subject's blood during treatment schedule. The cortisol levels are determined by ACTH (cosyntropin) stimulation test. The ACTH stimulation test measures how the adrenal glands respond to adrenocorticotrophic hormone (ACTH). ACTH is a hormone produced in the pituitary gland that stimulates the adrenal glands to release a hormone called cortisol. The man-made form of ACTH is called cosyntropin. The normal level of cortisol is less than 18 mcg/dL in a normal subject and cortisol level goes higher than 18 to 20 micrograms per deciliter (mcg/dL) after ACTH injection to the subject and similarly DHEA/DHEAS levels also changes in a subject who undergo treatment with topical corticosteroids, generally the standard reference range of DHEA is 280-640 µg/dL in men and 65-380 µg/dL is in women.

[0051] Clobetasol propionate is a highly potent topical corticosteroid, which is known to have effect on endocrine system which suppresses the HPA axis at doses as low as 2 grams per day. Shortcomings of the previously-described therapy include necessity of periodic evaluation for HPA axis suppression and modification in dosing and administering schedule due to the HPA axis suppression.

[0052] Distinctly, the topical composition of the present invention does not show significant adverse effect on endocrine system, when applied twice daily for 15 days (2 weeks) in the subjects having affected body surface area of at least 20% up to 50% excluding face, scalp, groin, axillae and other intertriginous areas.

[0053] In another aspect, the topical composition of the present invention comprises a therapeutically effective amount of clobetasol; an oil phase comprising at least one skin penetration enhancer; an aqueous phase and optionally one pharmaceutically acceptable excipient.

[0054] In another aspect, the present invention provides a method for prophylaxis, amelioration, or treatment of psoriasis, relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses, erythema, contact sensitivity

reactions, and other associated diseases or disorders, by administering to an individual the effective amount of topical composition comprising:

[0055] (a) a low dose of clobetasol propionate,

[0056] (b) an oil phase comprising: at least one penetration enhancing agent and a non-polymeric thickening agent,

[0057] (c) an aqueous phase; and

[0058] (d) optionally, at least one pharmaceutically acceptable excipient; wherein the composition is substantially free of propylene glycol and substantially free of polymers.

[0059] In another aspect, the clobetasol present in the composition amounts from about 0.005% to about 0.1% of the total weight of the composition. In an aspect, the clobetasol propionate is present in amounts from about 0.005% to about 0.05% of the composition, or in amounts up to about 0.025% of the total weight of the composition.

[0060] In some embodiments of the present invention, the clobetasol propionate is present in amounts up to about 0.005, 0.006, 0.007, 0.008, 0.009, 0.010, 0.011, 0.012, 0.013, 0.014, 0.015, 0.016, 0.017, 0.018, 0.019, 0.020, 0.021, 0.022, 0.023, 0.024, 0.025, 0.026, 0.027, 0.028, 0.029, 0.030, 0.031, 0.032, 0.033, 0.034, 0.035, 0.036, 0.037, 0.038, 0.039, 0.040, 0.041, 0.042, 0.043, 0.044, or 0.045% of the total weight of the composition. In some embodiments, the clobetasol propionate is present in amounts of less than 0.050% of the total weight of the composition. In some embodiments, the clobetasol propionate is present in amounts of about 0.010 to about 0.040% of the total weight of the composition. In some embodiments, the clobetasol propionate is present in amounts of about 0.015 to about 0.035% of the total weight of the composition. In some embodiments, the clobetasol propionate is present in amounts of about 0.020 to about 0.030% of the total weight of the composition.

[0061] In another aspect, the composition of the present invention comprises at least one penetration enhancing agent in an amount of from about 1% to about 30.0% of the weight of the composition, or in amounts of from about 0.01% to about 10.0% of the composition. In aspects of the present invention, the at least one penetration enhancing agent is provided in amounts up to about 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, or 10% of the weight of the composition.

[0062] In another embodiment, the present invention provides a topical pharmaceutical composition comprising: a low dose of clobetasol propionate in an amount selected from about 0.005% to about 0.1% of the total weight of the composition; an oil phase comprising at least one penetration enhancing agent in an amount from about 0.01% to about 15.0% of the total weight of the composition and a non-polymeric thickening agent, an aqueous phase, and optionally, at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of propylene glycol and substantially free of polymers.

[0063] In yet another embodiment, the present invention provides a method for prophylaxis, amelioration or treatment of skin diseases or disorders such as psoriasis/psoriatic plaques, relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses, erythema, contact sensitivity reactions, atopic dermatitis, seborrheic dermatitis, eczema, plaque psoriasis, erythrodermic psoriasis, psoriasis of the scalp, and other associated diseases or disorders, by administering to an individual an effective amount of a

topical composition comprising: (a) clobetasol propionate in an amount of about 0.025% of the total weight of the composition, (b) an oil phase comprising: at least one penetration enhancing agent and a non-polymeric thickening agent, (c) an aqueous phase, and (d) at least one pharmaceutically acceptable excipient,

wherein the composition is substantially free of propylene glycol and the composition has comparable or improved efficacy compared to the commercially available clobetasol propionate 0.05% w/w cream composition (TEMOVATE® cream). In an aspect, the topical composition is administered twice-a-day for a period of 4 weeks or topical composition is administered twice-a-day for a period of at least 2 weeks.

[0064] In another embodiment, the penetration enhancing agent used in the present invention is selected from the group consisting of polyols, glycols (except propylene glycol), ethers, glycol ethers, esters, sulfoxides, fatty acids, fatty acid esters, fatty alcohols, essential oils, terpenes, terpenoids, PEGylated fatty acids, PEGylated fatty acid esters, PEGylated fatty alcohols, and mixtures thereof

[0065] In another aspect of the present invention, the penetration enhancing agent is diethylene glycol monoethyl ether.

[0066] In one embodiment, a composition of the present invention comprises one or more additional active agents that are useful in the management of psoriasis and associated pathological conditions including synthetic, semi-synthetic, or naturally obtained active agents.

[0067] The composition of the present invention can be used for prophylaxis, amelioration, or treatment of skin diseases and disorders, by administering a pharmaceutically effective amount of the composition to a subject in need thereof. The compositions of the present invention are also useful in conjunction with other therapies, such as phototherapy.

[0068] In another aspect, the present invention provides a process for preparing a topical pharmaceutical composition, comprising:

[0069] (i) preparing an oil phase by melting and stirring thickening agent(s), emulsifier(s) followed by preservative(s) and emollient(s);

[0070] (ii) preparing an aqueous phase by heating water,

[0071] (iii) preparing an emulsion by adding the oil phase of step (i) to the aqueous phase of step (ii) or vice versa under constant homogenization,

[0072] (iv) dissolving a premixed solution of clobetasol in a solvent followed by addition of an antioxidant(s) and homogenizing to obtain a clobetasol solution, and

[0073] (v) adding the clobetasol solution obtained in step (iv) to the emulsion prepared in step (iii) followed by homogenization and cooling to obtain a cream composition.

[0074] In yet another aspect, the present invention provides a process for preparing topical pharmaceutical composition comprising:

[0075] (i) preparing an oil phase by melting and stirring stearyl alcohol, cetyl alcohol, whitewax; glyceryl stearate and PEG 100 stearate and emollient, followed by methyl paraben and propyl paraben, and the remaining part of the mineral oil,

[0076] (ii) preparing an aqueous phase by adding sorbitol solution into heated water,

[0077] (iii) preparing an emulsion by adding the oil phase of step (i) to the aqueous phase (ii) or vice versa under homogenization, dissolving a premixed solution of clobetasol propionate in a diethylene glycol monoethyl ether and the fol-

lowed by addition of BHT and homogenizing to obtain a clobetasol propionate solution, and

[0078] (iv) adding the steroid solution obtained in step (iv) to the emulsion prepared in step (iii) followed by homogenization to obtain a cream composition.

[0079] In further aspects, the compositions of the present invention using one or more other corticosteroids can be prepared by using a process similar to that described above.

[0080] The topical pharmaceutical composition of the present invention is useful in the prophylaxis, amelioration or treatment of skin diseases or disorders such as psoriasis/psoriatic plaques, relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses, erythema, contact sensitivity reactions, atopic dermatitis, seborrheic dermatitis, eczema, plaque psoriasis, erythrodermic psoriasis, psoriasis of the scalp, and other associated diseases or disorders.

[0081] In some embodiments of the present invention, it was surprisingly found that the topical compositions of the invention containing an oil phase that comprises at least one penetration enhancing agent, and an aqueous phase, provides an enhanced flux of clobetasol through the localized region of the body surface to reach the dermis layer; this advantageously allows for the use of a lower concentration of clobetasol, i.e., about 50% less than the commercially available dosage form TEMOVATE Cream® (which contains 0.05% of clobetasol propionate), while providing a similar or improved efficacy and provides no significant effect on endocrine system i.e., HPA axis suppression.

[0082] In yet another aspect of the invention, it has now been found that the pharmaceutical composition of the present invention containing 3% of penetration enhancing agent provides similar or improved efficacy as compared to TEMOVATE Cream® (which contains 0.05% of clobetasol propionate). In yet another aspect of the invention, the pharmaceutical composition of the present invention containing 10% of penetration enhancing agent.

[0083] Further, it is observed that the topical pharmaceutical composition of the present invention, which is free of propylene glycol, is non-irritating, non-toxic, and well-tolerated and are free of any undesired attributes, thereby providing a high degree of patient compliance.

[0084] In another aspect, compositions of the present application present invention are physically and chemically stable.

[0085] In another aspect, topical pharmaceutical compositions of the present invention are useful in the relief of the inflammatory and pruritic manifestations of steroid responsive dermatoses, and further can provide a moisturizing and/or soothing effect at the site of application to the skin. The composition of the application reduces the dryness that accompanies the build-up of skin in psoriatic plaques.

[0086] In another aspect, the composition of the application can be applied directly to the psoriatic lesions or dermatoses and can help reduce inflammation, remove built-up scale, reduce skin turnover, and/or clear affected skin of plaques.

[0087] In one embodiment, the compositions of the present invention can utilize any topical corticosteroids, either alone or in combination of others. Suitable examples of topical corticosteroids include, but not limited to, clobetasol propionate, alclometasone dipropionate, amcinonide, beclomethasone dipropionate, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, budesonide, clocortolone pivalate, desonide, desoximetasone, dexamethasone, dexamethasone acetate,

dexamethasone nicotinate, dexamethasone propionate, dexamethasone sodium phosphate, dexamethasone valerate, diflorasone diacetate, diflucortolone valerate, fluandrenolide, flumethasone pivalate, fluocinolone acetonide, fluocinonide, fluocortin butyl ester, fluticasone propionate, halcinonide, halobetasol propionate, halometasone monohydrate, hydrocortisone, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydrocortisone-17-butyrate-21-propionate, hydrocortisone aceponate, hydrocortisone acetate, hydrocortisone valerate, hydrocortisone butyrate, hydrocortisone probutate, methylprednisolone, methylprednisolone acetate, methylprednisolone aceponate, mometasone furoate, prednisolone, prednisolone sodium phosphate, prednisolone acetate, prednisolone-17-valerate-21-acetate, triamcinolone acetonide, triamcinolone acetate, triamcinolone diacetate, and prednicarbate. Other drug compounds are also useful, and this application further specifically contemplates the use of any combinations of steroid drugs.

[0088] The topical compositions of the present invention may be in the form of solution, suspension, emulsions, creams, ointments, lotions, microemulsions, nanoemulsions, emulgels, liposomes, micelle, reverse micelle, gels, hydrogels, sprays and the like.

[0089] In an embodiment, the topical composition of the present invention may be in form of compositions, comprising two phases: an oil phase and an aqueous phase and compositions of the present invention may be in the form of emulsions, creams, lotions, microemulsions, nanoemulsions, emulgels, liposomes, micelles, reverse micelle, spray and the like. In one embodiment, compositions may be in the form of an emulsion. The emulsion can be in the form of an oil-in-water type of emulsion or a water-in-oil type of emulsion. An aqueous-based emulsion, such as an oil-in-water emulsion, frequently has lower viscosity than other emulsion types and exhibits appreciable storage stability and patient compliance. Generally, oil-in-water emulsions have better skin feel properties, when applied to the skin, as these give sensations similar to an aqueous material.

[0090] In one embodiment, pharmaceutical compositions of the present invention are formulated as emulsions, comprising an oily or hydrophobic phase, an aqueous or hydrophilic phase, and an emulsifier. When the oily phase is dispersed as droplets within an aqueous continuous phase, this is called an "oil-in-water" type of emulsion. When the aqueous phase is dispersed as droplets within an oily continuous phase, this is called a "water-in-oil" type of emulsion.

[0091] In one embodiment, a pharmaceutical composition of the present invention is aqueous-based topical oil-in-water emulsion. The "aqueous-based" term is defined as an emulsion which comprises high percentage of water. The aqueous-based oil-in-water emulsion composition of the present invention comprises at least 60% of water in the final composition, or comprises at least 70% of water in the final composition.

[0092] In one embodiment, an aqueous-based topical oil-in-water emulsion composition of the present invention comprises: a therapeutically effective amount of a corticosteroid and at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of propylene glycol and substantially free of polymers.

[0093] In one embodiment, an aqueous-based topical oil-in-water emulsion composition of the present invention comprises: (a) a therapeutically acceptable amount of clobetasol (b) a discontinuous oil phase comprising: a solvent and at

least one penetration enhancing agent; (c) a continuous aqueous phase; and (d) at least one pharmaceutically acceptable excipient, wherein the composition is substantially free of propylene glycol and substantially free of polymers. In one embodiment, the topical composition comprises: (a) a therapeutically acceptable amount of clobetasol of about 0.025% w/w; (b) an oil phase comprising: at least one penetration enhancing agent, and a non-polymeric thickening agent; (c) an aqueous phase; and (d) optionally one pharmaceutically acceptable excipient; wherein the said topical composition is substantially free of propylene glycol and substantially free of polymers; wherein the topical composition provides no significant adverse effect on endocrine system.

[0094] In further embodiments, an aqueous based topical oil-in-water emulsion composition of the present invention has viscosity in the range of from about 10 cP to about 100000 cP. The viscosities of the aqueous-based emulsion compositions of the present invention may be in the range of about 0.01-100 Pascal second, "Pa-s" (10-1,00,000 cP), or about 0.1 to 100 Pa-s (100-1,00,000 cP) or about 1-50 Pa-s (1000-50,000 cP), or about 0.01-15 Pa-s (10-15,000 centipoise, "cP"), or about 0.02-1.5 Pa-s (20-1,500 cP), or about 0.05-1 Pa-s (50-1,000 cP).

[0095] The viscosity of topical compositions of the present invention is in the range of from about 0.1 cP to about 500 cP when measured by Brookfield viscometer Cap 2000+ with spindle no. 1 at 530 rpm at 25° C.

[0096] In another embodiment, pharmaceutical composition of the present invention includes one or more pharmaceutically acceptable excipient, which may act as carrier(s), emulsifier(s), co-emulsifier(s) solvent(s), co-solvents(s), emollient(s), antioxidant(s), preservative(s), gelling or thickening agent(s), polymer(s), surfactant(s), soothing agent(s), pH modifier(s), solubilizer(s), humectants(s), moisturizer(s), oily base(s), and the like.

[0097] The term "carrier" or "vehicle" denotes organic or inorganic ingredients, natural or synthetic, with which an active ingredient is combined to facilitate application of a composition. Examples of carriers include, but not limited to, water, acetone, alone or in combination with materials such as silicone fluids. In certain embodiments, the carrier can comprise, in addition to water, water-immiscible substances such as any pharmaceutically acceptable fatty esters of natural fatty acids, triglycerides of animal or vegetable, medium chain triglycerides, mixtures of mono-, di- and/or triglycerides, waxes, hydrogenated vegetable oils, and mixtures thereof

[0098] Examples of emulsifying agents include, but not limited to, disodium cocoampho diacetate, oxyethylenated glyceryl cocoate (7 EO), PEG-20 hexadecenyl succinate, PEG-15 stearyl ether, ricinoleic monoethanolamide monosulfosuccinate salts, oxyethylenated hydrogenated ricinoleic triglyceride containing 60 ethylene oxide units such as the products marketed by BASF under the trademarks CREMOPHOR® RH 60 or CREMOPHOR® RH 40 (polyoxyl 40 hydrogenated castor oil), polymers such as poloxamers, which are block copolymers of ethylene oxide and propylene oxide, and the nonsolid fatty substances at room temperature (that is to say, at temperatures ranging from about 20 to 35° C.) such as sesame oil, sweet almond oil, apricot stone oil, sunflower oil, octoxyglyceryl palmitate (or 2-ethylhexyl glyceryl ether palmitate), octoxyglyceryl behenate (or 2-ethylhexyl glyceryl ether behenate), dioctyl adipate, and tartrates of branched dialcohols. Sorbitan fatty acid esters are a

series of mixtures of partial esters of sorbitol and its mono- and dianhydrides with fatty acids. Sorbitan esters include products marketed as ARLACEL® 20, ARLACEL 40, ARLACEL 60, ARLACEL 80, ARLACEL83, ARLACEL 85, ARLACEL 987, ARLACEL C, PEG-6 stearate and glycol stearate and PEG-32 stearate (TEFOSE® 63), and PEG-6 stearate and PEG-32 stearate (TEFOSE® 1500), glyceryl stearate and PEG 100 stearate (TEFOSE® 165) and any mixtures thereof. Polyethylene glycol ethers of stearic acid are in another group of emulsifiers that can be used in the emulsions. Examples of polyethylene glycol ethers of stearic acid include, but not limited to, steareth-2, steareth-4, steareth-6, steareth-7, steareth-10, steareth-11, steareth-13, steareth-15, steareth-20, polyethylene glycol ethers of stearyl alcohol (steareth 21), and any mixtures thereof. Other emulsifying agents include sodium lauryl sulphate, cetyl trialkyl ammonium bromide, polyoxyethylene sorbitan fatty acid esters, and any mixtures thereof.

[0099] Nonionic emulsifying agents include those that can be broadly defined as condensation products of long chain alcohols, e.g., C8-30 alcohols, with sugar or starch polymers, i.e., glycosides. Various sugars include, but not limited to, glucose, fructose, mannose, and galactose, and various long chain alcohols include, but are not limited to, decyl alcohol, cetyl alcohol, stearyl alcohol, lauryl alcohol, myristyl alcohol, oleyl alcohol, and any mixtures thereof.

[0100] Other useful nonionic emulsifying agents include condensation products of alkylene oxides with fatty acids such as alkylene oxide esters of fatty acids. Other nonionic surfactants are the condensation products of alkylene oxides with 2 moles of fatty acids such as alkylene oxide diesters of fatty acids.

[0101] Emulsifying agents can also include any of a wide variety of cationic, anionic, zwitterionic, and amphoteric surfactants that are known in the art. Examples of anionic emulsifying agents include, but not limited to, alkyl isethionates, alkyl and alkyl ether sulfates and salts thereof, alkyl and alkenyl ether phosphates and salts thereof, alkyl methyl taurates, and soaps (e.g., alkali metal salts and sodium or potassium salts) of fatty acids.

[0102] Examples of amphoteric and zwitterionic emulsifying agents include those which are broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight or branched chain, wherein one of the aliphatic substituents contains from about 8 to about 22 carbon atoms and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Specific examples include, but not limited to, alkylimino acetates, iminodialkanoates and aminoalkanoates, imidazolium and ammonium derivatives. Other suitable amphoteric and zwitterionic emulsifying agents include betaines, sultaines, hydroxysultaines, alkyl sarcosinates, and alkanoyl sarcosinates.

[0103] Silicone emulsifying agents are typically organically modified organopoly siloxanes, sometimes called silicone surfactants. Useful silicone emulsifying agents include dimethicone copolyols. These materials are polydimethyl siloxanes, which have been modified to include polyether side chains such as polyethylene oxide chains, polypropylene oxide chains, mixtures of these chains, and polyether chains containing moieties derived from both ethylene oxide and propylene oxide.

[0104] Co-emulsifiers or secondary emulsifying agents include, but not limited to, polyoxylglycerides such as oleoyl

macroglycerides (LABRAFIL® M 1944CS), linoleoyl macroglycerides (LABRAFIL® M 2125CS), caprylocaproyl macroglycerides (LABRASOL®), cetyl alcohol (and) ceteth-20 (and) steareth-20 (EMULCIRE™ 61 WL 2659), glyceryl stearate (and) PEG-75 stearate (GELOT® 64), d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS) and any mixtures thereof.

[0105] The term “solvent” refers to components that aid in the dissolution of the drug in the formulation. Solvents serve to maintain a solution of the drug in the composition. Some solvents can also enhance percutaneous penetration of drug and/or act as humectants. For topical corticosteroids, solvents can include water-immiscible substances such as fatty esters of natural fatty acids, triglycerides of animal or vegetable, medium chain triglycerides, mixtures of mono-, di- and/or triglycerides, waxes, hydrogenated vegetable oils, and mixtures thereof. Some specific examples include, but not limited to, castor oil, isopropyl myristate, dimethyl isosorbide, oleyl alcohol, labrafil, labrasol, medium chain triglyceride, diethyl sebacate, lanolin oil, citrate triisocetyl triglycerides having 10-18 carbon atoms, caprylic/capric triglycerides, coconut oil, corn oil, cottonseed oil, linseed oil, oil of mink, olive oil, palm oil, sunflower oil, nut oil, saturated paraffin oils, mineral oils, vegetable oils or glycerides, and the like. Solvent can also be selected from the group comprising monoalkyl ether of diethylene glycol such as diethylene glycol monomethyl ether, diethylene glycol monoethyl ether or mixtures thereof. In an aspect, the solvent is diethylene glycol monoethyl ether. It is marketed by Gattefosse under the trade name TRANSCUTOL®, TRANSCUTOL-P®, TRANSCUTOL-CG®, and TRANSCUTOL-HP®.

[0106] In an embodiment, a solvent is selected from the group consisting of: mineral oil, isopropyl myristate, dimethyl isosorbide, oleyl Alcohol, labrafil, labrasol, medium chain triglyceride, diethyl sebacate, ammonium lauryl sulfate, lauramine oxide, sodium laureth sulfate, n-methyl-2-pyrrolidinone, octanoic acid, cocobetaine, dimethylsulfoxide, sodium laureth 2 sulfate, benzyl alcohol, ethylacetate, lactic acid, oleic acid, ethylacetate, spearmint oil, isostearic acid, ethanol, propylene glycol diacetate, dimethyl isosorbide, 1-butanol, methyl gluceth-10, sodium lauroylsarcosinate, polysorbate 20, isopropyl alcohol, 1-butanol, Capryol 90, sorbitanmonooleate, glyceryl ricinoleate, poloxamer, polyethylene glycol 200, polysorbate 65, triacetin, benzylalcohol, castor oil, arlacel 165, propylene glycol ricinoleate, glyceryl isostearate, propylene glycol, diethyl phthalate, glyceryl oleate, PEG-8 laurate, sorbitan sesquioleate, PPG-26 oleate, 1-octanol, Lauroglycol FCC, diisopropyladipate, laureth 4, and diethyl sebacate. for solubilizing clobetasol propionate. The compositions of the present invention comprising from about 1% w/w to 30% w/w of solvent based on total weight of the composition.

[0107] The term “emollients” are substances that soften and soothe the skin. They are used to prevent dryness and scaling of the skin. Examples of emollients that can be used in the present invention include, but not limited to, oils of natural origin such as almond oil, coconut oil, olive oil, palm oil, peanut oil and the like, fatty acids such as lauric acid, myristic acid, palmitic acid, and stearic acid, monohydric alcohol esters of the fatty acids such as ethyl laurate, isopropyl laurate, ethyl myristate, n-propyl myristate, isopropyl myristate, ethyl palmitate, isopropyl palmitate, methyl palmitate, methyl stearate, ethyl stearate, isopropyl stearate, butyl stearate, isobutyl stearate, amyl stearate, and isoamyl stearate,

glycols such as ethylene glycol, diethylene glycol, polyethylene glycol, branched aliphatic alcohols such as lauryl alcohol, myristyl alcohol, and stearyl alcohol, or mixtures thereof. Exemplary emollients include caprylic/capric triglycerides, castor oil, cetareth-20, cetareth-30, cetearyl alcohol, ceteth 20, cetostearyl alcohol, cetyl alcohol, cetyl stearyl alcohol, cocoa butter, diisopropyl adipate, glycerin, glyceryl monooleate, glyceryl monostearate, glyceryl stearate, isopropyl myristate, isopropyl palmitate, lanolin, lanolin alcohol, hydrogenated lanolin, liquid paraffins, linoleic acid, mineral oil, oleic acid, white petrolatum, polyethylene glycol, polyoxyethylene glycol fatty alcohol ethers, silicones and mixtures thereof.

[0108] Silicones are typically organically modified organopoly siloxanes, sometimes called silicone surfactants. Useful polysiloxane or silicone emollients include, but not limited to, polysiloxane polymer, dimethicone copolymers, cyclomethicones. These materials are polydimethyl siloxanes, which have been modified to include polyether side chains such as polyethylene oxide chains, polypropylene oxide chains, mixtures of these chains, and polyether chains containing moieties derived from both ethylene oxide and propylene oxide.

[0109] The term “antioxidants” are substances which inhibit oxidation or suppress reactions promoted by oxygen or peroxides. Antioxidants, especially lipid-soluble antioxidants, can be absorbed into the cellular membrane to neutralize oxygen radicals and thereby protect the membrane. Suitable antioxidants that can be used in the present invention include, but not limited to, ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, sorbic acid, carotenes, α -tocopherol (vitamin E), TPGS, ubiquinol, butylated hydroxyanisole, butylated hydroxytoluene, sodium benzoate, propyl gallate (PG, E310), and tertiary-butylhydroquinone.

[0110] The term “preservative” refers to a natural or synthetic chemical that prevents the decomposition of the composition by microbial growth or by undesirable chemical changes. Preservatives can desirably be incorporated into a composition for protecting against the growth of potentially harmful microorganisms. While microorganisms tend to grow in an aqueous phase and can also reside in a hydrophobic or oil phase. Examples of preservatives that can be used in the present invention include, but not limited to, methylparaben, propylparaben, benzyl alcohol, chlorocresol, benzalkonium chloride, cetrimonium chloride, sodium edetate, boric acid, sorbic acid, or any mixtures thereof.

[0111] The term “thickening agents” or “gelling agents” are used to give bulkiness to the composition. Examples of thickening agents or gelling agents that can be used in the present invention include, but not limited to carbomers, polyethylene glycols, acrylate polymers, methacrylate polymers, polyvinylpyrrolidones, copolymers based on butyl methacrylate and methyl methacrylate povidone, vinyl acetates, polyvinyl acetates, celluloses, gums, alginates, cellulose acetate phthalates, cellulose acetate butyrates, hydroxypropyl methyl cellulose phthalates, and the like. Examples include CARBOPOL® products, PEG 400, EUDRAGIT® 100, EUDRAGIT® RSPO, EUDRAGIT® RLPO, EUDRAGIT® ND40, PLASDONE®, copolymers based on butyl methacrylate and methyl methacrylate (PLASTOID® B), alkyl celluloses such as ethyl celluloses and methyl celluloses, hydroxyalkyl celluloses such as hydroxyethyl cellulose and hydroxypropyl cellulose, hydroxyalkyl alkyl celluloses such as hydroxypropyl methyl celluloses and hydroxybutyl methyl

celluloses, gums such as xanthan gum, tragacanth, guar gum, locust bean gum, acacia, and the like.

[0112] In an embodiment, the thickening agents are non-polymeric thickening agents, examples of non-polymeric thickening agent are fatty alcohol selected from group comprising: cetyl alcohol, paraffin, stearyl alcohol, white wax, wax cetyl esters, microcrystalline wax, anionic emulsifying wax, nonionic emulsifying wax, yellow wax, castor oil, ceresin, cetostearyl alcohol, cyclomethicone, glyceryl behenate, hectorite, myristyl alcohol, cetylstearyl alcohol, triolein, and lanolin. Fatty alcohols that can be used as non-polymeric thickening agent, include but not limited to stearyl alcohol, oleyl alcohol, cetyl alcohol, cetostearyl alcohol are long chain fatty alcohols. Stearyl Alcohol is a white, waxy solid with a faint odor, while oleyl alcohol and octyl dodecanol are clear, colorless liquids. Oleyl alcohol is an unsaturated fatty alcohol, similar to the saturated fatty alcohols stearyl alcohol and cetyl alcohol. In an embodiment, the topical compositions of the present invention are substantially free of polymers.

[0113] Other thickening agents or gelling agents or polymers that are useful in the present invention include, but not limited to, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof, cellulose ethers, cellulose esters, nitrocelluloses, polymers of acrylic and methacrylic esters, cellulose acetates, cellulose propionates, cellulose acetate butyrates, cellulose acetate phthalates, carboxylethyl celluloses, cellulose triacetates, cellulose sulphate sodium salts, poly(methyl methacrylate), poly(ethylmethacrylate), poly(butylmethacrylate), poly(isobutylmethacrylate), poly(hexylmethacrylate), poly(isodecylmethacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyethylenes, polypropylenes, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), poly(vinyl alcohol), poly(vinyl acetate), poly(vinyl chloride), polystyrenes, and the like, including their mixtures thereof

[0114] Examples of other useful polymers that can act as thickening agents or gelling agents include, but not limited to, synthetic polymers, such as polymers of lactic acid and glycolic acid, polyanhydrides, poly(ortho ester), polyurethanes, poly(butyric acid), poly(valeric acid), poly(caprolactone), poly(hydroxybutyrate), poly(lactide-co-glycolide), poly(lactide-co-caprolactone), and natural polymers such as alginate and other polysaccharides that include but not limited to arabinans, fructans, fucans, galactans, galacturonans, glucans, mannans, xylans (such as, for example, inulin), levan, fucoidan, carrageenan, galactocarlose, pectic acid, pectin, amylose, pullulan, glycogen, amylopectin, cellulose, dextran, pustulan, chitin, agarose, keratan, chondroitin, dermatan, hyaluronic acid, alginic acid, xanthan gum, starches, and various other natural homopolymers and heteropolymers, such as those containing one or more of aldoses, ketoses, acids or amines, erythrose, threose, ribose, arabinose, xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, mannitol, sorbitol, lactose, sucrose, trehalose, maltose, cellobiose, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine, glucuronic acid, gluconic acid, glucaric acid, galacturonic acid, mannuronic

acid, glucosamine, galactosamine, and neuraminic acid, and naturally occurring derivatives thereof, and including dextran and cellulose, collagen, albumin and other hydrophilic proteins, zein and other prolamines and hydrophobic proteins, copolymers and mixtures thereof.

[0115] The term “humectant” refers to a hygroscopic substance that is often a molecule with several hydrophilic groups, most often hydroxyl groups, but amines and carboxyl groups, sometimes esterified, can be encountered as well; the affinity to form hydrogen bonds with molecules of water is crucial here. Examples of humectants include, but not limited to, glycerol, and glyceryl triacetate (E1518). Others can be sugar polyols like sorbitol (E420), xylitol and maltitol (E965), polymeric polyols like polydextrose (E1200), or natural extracts like *quillaja* (E999), lactic acid or urea.

[0116] Some of the excipients described above can have more than one function in a composition. For example, an excipient can be both a solvent and a penetration enhancer, or both a solvent and a carrier. The categorizations of excipients described above are not to be construed as limiting or restricting in any manner.

[0117] The composition of the present application can be applied directly onto affected areas of the skin, such as psoriatic plaques or dermatoses. Cream compositions, are applied in the form of film on the affected areas and, in embodiments, can provide release of the active agent for an extended duration of time.

[0118] In an aspect, the topical composition of the present invention comprising: (a) a low dose of clobetasol; (b) an oil phase comprising: at least one penetration enhancing agent, and a non-polymeric thickening agent; (c) an aqueous phase; and (d) optionally, at least one pharmaceutically acceptable excipient; wherein the said topical composition comprising low dose of clobetasol has dose proportionate release rate as to be equivalent or more than the release rates of TEMOVATE® 0.05% cream. The term dose proportionate release rate as used herein means the topical composition of the present invention releases clobetasol such that concentration of clobetasol is equivalent to or more than the concentration delivered by 0.05% w/w topical clobetasol compositions such as TEMOVATE® cream. The dose proportionate release rate is cumulative percentage of drug release is at least about 6% of applied dose of clobetasol in about 9 hours.

[0119] In one aspect, the topical composition of the present invention forms a depot on the skin forming an occlusive film, thereby extending the duration of active agent action while allowing “breathing” of the skin.

[0120] In one embodiment, the compositions of the present invention may have pH values ranging from about 3.0 to about 7.0, or from about 3.5 to about 6.0.

[0121] The compositions of the present invention can be dispensed in any dispensing device such as laminated tubes or lacquered aluminum tubes. Laminated tubes contains propylene glycol-free topical compositions, wherein the device is a lamitube comprised of 5 layers White PE, Ethylene acrylic acid (EAA), Aluminum foil, EAA, Virgin natural PE such that the composition is consistently discharge on application. Used. In an embodiment, the compositions of the present invention are dispensed in lacquered aluminum tubes which are very useful and very effective in storing the cream.

[0122] The present invention is illustrated below by reference to the following examples. However, one skilled in the art will appreciate that the specific methods and results discussed are merely illustrative of the present invention, and not

to be construed as limiting the application. The following examples may include compilations of data that are representative of data gathered at various times during the course of development and experimentation related to the present invention.

EXAMPLES

[0123] The following general manufacturing processes were followed to prepare Examples 1-7:

[0124] Manufacturing Process I:

[0125] a) preparing an oil phase by melting and stirring stearyl alcohol, cetyl alcohol; glyceryl stearate and PEG 100 stearate and lanolin followed by methyl paraben and propyl paraben, and mineral oil,

[0126] b) preparing an aqueous phase by adding sorbitol solution into heated purified water,

[0127] c) preparing an emulsion by adding the oil phase of step (i) to the aqueous phase (ii) or vice versa under homogenization,

[0128] d) dissolving a premixed solution of clobetasol propionate in a diethylene glycol monoethyl ether and the followed by addition of BHT and homogenized to obtain a clobetasol propionate solution,

[0129] e) adding the clobetasol propionate solution obtained in step (iv) to the emulsion prepared in step (iii) followed by homogenization to obtain a cream composition.

[0130] Manufacturing Process II:

[0131] a) preparing an oil phase by melting and stirring cetostearyl alcohol; whitewax; glyceryl stearate and PEG 100 stearate and isopropyl myristate followed by methyl paraben and propyl paraben, and cyclomethicone,

[0132] b) preparing an aqueous phase by heating the purified water,

[0133] c) preparing an emulsion by adding the oil phase of step (i) to the aqueous phase (ii) or vice versa under homogenization,

[0134] d) dissolving a premixed solution of clobetasol propionate in a diethylene glycol monoethyl ether and the followed by addition of BHT and homogenized to obtain a clobetasol propionate solution,

[0135] e) adding the clobetasol propionate solution obtained in step (iv) to the emulsion prepared in step (iii) followed by homogenization to obtain a cream composition.

Example 1

Clobetasol Propionate (0.05% w/w) Cream

[0136] A composition of the present example was prepared by following Manufacturing Process-I using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.05
Stearyl alcohol	2
Cetyl alcohol	2
Glyceryl stearate & PEG 100	7.5
Lanolin	2
Mineral oil	5
Sorbitol solution, 70%	2
Diethylene glycol monoethyl ether	3
Butylated hydroxy toluene	0.05

-continued

Ingredient	Percentage w/w
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 2

Clobetasol Propionate (0.025% w/w) Cream

[0137] A composition of the present example was prepared by following Manufacturing Process-I using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.025
Stearyl alcohol	2
Cetyl alcohol	2
Glyceryl stearate & PEG 100	7.5
Lanolin	2
Mineral oil	5
Sorbitol solution, 70%	2
Diethylene glycol monoethyl ether	10
Butylated hydroxy toluene	0.05
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 3

Clobetasol Propionate (0.025% w/w) Cream

[0138] A composition of the present example was prepared by following Manufacturing Process-I using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.025
Stearyl alcohol	2
Cetyl alcohol	2
Glyceryl stearate & PEG 100	7.5
Lanolin	2
Mineral oil	5
Sorbitol solution, 70%	2
Diethylene glycol monoethyl ether	3
Butylated hydroxy toluene	0.05
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 4

Clobetasol Propionate (0.025% w/w) Cream

[0139] A composition of the present example was prepared by following Manufacturing Process-I using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.025
Stearyl alcohol	1.5
Cetyl alcohol	2.5
Glyceryl stearate & PEG 100	7.5
Lanolin	3
Mineral oil	4
Sorbitol solution, 70%	2
Diethylene glycol monoethyl ether	5
Butylated hydroxy toluene	0.05
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 5

Clobetasol Propionate (0.025% w/w) Cream

[0140] A composition of the present example was prepared by following Manufacturing Process-II using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.025
Cetostearyl alcohol	3
Glyceryl stearate & PEG 100	6
stearate	
White wax	1
Diethylene glycol monoethyl ether	3
Butylated hydroxy toluene	0.05
Isopropyl myristate	10
Cyclomethicone	5
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 6

Clobetasol Propionate (0.025% w/w) Cream

[0141] A composition of the present example was prepared by following Manufacturing Process-II using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.025
Cetostearyl alcohol	3
Glyceryl stearate & PEG 100	6
stearate	
White wax	1
Diethylene glycol monoethyl ether	10
Butylated hydroxy toluene	0.05
Isopropyl myristate	10
Cyclomethicone	5
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 7

Clobetasol propionate (0.05% w/w) cream

[0142] A composition of the present example was prepared by following Manufacturing Process-II using the following ingredient amounts.

Ingredient	Percentage w/w
Clobetasol propionate	0.05
Cetostearyl alcohol	3
Glyceryl stearate & PEG 100 stearate	6
White wax	1
Diethylene glycol monoethyl ether	10
Butylated hydroxy toluene	0.05
Isopropyl myristate	10
Cyclomethicone	5
Methyl paraben	0.2
Propyl paraben	0.4
Purified water	q.s to 100

Example 8

[0143] Physical and Chemical stability evaluation of the topical compositions of the present invention: All the compositions were evaluated for the physical changes such as color during the studies and all the compositions were remained in the off white to white cream throughout the study and did not show any significant changes.

[0144] The prepared formulation of example 1, example 2, example 3, example 5, example 6 and example 7 were filled into closed container and exposed to the various stability testing conditions such as 25° C. and 60% relative humidity (RH), 30° C. and 65% RH, and 40° C. and 75% RH for twelve months, and analyses at various storage points are shown in Tables.

TABLE 1

Specification	Assay	Related compound A	Highest single unknown impurity	% Total impurities
Example 1				
Initial	98.2	ND	ND	0.0
1 M 30° C./65% RH	100.7	ND	ND	0.0
1 M 40° C./75% RH	100.7	ND	ND	0.0
2 M 25° C./60% RH	100.4	ND	ND	0.0
2 M 40° C./75% RH	99.4	ND	ND	0.0
3 M 25° C./60% RH	99.6	ND	ND	0.0
3 M 30° C./65% RH	98.6	ND	ND	0.0
3 M 40° C./75% RH	99.0	ND	ND	0.0
Example 2				
Initial	102.0	ND	ND	0.0
1 M 30° C./65% RH	100.3	ND	ND	0.0
1 M 40° C./75% RH	100.1	ND	ND	0.0
2 M 30° C./65% RH	98.9	ND	ND	0.0
2 M 40° C./75% RH	98.7	ND	ND	0.0
3 M 25° C./60% RH	97.1	ND	ND	0.0
3 M 30° C./65% RH	97.1	ND	ND	0.0
3 M 40° C./75% RH	96.3	ND	ND	0.0
Example 3				
Initial	101.8	ND	0.14	0.19
1 M 25° C./60% RH	103.3	ND	0.10	0.27
1 M 30° C./65% RH	100.8	ND	0.09	0.19
1 M 40° C./75% RH	100.4	ND	0.11	0.30
2 M 30° C./65% RH	99.2	ND	0.182	0.309
2 M 40° C./75% RH	99.0	ND	0.193	0.404
3 M 25° C./60% RH	104.9	ND	0.17	0.40
3 M 30° C./65% RH	102.4	ND	0.17	0.46
Example 6				
Initial	102.9	ND	ND	0.0
1 M 30° C./65% RH	101.9	ND	ND	0.0
1 M 40° C./75% RH	101.3	ND	ND	0.0

TABLE 1-continued

Specification	Assay	Related compound A	Highest single unknown impurity	% Total impurities
2 M 30° C./65% RH	102.3	ND	ND	0.0
2 M 40° C./75% RH	101.1	ND	ND	0.0
3 M 30° C./65% RH	98.3	ND	ND	0.0
3 M 40° C./75% RH	99.5	ND	ND	0.0
6 M 25° C./60% RH	99.9	—	ND	ND
6 M 30° C./65% RH	99.1	—	ND	ND
6 M 40° C./75% RH	98.4	—	ND	ND
12 M 2-8° C.	100.5	—	0.10	0.17
12 M	101.1	—	0.10	0.22
25° C./60% RH				
12 M	100.9	—	0.21	0.21
30° C./65% RH				

Example 9

In Vitro Dissolution Study

[0145] Comparative in vitro dissolution profile testing, showing drug release from Example 3 and Example 7 Vs. TEMOVATE E® cream, was conducted. The cumulative percentage of drug released is shown in FIGS. 1 and 2 in comparison with TEMOVATE E® cream. The test was conducted as described below:

[0146] A Franz diffusion cell was fitted with a 0.45 µm nylon membrane clamped between the donor and receptor compartments. The receptor media was a mixture of water and acetone (35:65 by volume) with a replacement volume of 11.0 mL, a sampling volume of 2.0 mL was drawn at 30 min, 1, 2, 4, 6, and 8 hours respectively, and the temperature was maintained at 32±0.5° C. About 200 mg of the formulation was applied uniformly over the membrane. The donor compartment was covered using PARAFILM® (hydrocarbon wax and polyolefin blend). Receptor fluid was analyzed for the drug, using high performance liquid chromatography (HPLC).

Example 10

In Vivo Efficacy Study

[0147] The UV erythema test is a suitable and accepted procedure for standardized comparison of anti-inflammatory action of topical medications. In order to allow precise determination of the UV doses, individual sensitivity to UV were determined followed by performance of a light scale to determine the minimal erythema dose (MED).

[0148] UV exposure was performed using 1.5 MED, with less than 30 cm² skin surface was irradiated. The pharmaceutical compositions given in the examples and TEMOVATE E® cream were applied at the dose approximately 10 mg/cm² over the UV exposed skin surface. The assessment of erythema suppression will be determined by chromametric measurement.

[0149] The percent of inhibition of redness and AUC in comparison with TEMOVATE E® cream is shown in FIGS. 3 and 4, respectively.

[0150] While several particular forms of the application have been illustrated and described, it will be apparent that various modifications and combinations of the application detailed in the text can be made without departing from the spirit and scope of the application.

Example 11

Effect on Endocrine Systems
(Hypothalamic-Pituitary-Adrenal Axis Suppression Study)

[0151] The HPA axis suppression study enrolled 50 subjects with moderate to severe plaque psoriasis from 10 investigational sites in a ratio of 1:1 to test compositions (Example 5) to TEMOVATE cream. The subjects enrolled in the study were above 18 years to 90 years with body surface, having affected area (psoriasis) of at least 20% to 50% BSA (body surface area) on the body, not including the face, scalp, groin, axillae and other intertriginous areas. The subjects were having an IGA (investigator's global assessment score) grade of at least 3 (moderate) at the baseline visit. ACTH (cosyntropin) stimulation test were carried out in all the subjects. Cosyntropin is synthetic derivative of adrenocorticotrophic hormone (ACTH) and Cosyntropin was injected to the subjects.

[0152] The subjects whose post injection results were >18 ug/dL cortisol level at 30 minutes from the injection were considered normal and showed no other signs of abnormal HPA function or adrenal response and the subjects whose post injection results were <=18 mcg/dL at 30 minutes from the injection were considered abnormal.

[0153] The products were applied twice daily for 15 days to all affected areas on the body (20-50% BSA) 7 gm per day and results of cortisol levels, DHEA/DHEAS levels and changes in IGA score were evaluated on Day 1, Day 8, and Day 15. The change in IGA score from 3 to 0-1 was considered success in the treatment.

[0154] It is observed that no significant HPA axis suppression was noted with test composition. The results of the HPA suppression study showed a much lower potential for this adverse effect compared to Temovate (clobetasol propionate) Cream, 0.05%. The difference in the proportion of patients with HPA axis suppression between TEMOVATE and Test composition was minimum of about 8%.

[0155] While several particular forms of the application have been illustrated and described, it will be apparent that various modifications and combinations of the application detailed in the text can be made without departing from the spirit and scope of the application.

[0156] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

1. A topical composition for improving therapeutic efficacy and/or reducing the adverse effect of clobetasol comprising:

- a) a low dose of clobetasol;
- b) an oil phase comprising at least one penetration enhancing agent, and a non-polymeric thickening agent; and
- c) an aqueous phase;

wherein the said topical composition is substantially free of propylene glycol and substantially free of polymers.

2. The topical composition according to claim 1, and further comprising a pharmaceutically acceptable excipient.

3. The topical composition according to claim 1, wherein the adverse effect is on the endocrine system.

4. The topical composition according to claim 1, wherein the adverse effect is hypothalamic pituitary adrenal (HPA) axis suppression.

5. The topical composition according to claim 1, wherein the clobetasol is clobetasol propionate.

6. The topical composition according to the claim 5, wherein the clobetasol propionate is present in an amount from about 0.005% to about 0.1% of the total weight of the composition.

7. The topical composition according to the claim 5, wherein the clobetasol propionate is present in an amount from about 0.005% to about 0.05% of the total weight of the composition.

8. The topical composition according to the claim 5, wherein the clobetasol propionate is present in an amount up to about 0.025% of the total weight of the composition.

9. The topical composition according to claim 1, wherein the said penetration enhancing agent selected from mineral oil, isopropyl myristate, dimethyl isosorbide, oleyl alcohol, labrafil, labrasol, medium chain triglyceride, diethyl sebacate, ammonium lauryl sulfate, lauramine oxide, sodium laureth sulfate, n-methyl-2-pyrrolidinone, octanoic acid, cocobetaine, dimethylsulfoxide, sodium laureth 2 sulfate, benzyl alcohol, ethylacetate, lactic acid, oleic acid, ethylacetate, spearmint oil, isostearic acid, ethanol, propylene glycol diacetate, dimethyl isosorbide, 1-butanol, methyl gluceth-10, sodium lauroylsarcosinate, polysorbate 20, isopropyl alcohol, 1-butanol, Capryol 90, sorbitanmonooleate, glyceryl ricinoleate, poloxamer, polyethylene glycol 200, polysorbate 65, triacetin, benzylalcohol, castor oil, arlacel 165, propylene glycol ricinoleate, glyceryl isostearate, propylene glycol, diethyl phthalate, glyceryl oleate, PEG-8 laurate, sorbitan sesquioleate, PPG-26 oleate, 1-octanol, Lauroglycol_FCC, diisopropyladipate, laureth 4, and diethyl sebacate.

10. The topical composition according to claim 2, wherein the said penetration enhancing agent selected from mineral oil, isopropyl myristate, dimethyl isosorbide, oleyl alcohol, labrafil, labrasol, medium chain triglyceride, diethyl sebacate, ammonium lauryl sulfate, lauramine oxide, sodium laureth sulfate, n-methyl-2-pyrrolidinone, octanoic acid, cocobetaine, dimethylsulfoxide, sodium laureth 2 sulfate, benzyl alcohol, ethylacetate, lactic acid, oleic acid, ethylacetate, spearmint oil, isostearic acid, ethanol, propylene glycol diacetate, dimethyl isosorbide, 1-butanol, methyl gluceth-10, sodium lauroylsarcosinate, polysorbate 20, isopropyl alcohol, 1-butanol, Capryol 90, sorbitanmonooleate, glyceryl ricinoleate, poloxamer, polyethylene glycol 200, polysorbate 65, triacetin, benzylalcohol, castor oil, arlacel 165, propylene glycol ricinoleate, glyceryl isostearate, propylene glycol, diethyl phthalate, glyceryl oleate, PEG-8 laurate, sorbitan sesquioleate, PPG-26 oleate, 1-octanol, Lauroglycol_FCC, diisopropyladipate, laureth 4, and diethyl sebacate.

11. The topical composition according to claim 3, wherein the said penetration enhancing agent selected from mineral oil, isopropyl myristate, dimethyl isosorbide, oleyl alcohol, labrafil, labrasol, medium chain triglyceride, diethyl sebacate, ammonium lauryl sulfate, lauramine oxide, sodium laureth sulfate, n-methyl-2-pyrrolidinone, octanoic acid, cocobetaine, dimethylsulfoxide, sodium laureth 2 sulfate, benzyl alcohol, ethylacetate, lactic acid, oleic acid, ethylacetate, spearmint oil, isostearic acid, ethanol, propylene glycol diacetate, dimethyl isosorbide, 1-butanol, methyl gluceth-10, sodium lauroylsarcosinate, polysorbate 20, isopropyl alcohol, 1-butanol, Capryol 90, sorbitanmonooleate, glyceryl ricinoleate, poloxamer, polyethylene glycol 200, polysorbate 65, triacetin, benzylalcohol, castor oil, arlacel 165, propylene glycol ricinoleate, glyceryl isostearate, propylene glycol,

diethyl phthalate, glyceryl oleate, PEG-8 laurate, sorbitan sesquioleate, PPG-26 oleate, 1-octanol, Lauroglycol_FCC, diisopropyladipate, laureth 4, and diethyl sebacate.

12. The topical composition according to claim 1, wherein the penetration enhancing agent is present in an amounts from about 1% to about 30.0% of the total weight of the composition.

13. The topical composition according to claim 1, the said non-polymeric thickening agent selected from cetyl alcohol, paraffin, stearyl alcohol, white wax, wax cetyl esters, micro-crystalline wax, anionic emulsifying wax, nonionic emulsifying wax, yellow wax, castor oil, ceresin, cetostearyl alcohol, cyclomethicone, glyceryl behenate, hectorite, myristyl alcohol, cetylstearyl alcohol, triolein, and lanolin.

14. The topical composition according claim 1, comprising at least 60% w/w aqueous phase by weight based on the total weight of the composition.

15. The topical composition according claim 2, comprising at least 60% w/w aqueous phase by weight based on the total weight of the composition.

16. The topical composition according claim 3, comprising at least 60% w/w aqueous phase by weight based on the total weight of the composition.

17. A topical composition for improving therapeutic efficacy and/or reducing the adverse effect of clobetasol comprising:

- a) a low dose of about 0.025% w/w of clobetasol or its pharmaceutically acceptable salts thereof;
- b) an oil phase comprising at least one penetration enhancing agent comprising isopropyl myristate in the percentage of less than about 15% w/w, and a non-polymeric thickening agent comprising: cetostearyl alcohol; and
- c) an aqueous phase comprising water at least about 60% w/w;

wherein the said topical composition is substantially free of propylene glycol and substantially free of polymers.

18. A topical composition for improving therapeutic efficacy and/or reducing the adverse effect of clobetasol comprising:

- a) a low dose of about 0.025% w/w clobetasol;
- b) an oil phase comprising at least one penetration enhancing agent, and a non-polymeric thickening agent; and
- c) an aqueous phase;

wherein the said topical composition is substantially free of propylene glycol and substantially free of polymers.

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