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(71) Applicant: **ANACOR PHARMACEUTICALS, INC.** [US/US]; 1020 East Meadow Circle, Palo Alto, California 94303 (US).

(72) Inventors: **CORONADO, Dina Jean**; 170 Edinburgh Circle, Danville, California 94526 (US). **IMBERT, Delphine Caroline**; 8107 Hyannisport Drive, Cupertino, California 95014 (US). **LEE, Charles Edward**; 2452 Medallion Drive, Union City, California 94587 (US). **MERCHANT, Tejal**; 20125 Cedar Tree Lane, Cupertino, California 95014 (US). **YEP, Sylvia Zarela**; 272 Shimmer Court, Milpitas, California 95035 (US).

(74) Agent: **WALDRON, Roy F.**; PFIZER INC., 235 East 42nd Street, MS 235/9/S20, New York, New York 10017 (US).

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(54) Title: TOPICAL PHARMACEUTICAL FORMULATIONS FOR TREATING INFLAMMATORY-RELATED CONDITIONS

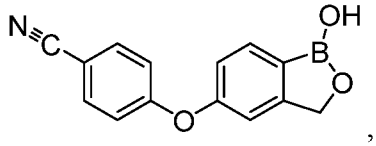
(57) Abstract: Topical pharmaceutical formulations, and methods of treating inflammatory conditions with these formulations, are disclosed.

TOPICAL PHARMACEUTICAL FORMULATIONS FOR TREATING INFLAMMATORY-RELATED CONDITIONS

BACKGROUND FOR THE INVENTION

Topical pharmaceutical formulations which are useful in the treatment of inflammatory-related conditions, such as atopic dermatitis and/or psoriasis, are known in the art. Topical pharmaceutical formulations which more quickly reduce the condition symptoms and/or resolve the underlying causes of the condition would be a significant advance in the art.

5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole,



is a non-steroidal PDE4 inhibitor useful in the treatment of inflammatory skin deseases, including mild to moderate atopic dermatitis and psoriasis. Crisaborole (tradename) is 2% 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole and is the first topical ointment PDE4 inhibitor for mild to moderate atopic dermatitis (AD) for patients two years of age and older and is recommended for twice daily application to the affected areas for about 28 days and up to an additional 48 weeks.

U.S. Patent Nos. 8,039,451, 8,168,614, 8,501,712 cover the compound and various method of treatments thereof. All references cited herein are incorporated in its entirety and for all purposes.

Formulation development of Crisaborole began with ointment and cream formulations for Phase I and Phase 2 clinical studies. It was determined that an ointment formulation was preferable for the treatment of inflammatory skin diseases, in part due to the beneficial emollient properties of an ointment. Early formulations were comprised of a partial suspension of Crisaborole, but chemical and physical stability issues became problematic requiring a different approach.

The present invention is directed to pharmaceutical compositions containing crisaborole, combinations of crisaborole and other active agents, and methods of using thereof.

SUMMARY OF THE INVENTION

In a first aspect, the invention provides a topical pharmaceutical formulation comprising:

a) an active agent which treats an inflammatory-related condition, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol; and

c) petrolatum.

In a second aspect, the invention provides a topical pharmaceutical formulation comprising:

a) from about 5% (w/w) to about 15% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) an emulsifying agent; and

f) a stiffening agent,

wherein the topical pharmaceutical formulation comprises the active agent, crisaborole.

The invention provides additional topical pharmaceutical formulations, as well as methods for their use and production, and combinations thereof.

The present invention also relates to crystalline forms or a non-crystalline form of 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. The present invention also relates to pharmaceutical compositions comprising a crystalline or non-crystalline form, and to methods for preparing such forms. The invention further relates to the use of a crystalline or non-crystalline form in the topical treatment of various diseases.

The invention also contemplates combinations of active ingredients for the treatment of atopic dermatitis.

DESCRIPTION OF FIGURES

Figure 1: The equation to calculate the volume of material that physically separated.

Figure 2: Powder x-ray spectrum of crisaborole Form 1

Figure 3: Powder X-ray spectrum of crisaborole Forms 1 (black), 2 (red) & 3 (blue).

Figure 4: Powder x-ray spectrum of crisaborole drug product placebo lot overlaid with Form 1.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions and Abbreviations

As used herein, the singular forms "a," "an", and "the" include plural references unless the context clearly dictates otherwise. For example, reference to "an active agent" includes a single active agent as well as two or more different active agents in combination. It is to be understood that present teaching is not limited to the specific dosage forms, carriers, or the like, disclosed herein and as such may vary.

The abbreviations used herein generally have their conventional meaning within the chemical and biological arts.

II. Introduction

The present invention relates to topical pharmaceutical formulations. These formulations can be useful in the treatment of inflammatory-related conditions. In one aspect, the formulation contains an active agent. In another aspect, the formulation does not contain an active agent. These formulations are useful in the treatment and/or prevention of atopic dermatitis and/or psoriasis.

IIa. Topical pharmaceutical formulations

In a first aspect, the invention comprises: a) an active agent, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof; b) from about 5% (w/w) to about 15% (w/w) of a solvent; and c) a base. In an exemplary embodiment, the topical pharmaceutical formulation further comprises up to about 0.5% (w/w) water. In an exemplary embodiment, the topical pharmaceutical formulation further comprises up to about 0.1% (w/w) water. In an exemplary embodiment, the topical pharmaceutical formulation further comprises up to about 0.01% (w/w) water.

In an exemplary embodiment, all of the components of pharmaceutical formulations are pharmaceutically acceptable.

II. a. i. Active Agent

In an exemplary embodiment, the topical pharmaceutical formulation comprises an active pharmaceutical ingredient ("active agent"). In an exemplary embodiment, the active agent is an anti-inflammatory agent. In an exemplary embodiment, the active agent is an anti-pruritic agent. In an exemplary embodiment, the active agent treats atopic dermatitis. In an exemplary embodiment, the active agent treats psoriasis. In an exemplary embodiment, the active agent is a compound described herein. In an exemplary embodiment, the active agent is a benzoxaborole.

In an exemplary embodiment, the active agent is disclosed in: PCT/US07/062350; 11/676,120 (now 8,168,614); 60/823,888; 60/774,532; PCT/US09/036250; 12/399,015 (now 8,039,450); 61/148,731; 61/143,700; 61/110,903; 61/105,990; 61/094,406; 61/052,637; 61/034,371; PCT/US11/022780; 13/015,487 (now 8,716,478); 61/298,860; 61/354,187; 61/368,211; PCT/US14/056800; and 61/881,343, the content of each of which is herein incorporated by reference for all purposes. In an exemplary embodiment, the active agent is 5-(3,4-dicyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In an exemplary embodiment, the active agent is crisaborole, also known as 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In an exemplary embodiment, the active agent is 5-(3-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, hydrate, or solvate thereof. In an exemplary embodiment, the active agent is 5-(2-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, hydrate, or solvate thereof.

In an exemplary embodiment, the active ingredient is a steroid. In an exemplary embodiment, the active ingredient is pimecrolimus or tazarotene or tacrolimus or triamcinolone or calcitriol or calcipotriene or betamethasone or clobatsol or halobetasol or diflorasone or mometasone.

In an exemplary embodiment, the active agent is present in a concentration of about 0.1% to about 3.0% (w/w). In an exemplary embodiment, the active agent is present in a concentration of about 0.1% to about 2.0% (w/w). In an exemplary embodiment, the active agent is present in a concentration of about 0.1% to about 1.0% (w/w). In an exemplary embodiment, the active agent is present in a concentration of about 1.0% to about 2.0% (w/w). In an exemplary embodiment, the active agent is present in a concentration of about 1.5% to about 2.0% (w/w). In an exemplary

embodiment, the active agent is present in a concentration of about 1.5% to about 2.5% (w/w). In an exemplary embodiment, the active agent is present in a concentration of about 1.0% to about 3.0% (w/w). In an exemplary embodiment, the active agent is present in a concentration of about 2.0% (w/w). In an exemplary embodiment, the active agent is present in a concentration of 2.0% (w/w).

In an exemplary embodiment, the invention provides an active agent described herein, or a salt, hydrate or solvate thereof, or a combination thereof. An exemplary embodiment is a combination of crisaborole as one active agent and a second active agent useful for the treatment of atopic dermatitis or psoriasis. The combination may be comprised of an admixture or co-formulation of the two active ingredients. Alternatively, the combination may be packaged in a dispenser wherein one active agent is in one chamber and another active ingredient is in a second chamber, but upon dispensing the two active agents are simultaneously delivered together such that administration of the combination may occur in one application. Alternatively, the active agents may individually be administered with the other active agent, wherein the second active agent may be administered either orally or topically.

Examples of second active agents that are contemplated in combination with crisaborole include but are not limited to:

Topical corticosteroids such as Fluocinonide, Desoximetasone, Mometasone, Triamcinolone, Betamethasone, Alclometasone, Desonide, Hydrocortisone and Mapracorat;

Topical Calcineurin inhibitors such as Tacrolimus, pimecrolimus and cyclosporine;

Topical formulations of PDE4 inhibitors such as apremilast, E-6005, OPA-15406, LEO 29102, DRM02, and Roflumilast;

Topical formulations of JAK kinase inhibitors such as Tofacitinib, JTE-052, Baricitinib, and Upadacitinib;

Topical Non-steroidal anti-inflammatories such as WBI-1001, and MRX-6;

Topcial ROR agents such as GSK2981278;

Injectable Anti- IL4, IL-31, IL-22, IL-33, IL-12, IL-23, IL-17, IgE, IL-4 treatments such as Dupilumab, Lebrikizumab, Nemolizumab, Tralokinumab, Etanercept, Adalimumab, Infliximab, Ustekinumab, Secukinumab, Omazumilab, CIM-331;

Vitamin D analogs such as calcipotriene ;

Oral Retinoic Acid derivatives such as alitretinoin;

Oral Liver X Receptor (LXR) selective agonists such as VTP-38543 ;

Oral H4 receptor antagonists such as ZPL-389 ;

Oral NK1 receptor antagonists such as Aprepitant and Tradipitant;

Oral CRTH2 receptor antagonists such as Fevipiprant and OC-459 ;

Oral Chymase inhibitors such as SUN 13834;

Oral GATA-3 inhibitors such as SB-011;

Oral ROR inverse agonists such as VTP-43742, ARN6039, TAK-828 and JTE-451;

Oral JAK inhibitors; including inhibitors of JAK1, JAK2, JAK3 and TYK2 such as PF-04965842, PF-06651600, and PF-06700841;

Oral PDE agents such as apremilast, roflumilast, and ibudilast;

Oral IRAK4 inhibitors such as PF-06650833;

Injectable aTNF inhibitors such as infliximab, adalimumab, golimumab, and certolizumab pegol;

Injectable galectin-3 inhibitor such as GR-MD-02

In an exemplary embodiment, the invention provides an active agent described herein, or a salt, hydrate or solvate thereof. In an exemplary embodiment, the invention provides an active agent described herein, or a salt thereof. In an exemplary embodiment, the salt is a pharmaceutically acceptable salt. In an exemplary embodiment, the invention provides an active agent described herein, or a hydrate thereof. In an exemplary embodiment, the invention provides an active agent described herein, or a solvate thereof. In an exemplary embodiment, the invention provides an active agent described herein, or a prodrug thereof. In an exemplary embodiment, the invention provides an active agent described herein. In an exemplary embodiment, the invention provides a pharmaceutically acceptable salt of an active agent described herein. In an exemplary embodiment, the invention provides a hydrate of an active agent described herein. In an exemplary embodiment, the invention provides a solvate

of an active agent described herein. In an exemplary embodiment, the invention provides a prodrug of an active agent described herein.

II. a. ii. Solvent

In an exemplary embodiment, the topical pharmaceutical formulation comprises a solvent. In an exemplary embodiment, the solvent is an alkylene glycol. In an exemplary embodiment, the solvent is propylene glycol. In an exemplary embodiment, the solvent is propylene glycol USP. In an exemplary embodiment, the solvent is butylene glycol.

In an exemplary embodiment, the solvent is present in a concentration of about 5.0% (w/w) to about 15.0% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 6.0% (w/w) to about 10.0% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 6.5% (w/w) to about 11.5% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 7.0% (w/w) to about 11.0% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 7.5% (w/w) to about 10.5% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 7.5% (w/w) to about 9.5% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 8.5% (w/w) to about 9.5% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 8.0% (w/w) to about 10.0% (w/w). In an exemplary embodiment, the solvent is present in a concentration of about 9.0% (w/w). In an exemplary embodiment, the solvent is present in a concentration of 9.0% (w/w).

II. a. iii. Base

In an exemplary embodiment, the topical pharmaceutical formulation comprises an ointment base. In an exemplary embodiment, the base is an ointment base. In an exemplary embodiment, the ointment base is white petrolatum. In an exemplary embodiment, the ointment base is white petrolatum USP. In an exemplary embodiment, the ointment base is mineral jelly or petroleum jelly or yellow petrolatum or yellow soft paraffin or yellow petroleum Jelly or white petrolatum jelly or white soft paraffin. In an exemplary embodiment, the base is mineral oil or light mineral oil or paraffin or lanolin alcohol.

The amount of base in the topical pharmaceutical formulations will be dependent on the amounts of the other components. More base may be added to compensate for smaller amounts of other components in the desired topical pharmaceutical formulation.

In an exemplary embodiment, the base is present in a quantum satis, q.s., concentration. In an exemplary embodiment, the base is present in a concentration of from about 65% (w/w) to about 90% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 65% (w/w) to about 85% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 67.955% (w/w) to about 89.8999% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 50% (w/w) to about 60% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 60% (w/w) to about 70% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 70% (w/w) to about 80% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 72% (w/w) to about 82% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 74% (w/w) to about 81% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 78% (w/w) to about 82% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 75% (w/w) to about 80% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 75% (w/w) to about 79% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 76% (w/w) to about 79% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 76% (w/w) to about 77% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 76.8% (w/w) to about 77% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 78% (w/w) to about 79% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 76.8% (w/w) to about 76.9% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 76.89% (w/w) to about 76.9% (w/w). In an exemplary embodiment, the base is present in a concentration of about 76.80% (w/w). In an exemplary embodiment, the base is present in a concentration of about 76.855% (w/w). In an exemplary embodiment, the base is present in a concentration of about 76.8965% (w/w). In an exemplary embodiment, the base is present in a concentration of about 76.8976% (w/w). In an exemplary embodiment, the base is present in a concentration of about 76.981% (w/w). In an exemplary embodiment, the base is present in a concentration of about 76.90% (w/w). In an exemplary embodiment, the base is present in a concentration of from about 78.89% (w/w) to about 78.9% (w/w). In an exemplary embodiment, the base is present in a concentration of about 78.80% (w/w). In an exemplary embodiment, the base is present in a concentration of about 78.855% (w/w). In an exemplary embodiment, the

base is present in a concentration of about 78.8965% (w/w). In an exemplary embodiment, the base is present in a concentration of about 78.8976% (w/w). In an exemplary embodiment, the base is present in a concentration of about 78.981% (w/w). In an exemplary embodiment, the base is present in a concentration of about 78.90% (w/w).

Optional components for the topical pharmaceutical formulation

II. a. iv. Antioxidant

In an exemplary embodiment, the topical pharmaceutical formulation further comprises an antioxidant. In an exemplary embodiment, the antioxidant is selected from the group consisting of butylated hydroxytoluene, ascorbic acid, ascorbic palmitate, butylated hydroxyanisole, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-*tert*-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone and a tocopherol, or a pharmaceutically acceptable salt or ester thereof, or a combination thereof. In an exemplary embodiment, the antioxidant is butylated hydroxytoluene. In an exemplary embodiment, the antioxidant is butylated hydroxytoluene NF.

In an exemplary embodiment, the antioxidant is present in a concentration of about 0.01% (w/w) to about 1% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.01% (w/w) to about 0.5% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.05% (w/w) to about 0.5% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.05% (w/w) to about 0.4% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.05% (w/w) to about 0.3% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.07% (w/w) to about 0.2% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.05% (w/w) to about 0.15% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of about 0.1% (w/w). In an exemplary embodiment, the antioxidant is present in a concentration of 0.1% (w/w).

II. a. v. Stabilizer

In an exemplary embodiment, the topical pharmaceutical formulation further comprises a stabilizer. In an exemplary embodiment, the stabilizer is ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the stabilizer is a pharmaceutically acceptable salt of

ethylenediaminetetraacetic acid, and this salt is a sodium salt or a potassium salt or a calcium salt, or a combination thereof. In an exemplary embodiment, the stabilizer is a pharmaceutically acceptable salt of ethylenediaminetetraacetic acid, and this salt is a sodium salt or a calcium salt, or a combination thereof. In an exemplary embodiment, the stabilizer is edetate calcium disodium. In an exemplary embodiment, the stabilizer is edetate calcium disodium USP.

In an exemplary embodiment, the stabilizer is present in a concentration of about 0.000010% (w/w) to about 0.0450% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0450% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0400% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0350% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0300% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0250% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0200% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0150% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.00010% (w/w) to about 0.0100% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0090% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.000010% (w/w) to about 0.0100% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0100% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0020% (w/w) to about 0.0100% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0024% (w/w) to about 0.0100% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0024% (w/w) to about 0.0090% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0035% (w/w) to about 0.0100% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0035% (w/w) to about 0.0090% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0080% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0010% (w/w) to about 0.0060% (w/w). In an exemplary embodiment, the stabilizer is present in a

concentration of about 0.0010% (w/w) to about 0.0050% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0020% (w/w) to about 0.0060% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0015% (w/w) to about 0.0045% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0025% (w/w) to about 0.0045% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0030% (w/w) to about 0.0040% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of about 0.0035% (w/w). In an exemplary embodiment, the stabilizer is present in a concentration of 0.0035% (w/w).

II. a. vi. Emulsifying Agent

In an exemplary embodiment, the topical pharmaceutical formulation further comprises an emulsifying agent. In an exemplary embodiment, the emulsifying agent is a glyceride blend. In an exemplary embodiment, the emulsifying agent is a glyceride blend, wherein the glyceride blend comprises a monoglyceride and a diglyceride. In an exemplary embodiment, the emulsifying agent is a glyceride blend, wherein the glyceride blend comprises a monoglyceride, a diglyceride, and a triglyceride. In an exemplary embodiment, the emulsifying agent is a glyceride blend, wherein the glyceride blend comprises a monoglyceride and a diglyceride, and wherein from about 40% (w/w) to about 55% (w/w) of the glyceride blend is a monoglyceride. In an exemplary embodiment, the emulsifying agent is a glyceride blend, wherein the glyceride blend comprises a monoglyceride, a diglyceride, and a triglyceride, and wherein from about 40% (w/w) to about 55% (w/w) of the glyceride blend is a monoglyceride. In an exemplary embodiment, the emulsifying agent is a glyceride blend, wherein the glyceride blend is Mono- and Di-glyceride NF.

In an exemplary embodiment, the monoglyceride is selected from the group consisting of glyceryl monostearate, glyceryl monopalmitate, glyceryl monooleate, or combinations thereof. In an exemplary embodiment, the monoglyceride is a monoglyceryl ester of a long chain, saturated or unsaturated fatty acid. In an exemplary embodiment, the monoglyceride is an alpha-monoglyceride. In an exemplary embodiment, the diglyceride is a diglyceryl ester of a long chain, saturated or unsaturated fatty acid.

In an exemplary embodiment, the glyceride blend is present in a concentration of about 3.0% (w/w) to about 10.0% (w/w). In an exemplary embodiment, the glyceride blend is present in a concentration of about 5.0% (w/w) to about 10.0% (w/w). In an

exemplary embodiment, the glyceride blend is present in a concentration of about 6.0% (w/w) to about 9.0% (w/w). In an exemplary embodiment, the glyceride blend is present in a concentration of about 5.0% (w/w) to about 8.0% (w/w). In an exemplary embodiment, the glyceride blend is present in a concentration of about 6.0% (w/w) to about 8.0% (w/w). In an exemplary embodiment, the glyceride blend is present in a concentration of about 6.5% (w/w) to about 7.5% (w/w). In an exemplary embodiment, the glyceride blend is present in a concentration of about 7.0% (w/w). In an exemplary embodiment, the glyceride blend is present in a concentration of 7.0% (w/w).

II. a. vii. Stiffening agent

In an exemplary embodiment, the topical pharmaceutical formulation further comprises a stiffening agent. In an exemplary embodiment, the stiffening agent is a wax. In an exemplary embodiment, the stiffening agent is a wax, and the wax is selected from the group consisting of beeswax, paraffin wax, and spermaceti wax. In an exemplary embodiment, the stiffening agent is paraffin wax. In an exemplary embodiment, the stiffening agent is paraffin wax NF.

In an exemplary embodiment, the stiffening agent is present in a concentration of about 2.0% (w/w) to about 6.0% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of about 2.0% (w/w) to about 8.0% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of about 3.0% (w/w) to about 5.0% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of about 4.0% (w/w) to about 6.0% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of about 4.0% (w/w) to about 5.0% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of about 4.5% (w/w) to about 5.5% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of about 5.0% (w/w). In an exemplary embodiment, the stiffening agent is present in a concentration of 5.0% (w/w).

<u>Specific topical pharmaceutical formulations</u>

II. a. viii.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol; and

c) petrolatum

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) an emulsifying agent; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) an emulsifying agent; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) edetate calcium disodium;

f) an emulsifying agent; and

g) a stiffening agent.

In an exemplary embodiment, the topical pharmaceutical formulation consists of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) from about 0.0020% (w/w) to about 0.0040% (w/w) edetate calcium disodium;

f) an emulsifying agent; and

g) a stiffening agent.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) from about 6% (w/w) to about 8% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) edetate calcium disodium;

f) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) an active agent which treats atopic dermatitis and/or psoriasis, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) from about 0.0020% (w/w) to about 0.0040% (w/w) edetate calcium disodium;

f) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) a stabilizer;

f) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) edetate calcium disodium;

f) from about 6% (w/w) to about 8% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides,

wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 8% (w/w) to about 10% (w/w) propylene glycol;

c) petrolatum;

d) an antioxidant;

e) from about 0.0020% (w/w) to about 0.0040% (w/w) edetate calcium disodium;

f) from about 6% (w/w) to about 8% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol;

c) petrolatum;

d) butylated hydroxytoluene;

e) edetate calcium disodium;

f) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides,

wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol;

c) petrolatum;

d) butylated hydroxytoluene;

e) edetate calcium disodium;

f) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) about 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) about 9% (w/w) propylene glycol;

c) white petrolatum;

d) about 0.1% (w/w) butylated hydroxytoluene;

e) about 0.0035% (w/w) edetate calcium disodium;

f) about 7% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists of:

a) 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) 9% (w/w) propylene glycol;

c) 76.8965% (w/w) white petrolatum;

d) 0.1% (w/w) butylated hydroxytoluene;

e) 0.0035% (w/w) edetate calcium disodium;

f) 7% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

g) 5% (w/w) paraffin wax.

Topical pharmaceutical formulation without an active agent

II. a.ix.

In another aspect, the invention comprises a topical pharmaceutical formulation which does not comprise an active agent which is useful in the treatment of inflammatory-related conditions. These topical pharmaceutical formulations which do not contain an active agent are also useful in the treatment of inflammatory conditions such as atopic dermatitis and/or psoriasis. In an exemplary embodiment, these topical pharmaceutical formulation do not contain one or more of the active agents listed herein. In an exemplary embodiment, the topical pharmaceutical formulation without an active agent further comprises up to about 0.5% (w/w) water. In an exemplary embodiment, the topical pharmaceutical formulation without an active agent further comprises up to about 0.1% (w/w) water. In an exemplary embodiment, the topical pharmaceutical formulation without an active agent further comprises up to about 0.01% (w/w) water.

The topical pharmaceutical formulation without an active agent may optionally contain a solvent, a base, an antioxidant, a stabilizer, an emulsifying agent, and a stiffening agent. The identity and concentrations for each of these components in the

topical pharmaceutical formulation without an active agent may be found in sections II. a. i.; II. a. ii.; II. a. iii.; II. a. iv.; II. a. v.; II. a. vi.; II. a. vii.; and II. a. viii. of this document.

Specific topical pharmaceutical formulations without an active agent

II. a.x.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) from about 5% (w/w) to about 15% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) an emulsifying agent; and

f) a stiffening agent,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) about 5% (w/w) of a solvent;

b) about 89.8999% (w/w) of petrolatum;

c) about 0.1% (w/w) of an antioxidant;

d) about 0.0001% (w/w) of a stabilizer;

e) about 3% (w/w) of an emulsifying agent; and

f) about 2% (w/w) of a stiffening agent,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) about 15% (w/w) of a solvent;

b) about 67.955% (w/w) of petrolatum;

c) about 1% (w/w) of an antioxidant;

d) about 0.0450% (w/w) of a stabilizer;

e) about 10% (w/w) of an emulsifying agent; and

f) about 6% (w/w) of a stiffening agent,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) from about 5% (w/w) to about 15% (w/w) of a solvent;

b) from about 67.955% (w/w) to about 89.8999% (w/w) of petrolatum;

c) from about 0.1% (w/w) to about 1% (w/w) of an antioxidant;

d) from about 0.0001% (w/w) to about 0.0450% (w/w) of a stabilizer;

e) from about 3% (w/w) to about 10% (w/w) of an emulsifying agent; and

f) from about 2% (w/w) to about 6% (w/w) of a stiffening agent,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) from about 5% (w/w) to about 15% (w/w) of propylene glycol;

b) from about 67.955% (w/w) to about 89.8999% (w/w) of petrolatum;

c) from about 0.1% (w/w) to about 1% (w/w) of butylated hydroxytoluene;

d) from about 0.0001% (w/w) to about 0.0450% (w/w) of edetate calcium disodium;

e) from about 3% (w/w) to about 10% (w/w) of a glyceride blend; and

f) from about 2% (w/w) to about 6% (w/w) of paraffin wax,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) from about 5% (w/w) to about 15% (w/w) of propylene glycol;

b) from about 67.955% (w/w) to about 89.8999% (w/w) of petrolatum;

c) from about 0.1% (w/w) to about 1% (w/w) of butylated hydroxytoluene;

d) from about 0.0001% (w/w) to about 0.0450% (w/w) of edetate calcium disodium;

e) from about 3% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides,

wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) from about 2% (w/w) to about 6% (w/w) of paraffin wax,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) an emulsifying agent; and

f) a stiffening agent,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation comprises:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) edetate calcium disodium;

e) an emulsifying agent; and

f) a stiffening agent,

wherein the topical pharmaceutical formulation does not comprise an active agent and wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) from about 0.0020% (w/w) to about 0.0040% (w/w) edetate calcium disodium;

e) an emulsifying agent; and

f) a stiffening agent.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) a stabilizer;

e) from about 6% (w/w) to about 8% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) edetate calcium disodium;

e) from about 6% (w/w) to about 8% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 8% (w/w) to about 10% (w/w) propylene glycol;

b) petrolatum;

c) an antioxidant;

d) from about 0.0020% (w/w) to about 0.0040% (w/w) edetate calcium disodium;

e) from about 6% (w/w) to about 8% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 5% (w/w) to about 15% (w/w) propylene glycol;

b) petrolatum;

c) butylated hydroxytoluene;

d) edetate calcium disodium;

e) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) a stiffening agent

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) from about 5% (w/w) to about 15% (w/w) propylene glycol;

b) petrolatum;

c) butylated hydroxytoluene;

d) edetate calcium disodium;

e) from about 5% (w/w) to about 10% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) paraffin wax

wherein the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of:

a) about 9% (w/w) propylene glycol;

b) white petrolatum;

c) about 0.1% (w/w) butylated hydroxytoluene;

d) about 0.0035% (w/w) edetate calcium disodium;

e) about 7% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) about 5% (w/w) paraffin wax.

In an exemplary embodiment, the topical pharmaceutical formulation consists of:

a) 9% (w/w) propylene glycol;

b) 78.8965% (w/w) white petrolatum;

c) 0.1% (w/w) butylated hydroxytoluene;

d) 0.0035% (w/w) edetate calcium disodium;

e) 7% (w/w) of a glyceride blend, wherein the glyceride blend comprises one or more monoglycerides and one or more diglycerides, wherein the one or more monoglycerides is in a total concentration of between 40% and 55% of the glyceride blend; and

f) 5% (w/w) paraffin wax

wherein the formulation comprises no more than about 0.5% (w/w) water.

Information regarding, excipients of use in the topical pharmaceutical formulations described herein, as well as making these topical pharmaceutical

formulations, can be found herein as well as in Remington: The Science and Practice of Pharmacy, 21st Ed., Pharmaceutical Press (2011), the content of which is incorporated by reference for all purposes.

III. The Methods

In another aspect of the invention, an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof, can be utilized in the methods described herein. In another aspect of the invention, the topical pharmaceutical formulation described herein can be utilized in the methods described herein. In another aspect of the invention, the topical pharmaceutical formulation with an active agent, described herein, can be utilized in the methods described herein. In another aspect of the invention, the topical pharmaceutical formulation without an active agent, described herein, can be utilized in the methods described herein. In an exemplary embodiment, in any of the methods described herein, the animal being administered an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof, or a topical pharmaceutical formulation described herein is not otherwise in need of treatment with said active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof, or the topical pharmaceutical formulation described herein. In an exemplary embodiment, in any of the methods described herein, the animal being administered an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof, or a topical pharmaceutical formulation described herein is in need of treatment with said active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof, or a topical pharmaceutical formulation described herein. In an exemplary embodiment, in any of the methods described herein, the animal being administered a topical pharmaceutical formulation without an active agent, described herein, is not otherwise in need of treatment with the topical pharmaceutical formulation without an active agent. In an exemplary embodiment, in any of the methods described herein, the animal being administered a topical pharmaceutical formulation without an active agent, described herein, is in need of treatment with the topical pharmaceutical formulation without an active agent.

III.a. Cytokine and/or Chemokine

In another aspect, the invention provides a method of decreasing the release of a cytokine and/or a chemokine, the method comprising contacting a cell with an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate

thereof. In an exemplary embodiment, the invention provides a method of decreasing the release of a cytokine and/or a chemokine, the method comprising contacting a cell with a topical pharmaceutical formulation with an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In an exemplary embodiment, the invention provides a method of decreasing the release of a cytokine and/or a chemokine, the method comprising contacting a cell with a topical pharmaceutical formulation without an active agent, described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In an exemplary embodiment, for any of the methods provided herein, the release of the cytokine and/or chemokine is decreased. In an exemplary embodiment, for any of the methods described herein, the cytokine and/or chemokine is decreased.

In another aspect, the invention provides a method of decreasing the release of a cytokine and/or a chemokine from a cell, the method comprising contacting the cell with an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In an exemplary embodiment, the active agent contacts the cell through administration of a topical pharmaceutical formulation described herein. In an exemplary embodiment, the invention provides a method of decreasing the release of a cytokine and/or a chemokine from a cell, the method comprising: contacting the cell with a topical pharmaceutical formulation without an active agent, described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In an exemplary embodiment, the release of the cytokine and/or chemokine by the cell is decreased. In an exemplary embodiment, the cell is a skin cell.

In another aspect, the invention provides a method of decreasing the release of a cytokine and/or a chemokine from a cell, the method comprising contacting the cell with a topical pharmaceutical formulation without an active agent, described herein. In an exemplary embodiment, the release of the cytokine and/or chemokine by the cell is decreased. In an exemplary embodiment, the cell is a skin cell.

In another aspect, the invention provides a method of decreasing the release of a cytokine and/or a chemokine by a skin cell, the method comprising contacting the skin cell with an active agent by administering a topical pharmaceutical formulation described herein. In an exemplary embodiment, the release of the cytokine and/or chemokine by the skin cell is decreased.

In another aspect, the invention provides a method of decreasing the release of a cytokine and/or a chemokine by a skin cell, the method comprising contacting the skin cell with a topical pharmaceutical formulation described herein. In an exemplary embodiment, the release of the cytokine and/or chemokine by the skin cell is decreased.

In another aspect, the invention provides a method of decreasing the release of a cytokine and/or a chemokine by a skin cell, the method comprising contacting the skin cell with a topical pharmaceutical formulation without an active agent, described herein. In an exemplary embodiment, the release of the cytokine and/or chemokine by the skin cell is decreased.

In an exemplary embodiment, the cytokine and/or chemokine is selected from the group consisting of TNF-α, IFN-γ, IL-2, IL-4, IL-5, IL-13, IL-22, IL-23, and IL-31. In an exemplary embodiment, the cytokine and/or chemokine is TNF-α. In an exemplary embodiment, the cytokine and/or chemokine is IL-23. In an exemplary embodiment, the cytokine and/or chemokine is IL-2. In an exemplary embodiment, the cytokine and/or chemokine is IL-17.

In an exemplary embodiment, for any of the methods described herein, the active agent or the topical pharmaceutical formulation is present in an amount which decreases the release of a cytokine and/or chemokine described herein by at least about 5 to about 100%, or at least about 30 to about 100%, 40 to about 100%, or at least about 50 to about 100%, or at least about 60 to about 100%, or at least about 70 to about 100%, or at least about 80 to about 100%, or at least about 90 to about 100%, or at least about 30 to about 70%, or at least about 40 to about 90%, or at least about 45 to about 80%, or at least about 55 to about 75%, or at least about 75 to about 98%, or at least about 55 to about 99%, or at least about 5% to about 20% or at least about 10% to about 25%.

III.b. Phosphodiesterase

In another aspect, the invention provides a method of inhibiting a phosphodiesterase (PDE), the method comprising contacting the phosphodiesterase with an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In an exemplary embodiment, the compound of the invention is a compound described herein or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, the compound of the invention is a compound described

herein. In an exemplary embodiment, the amount of the compound is a therapeutically effective amount. In an exemplary embodiment, the compound is according to a formula described herein. In an exemplary embodiment, for any of the methods described herein, the phosphodiesterase is inhibited.

In another aspect, the invention provides a method of inhibiting a phosphodiesterase (PDE) in a cell, the method comprising contacting the cell with a topical pharmaceutical formulation with an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In another aspect, the invention provides a method of inhibiting a phosphodiesterase (PDE) in a cell, the method comprising contacting the cell with a topical pharmaceutical formulation without an active agent described herein, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof. In an exemplary embodiment, the amount of the active agent is a therapeutically effective amount. In an exemplary embodiment, the amount of the topical pharmaceutical formulation with an active agent is a therapeutically effective amount. In an exemplary embodiment, the amount of the topical pharmaceutical formulation without an active agent is a therapeutically effective amount. In an exemplary embodiment, for any of the methods described herein, the cell is a skin cell. In an exemplary embodiment, for any of the methods described herein, the phosphodiesterase is inhibited.

In an exemplary embodiment, the phosphodiesterase is selected from the group consisting of PDE1, PDE2, PDE3, PDE4, PDE5, PDE6, PDE7, PDE8, PDE9, PDE10 and PDE11. In an exemplary embodiment, the phosphodiesterase is PDE4. In an exemplary embodiment, the PDE4 is selected from the group consisting of PDE4A, PDE4B, PDE4C and PDE4D. In an exemplary embodiment, the PDE4 is PDE4B. In an exemplary embodiment, the phosphodiesterase is PDE7.

In an exemplary embodiment, the invention provides a method for inhibiting a phosphodiesterase4 (PDE4), but not significantly inhibiting at least one PDE which is selected from the group consisting of PDE1, PDE2, PDE3, PDE5 and PDE6, involving contacting a cell with a topical pharmaceutical formulation described herein, thereby providing said inhibition.

In an exemplary embodiment, for any of the methods described herein, the active agent or the topical pharmaceutical formulation is present in an amount which inhibits a phosphodiesterase described herein by at least about 5 to about 100%, or at least about 30 to about 100%, 40 to about 100%, or at least about 50 to about 100%, or

at least about 60 to about 100%, or at least about 70 to about 100%, or at least about 80 to about 100%, or at least about 90 to about 100%, or at least about 30 to about 70%, or at least about 40 to about 90%, or at least about 45 to about 80%, or at least about 55 to about 75%, or at least about 75 to about 98%, or at least about 55 to about 99%, or at least about 5% to about 20% or at least about 10% to about 25%.

III.c. Conditions

In another aspect, the invention provides a method of treating and/or preventing a condition in an animal, the method comprising administering to the animal a therapeutically effective and/or prophylactically effective amount of a topical pharmaceutical formulation with an active agent, described herein. In an exemplary embodiment, the condition is treated and/or prevented. In an exemplary embodiment, the animal is in need of treatment and/or prophylaxis thereof. In an exemplary embodiment, the animal is not otherwise in need of treatment and/or prophylaxis thereof. In an exemplary embodiment, the condition is a condition of the skin. In an exemplary embodiment, the condition is pruritis.

In another aspect, the invention provides a method of treating and/or preventing a condition in an animal, the method comprising administering to the animal, a therapeutically effective and/or prophylactically effective amount of a topical pharmaceutical formulation without an active agent, described herein. In an exemplary embodiment, the condition is treated and/or prevented. In an exemplary embodiment, the animal is in need of treatment and/or prophylaxis thereof. In an exemplary embodiment, the condition is a condition of the skin. In an exemplary embodiment, the condition is pruritis.

In another aspect, the invention provides a method of treating and/or preventing an inflammatory-related condition in an animal, the method comprising administering to the animal a therapeutically effective and/or prophylactically effective amount of a topical pharmaceutical formulation with an active agent, described herein. In an exemplary embodiment, the inflammatory-related condition is treated and/or prevented. In an exemplary embodiment, the animal is in need of treatment and/or prophylaxis thereof. In an exemplary embodiment, the animal is not otherwise in need of treatment and/or prophylaxis thereof. In an exemplary embodiment, the inflammatory-related condition is a condition of the skin.

In another aspect, the invention provides a method of treating and/or preventing an inflammatory-related condition in an animal, the method comprising administering to the animal, a therapeutically effective and/or prophylactically effective amount of a topical pharmaceutical formulation without an active agent, described herein. In an exemplary embodiment, the inflammatory-related condition is treated and/or prevented. In an exemplary embodiment, the animal is in need of treatment and/or prophylaxis thereof.

In an exemplary embodiment, the inflammatory-related condition is psoriasis. In an exemplary embodiment, the inflammatory-related condition is plaque psoriasis or flexural psoriasis (inverse psoriasis) or guttate psoriasis or pustular psoriasis or nail psoriasis or psoriatic arthritis or erythrodermic psoriasis. In an exemplary embodiment, the inflammatory-related condition is plaque psoriasis. In an exemplary embodiment, the inflammatory-related condition is nail psoriasis.

In an exemplary embodiment, the inflammatory-related condition is dermatitis. In an exemplary embodiment, the inflammatory-related condition is contact dermatitis or atopic dermatitis or nummular dermatitis or seborrheic dermatitis or stasis dermatitis. In an exemplary embodiment, the inflammatory-related condition is atopic dermatitis. In an exemplary embodiment, the inflammatory-related condition is eczema.

In an exemplary embodiment, for any of the methods described herein, the animal is selected from the group consisting of human, cattle, deer, reindeer, goat, honey bee, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, camel, yak, elephant, ostrich, otter, chicken, duck, goose, guinea fowl, pigeon, swan, and turkey. In another exemplary embodiment, for any of the methods described herein, the animal is selected from the group consisting of a human, cattle, goat, pig, sheep, horse, cow, bull, dog, guinea pig, gerbil, rabbit, cat, chicken and turkey. In another exemplary embodiment, for any of the methods described herein, the animal is a human.

In another exemplary embodiment, the method involves preventing psoriasis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the psoriasis is prevented. In another exemplary embodiment, the method involves preventing psoriasis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the psoriasis is prevented. In another exemplary embodiment, the method involves treating psoriasis by

administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the psoriasis is treated.

In another exemplary embodiment, the method involves treating psoriasis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the psoriasis is treated.

In another exemplary embodiment, the method involves preventing plaque psoriasis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the plaque psoriasis is prevented.

In another exemplary embodiment, the method involves preventing plaque psoriasis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the plaque psoriasis is prevented.

In another exemplary embodiment, the method involves treating plaque psoriasis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the plaque psoriasis is treated. In another exemplary embodiment, the method involves treating plaque psoriasis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the plaque psoriasis is treated.

In another exemplary embodiment, the method involves preventing nail psoriasis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the nail psoriasis is prevented.

In another exemplary embodiment, the method involves preventing nail psoriasis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the nail psoriasis is prevented. In another exemplary embodiment, the method involves treating nail psoriasis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the nail psoriasis is treated. In another exemplary embodiment, the method involves treating nail psoriasis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the nail psoriasis is treated.

In another exemplary embodiment, the method involves preventing atopic dermatitis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the atopic dermatitis is prevented.

In another exemplary embodiment, the method involves preventing atopic dermatitis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the atopic dermatitis is prevented.

In another exemplary embodiment, the method involves treating atopic dermatitis by administering a topical pharmaceutical formulation with an active agent, described herein, to an animal. In an exemplary embodiment, the atopic dermatitis is treated.

In another exemplary embodiment, the method involves treating atopic dermatitis by administering a topical pharmaceutical formulation without an active agent, described herein, to an animal. In an exemplary embodiment, the atopic dermatitis is treated.

Exemplary embodiments are summarized herein below.

In an exemplary embodiment, the invention provides a topical pharmaceutical formulation comprising: a) an active agent which treats an inflammatory-related condition, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof; b) from about 5% (w/w) to about 15% (w/w) propylene glycol; and c) petrolatum.

In an exemplary embodiment, according to the above paragraph, the formulation comprises no more than about 0.5% (w/w) water.

In an exemplary embodiment, according to any of the above paragraphs, the amount of the propylene glycol is from about 7% (w/w) to about 11% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the propylene glycol is from about 6% (w/w) to about 10% (w/w). In an exemplary embodiment, according to any of the above paragraphs, the amount of the propylene glycol is from about 8% (w/w) to about 10% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the propylene glycol is about 9% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the propylene glycol is 9% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the propylene glycol is propylene glycol USP.

In an exemplary embodiment, according to any of the above paragraphs, the topical pharmaceutical formulation further comprises an emulsifying agent.

In an exemplary embodiment, according to any of the above paragraphs, wherein the emulsifying agent is a glyceride blend.

In an exemplary embodiment, according to any of the above paragraphs, wherein the emulsifying agent is a glyceride blend, and the glyceride blend comprises a monoglyceride and a diglyceride.

In an exemplary embodiment, according to any of the above paragraphs, the amount of the glyceride blend is from about 3% (w/w) to about 10% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the glyceride blend is from about 5% (w/w) to about 8% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the glyceride blend is from about 6% (w/w) to about 8% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the glyceride blend is about 7% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the glyceride blend is 7% (w/w). In an exemplary embodiment, according to any of the above paragraphs, the glyceride blend is is Mono- and Di-glyceride NF.

In an exemplary embodiment, according to any of the above paragraphs, from about 40% (w/w) to about 55% (w/w) of the glyceride blend is a monoglyceride.

In an exemplary embodiment, according to any of the above paragraphs, the topical pharmaceutical formulation further comprises a stabilizer. In an exemplary embodiment, according to any of the above paragraphs, the stabilizer is ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof. In an exemplary embodiment, according to any of the above paragraphs, further comprising a sodium salt or a potassium salt or a calcium salt, or a mixture thereof, of ethylenediaminetetraacetic acid. In an exemplary embodiment, according to any of the

above paragraphs, further comprising a sodium salt or a calcium salt, or a mixture thereof, of ethylenediaminetetraacetic acid.

In an exemplary embodiment, according to any of the above paragraphs, further comprising edetate calcium disodium.

In an exemplary embodiment, according to any of the above paragraphs, further comprising edetate calcium disodium USP.

In an exemplary embodiment, according to any of the above paragraphs, the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is from about 0.0001% (w/w) to about 0.01% (w/w). In an exemplary embodiment, according to any of the above paragraphs, the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is from about 0.001% (w/w) to about 0.01% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is from about 0.001% (w/w) to about 0.005% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is from about 0.0025% (w/w) to about 0.0045% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is about 0.0035% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is 0.0035% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the edetate calcium disodium USP is 0.0035% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, further comprising an antioxidant.

In an exemplary embodiment, according to any of the above paragraphs, the antioxidant is selected from the group consisting of butylated hydroxytoluene, ascorbic acid or a pharmaceutically acceptable salt thereof, ascorbic palmitate, butylated hydroxyanisole, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-*tert*-

butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone and tocopherols such as vitamin E, and the like, including pharmaceutically acceptable salts and esters thereof, and mixtures thereof.

In an exemplary embodiment, according to any of the above paragraphs, the antioxidant is butylated hydroxytoluene.

In an exemplary embodiment, according to any of the above paragraphs, the amount of the antioxidant is from about 0.01% (w/w) to about 1% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the antioxidant is from about 0.05% (w/w) to about 0.5% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the antioxidant is about 0.1% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the antioxidant is 0.1% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the antioxidant is butylated hydroxytoluene.

In an exemplary embodiment, according to any of the above paragraphs, the antioxidant is butylated hydroxytoluene NF.

In an exemplary embodiment, according to any of the above paragraphs, further comprising a stiffening agent.

In an exemplary embodiment, according to any of the above paragraphs, the amount of the stiffening agent is from about 2% (w/w) to about 8% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the stiffening agent is from about 4% (w/w) to about 6% (w/w). In an exemplary embodiment, according to any of the above paragraphs, the amount of the stiffening agent is about 5% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the stiffening agent is 5% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the stiffening agent is selected from the group consisting of beeswax, paraffin wax, wax, and spermaceti wax.

In an exemplary embodiment, according to any of the above paragraphs, the stiffening agent is paraffin wax.

In an exemplary embodiment, according to any of the above paragraphs, the stiffening agent is paraffin wax NF.

In an exemplary embodiment, according to any of the above paragraphs, the stiffening agent is 5% (w/w) paraffin wax NF.

In an exemplary embodiment, according to any of the above paragraphs, the active agent is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. In an exemplary embodiment, according to any of the above paragraphs, the amount of the active agent is from about 0.1% (w/w) to about 2.0% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole is from about 0.1% (w/w) to about 2.0% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the amount of the 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole is 2.0% (w/w).

In an exemplary embodiment, according to any of the above paragraphs, the remainder of the formulation is petrolatum. In an exemplary embodiment, according to any of the above paragraphs, the remainder of the formulation is White Petrolatum.

In an exemplary embodiment, according to any of the above paragraphs, the remainder of the formulation is White Petrolatum USP.

In an exemplary embodiment, the topical pharmaceutical formulation consists of: a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) propylene glycol; c) butylated hydroxytoluene; d) edetate calcium disodium; e) mono- and di- glycerides; f) paraffin wax; and g) white petrolatum.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of: a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) propylene glycol; c) butylated hydroxytoluene; d) edetate calcium disodium; e) mono- and di- glycerides; f) paraffin wax; and g) white petrolatum.

In an exemplary embodiment, the topical pharmaceutical formulation comprises: a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) propylene glycol;

c) butylated hydroxytoluene; d) edetate calcium disodium; e) mono- and di- glycerides; f) paraffin wax; and g) white petrolatum.

In an exemplary embodiment, the topical pharmaceutical formulation consists of: a) 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) 9% (w/w) propylene glycol; c) 0.1% (w/w) butylated hydroxytoluene; d) 0.0035% (w/w) edetate calcium disodium; e) 7% (w/w) mono- and di- glycerides; f) 5% (w/w) paraffin wax; and g) 76.8965% (w/w) white petrolatum.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of: a) 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) 9% (w/w) propylene glycol; c) 0.1% (w/w) butylated hydroxytoluene; d) 0.0035% (w/w) edetate calcium disodium; e) 7% (w/w) mono- and di- glycerides, wherein between 40% and 55% is the monoglyceride; f) 5% (w/w) paraffin wax; and g) 76.8965% (w/w) white petrolatum.

In an exemplary embodiment, the topical pharmaceutical formulation consists essentially of: a) about 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) about 9% (w/w) propylene glycol; c) about 0.1% (w/w) butylated hydroxytoluene; d) about 0.0035% (w/w) edetate calcium disodium; e) about 7% (w/w) mono- and di- glycerides, wherein between 40% and 55% is the monoglyceride; f) about 5% (w/w) paraffin wax; and g) about 76.8965% (w/w) white petrolatum.

In an exemplary embodiment, the topical pharmaceutical formulation consists of: a) about 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole; b) about 9% (w/w) propylene glycol; c) about 0.1% (w/w) butylated hydroxytoluene; d) about 0.0035% (w/w) edetate calcium disodium; e) about 7% (w/w) mono- and di-glycerides, wherein between 40% and 55% is the monoglyceride; f) about 5% (w/w) paraffin wax; and g) about 76.8965% (w/w) white petrolatum.

In an exemplary embodiment, the invention is a method of decreasing the release of a cytokine and/or a chemokine, the method comprising contacting a cell with the topical pharmaceutical formulation according to any of the above paragraphs.

In an exemplary embodiment, the invention is a method of treating an inflammatory-related condition in an animal, the method comprising administering to the animal a therapeutically effective amount of the topical pharmaceutical formulation according to any of the above paragraphs.

In an exemplary embodiment, according to any of the above method paragraphs, the inflammatory-related condition is psoriasis.

In an exemplary embodiment, according to any of the above method paragraphs, the inflammatory-related condition is atopic dermatitis.

In an exemplary embodiment, according to any of the above method paragraphs, the animal is a human.

In an exemplary embodiment, the invention is a method of treating atopic dermatitis in a human, the method comprising administering to the human a therapeutically effective amount of the topical pharmaceutical formulation according to any of the above paragraphs.

In an exemplary embodiment, the invention is a method of treating psoriasis in a human, the method comprising administering to the human a therapeutically effective amount of the topical pharmaceutical formulation according to any of the above paragraphs.

The invention is further illustrated by the Examples that follow. The Examples are not intended to define or limit the scope of the invention.

EXPERIMENTALS

Polymorphic Studies

Different crystalline solid forms of the same compound often possess different solid-state properties such as melting point, solubility, dissolution rate, hygroscopicity, powder flow, mechanical properties, chemical stability and physical stability. These solid-state properties may offer advantages in filtration, drying, and dosage form manufacturing unit operations. Thus, once different crystalline solid forms of the same compound have been identified, the optimum crystalline solid form under any given set of processing and manufacturing conditions may be determined as well as the different solid-state properties of each crystalline solid form.

Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation. Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), X-ray powder diffractometry

(XRPD), single crystal X-ray diffractometry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, and hot-stage optical microscopy.

During the development of the manufacturing process for crisaborole drug substance, attemps were directed towards identifying the polymorphs of crisaborole. Several solvent systems that involved polar protic solvents like water, polar aprotic sovletns like dimethoxyethane and nonpolar solvents such as heptanes were explored. These studies resulted in the identification of three polymorphs of crisaborole drug substance that were differentiated by X-ray Powder Diffraction. Form 2 was the form utilized in clinical studies through Phase 2. Form 1 was identified as the commercial form and was utilized in Phase 3 studies.

There are a number of analytical methods one of ordinary skill in the art in solid-state chemistry can use to analyze solid forms. The term "analyze" as used herein means to obtain information about the solid-state structure of solid forms. For example, X-ray powder diffraction is a suitable technique for differentiating amorphous solid forms from crystalline solid forms and for characterizing and identifying crystalline solid forms of a compound. X-ray powder diffraction is also suitable for quantifying the amount of a crystalline solid form (or forms) in a mixture. In X-ray powder diffraction, X-rays are directed onto a crystal and the intensity of the diffracted X-rays is measured as a function of twice the angle between the X-ray source and the beam diffracted by the sample. The intensity of these diffracted X-rays can be plotted on a graph as peaks with the x-axis being twice the angle (this is known as the "2θ" angle) between the X-ray source and the diffracted X-rays and with the y-axis being the intensity of the diffracted X-rays. This graph is called an X-ray powder diffraction pattern or powder pattern. Different crystalline solid forms exhibit different powder patterns because the location of the peaks on the x-axis is a property of the solid-state structure of the crystal.

Such powder patterns, or portions thereof, can be used as an identifying fingerprint for a crystalline solid form. Thus, one could take a powder pattern of an unknown sample and compare that powder pattern with a reference powder pattern. A positive match would mean that the unknown sample is of the same crystalline solid form as that of the reference. One could also analyze an unknown sample containing a mixture of solid forms by adding and subtracting powder patterns of known compounds.

When selecting peaks in a powder pattern to characterize a crystalline solid form or when using a reference powder pattern to identify a form, one identifies a peak or collection of peaks in one form that are not present in the other solid forms.

The term "characterize" as used herein means to select an appropriate set of data capable of distinguishing one solid form from another. That set of data in X-ray powder diffraction is the position of one or more peaks. Selecting which X-ray powder diffraction peaks define a particular form is said to characterize that form.

The term "identify" as used herein means taking a selection of characteristic data for a solid form and using those data to determine whether that form is present in a sample. In X-ray powder diffraction, those data are the x-axis positions of the one or more peaks characterizing the form in question as discussed above. For example, once one determines that a select number of X-ray diffraction peaks characterize a particular solid form, one can use those peaks to determine whether that form is present in a sample.

When characterizing and/or identifying crystalline solid forms of the same chemical compound with X-ray powder diffraction, it is often not necessary to use the entire powder pattern. A smaller subset of the entire powder pattern can often be used to perform the characterization and/or identification. By selecting a collection of peaks that differentiate the crystalline solid form from other crystalline solid forms of the compound, one can rely on those peaks to both characterize the form and to identify the form in, for example, an unknown mixture. Additional data can be added, such as from another analytical technique or additional peaks from the powder pattern, to characterize and/or identify the form should, for instance, additional polymorphs be identified later.

Due to differences in instruments, samples, and sample preparation, peak values is sometimes reported with the modifier "about" in front of the peak values. This is common practice in the solid-state chemical arts because of the variation inherent in peak values. A typical precision of the 2θ x-axis value of a peak in a powder pattern is on the order of plus or minus 0.2° 2θ. Thus, a powder diffraction peak that appears at "about 9.2° 2θ," means that the peak could be between 9.0° 2θ and 9.4° 2θ when measured on most X-ray diffractometers under most conditions. Variability in peak intensity is a result of how individual crystals are oriented in the sample container with respect to the external X-ray source (known as "preferred orientation"). This orientation effect does not provide structural information about the crystal. X-ray powder diffraction is just one of several analytical techniques one may use to characterize and/or identify

crystalline solid forms. Spectroscopic techniques such as Raman (including microscopic Raman), infrared, and solid state NMR spectroscopies may be used to characterize and/or identify crystalline solid forms. These techniques may also be used to quantify the amount of one or more crystalline solid forms in a mixture and peak values can also be reported with the modifier "about" in front of the peak values. A typical variability for a peak value associated with an FT-Raman and FT-Infrared measurement is on the order of plus or minus 2 cm^{-1}. A typical variability for a peak value associated with a ^{13}C chemical shift is on the order of plus or minus 0.2 ppm for crystalline material. A typical variability for a value associated with a differential scanning calorimetry onset temperature is on the order of plus or minus 5° C.

The term “room temperature” as used herein refers to the temperature range of 20 °C to 23 °C. .

1. Instrument Method (API and Drug Product Scans)

Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 ADVANCE diffractometer equipped with a Cu radiation source (K-α average). The system is equipped with a 2.5 axial Soller slits on the primary side. The secondary side utilizes 2.5 axial Soller slits and motorized slits. Diffracted radiation was detected by a Lynx Eye XE detector. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected in the Theta-Theta goniometer at the Cu wavelength from 3.0 to 40.0 degrees 2-Theta using a step size of 0.037 degrees and a step time of 1920 seconds. Samples were prepared by placing them in a low background holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software (Version 9.0.0.2) and analysis was performed by EVA diffract plus software.

The PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks selected with a threshold value of 1 and a width value of 0.3 were used to make preliminary peak assignments. The output of automated assignments was visually checked to ensure validity and adjustments were manually made if necessary. Peaks with relative intensity of ≥ 2% were generally chosen. The peaks which were not resolved or were consistent with noise were not selected. A typical error associated with the peak position from PXRD stated in USP up to +/- 0.2° 2-Theta (USP-941). The peak fitting associated with Forms 1, 2 and 3 are listed in Tables 1-3; Table 4 lists the peaks for Form 1 that can be distinguished from

the placebo drug product. For example, 6.0, 12.1, 14.1 and 15.4 peaks are associated with crisaborole. In particular, peaks 6.0 and 15.4 are preferred associated peaks.

Table 1: PXRD peak list for Form 1 API. Asterisked peak positions represent characteristic peaks.

Angle	Rel. Intensity
6.1*	100
12.2	14
14.2	9
15.4*	31
16.1	6
17.7	2
18.2	46
21.5	11
23.1	5
24.3	8
24.9	12
26.2	61
26.5	7
28.5	12
29.1	3
31.6	7
31.4	17
31.7	7
32.8	2
33.8	3
37.0	2

Table 2: PXRD peak list for Form 2 API

Angle 2Theta°	Relative Intensity %
7.1	6
12.3	12
14.3	18
14.9	4
15.5	2
16.4	13
16.7	75
17.7	43
17.9	7
18.4	10
20.0	8
20.9	100
21.4	29
21.8	36
22.2	5
22.7	59
23.2	30
23.5	8
24.2	4
24.9	31
24.9	26
26.1	11
26.4	7
26.5	7
27.1	8
27.5	9
27.8	15
28.0	32
28.8	6
29.1	3
30.1	10

31.0	3
31.5	5
32.1	3
33.7	3
34.4	2
34.9	5
37.4	7
38.9	2
39.9	2
43.1	4
45.6	2
46.5	3

Table 3: PXRD peak list for crisaborole Form 3 API.

Angle 2-Theta°	**Rel. Intensity %**
13.8	2
14.3	2
15.8	5
16.4	6
16.6	13
16.7	13
16.8	7
17.7	8
18.4	9
18.4	8
18.8	15
19.7	12
20.8	100
21.4	13
21.9	9
22.7	16
23.2	4
23.5	4

23.9	17
24.9	4
26.4	3
26.2	8
26.5	3
27.1	3
27.6	6
27.9	33
28.8	5
29.1	3
31.4	6
32.3	2
34.9	2
37.3	6

Table 4: PXRD peak list for Crisaborole Form 1 drug product.

Angle 2-Theta°	**Relative Intensity %**
6.0	89
12.1	11
14.1	33
15.4	100
16.0	17
17.7	6
18.2	40
18.6	2
21.5	33
23.1	6
24.9	37
26.2	87
26.5	14
27.6	2
28.5	33
28.5	27

29.1	7
31.0	6
31.4	11
31.7	9
31.8	8
32.8	3
33.8	7
37.1	3
39.3	2

2. Method for Producing Form 1

Crisaborole was dissolved in acetic acid (~3.5 vol) at 70°C followed by the addition of about 0.75 vol water. The mixture was cooled to ~ 61°C (range: between 58°C and 63°C), seeded with crisaborole (1% seeding ± 1%) and maintained at that temperature for approximately 15 minutes. The reaction mixture was then cooled to 50°C (± 3°C) over a 45 to 60 minute period and monitored by Raman Spectroscopy until the appropriate end point was reached. The reaction mixture was then further cooled to 20°C (± 5°C) over 3 to 5 hours (target: 4 hours) and monitored by Raman Spectroscopy until the appropriate end point is reached. The solids were filtered and washed with 3 X 2 volumes of water and dried at 45°C (± 10°C). See Table 1 and Figure 2: PXRD spectrum of Form 1 and Figure 4: PXRD of crisaborole drug product placebo lot overlaid with Form 1.

3. Method for Producing Form 2

Crisaborole was dissolved in acetonitrile at 70C and approximately 2 volumes of water were added to the solution, affording immediate precipitation of Form 2. See Table 2 and Figure 3: PXRD spectrum of Forms 1, 2 and 3.

4. Method for Producing Form 3

Polymorphic Form 3 was typically only found during polymorph screening utilizing fast evaporation studies from solvents such as ethyl acetate, methyl ethyl ketone, and methyl *tert*-butyl ether. Approximately 1 g of Crisaborole was dissolved in acetonitrile at 75°C, followed by filtration. Water was added to the filtrate as an anti-solvent at 75°C. The resulting mixture was a clear solution, and it was seeded with approximately 2 mg of Form III seed crystal. The mixtures were then cooled to ambient

temperature at 20 °C/h and stirred overnight. The solids were isolated by filtration and washed with approximately 2 mL of water. The solids were dried under vacuum at ambient temperature for 20 hours, which was then analyzed by XRPD to confirm the formation of Form III. See Figure 2: PXRD spectrum of Forms 1, 2 and 3.

Solvent Selection

One of the key aspects encountered in reformulating crisaborole was that the active agent be fully dissolved within its solvent. A selection criterion of greater than 10% w/w crisaborole solubility was used to select solvents capable of carrying at least 1% crisaborole in a final drug product formulation, assuming the drug product contained 10% solvent. The solubility of crisaborole in ten solvents was evaluated to identify those with crisaborole solubility greater than 10% w/w by visual assessment. The equilibrium solubity of the best solvents was subsequently verified by HPLC. See **Table 5**.

Table 5: Solubility Studies of Crisaborole Form II

Solvent	Visual Solubity[a] (% w/w)	Solubity by HPLC[b] (mg/mL)
Transcutol® P, NF	28.6%	21.2
Hexylene Glycol, NF	25.9%	356
Propylene Glycol, USP	24.0%	274
Polyethylene Glycol (PEG) 400, USP	15.0%	164
Propylene Carbonate, NF	9.9%	96
Diisopropyl Adipate	7.7%	--
Oleyl Alcohol, NF	2.3%	33
Ethylhexyl Hydroxystearate	1.6%	21
Isopropyl Myristate, NF	0.6%	--
Oleic Acid, NF	<0.1%	--

--Not tested

a. Crisaborole polymorph Form 2

b. Transcutol P is equivalent to diethylene glycol monoethyl ether

The solvents that satisfied the greater than 10% w/w solubility requirement were also evaluated for crisaborole compatibility by assessing degradant formation in

crisaborole solutions at 80% saturation after storage at 50º C and 40 º C/75% RH for seven days.

Crisaborole solutions of three of the seven evaluated solvents (propylene glycol, propylene carbonate and PEG400) exhibited two main degradants, including Impurity 1. Of these three, the propylene glycol solutions had the lowest overall degradation and the highest crisaborole solubility. Crisaborole solutions of the four remaining solvents all exhibited an additional degradant and, therefore, were excluded from development. (See **Table 6**)

Table 6: Crisaborole Compatibility with Various Solvents

		Degradant (% Peak Area)			
Solvent	**Condition**	Impurity 2	Impurity 1	Impurity 3	Total
Propylene Glycol, USP	T_0	—	—	—	—
	7 day, 40°C/75% RH	0.0	0.0	—	0.15
	7 day, 50°C	0.1	0.1	—	0.26
Propylene Carbonate, NF	T_0	—	—	—	—
	7 day, 40°C/75% RH	—	1.3	—	1.37
	7 day, 50°C	0.0	2.0	—	2.08
PEG 400, USP	T_0	0.2	—	—	0.27
	7 day, 40°C/75% RH	0.7	0.0	—	0.82
	7 day, 50°C	0.9	0.1	—	1.09
Hexylene Glycol, NF	T_0	—	—	—	—
	7 day, 40°C/75% RH	0.1	0.0	0.1	0.30
	7 day, 50°C	0.2	0.1	0.3	0.74
Transcutol P, NF [a]	T_0	0.1	—	—	0.12
	7 day, 40°C/75% RH	0.2	—	—	0.22
	7 day, 50°C	0.2	0.0	0.1	0.47
Oleyl Alcohol, NF	T_0	0.4	—	0.0	0.53
	7 day, 40°C/75% RH	5.9	—	0.1	6.02
	7 day, 50°C	9.1	0.10	0.2	9.48
Ethylhexyl	T_0	0.1	—	7.8	7.97
	7 day, 40°C/75% RH	0.2	—	11.	11.78
	7 day, 50°C	0.4	—	13.	13.81

RRT, relative retention time; —, not detected.

a Transcutol P is equivalent to diethylene glycol monoethyl ether.

Emulsifier Selection

To form an ointment containing propylene glycol phase dispersed within a petrolatum base, studies were conducted to identify an emulsifier with an appropriate hydrophilic-lipophilic balance (HLB) value, acceptable crisaborole compatibility, and demonstrated emulsifying ability. An emulsifier with an HLB value of 4-6 was desired for a water-in-oil type emulsion, and four potential emulsifiers were evaluated for

crisaborole compatibility: mono- and di-glycerides (MDG), sorbitan sesquioleate, sorbitan monooleate, and glyceryl monooleate with HLB values of 3.8, 3.7, 4.3, and 3.8 respectively.

Crisaborole was dissolved in propylene glycol to which each emulsifier was added, forming either a solution or partial suspension. The levels of each were approximately equivalent to levels in an ointment formulation containg 10% propylene glycol, 2% crisaborole and 5% emulsifier. The samples were stored at 50º C for 7 days before they were analyzed for degradation of crisaborole. The compatibility results are summarized in Table 7.

Table 7: Crisaborole Compatibility with Various Emulsifiers

Emulsifier	Condition	Degradant (% Peak Area)	
		Impurity X	Impurity 1
Mono- and Di-glycerides [a]	7 day, 50°C	—	1.2
Sorbitan Sesquioleate, NF	7 day, 50°C	—	13.2
Sorbitan Monooleate, NF	7 day, 50°C	0.45	8.4
Glyceryl Monooleate, NF	7 day, 50°C	.15	18.9

—, not detected.

a Identified as Glycerol monostearate, purified.

The MDG grade initially evaluated for crisaborole compatibility was non-compendial and identified as glycerol monostearate, purified. Testing demonstrated, however, that the material conformed more closely to the mono- and di-glycerides, NF compendial specification than to the glyceryl monostearate, NF (GMS) compendial specifications. It is, therefore described herein, as MDG. In an effort to improve the formulation, the non-compendial MDG was replaced with a compendial grade of glyceryl monostearate, NF (Sasol Imwitor® 491). Sasol Imwitor® 491, however, exhibited poor emulsifying properties, likely due to different proportions of mono-glyceride and di-gyceride that is inherent between MDG and GMS.

A variety of compendial and non-compendial MDG and GMS grades were subsequently evaluated for crisaborole compatibility. For the emulsifier evaluation:

(a) a solution of the ointment active phase was prepared: 2 g crisaborole, 8.91 g propylene glycol, 0.09 g water, and 0.1 g boric acid;

(b) 1 gram of active phase was mixed with 0.6 gram of emulsifier, and

(c) the samples were stored at 50°C for 7 days.

The crisaborole compatibility results are presented in Table 8.

Table 8: Crisaborole Compatibility with Potential Emulsifier Grades

Source (Material)	Grade	Compendial Status	Mono-glyceride Content (%)	Degradant (% Peak)	
				Impurity	Impurity 1
Control A[a]	—	—	—	0.	0.
Gattefosse (Geleol™)	MDG	NF	5	0.	0.
Alfa Aesar (Glycerol	MDG	none	4	0.	0.
Sasol (Imwitor® 491)	GMS	NF	9	0.	0.
Sasol (Imwitor® 900K)	MDG	NF	4	0.	1.
Caravan (BFP® 74K)	MDG	none	4	0.	1.
Caravan (BFP® 74E)	MDG	none	4	0.	3.
Abitec (Capmul® MCM)	MDG	NF	5	0.	2.
Control B[a]	—	—	—	0.	0.
Cognis (Cutina® GMS V)	MDG	NF	5	0.	0.

GMS, glyceryl monostearate; MDG, mono- and di-glycerides; RRT, relative retention time;

—, not applicable.

a Control A was conducted concurrently with all emulsifiers except Cutina, which was conducted concurrently with Control B.

Multiple sources of mono- and di-glycerides exhibited acceptable compatibility with crisaborole under these stability conditions. Exemplary sources included Gattefosse (Geleol™), Alfa Aesar (Glycerol monostearate), Sasol (Imwitor® 491), Sasol (Imwitor® 900K), Caravan (BFP® 74K), Caravan (BFP® 74E), Abitec (Capmul® MCM NF), Cognis (Cutina® GMS V PH). Mono- and di-glycerides, NF was selected to be the emulsifier for Crisaborole Topical Ointment, 2% on the basis of compendial status, HLB value, chemical compatibility, and established emulsifying capability.

Stabilizer Selection

Early prototype formulations demonstrated improved stability, particularly with regard to protodeboronation, when approximately 1% of the propylene glycol solvent was replaced with water. Further improvement in stability was found when a small percentage of boric acid was added to the formulation. The Crisaborole Ointment Z6

formulation, therefore, included small amounts of both water and boric acid. However, the mechanism by which water and boric acid reduced the rate of protodeboronation was not well understood.

During scale-up procedures, however, the presence of water in propylene glycol reduced the solubility of crisaborole Form I (the commercial polymorphic Form), presenting potential formulation challenges. Furthermore, the water and boric acid combination did not adequately stabilize crisaborole and an alternative stabilizer was therefore pursued.

Edetate calcium disodium (EDTA) was evaluated as a stabilizer at various levels within drug product formulations utilizing the same excipients used in Crisaborole Topical Ointment, 2%. The drug product formulations were evaluated in multiple candidate tubes, including 60-g laminate tubes equivalent to the commercial primary container closure system (with the exception of not having an orifice seal), at both 25°C/60% RH and 40°C/75% RH.

The evaluated formulations differed from Crisaborole Topical Ointment, 2% only in the stabilizers used: 0 ppm EDTA, **Z10**, 24 ppm EDTA (Ointment **Z7**), 90 ppm EDTA, 450 ppm EDTA, and 0.09% water with 0.10% boric acid (equivalent to Ointment **Z6**, but utilizing MDG rather than GMS). Results from the evaluation in the 60-g laminate tubes are presented in **Tables 5** and **6**. After six months, the formulation without stabilizer exhibited the greatest total crisaborole degradation and lowest assay at the 40°C/75% RH condition, followed by the Ointment **Z6** formulation (water and boric acid as stabilizer). The greatest stabilizing effect was observed at the 24 ppm EDTA and 90 ppm EDTA levels. The 24 ppm EDTA formulation (Ointment **Z7**) was subsequently utilized in clinical studies

EXAMPLES

EXAMPLE 1

Manufacture of Topical Pharmaceutical Formulations of the invention

a) Topical pharmaceutical formulation with an active agent

Step 1: Preparation of Oil Phase

In a primary compounding vessel, white petrolatum, paraffin wax and mono and diglycerides were added with continuous propeller mixing while being heated to 70-80 °C. The temperature of this mixture was maintained at 70-80°C with the mixture appearing visually melted and uniform. With propeller stirring, butylated hydroxytoluene

was added and mixed to dissolve while maintaining the temperature to 70-80°C. While being stirred, the mixture was cooled down to 40-46 °C and maintained until addition of drug solution phase.

Step 2: Preparation of Drug Solution Phase

In a secondary compounding vessel, edetate calcium disodium was added to propylene glycol with continuous propeller mixing while being heated to 40-46°C. The temperature of this mixture was maintained at 40-46°C with the mixture appearing visually dissolved and uniform. With continuous mixing, crisaborole was added to dissolve while maintaining the temperature at 40-46°C.

Step 3: Emulsification

The drug solution phase was filtered through 80 mesh filter and added to the oil phase. It was then homogenized for 10 minutes while maintaining the temperature at 40-46°C. The final composition was cooled to 25°C with propeller mixing until a homogenous ointment was obtained.

All components were compendial. The 2% ointment formulation, **Z**, was produced according to the procedure above and had the following components:

Component	**Z % w/w**
Crisaborole	2.000
Propylene Glycol	9.000
Butylated Hydroxytoluene	0.100
Mono- and Di- glycerides	7.000
Paraffin Wax	5.000
White Petrolatum	76.8965
Edetate Calcium Disodium	0.0035

b) Topical pharmaceutical formulation without an active agent

Step 1: Preparation of Oil Phase

In a primary compounding vessel, white petrolatum, paraffin wax and mono and diglycerides were added with continuous propeller mixing while being heated to 70-80 °C. The temperature of this mixture was maintained at 70-80 °C with the mixture

appearing visually melted and uniform. With propeller stirring, butylated hydroxytoluene was added and mixed to dissolve while maintaining the temperature to 70-80 °C. While being stirred, the mixture was cooled down to 40-46 °C and maintained until addition of drug solution phase.

Step 2: Preparation of Solvent Phase

In a secondary compounding vessel, edetate calcium disodium was added to propylene glycol with continuous propeller mixing while being heated to 40-46 °C. The temperature of this mixture was maintained at 40-46 °C with the mixture appearing visually dissolved and uniform.

Step 3: Emulsification

The solvent phase was filtered through 80 mesh filter and added to the oil phase. It was then homogenized for 10 minutes while maintaining the temperature at 40-46°C. The final composition was cooled to 25°C with propeller mixing until a homogenous ointment was obtained.

All components were compendial. The 2% ointment formulation, **Y**, was produced according to the procedure above and had the following components:

Component	**Y % w/w**
Propylene Glycol	9.000
Butylated Hydroxytoluene	0.100
Mono- and Di- glycerides	7.000
Paraffin Wax	5.000
White Petrolatum	78.8965
Edetate Calcium Disodium	0.0035

EXAMPLE 2

Flux tests for 2% and 5% crisaborole creams—

In vitro penetration of crisaborole in cream formulations through human ex vivo cadaver skin was measured. The composition of the 2% crisaborole cream formulation, **Z1**, and the 5% crisaborole cream formulation, **Z2**, are provided below. Both **Z1** and **Z2**

are disclosed in U.S. Pat. App. No. 12/399,015 (U.S. Pat. Pub. No. US2009/0291917) and PCT Pat. App. No. PCT/US09/036250 (PCT Pat. Pub. No. WO2009/111676).

Component	Z1 % w/w	Z2 % w/w
Crisaborole	2.0	5.0
Methylparaben	0.15	0.15
Propylparaben	0.03	0.03
Glyceryl Monostearate SE	8.0	8.0
Butylated Hydroxytoluene	0.02	0.02
Edetate Disodium	0.05	0.05
Pemulen TR-2	0.25	0.25
Carbopol Ultrez 10	0.20	0.20
25% Trolamine	0.84	0.84
Propylene Glycol	5.0	5.0
Octyldodecanol	10.0	10.0
Oleyl Alcohol	10.0	10.0
Benzyl Alcohol	2.0	2.0
Diisopropyl Adipate	10.0	10.0
Purified Water	QS 100	QS 100

25% Trolamine Solution

Component	% w/w
Trolamine	25.0
Purified Water	75.0

Testing was conducted according to the following protocol.

Study Skin Preparation

Percutaneous penetration was measured using the *in vitro* cadaver skin finite dose technique. Human, *ex vivo*, trunk skin, within 1 year of collection without obvious signs of skin disease was used in this study. It was dermatomed, prepared for cryopreservation, sealed in a water impermeable plastic bag, and stored at ≤ -70°C until

the day of the experiment. Prior to use it was thawed in ~37°C water, then rinsed in water to remove any adherent blood or other material from the surface.

Skin from a single donor was cut into multiple smaller sections large enough to fit on static 1.0 cm^2 Franz diffusion cells. The dermal chamber was filled to capacity with a reservoir solution of phosphate-buffered isotonic saline (PBS), pH 7.4 ± 0.1, and the epidermal cell (chimney) left open to ambient laboratory conditions. All cells were mounted in a diffusion apparatus in which the dermal bathing solution was stirred magnetically at approximately 600 RPM and the skin surface temperature maintained at 32.0 ± 1.0 °C.

To assure the integrity of each skin section, its permeability to tritiated water was determined before application of the test products. Franz TJ et al., Abst. J Invest Dermatol 1990, 94:525. Following a brief (0.5-1 hour) equilibrium period, ^3H_2O (NEN, Boston, MA, sp. Act. ~ 0.5 µCi/mL) was layered across the top of the skin by dropper so that the entire exposed surface was covered (approximately 250 - 500 µL). After 5 minutes the ^3H_2O aqueous layer was removed. At 30 minutes the receptor solution was collected and analyzed for radioactive content by liquid scintillation counting. Skin specimens in which absorption of ^3H_2O was less than 1.56 µL-equ/cm^2 were considered acceptable.

Following the water test the chambers were arranged in formulation groups so that there was an even raked distribution of the chambers with associated water penetration within each group for each formulation.

Dosing and Sample Collection

Just prior to dosing, a pre-dose sample was taken and the reservoir solution was replaced with a fresh solution of 0.1x PBS with 0.1% Volpo. The chimney was removed from the Franz Cell to allow full access to the epidermal surface of the skin. All formulations were then applied to the skin sections using a positive displacement pipette set to deliver 5 µL formulation/cm^2. The dose was spread across the surface with the Teflon tip of the pipette. Five to ten minutes after application the chimney portion of the Franz Cell was replaced. Care was taken to keep containers of dosing solution capped when not in use and to leave them open as little as possible during dosing in order to minimize evaporation.

At pre-selected times after dosing, (4, 8, 12, 24, and 48 hours) the reservoir solution was removed in its entirety, replaced with fresh reservoir solution, and a

predetermined volume aliquot saved for subsequent analysis. All samples were collected in 2 mL Boil-Proof Microtubes (Axygen Scientific MCT-200-C).

Spare cells were available which were not dosed but used to evaluate for the appearance of substances diffusing out of the skin that might interfere with the analytic method.

After the last sample was collected, the surfaces were washed twice (0.5 mL volume each) with acetonitrile to collect un-absorbed formulation from the surface of the skin. Following the wash, the skin was tape stripped (Transpore® Tape, 3M) no more than 10 times to remove the stratum corneum. The tape strips were extracted overnight in acetonitrile. The skin was then removed from the chamber, split into epidermis and dermis. Each was extracted overnight in acetonitrile. In addition, at the end of the study, the chamber parts (dosing chimney and reservoir chamber) were rinsed separately with acetonitrile and the samples retained for analysis.

Results:

Total percutaneous penetration through human cadaver skin over 48 hours for Z1 and Z2 are provided below:

Mean Cumulative Amounts (µg/cm^2) of Crisaborole through Human Cadaver Skin over 48 Hours (Creams)

	Z1	Z2
Mean ± SD N=3 donors, 3 replicates per donor.	1.13 ±0.67 µg/cm^2	4.57± 3.51 µg/cm^2

EXAMPLE 3

Flux tests for 2% crisaborole ointment Z3 and 5% crisaborole ointment Z4—

In vitro penetration of crisaborole in two ointment formulations through human ex vivo cadaver skin was measured. The composition of the 2% crisaborole ointment formulation, Z3, and the 5% crisaborole ointment formulation, Z4, are provided below. Both Z3 and Z4 are disclosed in U.S. Pat. App. No. 12/399,015 (U.S. Pat. Pub. No. US2009/0291917) and PCT Pat. App. No. PCT/US09/036250 (PCT Pat. Pub. No. WO2009/111676).

Component	Z3 % w/w	Z4 % w/w
Crisaborole	2.0	5.0
Ethylhexyl Hydroxystearate	10.0	10.0
Oleyl Alcohol	10.0	10.0
White Petrolatum	78.0	75.0

Testing was conducted according to the protocol of Example 2.

Results:

Total percutaneous penetration through human cadaver skin over 48 hours for **Z3** and **Z4** are provided below:

Mean Cumulative Amounts (µg/cm^2) of Crisaborole through Human Cadaver Skin over 48 Hours (Ointments)

	Z3	Z4
Mean ± SD N=3 donors, 3 replicates per donor.	3.89 ± 0.87 µg/cm^2	4.43±1.81 µg/cm^2

EXAMPLE 4

Flux tests for 2% crisaborole cream Z1 and 2% crisaborole ointment Z —

In vitro penetration of crisaborole in 2% cream formulation **Z1** and ointment formulation **Z**, through human ex vivo cadaver skin was measured.

The composition of the 2% crisaborole cream, **Z1**, is described in Example 2. The composition of the 2% crisaborole ointment, **Z**, is described in Example 1.

Skin Samples & Donor Demographics

Human ex vivo cadaver skin was supplied by Allosource (6278 South Troy Circle, Centennial, CO) and stored at -80°C until use. The thickness of dermatomed skin was approximately 500 µm. Human cadaver skin without obvious signs of skin disease from three donors was used during the study.

Test Procedure

Human ex vivo cadaver skin was stored at -80°C until the morning of the study. Skin was thawed by submerging in pre-warmed phosphate buffered saline (PBS) (37°C), and was inspected for any visible holes or damage. Skin was carefully sectioned using a scalpel to the appropriate size for placement onto the vertical diffusion cell.

Receiving media (90:10 water:propylene glycol v/v) that was pre-warmed to 37°C, and a stir bar, were added to each diffusion cell and allowed to equilibrate for a minimum of 30 minutes. A section of skin was placed on top of each cell, and cells were assembled using clamps to secure the skin in place. Any air bubbles that were introduced during the assembly of the cells were removed. Skin and media were allowed to equilibrate for a minimum of thirty minutes after assembly of the cells.

A 400 µL pre-dose sample of receptor media was collected for analysis, and an equal volume was replaced with pre-warmed fresh media. Formulations were warmed to 31 ± 1°C and equilibrated for approximately 1 hour prior to dosing. Immediately prior to dosing, formulations were briefly mixed using the pipette tip. At one minute intervals, each cell was dosed once with approximately 5 µL/cm^2 of respective formulation using a positive displacement pipette. A glass rod was used to spread the formulation evenly covering the entire surface area of the skin. The sampling port was occluded with parafilm to prevent evaporation of the receptor media during the study. Each glass rod was saved and the tip extracted overnight in 400 µL extraction solution (0.1% formic acid in acetonitrile).

At 3, 6, 12, 24 and 48 hours following dose administration, a 400 µL aliquot of receiving media was removed through the sampling stem of each cell with a pipette. After removing the media, an equal volume of pre-warmed fresh receiving medium was added to replace the volume removed during sampling. Care was taken to avoid

generation of any air bubbles during sampling, and any bubbles were carefully removed if necessary.

At the conclusion of the study, the cells were disassembled and the skin was carefully removed from each cell. Each skin section was washed twice with 0.5 mL of extraction solution (0.1% formic acid in acetonitrile) to collect un-absorbed formulation from the surface of the skin. The skin surface was gently cleansed with lab tissue to remove any residual liquid from the wash. Tissues were tape stripped 1-2 times with 3M Transpore tape to collect the stratum corneum. Tape strips were collected, combined, and extracted in 1 mL extraction solvent (0.1% formic acid in acetonitrile).

Following tape stripping, the skin was carefully separated into epidermis and dermis using forceps. Each section was added to a tared vial and weights collected. To each epidermis vial, homogenization solution (0.1% formic acid in water/propylene glycol [10:90 v/v]) was added at a ratio of 10× tissue weight. To each dermis vial, homogenization solution was added at a ratio of 4× tissue weight. Tissues were homogenized using a bead homogenizer (Omni BeadRuptor with 2 mL micro tubes containing 2.8 mm ceramic beads) at the following settings:

Speed: 7.45 m/sec; Cycle time: 15 sec; # of Cycles: 2; Dwell time: 1 min

Sample Analysis

The receiving medium collected from the diffusion cell assemblies was aliquotted into 96 well plates and frozen at -20°C. Epidermis and dermis homogenates and tape strip extracts of stratum corneum prepared at the conclusion of the experiment were also frozen at -20°C.

Results

The receiving medium collected from the diffusion cell assemblies was aliquotted into 96 well plates and frozen at -20°C.

Mean Cumulative Amounts (µg/cm^2) of Crisaborole penetrated through human cadaver skin into the receiving medium over 48 Hours

	Z	**Z1**
Mean ± SD N=3 donors, 2 replicates per donor.	35.04 ± 10.81 µg/cm^2	20.60±10.18 µg/cm^2

The penetration of **Z** into and through human skin is greater than the penetration of **Z1**.

EXAMPLE 5

Flux tests for 2% crisaborole ointment Z3 with oleyl alcohol and 2% crisaborole ointment Z6 with propylene glycol—

In vitro penetration of crisaborole in two ointment formulations through human ex vivo cadaver skin was measured. The composition of the 2% crisaborole ointment formulation with oleyl alcohol, **Z3**, and the 2% crisaborole ointment formulation with propylene glycol, **Z6**, are provided below.

Component	**Z3 % w/w**
Crisaborole	2.0
Ethylhexyl Hydroxystearate	10.0
Oleyl Alcohol	10.0
White Petrolatum	78.0

Component	Z6 % w/w
Crisaborole	2.00
Propylene Glycol	8.91
Boric Acid	0.10
Purified Water	0.09
Butylated Hydroxytoluene	0.10
Mono- and Di- Glycerides, 40-55% Monoglycerides	7.00
Paraffin wax	5.00
White Petrolatum	76.80

Skin Samples & Donor Demographics:

Human ex vivo cadaver skin without obvious signs of skin disease was used in the study. It was stored at ~-70°C until use. It was dermatomed, prepared for cryopreservation, sealed in a water impermeable plastic bag, and stored at ~ -70°C until the day of the experiment.

Test Procedure:

Human ex vivo cadaver skin was stored at ~-70°C until the morning of the study. Skin was thawed by submerging in pre-warmed water (37°C), and was inspected for any visible holes or damage. Skin from a single donor was cut into multiple smaller sections large enough to fit on nominal 1.0 cm^2 static Franz diffusion cells.

Skin from a single donor was cut into multiple smaller sections large enough to fit on nominal 1.0 cm^2 static Franz diffusion cells. The dermal chamber was filled to capacity with a reservoir solution of phosphate-buffered isotonic saline (PBS), pH 7.4 ± 0.1, and the epidermal cell (chimney) left open to ambient laboratory conditions. All cells were mounted in a diffusion apparatus in which the dermal bathing solution was stirred magnetically at approximately 600 RPM and the skin surface temperature maintained at 32.0 ± 1.0 °C.

A water integrity test was determined before application of the test products. Following a brief (0.5-1 hour) equilibrium period, ^3H_2O (Perkin Elmer, sp. Act. ~ 0.5 µCi/mL) was layered across the top of the skin so that the entire exposed surface was covered (approximately 250 - 500 µL). After 5 minutes the ^3H_2O aqueous layer was removed. At 30 minutes the receptor solution was collected and analyzed for

radioactive content by liquid scintillation counting. Skin specimens in which absorption of ^3H_2O was less than 1.56 µL-equ/cm^2 were considered acceptable.

Just prior to dosing, the reservoir solution was replaced with a fresh solution of distilled deionized water (ddH_2O) with 80 µg/mL gentamicin. The chimney was removed from the Franz Cell to allow full access to the epidermal surface of the skin. The test formulations were warmed slightly at a controlled temperature of 30 ± 2 °C and equilibrated at the maintained temperature for approximately 2 hours prior to dosing.

The product was applied to five replicate sections of the same donor skin. Dosing was performed using a positive displacement pipette set to deliver 5µL formulation/cm^2, or by weight (5 mg/cm^2) if not of sufficient viscosity to pipette.

Results:

Total percutaneous penetration through human cadaver skin over 48 hours for **Z3** and **Z6** are provided below:

Mean Cumulative Amounts (µg/cm^2) of Crisaborole penetrated through human cadaver skin into the receiving medium over 48 Hours

	Z3	**Z6**
Mean ± SD N=2 donors, 5 replicates per donor.	68.047± 8.15 µg/cm^2	82.212± 5.18 µg/cm^2

Flux of crisaborole through the skin was surprisingly greater with **Z6** than with **Z3**.

EXAMPLE 6

Physical Stability Centrifugation Stress Tests

Pharmaceutical formulation Z5 contained the following ingredients:

Component	Z5 % w/w
Crisaborole	2.00
Propylene Glycol	8.91
Boric Acid	0.10
Purified Water	0.09
Butylated Hydroxytoluene	0.10
Mono- and Di- Glycerides, 90% Monoglycerides	7.00
Paraffin wax	5.00
White Petrolatum	76.80

and was prepared as described in Example 1 above, but with boric acid and water being added in Step 2A instead of EDTA.

Pharmaceutical formulation **Z6** contained the following ingredients:

Component	Z6 % w/w
Crisaborole	2.00
Propylene Glycol	8.91
Boric Acid	0.10
Purified Water	0.09
Butylated Hydroxytoluene	0.10
Mono- and Di- Glycerides, 40-55% Monoglycerides	7.00
Paraffin wax	5.00
White Petrolatum	76.80

and was prepared as described for Z5 above.

The physical stability of **Z5** and **Z6** were tested by centrifugation. Samples of each ointment were placed in 15 mL low density polyethylene centrifuge tubes. The

sample size was approximately 10 mL per centrifuge tube. Samples were equilibrated for about one hour in a 25°C/60% RH oven before centrifugation. The tubes were placed in a Beckman Coulter Allegra 6R Series Centrifuge and spun at 2890 rpm. After spinning for 1.5 hours, the percentage of internal volume separation was measured.

The volume of material that physically separated was determined by measuring the height of the separated phase and calculating the volume using the equation provided in Figure 1. The percent of the total sample that separated was then calculated by dividing the volume of the separated phase by the total ointment volume.

Z6 measured 0% internal volume separation while **Z5** measured 1.4% internal volume separation. The ointments were next spun for an additional 1.5 hours (3.0 hours total), and the percentage of internal volume separation was measured again. **Z6** measured 0% internal volume separation while **Z5** measured 1.5% internal volume separation.

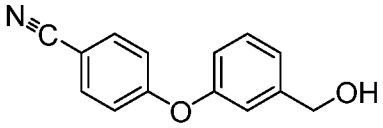
Ointment formulations utilizing mono- and di- glycerides (MDG) in which the monoglyceride percentage is between 40-55% possess greater physical stability over ointment formulations utilizing mono- and di- glycerides (MDG) in which the monoglyceride percentage is at least 90%.

EXAMPLE 7

Degradant Reduction Tests:

Impurities in stability batches have been observed and monitored, including Impurity 1, which is believed to be a stability protodeboronation product of crisaborole.

Impurity 1:



Impurity 1 was characterized with nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS) and the retention time of high-performance chromatography (HPLC) was confirmed against the standard. The H and C position assignments for Impurity 1 based on the NMR data are listed in **Table 2**.

Table 2: ^{1}H NMR and ^{13}C NMR Assignments for Impurity1

Position [a]	$\delta^{1}H$ (ppm)	Multiplicity J_{HH} (Hz)	$\delta^{13}C$ (ppm)
1	—	—	105.02
2	7.84	d,	134.63
3	7.08	m	118.04
4	—	—	161.16
5	7.08	m	118.04
6	7.84	d,	134.63
7	7.00	dd, 7.9, 2.4	118.37
8	7.41	apparent t, 7.8	130.08
9	7.21	d,	122.96
10	—	—	145.57
11	7.08	m	117.79
12	—	—	154.44
13	4.52	d,	69.26
14	5.28	t, 5.8	—
15	—	—	118.73

d, doublet; dd, doublet of a doublet; m, multiplet; t, triplet.

a Position assignment was confirmed by extended NMR (gCOSY, NOESY 1D, gHSQC and gHMBC).

The proposed acceptance criterion to the FDA for Impurity 1 is not more than 2.0% crisaborole label strength, based upon stability data. Impurity 1 levels were observed to increase over time, up to 1.2% label strength and 1.4% label strength for the primary and supporting stability lots under long-term (25° C, 60% relative humidity) and accelerated (40° C, 75% relative humidity) storage conditions, respectively.

Accordingly, minimizing the amount of degradation of crisaborole is a goal of the formulation.

Pharmaceutical formulations with different types and amounts of stabilizers (**Z**, **Z6**, **Z7**, **Z8**, **Z9**, and **Z10**) were tested for their ability to reduce the amount of **Impurity 1**.

The compositions of **Z** and **Z6** are described herein. The 2% ointment formulations **Z7**, **Z8**, **Z9**, and **Z10**, have the following components and were produced according to the methods described herein:

Component	Z7 % w/w	Z8 % w/w	Z9 % w/w	Z10 % w/w
Crisaborole	2.000	2.000	2.000	2.000
Propylene Glycol	9.000	9.000	9.000	9.000
Butylated Hydroxytoluene	0.100	0.100	0.100	0.100
Mono- and Di- glycerides	7.000	7.000	7.000	7.000
Paraffin Wax	5.000	5.000	5.000	5.000
White Petrolatum	76.8976	76.9810	76.855	76.900
Edetate Calcium Disodium	0.0024	0.0090	0.0450	0.0000

In summary, these formulations contain the following types and amounts of stabilizers.

Z6: Stabilizer: Boric Acid; Water Amt: 0.1% w/w; 0.09% w/w

Z7: Stabilizer: Edetate Calcium Disodium Amt: 0.0024% w/w

Z8: Stabilizer: Edetate Calcium Disodium Amt: 0.0090% w/w

Z9: Stabilizer: Edetate Calcium Disodium Amt: 0.0450% w/w

Z10: Stabilizer: None

Z: Stabilizer: Edetate Calcium Disodium Amt: 0.0035% w/w

Analytical method for analysis of Impurity 1:

Crisaborole containing ointments are assayed using a reverse phase HPLC method using a BDS Hypersil C18 column (150x4.6mm, 5 micron) and a 1.0 mL/min flow rate, a 10 µL injection volume, with UV detection at 254 nm. The mobile phase (gradient) are described below:

Mobile Phase A: 0.1%phosphoric acid solution/acetonitrile 95%/5% (v/v)

Mobile Phase B: 0.1%phosphoric acid solution/acetonitrile 5%/95% (v/v)

The topical pharmaceutical formulations were subjected to chemical stability testing with the following results in Table 5:

Table 5: Effect of Stabilizer on Impurity 1 formation in ointments under various conditions

	Impurity 1 (%)				
Time (Months)	**Z6**	**Z7**	**Z8**	**Z9**	**Z10**
0	0.07	0.12			ND
40 °C/75% RH					
1	0.31	0.16	0.18	0.27	0.35
3	0.88	0.53	0.64	0.88	1.13
6	1.73	1.07	1.25	1.63	2.08
25 °C/60% RH					
1	0.07	0.03	0.04	0.06	0.08
3	0.14	0.09	0.10	0.15	0.17
6	0.25	0.18	0.20	0.29	0.30

ND, not detected; RH, relative humidity.

Table 5 demonstrates that among these recited formulations, the formulation without stabilizer, **Z10**, exhibited the highest Impurity 1 levels. The greatest stabilizing effect was observed at the 24 ppm EDTA (**Z7**) and 90 ppm EDTA (**Z8**) levels.

Additional stability testing was performed on **Z6**, **Z7**, and **Z** and presented in **Table 6**:

Table 6: Effect of Stabilizer on Impurity 1 formation in ointments under various conditions

	Impurity 1 (%)		
Time (Months)	**Z6**	**Z7**	**Z**
0	0.12	0.12	ND
40 °C/75% RH			
1	0.69	0.49	0.21
3	1.6	1.0	0.62
6	2.5	1.6	1.2
25 °C/60% RH			
1	0.22	0.19	0.07
3	0.46	0.35	0.12
6	0.66	0.54	0.25
9	0.82	0.74	0.29
12	1.1	0.89	0.37
18	1.7	1.2	0.54
24	2.0	1.6	0.73

ND, not detected; RH, relative humidity.

These tests demonstrate that a much lower amount of Impurity 1 occurs with pharmaceutical formulation **Z** over formulations **Z6** and **Z7**.

EXAMPLE 8

Safety and Efficacy of Z and Y in the treatment of mild-to-moderate atopic dermatitis (AD)

The objective of the trial was to determine the safety and efficacy of **Z** applied twice daily (BID) compared to **Y** in the treatment of mild-to-moderate atopic dermatitis (AD) in children, adolescents, and adults (ages 2 years and older). The composition of **Z** is:

Component	Z % w/w
Crisaborole	2.000
Propylene Glycol	9.000
Butylated Hydroxytoluene	0.100
Mono- and Di- glycerides	7.000
Paraffin Wax	5.000
White Petrolatum	76.8965
Edetate Calcium Disodium	0.0035

The composition of **Y** is:

Component	Y % w/w
Propylene Glycol	9.000
Butylated Hydroxytoluene	0.100
Mono- and Di- glycerides	7.000
Paraffin Wax	5.000
White Petrolatum	78.8965
Edetate Calcium Disodium	0.0035

Two multi-center, double-blind, vehicle-controlled studies were conducted in the U.S. which enrolled over 750 patients each. Patients enrolled were aged 2 years and older with mild-to-moderate atopic dermatitis affecting >5% body surface area. Patients were randomized 2:1 (**Z**:**Y**) and treated twice daily for 28 days.

The primary efficacy endpoint was defined as the achievement of "Clear" (0) or "Almost Clear" (1) status, with 2 or greater grade improvement from baseline, at Day 29 according to the Investigator's Static Global Assessment (ISGA).

The secondary efficacy endpoint was defined as the achievement of "Clear" (0) or "Almost Clear" (1) status, irrespective of improvement from baseline, at Day 29 according to the Investigator's Static Global Assessment (ISGA).

In one trial, 503 patients received Z while 256 received **Y**. The mean age of those receiving **Z** was 12 years, with a range of 2 to 65 years. The mean age of those receiving **Y** was 12.4 years, with a range of 2 to 63 years. 39.0% of those receiving **Z** had a baseline ISGA of "Mild" (2), while 61.0% of those receiving **Z** had a baseline

ISGA of "Moderate" (3). 36.3% of those receiving **Y** had a baseline ISGA of "Mild" (2), while 63.7% of those receiving **Y** had a baseline ISGA of "Moderate" (3). The mean % of Body Surface Area affected by atopic dermatitis for those receiving **Z** was 18.8%, with a range of from between 5% to 95%. The mean % of Body Surface Area affected by atopic dermatitis for those receiving **Y** was 18.6%, with a range of from between 5% to 90%.

From this trial, 32.8% of those receiving **Z** achieved the primary endpoint, while 25.4% of those receiving **Y** achieved the primary endpoint. 51.7% of those receiving **Z** achieved the secondary endpoint, while 40.6% of those receiving **Y** achieved the secondary endpoint.

In another trial, 513 patients received **Z** while 250 received **Y**. The mean age of those receiving **Z** was 12.6 years, with a range of 2 to 79 years. The mean age of those receiving **Y** was 11.8 years, with a range of 2 to 79 years. 38.4% of those receiving **Z** had a baseline ISGA of "Mild" (2), while 61.6% of those receiving **Z** had a baseline ISGA of "Moderate" (3). 40.0% of those receiving **Y** had a baseline ISGA of "Mild" (2), while 60.0% of those receiving Y had a baseline ISGA of "Moderate" (3). The mean % of Body Surface Area affected by atopic dermatitis for those receiving **Z** was 17.9%, with a range of from between 5% to 95%. The mean % of Body Surface Area affected by atopic dermatitis for those receiving **Y** was 17.7%, with a range of from between 5% to 90%.

From this trial, 31.4% of those receiving **Z** achieved the primary endpoint, while 18.0% of those receiving **Y** achieved the primary endpoint. 48.5% of those receiving **Z** achieved the secondary endpoint, while 29.7% of those receiving **Y** achieved the secondary endpoint.

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A topical pharmaceutical formulation comprising:

(a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

(b) from about 5% (w/w) to about 15% (w/w) propylene glycol; and

(c) petrolatum.

2. The topical pharmaceutical formulation of claim 1, wherein the formulation comprises no more than about 0.5% (w/w) water.

3. The topical pharmaceutical formulation of claim 2, wherein the amount of the propylene glycol is about 9% (w/w).

4. The topical pharmaceutical formulation of claim 3, further comprising a glyceride blend from about 3% (w/w) to about 10% (w/w), wherein the glyceride blend comprises a monoglyceride and a diglyceride.

5. The topical pharmaceutical formulation of claim 4, wherein the amount of the glyceride blend is about 7% (w/w) and the glyceride blend is Mono- and Di-glyceride NF.

6. The topical pharmaceutical formulation of claim 5, wherein from about 40% (w/w) to about 55% (w/w) of the glyceride blend is a monoglyceride.

7. The topical pharmaceutical formulation of a preceding claim, further comprising ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, from about 0.0001% (w/w) to about 0.01% (w/w).

8. The topical pharmaceutical formulation of claim 7, further comprising a sodium salt or a potassium salt or a calcium salt, or a mixture thereof, of ethylenediaminetetraacetic acid.

9. The topical pharmaceutical formulation of claim 7, further comprising edetate calcium disodium.

10. The topical pharmaceutical formulation of claim 7 or 9, wherein the amount of the ethylenediaminetetraacetic acid, or a pharmaceutically acceptable salt thereof, is about 0.0035% (w/w).

11. The topical pharmaceutical formulation of a preceding claim, further comprising an antioxidant from about 0.01% (w/w) to about 1% (w/w) selected from the group consisting of butylated hydroxytoluene, ascorbic acid or a pharmaceutically acceptable salt thereof, ascorbic palmitate, butylated hydroxyanisole, 2,4,5-trihydroxybutyrophenone, 4-hydroxymethyl-2,6-di-*tert*-butylphenol, erythorbic acid, gum guaiac, propyl gallate, thiodipropionic acid, dilauryl thiodipropionate, tert-butylhydroquinone and tocopherols such as vitamin E, and the like, including pharmaceutically acceptable salts and esters thereof, and mixtures thereof.

12. The topical pharmaceutical formulation of claim 11, wherein the antioxidant is butylated hydroxytoluene.

13. The topical pharmaceutical formulation of claim 11 or 12, wherein the amount of the antioxidant is 0.1% (w/w).

14. The topical pharmaceutical formulation of a preceding claim, further comprising a stiffening agent from about 2% (w/w) to about 8% (w/w).

15. The topical pharmaceutical formulation of claim 14, wherein the stiffening agent is selected from the group consisting of beeswax, paraffin wax, wax, and spermaceti wax.

16. The topical pharmaceutical formulation of claim 15, wherein the stiffening agent is 5% (w/w) paraffin wax NF.

17. A topical pharmaceutical formulation comprising:

a) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol;

c) butylated hydroxytoluene;

d) edetate calcium disodium;

e) mono- and di- glycerides;

f) paraffin wax; and

g) white petrolatum.

18. The topical pharmaceutical formulation of claim 17 comprising:

a) from about 0.1% (w/w) to about 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole;

b) from about 5% (w/w) to about 15% (w/w) propylene glycol USP;

c) 0.1% (w/w) butylated hydroxytoluene;

d) 0.0035% (w/w) edetate calcium disodium;

e) 7% (w/w) mono- and di- glycerides NF;

f) 5% (w/w) paraffin wax; and

g) 76.8965% (w/w) white petrolatum.

19. The topical pharmaceutical formulation of claim 18 consisting of:

a) about 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof;

b) about 9% (w/w) propylene glycol USP;

c) about 0.1% (w/w) butylated hydroxytoluene;

d) about 0.0035% (w/w) edetate calcium disodium;

e) about 7% (w/w) mono- and di- glycerides NF, wherein between 40% and 55% is said monoglyceride;

f) about 5% (w/w) paraffin wax; and

g) about 76.8965% (w/w) white petrolatum.

20. A method of decreasing the release of a cytokine and/or a chemokine, the method comprising contacting a cell with the topical pharmaceutical formulation of a preceding claim.

21. A method of treating an inflammatory-related condition in an animal, the method comprising administering to the animal a therapeutically effective amount of the topical pharmaceutical formulation of a preceding claim.

22. The method of claim 21, wherein the inflammatory-related condition is psoriasis.

23. The method of claim 22, wherein the inflammatory-related condition is atopic dermatitis.

24. A method of treating atopic dermatitis in a human, the method comprising administering to the human a therapeutically effective amount of the topical pharmaceutical formulation of a preceding claim.

25. The method of claim 24 further comprising administrating the pharmaceutical formulation to an affected area of the human on a twice daily basis.

26. The method of claim 25 further comprising administering the pharmaceutical formulation over a period of about 28 days.

27. The method of claims 24 further comprising a second active agent administered in combination with pharmaceutical formulation.

28. The method of claim 27 wherein the second active agent is a JAK kinase inhibitor such as Tofacitinib, JTE-052, Baricitinib, or Upadacitinib.

29. A stable pharmaceutical composition in a topical dosage form consisting essentially of:

(a) an active agent which is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole or crisaborole, a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

(b) one or more pharmaceutically acceptable excipients that do not promote protodeboronation of more than 2.0% by weight of the active agent to Impurity 1 when stored at 25° C and a relative humidity of 75% for a period of about 24 months.

30. The pharmaceutical composition of claim 29, wherein the Impurity 1 is less than 1% by weight of the active agent.

31. The pharmaceutical composition of claim 30, wherein the Impurity 1 is less than 0.75% by weight of the active agent.

32. The pharmaceutical composition of claim 31 wherein the dosage form is an ointment and the active agent is 2.0% of the composition.

33. The pharmaceutical composition of claim 32 wherein the active ingredient is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole.

34. The pharmaceutical composition of claim 33 wherein the excipient is a stabilizer; and less than 0.25% (w/w) degradation byproducts or impurities.

35. The pharmaceutical composition of claim 34, further comprising

(a) about 2% (w/w) 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole;

b) about 9% (w/w) propylene glycol;

c) about 0.1% (w/w) butylated hydroxytoluene;

d) about 0.0035% (w/w) edetate calcium disodium;

e) about 7% (w/w) mono- and di- glycerides, wherein between 40% and 55% is said monoglyceride;

f) about 5% (w/w) paraffin wax; and

g) about 76.8965% (w/w) white petrolatum.

36. A stable pharmaceutical composition in a topical dosage form consisting essentially of:

(a) an active agent which is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole or crisaborole, a pharmaceutically acceptable salt, or a hydrate or a solvate thereof;

(b) one or more pharmaceutically acceptable excipients that do not promote protodeboronation of more than about 0.75% by weight of the active agent

to Impurity 1 when stored at 40° C and a relative humidity of 75% for a period of about 1 month.

37. The pharmaceutical composition of claim 36, wherein the Impurity 1 is less than about 0.5% by weight of the active agent.

38. The pharmaceutical composition of claim 37, wherein the Impurity 1 is less than about 0.3% by weight of the active agent.

39. The pharmaceutical composition of claim 38 wherein the dosage form is an ointment and the active agent is 2.0% of the composition.

40. The pharmaceutical composition of claim 39 wherein the active ingredient is 5-(4-cyanophenoxy)-1,3-dihydro-1-hydroxy-2,1-benzoxaborole.

41. The pharmaceutical composition of claim 40 wherein the excipient is a stabilizer; and less than 0.25% (w/w) degradation byproducts or impurities.

42. A crystalline Form 1 of any of the preceding claims having characteristic peaks selected from an X-ray powder diffraction pattern containing the following 2θ values measured using Cu $K_{\alpha 1}$ radiation (λ = 1.54056 Å): 6.0, 12.1, 14.1 and 15.4 °2θ ± 0.2 ° 2θ.

43. The crystalline Form of claim 42 wherein the characteristic peaks are 6.0 and 15.4 °2θ ± 0.2 ° 2θ.

FIG. 1

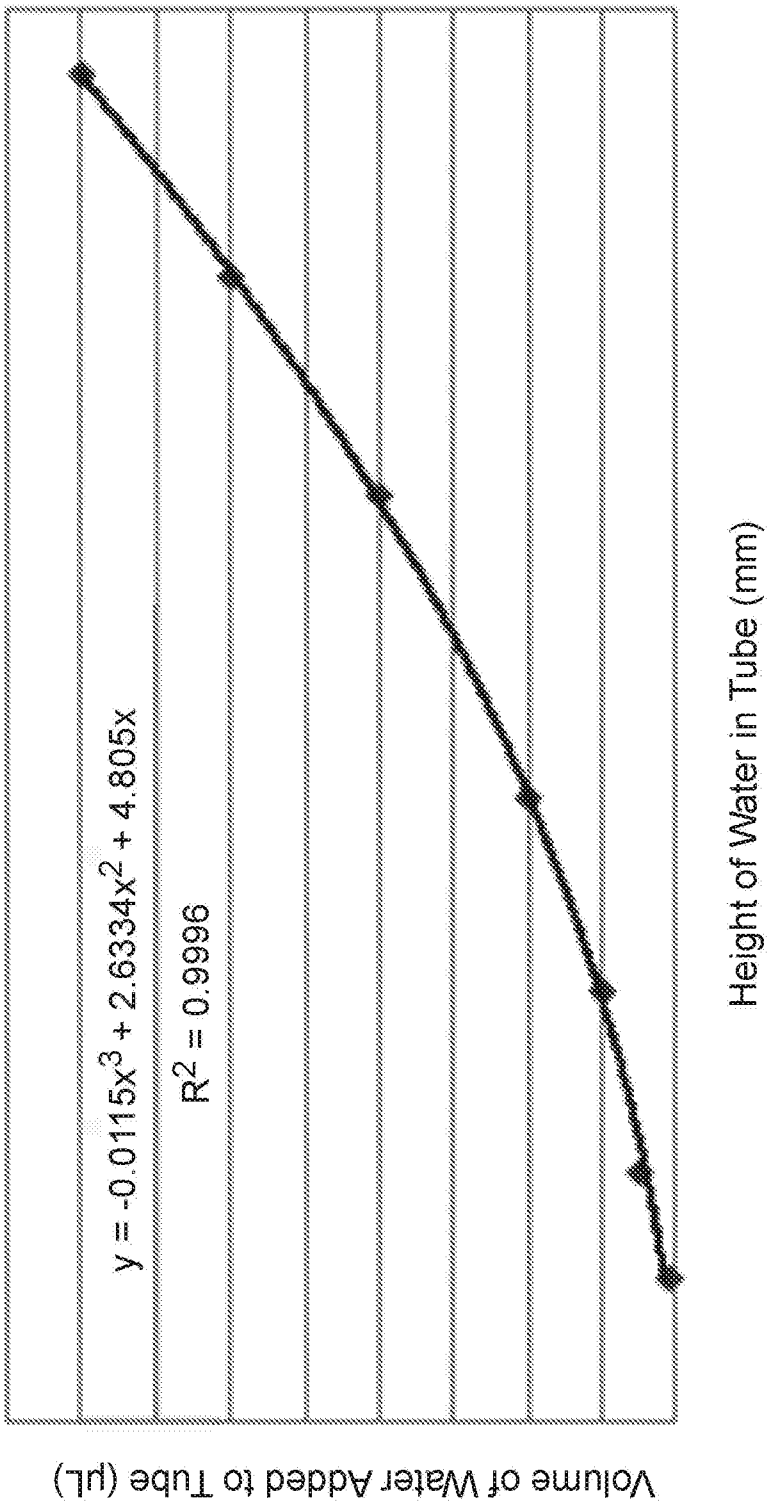

y = -0.0115x3 + 2.6334x2 + 4.805x
R2 = 0.9996
Volume of Water Added to Tube (µL)
Height of Water in Tube (mm)

FIG. 2

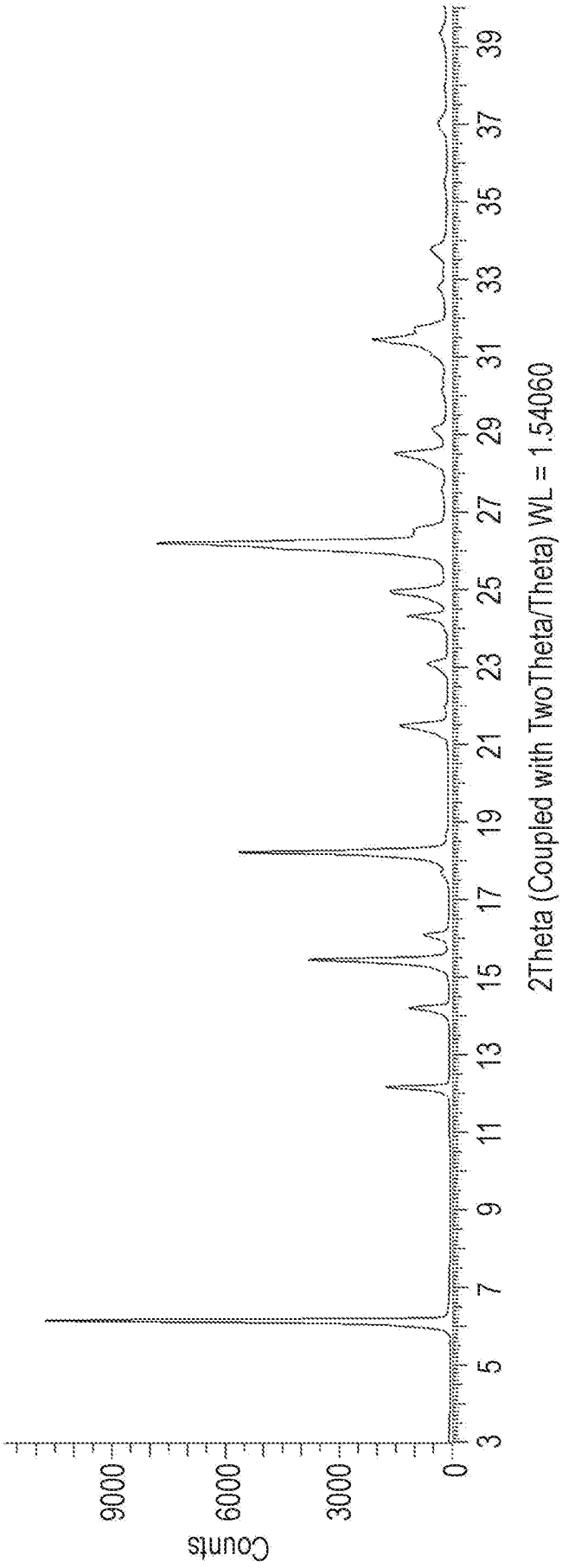

Powder x-ray spectrum of crisaborole Form 1
Counts
9000
6000
3000
0
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2Theta (Coupled with TwoTheta/Theta) WL = 1.54060

FIG. 3

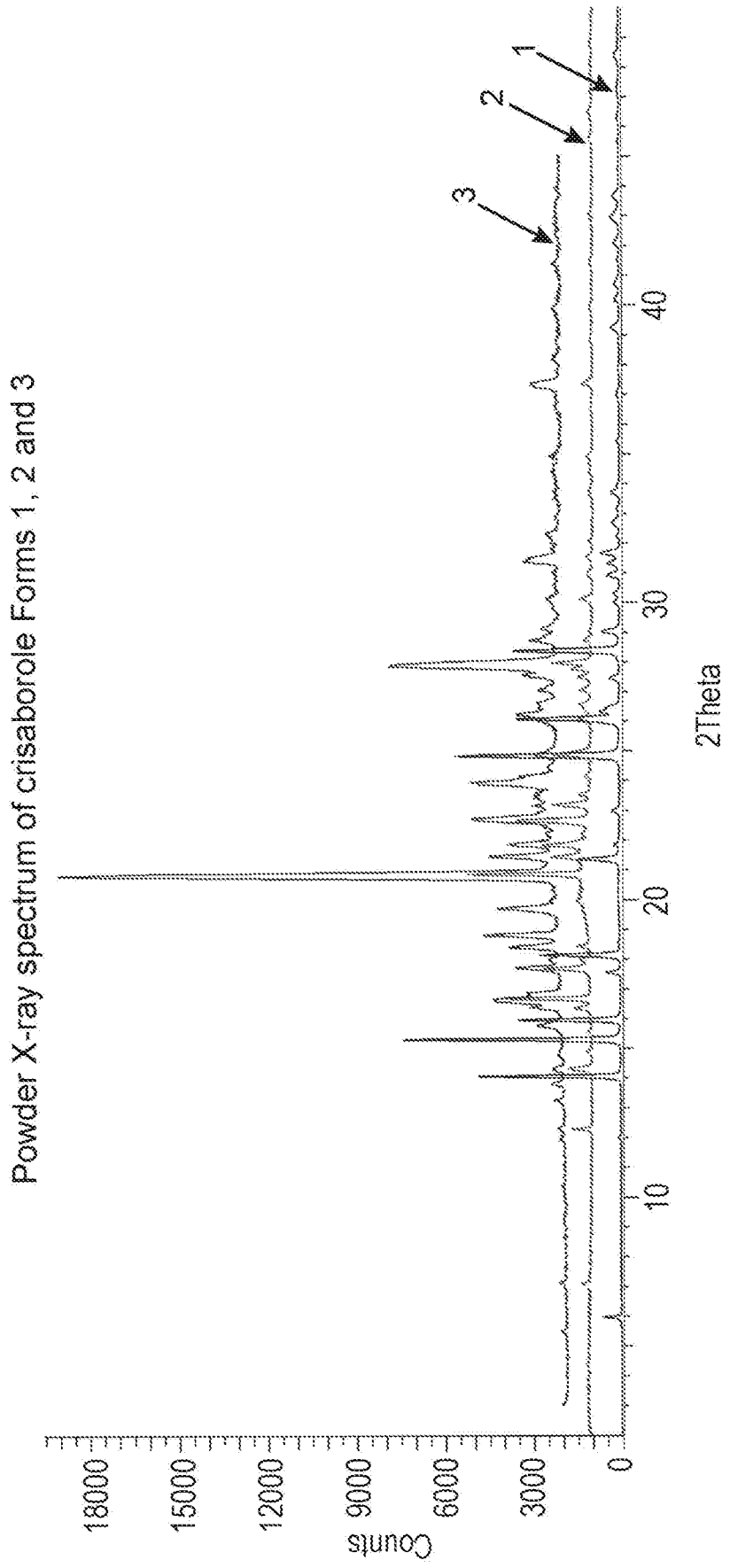
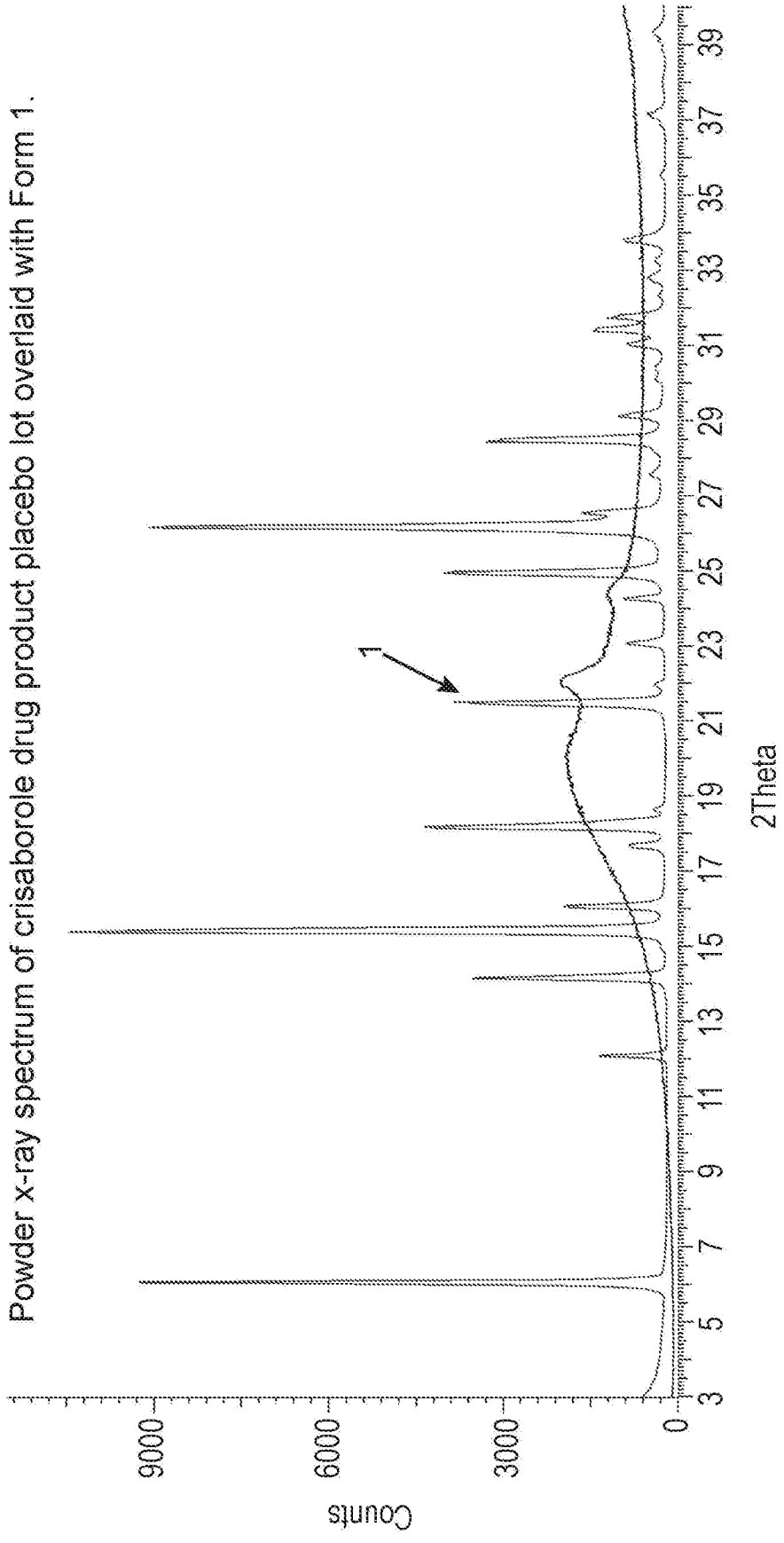

Powder X-ray spectrum of crisaborole Forms 1, 2 and 3
Counts
18000
15000
12000
9000
6000
3000
0
2Theta
10
20
30
40
1
2
3

FIG. 4


Powder x-ray spectrum of crisaborole drug product placebo lot overlaid with Form 1.
1
Counts
9000
6000
3000
0
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2Theta

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/057073

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K45/06 A61K47/06 A61K9/06 A61K31/69
A61P17/00
ADD.
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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/291917 A1 (AKAMA TSUTOMU [US] ET AL) 26 November 2009 (2009-11-26) cited in the application examples 24-28	1-16, 20-43
X	IP E ET AL: "Formulation, skin penetration, and anti-inflammatory activity of AN2728: A novel borinic acid ester", JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY, MOSBY, INC, US, vol. 56, no. 2, 1 February 2007 (2007-02-01), page AB177, XP005937376, ISSN: 0190-9622 abstract	1-16, 20-43

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but 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 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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2017	10/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ganschow, Silke

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/057073

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAZARIAN R ET AL: "AN-2728, a PDE4 inhibitor for the potential topical treatment of psoriasis and atopic dermatitis", CURRENT OPINION IN INVESTIGATIONAL DRUGS, PHARMAPRESS, US, vol. 10, no. 11, 1 November 2009 (2009-11-01), pages 1236-1242, XP009193262, ISSN: 1472-4472 page 1238, right-hand column, paragraph 2	1-16, 20-43
X	DeDe Sheel: "Anacor Pharmaceuticals Announces Positive Top-Line Results From Two Phase 3 Pivotal Studies of Crisaborole Topical Ointment, 2% in Patients With Mild-to-Moderate Atopic Dermatitis", Internet , 13 July 2015 (2015-07-13), XP002766381, Retrieved from the Internet: URL:http://files.shareholder.com/downloads/ANCR/0x0x838819/10BD159B-4ADA-44F2-9636-C68CBD7F927F/ANAC_News_2015_7_13_Press_Releases.pdf [retrieved on 2017-01-25] the whole document	42,43
X	FREUND Y ET AL: "AN2728, a new boron-based topical anti-inflammatory agent, inhibits phosphodiesterase 4 (PDE4)", JOURNAL OF INVESTIGATIVE DERMATOLOGY, NATURE PUBLISHING GROUP, US, vol. 135, no. Suppl.1, 1 May 2015 (2015-05-01), page S87, XP009193269, ISSN: 0022-202X abstract	42,43

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/057073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2016318955 A1	03-11-2016

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(71)申请人 安那卡药品公司
地址 美国纽约

(72)发明人 D·J·科罗纳多 D·C·英伯特
C·E·李 T·麦钱特
S·Z·耶普

(74)专利代理机构 永新专利商标代理有限公司 72002
代理人 张晓威

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A61K 31/69(2006.01)
A61P 17/00(2006.01)

权利要求书3页 说明书44页 附图4页

(54)发明名称

用于治疗炎症相关病症的局部药物制剂

(57)摘要

本发明公开局部药物制剂和使用这些制剂治疗炎症病症的方法。

CN 108366958 A

1.局部药物制剂,其包含:

(a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物;

(b)约5%(w/w)至约15%(w/w)丙二醇;和

(c)矿脂。

2.如权利要求1的局部药物制剂,其中所述制剂包含不多于约0.5%(w/w)水。

3.如权利要求2的局部药物制剂,其中所述丙二醇的量是约9%(w/w)。

4.如权利要求3的局部药物制剂,其还包含约3%(w/w)至约10%(w/w)甘油酯混合物,其中所述甘油酯混合物包含甘油单酯和甘油二酯。

5.如权利要求4的局部药物制剂,其中所述甘油酯混合物的量是约7%(w/w)且所述甘油酯混合物是甘油单酯和甘油二酯NF。

6.如权利要求5的局部药物制剂,其中所述甘油酯混合物的约40%(w/w)至约55%(w/w)是甘油单酯。

7.如前述权利要求的局部药物制剂,其还包含约0.0001%(w/w)至约0.01%(w/w)乙二胺四乙酸或其药学上可接受的盐。

8.如权利要求7的局部药物制剂,其还包含乙二胺四乙酸的钠盐或钾盐或钙盐或其混合物。

9.如权利要求7的局部药物制剂,其还包含依地酸钙二钠。

10.如权利要求7或9的局部药物制剂,其中所述乙二胺四乙酸或其药学上可接受的盐的量是约0.0035%(w/w)。

11.如前述权利要求的局部药物制剂,其还包含约0.01%(w/w)至约1%(w/w)的选自以下的抗氧化剂:丁基化羟基甲苯、抗坏血酸或其药学上可接受的盐、抗坏血酸棕榈酸酯、丁基化羟基苯甲醚、2,4,5-三羟基苯丁酮、4-羟甲基-2,6-二-叔丁基苯酚、异抗坏血酸、愈创树脂、没食子酸丙酯、硫代二丙酸、硫代二丙酸二月桂酯、叔丁基对苯二酚和生育酚如维生素E,等,包括其药学上可接受的盐和酯及其混合物。

12.如权利要求11的局部药物制剂,其中所述抗氧化剂是丁基化羟基甲苯。

13.如权利要求11或12的局部药物制剂,其中所述抗氧化剂的量是0.1%(w/w)。

14.如前述权利要求的局部药物制剂,其还包含约2%(w/w)至约8%(w/w)硬化剂。

15.如权利要求14的局部药物制剂,其中所述硬化剂选自蜂蜡、石蜡、蜡和鲸蜡。

16.如权利要求15的局部药物制剂,其中所述硬化剂是5%(w/w)石蜡NF。

17.局部药物制剂,其包含:

a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯、其药学上可接受的盐或水合物或溶剂合物;

b)约5%(w/w)至约15%(w/w)丙二醇;

c)丁基化羟基甲苯;

d)依地酸钙二钠;

e)甘油单酯和甘油二酯;

f)石蜡;和

g)白矿脂。

18.如权利要求17的局部药物制剂,其包含:

a)约0.1%(w/w)至约2%(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯;

b)约5%(w/w)至约15%(w/w)丙二醇USP;

c)0.1%(w/w)丁基化羟基甲苯;

d)0.0035%(w/w)依地酸钙二钠;

e)7%(w/w)甘油单酯和甘油二酯NF;

f)5%(w/w)石蜡;和

g)76.8965%(w/w)白矿脂。

19.如权利要求18的局部药物制剂,其由以下组成:

a)约2%(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐;

b)约9%(w/w)丙二醇USP;

c)约0.1%(w/w)丁基化羟基甲苯;

d)约0.0035%(w/w)依地酸钙二钠;

e)约7%(w/w)甘油单酯和甘油二酯NF,其中40%至55%是所述甘油单酯;

f)约5%(w/w)石蜡;和

g)约76.8965%(w/w)白矿脂。

20.减少细胞因子和/或趋化因子释放的方法,所述方法包括使细胞与前述权利要求的局部药物制剂接触。

21.治疗动物的炎症相关病症的方法,所述方法包括将治疗有效量的前述权利要求的局部药物制剂给药所述动物。

22.如权利要求21的方法,其中所述炎症相关病症是银屑病。

23.如权利要求22的方法,其中所述炎症相关病症是特应性皮炎。

24.治疗人类的特应性皮炎的方法,所述方法包括将治疗有效量的前述权利要求的局部药物制剂给药所述人类。

25.如权利要求24的方法,其还包括将所述药物制剂每天两次给药所述人类的受影响区域。

26.如权利要求25的方法,其还包括将所述药物制剂给药约28天的时间。

27.如权利要求24的方法,其还包括第二活性剂与药物制剂组合给药。

28.如权利要求27的方法,其中所述第二活性剂是JAK激酶抑制剂,诸如托法替尼、JTE-052、巴瑞替尼或乌帕替尼。

29.局部剂型的稳定药物组合物,其基本上由以下组成:

(a)活性剂,其是5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或克瑞沙硼、其药学上可接受的盐或水合物或溶剂合物;

(b)一种或多种药学上可接受的赋形剂,其在25℃和75%的相对湿度下储存约24个月的时间不会促进多于2.0重量%的所述活性剂质子去硼化至杂质1。

30.如权利要求29的药物组合物,其中所述杂质1少于所述活性剂的1重量%。

31.如权利要求30的药物组合物,其中所述杂质1少于所述活性剂的0.75重量%。

32.如权利要求31的药物组合物，其中所述剂型是软膏剂且所述活性剂是所述组合物的2.0％。

33.如权利要求32的药物组合物，其中所述活性成分是5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯。

34.如权利要求33的药物组合物，其中所述赋形剂是稳定剂；且少于0.25％(w/w)降解副产物或杂质。

35.如权利要求34的药物组合物，其还包含

a)约2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；

b)约9％(w/w)丙二醇；

c)约0.1％(w/w)丁基化羟基甲苯；

d)约0.0035％(w/w)依地酸钙二钠；

e)约7％(w/w)甘油单酯和甘油二酯，其中40％至55％是所述甘油单酯；

f)约5％(w/w)石蜡；和

g)约76.8965％(w/w)白矿脂。

36.局部剂型的稳定药物组合物，其基本上由以下组成：

(a)活性剂，其是5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或克瑞沙硼、其药学上可接受的盐或水合物或溶剂合物；

(b)一种或多种药学上可接受的赋形剂，其在40℃和75％的相对湿度下储存约1个月的时间不会促进多于约0.75重量％的所述活性剂质子去硼化至杂质1。

37.如权利要求36的药物组合物，其中所述杂质1少于所述活性剂的约0.5重量％。

38.如权利要求37的药物组合物，其中所述杂质1少于所述活性剂的约0.3重量％。

39.如权利要求38的药物组合物，其中所述剂型是软膏剂且所述活性剂是所述组合物的2.0％。

40.如权利要求39的药物组合物，其中所述活性成分是5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯。

41.如权利要求40的药物组合物，其中所述赋形剂是稳定剂；且少于0.25％(w/w)降解副产物或杂质。

42.前述权利要求中任一项的结晶形式1，其具有选自使用Cu $K_{\alpha 1}$辐射(λ = 1.54056 Å)所测量的含有以下2θ值的X射线粉末衍射图案的特征峰：6.0°、12.1°、14.1°和15.4°2θ±0.2°2θ。

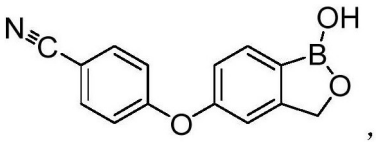
43.如权利要求42的结晶形式，其中所述特征峰是6.0°和15.4°2θ±0.2°2θ。

用于治疗炎症相关病症的局部药物制剂

[0001] 发明背景

[0002] 可用于治疗炎症相关病症(如特应性皮炎和/或银屑病)的局部药物制剂是本领域已知的。更快速地减小病症症状和/或解决病症的潜在病因的局部药物制剂会是本领域的显著进步。

[0003] 5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯(benzoxaborole),

[0004] 

,

[0005] 是可用于治疗炎症皮肤疾病(包括轻度至中度特应性皮炎和银屑病)的非甾体PDE4抑制剂。克瑞沙硼(Crisaborole)(商品名)是2%5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯且是用于2岁及以上患者的轻度至中度特应性皮炎(AD)的第一个局部软膏剂PDE4抑制剂,且推荐每天两次施用至受影响区域持续约28天且至多额外48周。

[0006] 美国专利第8,039,451号、第8,168,614号、第8,501,712号涉及该化合物及其各种治疗方法。本文中引用的所有参考文献均全部并入本文中且用于所有目的。

[0007] 克瑞沙硼的制剂研发开始于软膏剂及乳膏制剂,用于I期及2期临床研究。经确定软膏剂制剂优选用于治疗炎症皮肤疾病,部分由于软膏剂的有利的润肤性质。早期制剂包含克瑞沙硼的部分混悬剂,但化学和物理稳定性问题变得成问题,从而需要不同途径。

[0008] 本发明涉及含有克瑞沙硼、克瑞沙硼和其他活性剂的组合的药物组合物及其使用方法。

[0009] 发明概述

[0010] 在第一方面中,本发明提供局部药物制剂,其包含:

[0011] a)治疗炎症相关病症的活性剂或其药学上可接受的盐、或水合物或溶剂合物;

[0012] b)约5%(w/w)至约15%(w/w)丙二醇;和

[0013] c)矿脂(petrolatum)。

[0014] 在第二方面中,本发明提供局部药物制剂,其包含:

[0015] a)约5%(w/w)至约15%(w/w)丙二醇;

[0016] b)矿脂;

[0017] c)抗氧化剂;

[0018] d)稳定剂;

[0019] e)乳化剂;和

[0020] f)硬化剂,

[0021] 其中局部药物制剂包含活性剂克瑞沙硼。

[0022] 本发明提供其他局部药物制剂以及其使用和生产方法及其组合。

[0023] 本发明还涉及结晶形式或非结晶形式的5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,

1-苯并氧杂硼杂环戊二烯。本发明还涉及包含结晶或非结晶形式的药物组合物及用于制备这样的形式的方法。本发明还涉及结晶或非结晶形式在各种疾病的局部治疗中的用途。

[0024] 本发明还涵盖用于治疗特应性皮炎的活性成分的组合。

附图说明

[0025] 图1:计算物理分离的材料体积的方程。

[0026] 图2:形式1克瑞沙硼的粉末x射线光谱。

[0027] 图3:形式1(黑色)、2(红色)和3(蓝色)克瑞沙硼的粉末X射线光谱。

[0028] 图4:克瑞沙硼药品安慰剂批次与形式1叠加的粉末x射线光谱。

[0029] 发明详述

[0030] I.定义和缩写

[0031] 除非上下文另外清楚指示,否则如本文所用单数形式“一(a、an)”和“该”包括复数个参考。例如,对“活性剂”的提及包括单一活性剂以及两种或更多种不同活性剂组合。应理解,本发明教导不限于本文中所公开的特定剂型、载体等,因此可变化。

[0032] 本文所用的缩写通常具有其化学和生物领域内的常规含义。

[0033] II.引言

[0034] 本发明涉及局部药物制剂。这些制剂可用于炎症相关病症的治疗。在一方面中,制剂含有活性剂。在另一方面中,制剂不含有活性剂。这些制剂可用于特应性皮炎和/或银屑病的治疗和/或预防。

[0035] IIa.局部药物制剂

[0036] 在第一方面中,本发明包含:a)活性剂或其药学上可接受的盐或水合物或溶剂合物;b)约5%(w/w)至约15%(w/w)的溶剂;和c)基质。在示例性实施方案中,局部药物制剂还包含至多约0.5%(w/w)水。在示例性实施方案中,局部药物制剂还包含至多约0.1%(w/w)水。在示例性实施方案中,局部药物制剂还包含至多约0.01%(w/w)水。

[0037] 在示例性实施方案中,药物制剂的所有组分均为药学上可接受的。

[0038] II.a.i.活性剂

[0039] 在示例性实施方案中,局部药物制剂包含活性药物成分(“活性剂”)。在示例性实施方案中,活性剂是抗炎剂。在示例性实施方案中,活性剂是抗瘙痒剂。在示例性实施方案中,活性剂治疗特应性皮炎。在示例性实施方案中,活性剂治疗银屑病。在示例性实施方案中,活性剂是本文所述化合物。在示例性实施方案中,活性剂是苯并氧杂硼杂环戊二烯。

[0040] 在示例性实施方案中,活性剂公开于PCT/US07/062350;11/676,120(现8,168,614);60/823,888;60/774,532;PCT/US09/036250;12/399,015(现8,039,450);61/148,731;61/143,700;61/110,903;61/105,990;61/094,406;61/052,637;61/034,371;PCT/US11/022780;13/015,487(现8,716,478);61/298,860;61/354,187;61/368,211;PCT/US14/056800;和61/881,343中,其中每一个的内容均援引加入本文中以用于所有目的。在示例性实施方案中,活性剂是5-(3,4-二氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐、水合物或溶剂合物。在示例性实施方案中,活性剂是克瑞沙硼,还称为5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐、水合物或溶剂合物。在示例性实施方案中,活性剂是5-(3-氰基苯氧基)-

1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐、水合物或溶剂合物。在示例性实施方案中,活性剂是5-(2-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐、水合物或溶剂合物。

[0041] 在示例性实施方案中,活性成分是类固醇。在示例性实施方案中,活性成分是吡美莫司、或他扎罗汀、或他克莫司、或曲安西龙、或骨化三醇、或卡泊三醇、或倍他米松、或氯倍他索(clobatsol)、或卤贝他索、或二氟拉松或莫美他松。

[0042] 在示例性实施方案中,活性剂以约0.1%(w/w)至约3.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以约0.1%(w/w)至约2.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以约0.1%(w/w)至约1.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以约1.0%(w/w)至约2.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以约1.5%(w/w)至约2.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以约1.5%(w/w)至约2.5%(w/w)的浓度存在。在示例性实施方案中,活性剂以约1.0%(w/w)至约3.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以约2.0%(w/w)的浓度存在。在示例性实施方案中,活性剂以2.0%(w/w)的浓度存在。

[0043] 在示例性实施方案中,本发明提供本文所述活性剂或其盐、水合物或溶剂合物或其组合。示例性实施方案是作为一种活性剂的克瑞沙硼和可用于治疗特应性皮炎或银屑病的第二活性剂的组合。该组合可包含两种活性成分的混合物或共制剂。或者,该组合可包装于分配器中,其中一种活性剂是在一个室中且另一活性成分是在另一室中,但经分配将该两种活性剂同时一起递送,使得该组合的给药可在一次施用中发生。或者,活性剂可与其他活性剂单独给药,其中第二活性剂可经口或局部给药。

[0044] 涵盖在与克瑞沙硼组合的第二活性剂的实例包括但不限于:

[0045] 局部皮质类固醇,诸如氟轻松醋酸酯、去羟米松、莫美他松、曲安西龙、倍他米松、阿氯米松、地索奈德、氢化可体松和美普克莱(Mapracorat);

[0046] 局部钙调磷酸酶抑制剂,诸如他克莫司、吡美莫司和环孢素;

[0047] PDE4抑制剂的局部制剂,诸如阿普司特、E-6005、OPA-15406、LEO 29102、DRM02和罗氟司特;

[0048] JAK激酶抑制剂的局部制剂,诸如托法替尼、JTE-052、巴瑞替尼和乌帕替尼;

[0049] 局部非甾体抗炎药物,诸如WBI-1001和MRX-6;

[0050] 局部ROR药剂,诸如GSK2981278;

[0051] 可注射抗IL4、IL-31、IL-22、IL-33、IL-12、IL-23、IL-17、IgE、IL-4治疗药物,诸如杜鲁单抗(Dupilumab)、来金珠单抗、尼莫利珠单抗(Nemolizumab)、曲洛吉努单抗、依那西普、阿达木单抗、英夫利昔单抗、优特克单抗、塞库吉努(Secukinumab)、奥马珠(Omazumilab)、CIM-331;

[0052] 维生素D类似物,诸如卡泊三醇;

[0053] 口服视黄酸衍生物,诸如阿利维A酸;

[0054] 口服肝X受体(LXR)选择性激动剂,诸如VTP-38543;

[0055] 口服H4受体拮抗剂,诸如ZPL-389;

[0056] 口服NK1受体拮抗剂,诸如阿瑞匹坦和曲地匹坦(Tradipitant);

[0057] 口服CRTH2受体拮抗剂,诸如弗维普兰特(Fevipiprant)和OC-459;

[0058] 口服糜蛋白酶抑制剂，诸如SUN 13834；

[0059] 口服GATA-3抑制剂，诸如SB-011；

[0060] 口服ROR反激动剂，诸如VTP-43742、ARN6039、TAK-828和JTE-451；

[0061] 口服JAK抑制剂；包括JAK1、JAK2、JAK3及TYK2的抑制剂，诸如PF-04965842、PF-06651600和PF-06700841；

[0062] 口服PDE药剂，诸如阿普司特、罗氟司特和异丁司特；

[0063] 口服IRAK4抑制剂，诸如PF-06650833；

[0064] 可注射aTNF抑制剂，诸如英夫利昔单抗、阿达木单抗、戈利木单抗和聚乙二醇化赛妥珠单抗；

[0065] 可注射半乳凝素-3抑制剂，诸如GR-MD-02。

[0066] 在示例性实施方案中，本发明提供本文所述活性剂或其盐、水合物或溶剂合物。在示例性实施方案中，本发明提供本文所述活性剂或其盐。在示例性实施方案中，盐是药学上可接受的盐。在示例性实施方案中，本发明提供本文所述活性剂或其水合物。在示例性实施方案中，本发明提供本文所述活性剂或其溶剂合物。在示例性实施方案中，本发明提供本文所述活性剂或其前药。在示例性实施方案中，本发明提供本文所述活性剂。在示例性实施方案中，本发明提供本文所述活性剂的药学上可接受的盐。在示例性实施方案中，本发明提供本文所述活性剂的水合物。在示例性实施方案中，本发明提供本文所述活性剂的溶剂合物。在示例性实施方案中，本发明提供本文所述活性剂的前药。

[0067] II.a.ii.溶剂

[0068] 在示例性实施方案中，局部药物制剂包含溶剂。在示例性实施方案中，溶剂是亚烷基二醇。在示例性实施方案中，溶剂是丙二醇。在示例性实施方案中，溶剂是丙二醇USP。在示例性实施方案中，溶剂是丁二醇。

[0069] 在示例性实施方案中，溶剂是以约5.0％(w/w)至约15.0％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约6.0％(w/w)至约10.0％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约6.5％(w/w)至约11.5％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约7.0％(w/w)至约11.0％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约7.5％(w/w)至约10.5％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约7.5％(w/w)至约9.5％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约8.5％(w/w)至约9.5％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约8.0％(w/w)至约10.0％(w/w)的浓度存在。在示例性实施方案中，溶剂是以约9.0％(w/w)的浓度存在。在示例性实施方案中，溶剂是以9.0％(w/w)的浓度存在。

[0070] II.a.iii.基质

[0071] 在示例性实施方案中，局部药物制剂包含软膏基质。在示例性实施方案中，基质是软膏基质。在示例性实施方案中，软膏基质是白矿脂。在示例性实施方案中，软膏基质是白矿脂USP。在示例性实施方案中，软膏基质是矿物冻或凡士林(petroleum jelly)或黄矿脂或黄软石蜡或黄凡士林或白凡士林(petrolatum jelly)或白软石蜡。在示例性实施方案中，基质是矿物油或轻质矿物油或石蜡或羊毛脂醇。

[0072] 局部药物制剂中基质的量会取决于其他组分的量。可添加更多基质以补偿期望局部药物制剂中的其他组分的较少量。在示例性实施方案中，基质是以适量(q.s.)浓度存在。

在示例性实施方案中，基质是以约65％(w/w)至约90％(w/w)的浓度存在。在示例性实施方案中，基质是以约65％(w/w)至约85％(w/w)的浓度存在。在示例性实施方案中，基质是以约67.955％(w/w)至约89.8999％(w/w)的浓度存在。在示例性实施方案中，基质是以约50％(w/w)至约60％(w/w)的浓度存在。在示例性实施方案中，基质是以约60％(w/w)至约70％(w/w)的浓度存在。在示例性实施方案中，基质是以约70％(w/w)至约80％(w/w)的浓度存在。在示例性实施方案中，基质是以约72％(w/w)至约82％(w/w)的浓度存在。在示例性实施方案中，基质是以约74％(w/w)至约81％(w/w)的浓度存在。在示例性实施方案中，基质是以约78％(w/w)至约82％(w/w)的浓度存在。在示例性实施方案中，基质是以约75％(w/w)至约80％(w/w)的浓度存在。在示例性实施方案中，基质是以约75％(w/w)至约79％(w/w)的浓度存在。在示例性实施方案中，基质是以约76％(w/w)至约79％(w/w)的浓度存在。在示例性实施方案中，基质是以约76％(w/w)至约77％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.8％(w/w)至约77％(w/w)的浓度存在。在示例性实施方案中，基质是以约78％(w/w)至约79％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.8％(w/w)至约76.9％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.89％(w/w)至约76.9％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.80％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.855％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.8965％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.8976％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.981％(w/w)的浓度存在。在示例性实施方案中，基质是以约76.90％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.89％(w/w)至约78.9％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.80％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.855％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.8965％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.8976％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.981％(w/w)的浓度存在。在示例性实施方案中，基质是以约78.90％(w/w)的浓度存在。

[0073] 用于局部药物制剂的任选组分

[0074] II.a.iv.抗氧化剂

[0075] 在示例性实施方案中，局部药物制剂还包含抗氧化剂。在示例性实施方案中，抗氧化剂选自丁基化羟基甲苯、抗坏血酸、抗坏血酸棕榈酸酯、丁基化羟基苯甲醚、2,4,5-三羟基苯丁酮、4-羟甲基-2,6-二-叔丁基苯酚、异抗坏血酸、愈创树脂、没食子酸丙酯、硫代二丙酸、硫代二丙酸二月桂酯、叔丁基对苯二酚和生育酚或其药学上可接受的盐或酯或其组合。在示例性实施方案中，抗氧化剂是丁基化羟基甲苯。在示例性实施方案中，抗氧化剂是丁基化羟基甲苯NF。

[0076] 在示例性实施方案中，抗氧化剂是以约0.01％(w/w)至约1％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.01％(w/w)至约0.5％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.05％(w/w)至约0.5％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.05％(w/w)至约0.4％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.05％(w/w)至约0.3％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.07％(w/w)至约0.2％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.05％(w/w)至约0.15％(w/w)的浓度存在。在示例性实施方案中，抗氧化剂是以约0.1％(w/w)的

浓度存在。在示例性实施方案中，抗氧化剂是以0.1％(w/w)的浓度存在。

[0077] II.a.v.稳定剂

[0078] 在示例性实施方案中，局部药物制剂还包含稳定剂。在示例性实施方案中，稳定剂是乙二胺四乙酸或其药学上可接受的盐。在示例性实施方案中，稳定剂是乙二胺四乙酸的药学上可接受的盐且该盐是钠盐或钾盐或钙盐或其组合。在示例性实施方案中，稳定剂是乙二胺四乙酸的药学上可接受的盐且该盐是钠盐或钙盐或其组合。在示例性实施方案中，稳定剂是依地酸钙二钠。在示例性实施方案中，稳定剂是依地酸钙二钠USP。

[0079] 在示例性实施方案中，稳定剂是以约0.000010％(w/w)至约0.0450％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0450％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0400％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0350％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0300％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0250％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0200％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0150％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.00010％(w/w)至约0.0100％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0090％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.000010％(w/w)至约0.0100％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0100％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0020％(w/w)至约0.0100％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0024％(w/w)至约0.0100％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0024％(w/w)至约0.0090％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0035％(w/w)至约0.0100％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0035％(w/w)至约0.0090％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0080％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0060％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0010％(w/w)至约0.0050％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0020％(w/w)至约0.0060％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0015％(w/w)至约0.0045％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0025％(w/w)至约0.0045％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0030％(w/w)至约0.0040％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以约0.0035％(w/w)的浓度存在。在示例性实施方案中，稳定剂是以0.0035％(w/w)的浓度存在。

[0080] II.a.vi.乳化剂

[0081] 在示例性实施方案中，局部药物制剂还包含乳化剂。在示例性实施方案中，乳化剂是甘油酯混合物。在示例性实施方案中，乳化剂是甘油酯混合物，其中甘油酯混合物包含甘油单酯和甘油二酯。在示例性实施方案中，乳化剂是甘油酯混合物，其中甘油酯混合物包含甘油单酯、甘油二酯和甘油三酯。在示例性实施方案中，乳化剂是甘油酯混合物，其中甘油酯混合物包含甘油单酯和甘油二酯且其中约40％(w/w)至约55％(w/w)的甘油酯混合物是甘油单酯。在示例性实施方案中，乳化剂是甘油酯混合物，其中甘油酯混合物包含甘油单

酯、甘油二酯和甘油三酯且其中约40％(w/w)至约55％(w/w)的甘油酯混合物是甘油单酯。在示例性实施方案中，乳化剂是甘油酯混合物，其中甘油酯混合物是甘油单酯NF和甘油二酯NF。

[0082] 在示例性实施方案中，甘油单酯选自单硬脂酸甘油酯、单棕榈酸甘油酯、单油酸甘油酯或其组合。在示例性实施方案中，甘油单酯是长链、饱和或不饱和脂肪酸的一甘油酯。在示例性实施方案中，甘油单酯是α-甘油单酯。在示例性实施方案中，甘油二酯是长链、饱和或不饱和脂肪酸的二甘油酯。

[0083] 在示例性实施方案中，甘油酯混合物是以约3.0％(w/w)至约10.0％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以约5.0％(w/w)至约10.0％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以约6.0％(w/w)至约9.0％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以约5.0％(w/w)至约8.0％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以约6.0％(w/w)至约8.0％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以约6.5％(w/w)至约7.5％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以约7.0％(w/w)的浓度存在。在示例性实施方案中，甘油酯混合物是以7.0％(w/w)的浓度存在。

[0084] II.a.vii.硬化剂

[0085] 在示例性实施方案中，局部药物制剂还包含硬化剂。在示例性实施方案中，硬化剂是蜡。在示例性实施方案中，硬化剂是蜡，且该蜡选自由蜂蜡、石蜡和鲸蜡。在示例性实施方案中，硬化剂是石蜡。在示例性实施方案中，硬化剂是石蜡NF。

[0086] 在示例性实施方案中，硬化剂是以约2.0％(w/w)至约6.0％(w/w)的浓度存在。在示例性实施方案中，硬化剂是以约2.0％(w/w)至约8.0％(w/w)的浓度存在。在示例性实施方案中，硬化剂是以约3.0％(w/w)至约5.0％(w/w)的浓度存在。在示例性实施方案中，硬化剂是以约4.0％(w/w)至约6.0％(w/w)的浓度存在。在示例性实施方案中，硬化剂是以约4.0％(w/w)至约5.0％(w/w)的浓度存在。在示例性实施方案中，硬化剂是以约4.5％(w/w)至约5.5％(w/w)的浓度存在。在示例性实施方案中，硬化剂以约5.0％(w/w)的浓度存在。在示例性实施方案中，硬化剂以5.0％(w/w)的浓度存在。

[0087] 特定局部药物制剂

[0088] II.a.viii.

[0089] 在示例性实施方案中，局部药物制剂包含：

[0090] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0091] b)约5％(w/w)至约15％(w/w)丙二醇；和

[0092] c)矿脂

[0093] 其中制剂包含不多于约0.5％(w/w)水。

[0094] 在示例性实施方案中，局部药物制剂包含：

[0095] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0096] b)约5％(w/w)至约15％(w/w)丙二醇；

[0097] c)矿脂；

[0098] d)抗氧化剂；

[0099] e)稳定剂；

[0100] f)乳化剂;和

[0101] g)硬化剂

[0102] 其中制剂包含不多于约0.5％(w/w)水。

[0103] 在示例性实施方案中,局部药物制剂包含：

[0104] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0105] b)约8％(w/w)至约10％(w/w)丙二醇；

[0106] c)矿脂；

[0107] d)抗氧化剂；

[0108] e)稳定剂；

[0109] f)乳化剂;和

[0110] g)硬化剂

[0111] 其中制剂包含不多于约0.5％(w/w)水。

[0112] 在示例性实施方案中,局部药物制剂由以下组成：

[0113] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0114] b)约8％(w/w)至约10％(w/w)丙二醇；

[0115] c)矿脂；

[0116] d)抗氧化剂；

[0117] e)依地酸钙二钠；

[0118] f)乳化剂;和

[0119] g)硬化剂。

[0120] 在示例性实施方案中,局部药物制剂由以下组成：

[0121] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0122] b)约8％(w/w)至约10％(w/w)丙二醇；

[0123] c)矿脂；

[0124] d)抗氧化剂；

[0125] e)约0.0020％(w/w)至约0.0040％(w/w)依地酸钙二钠；

[0126] f)乳化剂;和

[0127] g)硬化剂。

[0128] 在示例性实施方案中,局部药物制剂基本上由以下组成：

[0129] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0130] b)约8％(w/w)至约10％(w/w)丙二醇；

[0131] c)矿脂；

[0132] d)抗氧化剂；

[0133] e)稳定剂；

[0134] f)甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯；和

[0135] g)硬化剂

[0136] 其中制剂包含不多于约0.5％(w/w)水。

[0137] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0138] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0139] b)约8％(w/w)至约10％(w/w)丙二醇；

[0140] c)矿脂；

[0141] d)抗氧化剂；

[0142] e)稳定剂；

[0143] f)甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0144] g)硬化剂

[0145] 其中制剂包含不多于约0.5％(w/w)水。

[0146] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0147] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0148] b)约8％(w/w)至约10％(w/w)丙二醇；

[0149] c)矿脂；

[0150] d)抗氧化剂；

[0151] e)稳定剂；

[0152] f)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0153] g)硬化剂

[0154] 其中制剂包含不多于约0.5％(w/w)水。

[0155] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0156] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0157] b)约8％(w/w)至约10％(w/w)丙二醇；

[0158] c)矿脂；

[0159] d)抗氧化剂；

[0160] e)稳定剂；

[0161] f)约6％(w/w)至约8％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0162] g)硬化剂

[0163] 其中制剂包含不多于约0.5％(w/w)水。

[0164] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0165] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0166] b)约8％(w/w)至约10％(w/w)丙二醇；

[0167] c)矿脂；

[0168] d)抗氧化剂；

[0169] e)依地酸钙二钠；

[0170] f)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0171] g)硬化剂

[0172] 其中制剂包含不多于约0.5％(w/w)水。

[0173] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0174] a)治疗特应性皮炎和/或银屑病的活性剂或其药学上可接受的盐或水合物或溶剂合物；

[0175] b)约8％(w/w)至约10％(w/w)丙二醇；

[0176] c)矿脂；

[0177] d)抗氧化剂；

[0178] e)约0.0020％(w/w)至约0.0040％(w/w)依地酸钙二钠；

[0179] f)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0180] g)硬化剂

[0181] 其中制剂包含不多于约0.5％(w/w)水。

[0182] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0183] a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物；

[0184] b)约8％(w/w)至约10％(w/w)丙二醇；

[0185] c)矿脂；

[0186] d)抗氧化剂；

[0187] e)稳定剂；

[0188] f)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0189] g)硬化剂

[0190] 其中制剂包含不多于约0.5％(w/w)水。

[0191] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0192] a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上

可接受的盐或水合物或溶剂合物；

[0193] b)约8％(w/w)至约10％(w/w)丙二醇；

[0194] c)矿脂；

[0195] d)抗氧化剂；

[0196] e)依地酸钙二钠；

[0197] f)约6％(w/w)至约8％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0198] g)硬化剂

[0199] 其中制剂包含不多于约0.5％(w/w)水。

[0200] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0201] a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物；

[0202] b)约8％(w/w)至约10％(w/w)丙二醇；

[0203] c)矿脂；

[0204] d)抗氧化剂；

[0205] e)约0.0020％(w/w)至约0.0040％(w/w)依地酸钙二钠；

[0206] f)约6％(w/w)至约8％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0207] g)硬化剂

[0208] 其中制剂包含不多于约0.5％(w/w)水。

[0209] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0210] a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物；

[0211] b)约5％(w/w)至约15％(w/w)丙二醇；

[0212] c)矿脂；

[0213] d)丁基化羟基甲苯；

[0214] e)依地酸钙二钠；

[0215] f)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0216] g)硬化剂

[0217] 其中制剂包含不多于约0.5％(w/w)水。

[0218] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0219] a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物；

[0220] b)约5％(w/w)至约15％(w/w)丙二醇；

[0221] c)矿脂；

[0222] d)丁基化羟基甲苯；

[0223] e)依地酸钙二钠；

[0224] f)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0225] g)硬化剂

[0226] 其中制剂包含不多于约0.5％(w/w)水。

[0227] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0228] a)约2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物；

[0229] b)约9％(w/w)丙二醇；

[0230] c)白矿脂；

[0231] d)约0.1％(w/w)丁基化羟基甲苯；

[0232] e)约0.0035％(w/w)依地酸钙二钠；

[0233] f)约7％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0234] g)硬化剂

[0235] 其中制剂包含不多于约0.5％(w/w)水。

[0236] 在示例性实施方案中，局部药物制剂由以下组成：

[0237] a)2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯或其药学上可接受的盐或水合物或溶剂合物；

[0238] b)9％(w/w)丙二醇；

[0239] c)76.8965％(w/w)白矿脂；

[0240] d)0.1％(w/w)丁基化羟基甲苯；

[0241] e)0.0035％(w/w)依地酸钙二钠；

[0242] f)7％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0243] g)5％(w/w)石蜡。

[0244] 不具有活性剂的局部药物制剂

[0245] II.a.ix.

[0246] 在另一方面中，本发明包含局部药物制剂，该药物制剂不包含可用于治疗炎症相关病症的活性剂。这些不含有活性剂的局部药物制剂还可用于治疗诸如特应性皮炎和/或银屑病的炎症病症。在示例性实施方案中，这些局部药物制剂不含有本文中所列的活性剂的一种或多种。在示例性实施方案中，不具有活性剂的局部药物制剂还包含至多约0.5％(w/w)水。在示例性实施方案中，不具有活性剂的局部药物制剂还包含至多约0.1％(w/w)水。在示例性实施方案中，不具有活性剂的局部药物制剂还包含至多约0.01％(w/w)水。

[0247] 不具有活性剂的局部药物制剂可任选地含有溶剂、基质、抗氧化剂、稳定剂、乳化剂和硬化剂。不具有活性剂的局部药物制剂中的这些组分中的每一种的特性和浓度可见此文件的II.a.i.；II.a.ii.；II.a.iii.；II.a.iv.；II.a.v.；II.a.vi.；II.a.vii.；和

II.a.viii.部分。

[0248] 不具有活性剂的特定局部药物制剂

[0249] II.a.x.

[0250] 在示例性实施方案中,局部药物制剂包含:

[0251] a)约5%(w/w)至约15%(w/w)丙二醇;

[0252] b)矿脂;

[0253] c)抗氧化剂;

[0254] d)稳定剂;

[0255] e)乳化剂;和

[0256] f)硬化剂,

[0257] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5%(w/w)水。

[0258] 在示例性实施方案中,局部药物制剂包含:

[0259] a)约5%(w/w)的溶剂;

[0260] b)约89.8999%(w/w)的矿脂;

[0261] c)约0.1%(w/w)的抗氧化剂;

[0262] d)约0.0001%(w/w)的稳定剂;

[0263] e)约3%(w/w)的乳化剂;和

[0264] f)约2%(w/w)的硬化剂,

[0265] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5%(w/w)水。

[0266] 在示例性实施方案中,局部药物制剂包含:

[0267] a)约15%(w/w)的溶剂;

[0268] b)约67.955%(w/w)的矿脂;

[0269] c)约1%(w/w)的抗氧化剂;

[0270] d)约0.0450%(w/w)的稳定剂;

[0271] e)约10%(w/w)的乳化剂;和

[0272] f)约6%(w/w)的硬化剂,

[0273] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5%(w/w)水。

[0274] 在示例性实施方案中,局部药物制剂包含:

[0275] a)约5%(w/w)至约15%(w/w)的溶剂;

[0276] b)约67.955%(w/w)至约89.8999%(w/w)的矿脂;

[0277] c)约0.1%(w/w)至约1%(w/w)的抗氧化剂;

[0278] d)约0.0001%(w/w)至约0.0450%(w/w)的稳定剂;

[0279] e)约3%(w/w)至约10%(w/w)的乳化剂;和

[0280] f)约2%(w/w)至约6%(w/w)的硬化剂,

[0281] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5%(w/w)水。

[0282] 在示例性实施方案中,局部药物制剂包含:

[0283] a)约5%(w/w)至约15%(w/w)的丙二醇;

[0284] b)约67.955%(w/w)至约89.8999%(w/w)的矿脂;

[0285] c)约0.1%(w/w)至约1%(w/w)的丁基化羟基甲苯;

[0286] d)约0.0001％(w/w)至约0.0450％(w/w)的依地酸钙二钠；

[0287] e)约3％(w/w)至约10％(w/w)的甘油酯混合物；和

[0288] f)约2％(w/w)至约6％(w/w)的石蜡，

[0289] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5％(w/w)水。

[0290] 在示例性实施方案中，局部药物制剂包含：

[0291] a)约5％(w/w)至约15％(w/w)的丙二醇；

[0292] b)约67.955％(w/w)至约89.8999％(w/w)的矿脂；

[0293] c)约0.1％(w/w)至约1％(w/w)的丁基化羟基甲苯；

[0294] d)约0.0001％(w/w)至约0.0450％(w/w)的依地酸钙二钠；

[0295] e)约3％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0296] f)约2％(w/w)至约6％(w/w)的石蜡，

[0297] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5％(w/w)水。

[0298] 在示例性实施方案中，局部药物制剂包含：

[0299] a)约8％(w/w)至约10％(w/w)丙二醇；

[0300] b)矿脂；

[0301] c)抗氧化剂；

[0302] d)稳定剂；

[0303] e)乳化剂；和

[0304] f)硬化剂，

[0305] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5％(w/w)水。

[0306] 在示例性实施方案中，局部药物制剂包含：

[0307] a)约8％(w/w)至约10％(w/w)丙二醇；

[0308] b)矿脂；

[0309] c)抗氧化剂；

[0310] d)依地酸钙二钠；

[0311] e)乳化剂；和

[0312] f)硬化剂，

[0313] 其中局部药物制剂不包含活性剂且其中制剂包含不多于约0.5％(w/w)水。

[0314] 在示例性实施方案中，局部药物制剂由以下组成：

[0315] a)约8％(w/w)至约10％(w/w)丙二醇；

[0316] b)矿脂；

[0317] c)抗氧化剂；

[0318] d)约0.0020％(w/w)至约0.0040％(w/w)依地酸钙二钠；

[0319] e)乳化剂；和

[0320] f)硬化剂。

[0321] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0322] a)约8％(w/w)至约10％(w/w)丙二醇；

[0323] b)矿脂；

[0324] c)抗氧化剂；

[0325] d)稳定剂；

[0326] e)甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯；和

[0327] f)硬化剂

[0328] 其中制剂包含不多于约0.5％(w/w)水。

[0329] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0330] a)约8％(w/w)至约10％(w/w)丙二醇；

[0331] b)矿脂；

[0332] c)抗氧化剂；

[0333] d)稳定剂；

[0334] e)甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0335] f)硬化剂

[0336] 其中制剂包含不多于约0.5％(w/w)水。

[0337] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0338] a)约8％(w/w)至约10％(w/w)丙二醇；

[0339] b)矿脂；

[0340] c)抗氧化剂；

[0341] d)稳定剂；

[0342] e)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0343] f)硬化剂

[0344] 其中制剂包含不多于约0.5％(w/w)水。

[0345] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0346] a)约8％(w/w)至约10％(w/w)丙二醇；

[0347] b)矿脂；

[0348] c)抗氧化剂；

[0349] d)稳定剂；

[0350] e)约6％(w/w)至约8％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0351] f)硬化剂

[0352] 其中制剂包含不多于约0.5％(w/w)水。

[0353] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0354] a)约8％(w/w)至约10％(w/w)丙二醇；

[0355] b)矿脂；

[0356] c)抗氧化剂；

[0357] d)依地酸钙二钠；

[0358] e)约6％(w/w)至约8％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0359] f)硬化剂

[0360] 其中制剂包含不多于约0.5％(w/w)水。

[0361] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0362] a)约8％(w/w)至约10％(w/w)丙二醇；

[0363] b)矿脂；

[0364] c)抗氧化剂；

[0365] d)约0.0020％(w/w)至约0.0040％(w/w)依地酸钙二钠；

[0366] e)约6％(w/w)至约8％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0367] f)硬化剂

[0368] 其中制剂包含不多于约0.5％(w/w)水。

[0369] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0370] a)约5％(w/w)至约15％(w/w)丙二醇；

[0371] b)矿脂；

[0372] c)丁基化羟基甲苯；

[0373] d)依地酸钙二钠；

[0374] e)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0375] f)硬化剂

[0376] 其中制剂包含不多于约0.5％(w/w)水。

[0377] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0378] a)约5％(w/w)至约15％(w/w)丙二醇；

[0379] b)矿脂；

[0380] c)丁基化羟基甲苯；

[0381] d)依地酸钙二钠；

[0382] e)约5％(w/w)至约10％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0383] f)石蜡

[0384] 其中制剂包含不多于约0.5％(w/w)水。

[0385] 在示例性实施方案中，局部药物制剂基本上由以下组成：

[0386] a)约9％(w/w)丙二醇；

[0387] b)白矿脂；

[0388] c)约0.1％(w/w)丁基化羟基甲苯；

[0389] d)约0.0035％(w/w)依地酸钙二钠；

[0390] e)约7％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0391] f)约5％(w/w)石蜡。

[0392] 在示例性实施方案中，局部药物制剂由以下组成：

[0393] a)9％(w/w)丙二醇；

[0394] b)78.8965％(w/w)白矿脂；

[0395] c)0.1％(w/w)丁基化羟基甲苯；

[0396] d)0.0035％(w/w)依地酸钙二钠；

[0397] e)7％(w/w)的甘油酯混合物，其中甘油酯混合物包含一种或多种甘油单酯和一种或多种甘油二酯，其中一种或多种甘油单酯的总浓度是甘油酯混合物的40％至55％；和

[0398] f)5％(w/w)石蜡

[0399] 其中制剂包含不多于约0.5％(w/w)水。

[0400] 关于用于本文所述局部药物制剂中以及制备这些局部药物制剂的赋形剂的信息，可见本文以及Remington:The Science and Practice of Pharmacy，第21版，Pharmaceutical Press(2011)，其内容援引加入以用于所有目的。

[0401] III.方法

[0402] 在本发明的另一方面中，本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物可用于本文所述方法中。在本发明的另一方面中，本文所述局部药物制剂可用于本文所述方法中。在本发明的另一方面中，本文所述的具有活性剂的局部药物制剂可用于本文所述方法中。在本发明的另一方面中，本文所述的不具有活性剂的局部药物制剂可用于本文所述方法中。在示例性实施方案中，在本文所述方法中的任一种中，经给药本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物或本文所述局部药物制剂的动物原本不需要使用本文所述的所述活性剂或其药学上可接受的盐或水合物或溶剂合物或本文所述局部药物制剂治疗。在示例性实施方案中，在本文所述方法中的任一种中，经给药本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物或本文所述局部药物制剂的动物需要使用本文所述的所述活性剂或其药学上可接受的盐或水合物或溶剂合物或本文所述局部药物制剂治疗。在示例性实施方案中，在本文所述方法中的任一种中，经给药本文所述的不具有活性剂的局部药物制剂的动物原本不需要使用不具有活性剂的局部药物制剂治疗。在示例性实施方案中，在本文所述方法中的任一种中，经给药本文所述的不具有活性剂的局部药物制剂的动物需要使用不具有活性剂的局部药物制剂治疗。

[0403] III.a.细胞因子和/或趋化因子

[0404] 在另一方面中，本发明提供减少细胞因子和/或趋化因子释放的方法，该方法包括使细胞与本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物接触。在示例性实施方案中，本发明提供减少细胞因子和/或趋化因子释放的方法，该方法包括使细胞与具有本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物的局部药物制剂接触。在示例性实施方案中，本发明提供减少细胞因子和/或趋化因子释放的方法，该方法包括使细胞与本

文所述的不具有活性剂或其药学上可接受的盐或水合物或溶剂合物的局部药物制剂接触。在示例性实施方案中，对于本文中所提供方法中的任一种，细胞因子和/或趋化因子的释放均减少。在示例性实施方案中，对于本文所述方法中的任一种，细胞因子和/或趋化因子均减少。

[0405] 在另一方面中，本发明提供减少细胞因子和/或趋化因子从细胞释放的方法，该方法包括使细胞与本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物接触。在示例性实施方案中，通过给药本文所述的局部药物制剂来使活性剂接触细胞。在示例性实施方案中，本发明提供减少细胞因子和/或趋化因子从细胞释放的方法，该方法包括：使细胞与本文所述的不具有活性剂或其药学上可接受的盐或水合物或溶剂合物的局部药物制剂接触。在示例性实施方案中，细胞因子和/或趋化因子经细胞的释放减少。在示例性实施方案中，细胞是皮肤细胞。

[0406] 在另一方面中，本发明提供减少细胞因子和/或趋化因子从细胞释放的方法，该方法包括使细胞与本文所述的不具有活性剂的局部药物制剂接触。在示例性实施方案中，细胞因子和/或趋化因子经细胞的释放减少。在示例性实施方案中，细胞是皮肤细胞。

[0407] 在另一方面中，本发明提供减少细胞因子和/或趋化因子经皮肤细胞释放的方法，该方法包括通过给药本文所述局部药物制剂来使皮肤细胞与活性剂接触。在示例性实施方案中，细胞因子和/或趋化因子经皮肤细胞的释放减少。

[0408] 在另一方面中，本发明提供减少细胞因子和/或趋化因子经皮肤细胞释放的方法，该方法包括使皮肤细胞与本文所述局部药物制剂接触。在示例性实施方案中，细胞因子和/或趋化因子经皮肤细胞的释放减少。

[0409] 在另一方面中，本发明提供减少细胞因子和/或趋化因子经皮肤细胞释放的方法，该方法包括使皮肤细胞与本文所述的不具有活性剂的局部药物制剂接触。在示例性实施方案中，细胞因子和/或趋化因子经皮肤细胞的释放减少。

[0410] 在示例性实施方案中，细胞因子和/或趋化因子选自：TNF-α、IFN-γ、IL-2、IL-4、IL-5、IL-13、IL-22、IL-23和IL-31。在示例性实施方案中，细胞因子和/或趋化因子是TNF-α。在示例性实施方案中，细胞因子和/或趋化因子是IL-23。在示例性实施方案中，细胞因子和/或趋化因子是IL-2。在示例性实施方案中，细胞因子和/或趋化因子是IL-17。

[0411] 在示例性实施方案中，对于本文所述方法中的任一种，活性剂或局部药物制剂是以使本文所述细胞因子和/或趋化因子的释放减少以下的量存在：至少约5％至约100％、或至少约30％至约100％、40％至约100％、或至少约50％至约100％、或至少约60％至约100％、或至少约70％至约100％、或至少约80％至约100％、或至少约90％至约100％、或至少约30％至约70％、或至少约40％至约90％、或至少约45％至约80％、或至少约55％至约75％、或至少约75％至约98％、或至少约55％至约99％、或至少约5％至约20％或至少约10％至约25％。

[0412] III.b.磷酸二酯酶

[0413] 在另一方面中，本发明提供抑制磷酸二酯酶(PDE)的方法，该方法包括使磷酸二酯酶与本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物接触。在示例性实施方案中，本发明化合物是本文所述化合物或其药学上可接受的盐。在示例性实施方案中，本发明化合物是本文所述化合物。在示例性实施方案中，化合物的量是治疗有效量。在示例性实施

方案中，化合物是根据本文所述的式。在示例性实施方案中，对于本文所述方法中的任一种，磷酸二酯酶被抑制。

[0414] 在另一方面中，本发明提供抑制细胞中的磷酸二酯酶(PDE)的方法，该方法包括使细胞与具有本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物的局部药物制剂接触。在另一方面中，本发明提供抑制细胞中的磷酸二酯酶(PDE)的方法，该方法包括使细胞与不具有本文所述活性剂或其药学上可接受的盐或水合物或溶剂合物的局部药物制剂接触。在示例性实施方案中，活性剂的量是治疗有效量。在示例性实施方案中，具有活性剂的局部药物制剂的量是治疗有效量。在示例性实施方案中，不具有活性剂的局部药物制剂的量是治疗有效量。在示例性实施方案中，对于本文所述方法中的任一种，细胞是皮肤细胞。在示例性实施方案中，对于本文所述方法中的任一种，磷酸二酯酶被抑制。

[0415] 在示例性实施方案中，磷酸二酯酶选自:PDE1、PDE2、PDE3、PDE4、PDE5、PDE6、PDE7、PDE8、PDE9、PDE10和PDE11。在示例性实施方案中，磷酸二酯酶是PDE4。在示例性实施方案中，PDE4选自:PDE4A、PDE4B、PDE4C和PDE4D。在示例性实施方案中，PDE4是PDE4B。在示例性实施方案中，磷酸二酯酶是PDE7。

[0416] 在示例性实施方案中，本发明提供用于抑制磷酸二酯酶4(PDE4)，但并不显著抑制至少一种选自PDE1、PDE2、PDE3、PDE5和PDE6的PDE的方法，其涉及使细胞与本文所述局部药物制剂接触，由此提供所述抑制。

[0417] 在示例性实施方案中，对于本文所述方法中的任一种，活性剂或局部药物制剂是以将本文所述磷酸二酯酶抑制以下的量存在:至少约5％至约100％、或至少约30％至约100％、40％至约100％、或至少约50％至约100％、或至少约60％至约100％、或至少约70％至约100％、或至少约80％至约100％、或至少约90％至约100％、或至少约30％至约70％、或至少约40％至约90％、或至少约45％至约80％、或至少约55％至约75％、或至少约75％至约98％、或至少约55％至约99％、或至少约5％至约20％或至少约10％至约25％。

[0418] III.c.病症

[0419] 在另一方面中，本发明提供治疗和/或预防动物的病症的方法，该方法包括将治疗有效量和/或预防有效量的本文所述的具有活性剂的局部药物制剂给药动物。在示例性实施方案中，病症经治疗和/或经预防。在示例性实施方案中，动物需要其治疗和/或预防。在示例性实施方案中，动物原本不需要其治疗和/或预防。在示例性实施方案中，病症是皮肤的病症。在示例性实施方案中，病症是搔痒。

[0420] 在另一方面中，本发明提供治疗和/或预防动物的病症的方法，该方法包括将治疗有效量和/或预防有效量的本文所述的不具有活性剂的局部药物制剂给药动物。在示例性实施方案中，病症经治疗和/或经预防。在示例性实施方案中，动物需要其治疗和/或预防。在示例性实施方案中，病症是皮肤的病症。在示例性实施方案中，病症是搔痒。

[0421] 在另一方面中，本发明提供治疗和/或预防动物的炎症相关病症的方法，该方法包括将治疗有效量和/或预防有效量的本文所述的具有活性剂的局部药物制剂给药动物。在示例性实施方案中，炎症相关病症经治疗和/或经预防。在示例性实施方案中，动物需要其治疗和/或预防。在示例性实施方案中，动物原本不需要其治疗和/或预防。在示例性实施方案中，炎症相关病症是皮肤的病症。

[0422] 在另一方面中，本发明提供治疗和/或预防动物的炎症相关病症的方法，该方法包

括将治疗有效量和/或预防有效量的本文所述的不具有活性剂的局部药物制剂给药动物。在示例性实施方案中，炎症相关病症经治疗和/或经预防。在示例性实施方案中，动物需要其治疗和/或预防。

[0423] 在示例性实施方案中，炎症相关病症是银屑病。在示例性实施方案中，炎症相关病症是斑块状银屑病或屈侧银屑病(反转型银屑病)或点滴状银屑病或脓疱性银屑病或指甲银屑病或银屑病关节炎或红皮病型银屑病。在示例性实施方案中，炎症相关病症是斑块状银屑病。在示例性实施方案中，炎症相关病症是指甲银屑病。

[0424] 在示例性实施方案中，炎症相关病症是皮炎。在示例性实施方案中，炎症相关病症是接触性皮炎或特应性皮炎或钱币状皮炎或脂溢性皮炎或郁滞性皮炎。在示例性实施方案中，炎症相关病症是特应性皮炎。在示例性实施方案中，炎症相关病症是湿疹。

[0425] 在示例性实施方案中，对于本文所述方法中的任一种，动物选自：人类、牛、鹿、驯鹿、山羊、蜜蜂、猪、绵羊、马、母牛、公牛、狗、豚鼠、沙鼠、兔、猫、骆驼、牦牛、象、鸵鸟、水獭、鸡、鸭、鹅、珠鸡、鸽、天鹅和火鸡。在另一示例性实施方案中，对于本文所述方法中的任一种，动物选自：人类、牛、山羊、猪、绵羊、马、母牛、公牛、狗、豚鼠、沙鼠、兔、猫、鸡和火鸡。在另一示例性实施方案中，对于本文所述方法中的任一种，动物是人类。

[0426] 在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来预防银屑病。在示例性实施方案中，银屑病经预防。在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来预防银屑病。在示例性实施方案中，银屑病经预防。在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来治疗银屑病。在示例性实施方案中，银屑病经治疗。

[0427] 在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来治疗银屑病。在示例性实施方案中，银屑病经治疗。

[0428] 在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来预防斑块状银屑病。在示例性实施方案中，斑块状银屑病经预防。

[0429] 在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来预防斑块状银屑病。在示例性实施方案中，斑块状银屑病经预防。

[0430] 在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来治疗斑块状银屑病。在示例性实施方案中，斑块状银屑病经治疗。在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来治疗斑块状银屑病。在示例性实施方案中，斑块状银屑病经治疗。

[0431] 在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来预防指甲银屑病。在示例性实施方案中，指甲银屑病经预防。

[0432] 在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来预防指甲银屑病。在示例性实施方案中，指甲银屑病经预防。在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来治疗指甲银屑病。在示例性实施方案中，指甲银屑病经治疗。在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来治疗指甲银屑病。在示例性实施方案中，指甲银屑病经治疗。

[0433] 在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来预防特应性皮炎。在示例性实施方案中，特应性皮炎经预防。

[0434] 在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来预防特应性皮炎。在示例性实施方案中，特应性皮炎经预防。

[0435] 在另一示例性实施方案中，该方法涉及通过将本文所述的具有活性剂的局部药物制剂给药动物来治疗特应性皮炎。在示例性实施方案中，特应性皮炎经治疗。

[0436] 在另一示例性实施方案中，该方法涉及通过将本文所述的不具有活性剂的局部药物制剂给药动物来治疗特应性皮炎。在示例性实施方案中，特应性皮炎经治疗。

[0437] 示例性实施方案概述于下文中。

[0438] 在示例性实施方案中，本发明提供局部药物制剂，其包含：a)治疗炎症相关病症的活性剂或其药学上可接受的盐或水合物或溶剂合物；b)约5％(w/w)至约15％(w/w)丙二醇；及c)矿脂。

[0439] 在示例性实施方案中，根据以上段落，制剂包含不多于约0.5％(w/w)水。

[0440] 在示例性实施方案中，根据以上段落中的任一个，丙二醇的量是约7％(w/w)至约11％(w/w)。

[0441] 在示例性实施方案中，根据以上段落中的任一个，丙二醇的量是约6％(w/w)至约10％(w/w)。在示例性实施方案中，根据以上段落中的任一个，丙二醇的量是约8％(w/w)至约10％(w/w)。

[0442] 在示例性实施方案中，根据以上段落中的任一个，丙二醇的量是约9％(w/w)。

[0443] 在示例性实施方案中，根据以上段落中的任一个，丙二醇的量是9％(w/w)。

[0444] 在示例性实施方案中，根据以上段落中的任一个，丙二醇是丙二醇USP。

[0445] 在示例性实施方案中，根据以上段落中的任一个，局部药物制剂还包含乳化剂。

[0446] 在示例性实施方案中，根据以上段落中的任一个，其中乳化剂是甘油酯混合物。

[0447] 在示例性实施方案中，根据以上段落中的任一个，其中乳化剂是甘油酯混合物，且甘油酯混合物包含甘油单酯和甘油二酯。

[0448] 在示例性实施方案中，根据以上段落中的任一个，甘油酯混合物的量是约3％(w/w)至约10％(w/w)。

[0449] 在示例性实施方案中，根据以上段落中的任一个，甘油酯混合物的量是约5％(w/w)至约8％(w/w)。

[0450] 在示例性实施方案中，根据以上段落中的任一个，甘油酯混合物的量是约6％(w/w)至约8％(w/w)。

[0451] 在示例性实施方案中，根据以上段落中的任一个，甘油酯混合物的量是约7％(w/w)。

[0452] 在示例性实施方案中，根据以上段落中的任一个，甘油酯混合物的量是7％(w/w)。在示例性实施方案中，根据以上段落中的任一个，甘油酯混合物是甘油单酯NF和甘油二酯NF。

[0453] 在示例性实施方案中，根据以上段落中的任一个，约40％(w/w)至约55％(w/w)的甘油酯混合物是甘油单酯。

[0454] 在示例性实施方案中，根据以上段落中的任一个，局部药物制剂还包含稳定剂。在

示例性实施方案中，根据以上段落中的任一个，稳定剂是乙二胺四乙酸或其药学上可接受的盐。在示例性实施方案中，根据以上段落中的任一个，其还包含乙二胺四乙酸的钠盐或钾盐或钙盐或其混合物。在示例性实施方案中，根据以上段落中的任一个，其还包含乙二胺四乙酸的钠盐或钙盐或其混合物。

[0455] 在示例性实施方案中，根据以上段落中的任一个，其还包含依地酸钙二钠。

[0456] 在示例性实施方案中，根据以上段落中的任一个，其还包含依地酸钙二钠USP。

[0457] 在示例性实施方案中，根据以上段落中的任一个，乙二胺四乙酸或其药学上可接受的盐的量是约0.0001％(w/w)至约0.01％(w/w)。在示例性实施方案中，根据以上段落中的任一个，乙二胺四乙酸或其药学上可接受的盐的量是约0.001％(w/w)至约0.01％(w/w)。

[0458] 在示例性实施方案中，根据以上段落中的任一个，乙二胺四乙酸或其药学上可接受的盐的量是约0.001％(w/w)至约0.005％(w/w)。

[0459] 在示例性实施方案中，根据以上段落中的任一个，乙二胺四乙酸或其药学上可接受的盐的量是约0.0025％(w/w)至约0.0045％(w/w)。

[0460] 在示例性实施方案中，根据以上段落中的任一个，乙二胺四乙酸或其药学上可接受的盐的量是约0.0035％(w/w)。

[0461] 在示例性实施方案中，根据以上段落中的任一个，乙二胺四乙酸或其药学上可接受的盐的量是0.0035％(w/w)。

[0462] 在示例性实施方案中，根据以上段落中的任一个，依地酸钙二钠USP的量是0.0035％(w/w)。

[0463] 在示例性实施方案中，根据以上段落中的任一个，其还包含抗氧化剂。

[0464] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂选自：丁基化羟基甲苯、抗坏血酸或其药学上可接受的盐、抗坏血酸棕榈酸酯、丁基化羟基茴香醚、2,4,5-三羟基苯丁酮、4-羟甲基-2,6-二-叔丁基苯酚、异抗坏血酸、愈创树脂、没食子酸丙酯、硫二丙酸、硫代二丙酸二月桂酯、叔丁基对苯二酚和生育酚(如维生素E)等，包括其药学上可接受的盐和酯及其混合物。

[0465] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂是丁基化羟基甲苯。

[0466] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂的量是约0.01％(w/w)至约1％(w/w)。

[0467] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂的量是约0.05％(w/w)至约0.5％(w/w)。

[0468] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂的量是约0.1％(w/w)。

[0469] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂的量是0.1％(w/w)。

[0470] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂是丁基化羟基甲苯。

[0471] 在示例性实施方案中，根据以上段落中的任一个，抗氧化剂是丁基化羟基甲苯NF。

[0472] 在示例性实施方案中，根据以上段落中的任一个，其还包含硬化剂。

[0473] 在示例性实施方案中，根据以上段落中的任一个，硬化剂的量是约2％(w/w)至约8％(w/w)。

[0474] 在示例性实施方案中，根据以上段落中的任一个，硬化剂的量是约4％(w/w)至约6％(w/w)。在示例性实施方案中，根据以上段落中的任一个，硬化剂的量是约5％(w/w)。

[0475] 在示例性实施方案中，根据以上段落中的任一个，硬化剂的量是5％(w/w)。

[0476] 在示例性实施方案中，根据以上段落中的任一个，硬化剂选自蜂蜡、石蜡、蜡和鲸蜡。

[0477] 在示例性实施方案中，根据以上段落中的任一个，硬化剂是石蜡。

[0478] 在示例性实施方案中，根据以上段落中的任一个，硬化剂是石蜡NF。

[0479] 在示例性实施方案中，根据以上段落中的任一个，硬化剂是5％(w/w)石蜡NF。

[0480] 在示例性实施方案中，根据以上段落中的任一个，活性剂是5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯。在示例性实施方案中，根据以上段落中的任一个，活性剂的量是约0.1％(w/w)至约2.0％(w/w)。

[0481] 在示例性实施方案中，根据以上段落中的任一个，5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯的量是约0.1％(w/w)至约2.0％(w/w)。

[0482] 在示例性实施方案中，根据以上段落中的任一个，5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯的量是2.0％(w/w)。

[0483] 在示例性实施方案中，根据以上段落中的任一个，制剂的剩余物是矿脂。在示例性实施方案中，根据以上段落中的任一个，制剂的剩余物是白矿脂。

[0484] 在示例性实施方案中，根据以上段落中的任一个，制剂的剩余物是白矿脂USP。

[0485] 在示例性实施方案中，局部药物制剂由以下组成：a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)丙二醇；c)丁基化羟基甲苯；d)依地酸钙二钠；e)甘油单酯和甘油二酯；f)石蜡；和g)白矿脂。

[0486] 在示例性实施方案中，局部药物制剂基本上由以下组成：a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)丙二醇；c)丁基化羟基甲苯；d)依地酸钙二钠；e)甘油单酯和甘油二酯；f)石蜡；和g)白矿脂。

[0487] 在示例性实施方案中，局部药物制剂包含：a)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)丙二醇；c)丁基化羟基甲苯；d)依地酸钙二钠；e)甘油单酯和甘油二酯；f)石蜡；和g)白矿脂。

[0488] 在示例性实施方案中，局部药物制剂由以下组成：a)2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)9％(w/w)丙二醇；c)0.1％(w/w)丁基化羟基甲苯；d)0.0035％(w/w)依地酸钙二钠；e)7％(w/w)甘油单酯和甘油二酯；f)5％(w/w)石蜡；和g)76.8965％(w/w)白矿脂。

[0489] 在示例性实施方案中，局部药物制剂基本上由以下组成：a)2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)9％(w/w)丙二醇；c)0.1％(w/w)丁基化羟基甲苯；d)0.0035％(w/w)依地酸钙二钠；e)7％(w/w)甘油单酯和甘油二酯，其中40％至55％是甘油单酯；f)5％(w/w)石蜡；和g)76.8965％(w/w)白矿脂。

[0490] 在示例性实施方案中，局部药物制剂基本上由以下组成：a)约2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)约9％(w/w)丙二醇；c)约0.1％(w/w)丁基化羟基甲苯；d)约0.0035％(w/w)依地酸钙二钠；e)约7％(w/w)甘油单酯和甘油二酯，其中40％至55％是甘油单酯；f)约5％(w/w)石蜡；和g)约76.8965％(w/w)白矿脂。

[0491] 在示例性实施方案中，局部药物制剂由以下组成：a)约2％(w/w)5-(4-氰基苯氧基)-1,3-二氢-1-羟基-2,1-苯并氧杂硼杂环戊二烯；b)约9％(w/w)丙二醇；c)约0.1％(w/

w)丁基化羟基甲苯;d)约0.0035%(w/w)依地酸钙二钠;e)约7%(w/w)甘油单酯和甘油二酯,其中40%至55%是甘油单酯;f)约5%(w/w)石蜡;和g)约76.8965%(w/w)白矿脂。

[0492] 在示例性实施方案中,本发明是减少细胞因子和/或趋化因子的释放的方法,该方法包括使细胞与以上段落中的任一个的局部药物制剂接触。

[0493] 在示例性实施方案中,本发明是治疗动物的炎症相关病症的方法,该方法包括将治疗有效量的以上段落中的任一个的局部药物制剂给药动物。

[0494] 在示例性实施方案中,根据以上方法段落中的任一个,炎症相关病症是银屑病。

[0495] 在示例性实施方案中,根据以上方法段落中的任一个,炎症相关病症是特应性皮炎。

[0496] 在示例性实施方案中,根据以上方法段落中的任一个,动物是人类。

[0497] 在示例性实施方案中,本发明是治疗人类的特应性皮炎的方法,该方法包括将治疗有效量的以上段落中的任一个的局部药物制剂给药人类。

[0498] 在示例性实施方案中,本发明是治疗人类的银屑病的方法,该方法包括将治疗有效量的以上段落中的任一个的局部药物制剂给药人类。

[0499] 通过随后的实施例进一步说明本发明。实施例不意在限定或限制本发明的范围。

[0500] 实验

[0501] 多晶型研究

[0502] 同一化合物的不同结晶固体形式通常具有不同固态性质,诸如熔点、溶解度、溶解速率、吸湿性、粉末流动、机械性质、化学稳定性和物理稳定性。这些固态性质可提供过滤、干燥和剂型制造单元操作的优点。因此,一旦鉴别同一化合物的不同结晶固体形式,即可确定在任何给定一组处理和制造条件下的最佳结晶固体形式以及每个结晶固体形式的不同固态性质。

[0503] 分子的多晶型可通过多种本领域已知方法获得。这样的方法包括但不限于熔融再结晶、熔融冷却、溶剂再结晶、去溶剂化、快速蒸发、快速冷却、缓慢冷却、蒸气扩散和升华。可使用公知的技术来检测、鉴别、分类和表征多晶型,这些技术诸如但不限于差示扫描量热法(DSC)、热重分析法(TGA)、X射线粉末衍射法(XRPD)、单晶X射线衍射法、固态核磁共振(NMR)、红外(IR)光谱、拉曼光谱(Raman spectroscopy)和热台光学显微术。

[0504] 在克瑞沙硼原料药的制造过程的发展期间,尝试鉴别克瑞沙硼的多晶型。探索涉及极性质子溶剂(如水)、极性非质子溶剂(如二甲氧基乙烷)和非极性溶剂(例如庚烷)的若干溶剂系统。这些研究使得鉴别通过X射线粉末衍射区分的克瑞沙硼原料药的3种多晶型。形式2是在临床研究中在整个2期中所使用的形式。形式1鉴别为商业形式且用于3期研究中。

[0505] 固态化学中存在本领域技术人员可使用以分析固体形式的多种分析方法。如本文所用,术语“分析”意指获得关于固体形式的固态结构的信息。例如,X射线粉末衍射是适用于区分无定形固体形式与结晶固体形式且用于表征及鉴别化合物的结晶固体形式的技术。X射线粉末衍射还适于定量混合物中之一(或多种)结晶固体形式的量。在X射线粉末衍射中,将X射线引导至晶体上并测量衍射X射线的强度作为X射线源与由样品所衍射的束之间的两倍角度的函数。可将这些衍射X射线的强度在图上绘制为峰,其中x轴是X射线源与衍射X射线之间的两倍角度(这称为“2θ”角)且其中y轴是衍射X射线的强度。此图称为X射线粉末

衍射图案或粉末图案。不同结晶固体形式展现不同粉末图案，因为x轴上峰的位置是晶体固态结构的性质。

[0506] 这样的粉末图案或其部分，可用作结晶固体形式的鉴别指纹。因此，可获取未知样品的粉末图案且比较该粉末图案与参照粉末图案。阳性匹配会意味着未知样品具有与参照相同的结晶固体形式。通过将已知化合物的粉末图案相加和相减，还可分析含有固体形式混合物的未知样品。

[0507] 当选择粉末图案中的峰来表征结晶固体形式或在使用参照粉末图案来鉴别形式时，鉴别在其他固体形式中不存在的一种形式的峰或峰集合。

[0508] 如本文所用，术语“表征”意指选择能够区别一种固体形式与另一种固体形式的适当数据集。X射线粉末衍射中的该数据集是一或多个峰的位置。选择哪些X射线粉末衍射峰来限定具体形式称为表征该形式。

[0509] 如本文所用的术语“鉴别”意指对固体形式的特征数据进行选择且使用那些数据来确定该形式是否存在于样品中。在X射线粉末衍射中，那些数据是表征如以上论述所讨论形式的一个或多个峰的x轴位置。例如，在确定选择数目的X射线衍射峰表征具体固体形式后，可使用那些峰来确定该形式是否存在于样品中。

[0510] 在使用X射线粉末衍射来表征和/或鉴别相同化学化合物的结晶固体形式时，通常不需要使用整个粉末图案。整个粉末图案的较小子集通常可用于实施表征和/或鉴别。通过选择将化合物的结晶固体形式与其他结晶固体形式区分开的峰的集合，可依靠那些峰来表征该形式并鉴别(例如)未知混合物中的该形式。可增加(诸如)来自另一分析技术或来自粉末图案的其他峰的其他数据来表征和/或鉴别该形式，例如会稍后鉴别其他多晶型。

[0511] 由于仪器、样品和样品制备的差异，有时在峰值前使用修饰语“约”来报告峰值。因为峰值的固有变化，这是固态化学领域中的常见实践。粉末图案中峰的2θx轴值的典型精密度是大约加或减0.2°2θ。因此，在大多X射线衍射仪上在大多条件下测量时，在“约9.2°2θ”处出现的粉末衍射峰意指该峰可以为9.0°2θ至9.4°2θ。峰强度的可变性是由于单独晶体在样品容器中相对于外部X射线源的定向方式(称为“优选定向”)。此定向效应不提供关于晶体的结构信息。X射线粉末衍射仅是可用于表征和/或鉴别结晶固体形式的若干分析技术中之一。诸如拉曼(包括显微拉曼)、红外和固态NMR光谱等光谱技术可用于表征和/或鉴别结晶固体形式。这些技术还可用于定量混合物中一种或多种结晶固体形式的量且还可在峰值前使用修饰语“约”来报告峰值。与FT-拉曼和FT-红外测量值相关的峰值的典型可变性是大约加或减2cm^{-1}。对于结晶材料，与^{13}C化学位移相关的峰值的典型可变性是大约加或减0.2ppm。与差示扫描量热法起始温度相关的值的典型可变性是大约加或减5℃。

[0512] 如本文所用的术语“室温”是指在20℃至23℃的温度。

[0513] 1.仪器方法(API和药品扫描)

[0514] 使用配备有Cu辐射源(K-α平均)的Bruker AXS D8ADVANCE衍射仪来实施粉末X射线衍射分析。该系统在初级侧上配备有2.5轴向索勒狭缝(Soller slits)。次级侧使用2.5轴向索勒狭缝和电动狭缝。通过Lynx Eye XE检测器检测衍射辐射。将X射线管电压及安培数分别设定至40kV和40mA。在Cu波长下自3.0度至40.0度2θ使用0.037度的步长及1920秒的步时于θ-θ测角器中收集数据。通过将其置于低背景夹持器中来制备样品并在收集期间旋转。使用Bruker DIFFRAC Plus软件(9.0.0.2版)来收集数据且通过EVA diffract plus软

件来实施分析。

[0515] PXRD数据文件在峰搜索前不进行处理。使用EVA软件中的峰搜索算法，以阈限值为1且宽度值为0.3选择峰以用于进行初步峰指定。目视检查自动指定的输出以确保正确性且若需要手动进行调整。通常选择相对强度≥2％的峰。不选择未解析或与噪音一致的峰。USP中所阐明与来自PXRD的峰位置相关的典型误差至多+/-0.2°2-θ(USP-941)。与形式1、形式2和形式3相关的峰拟合列示于表1-3中；表4列示可与安慰剂药品区别的形式1的峰。例如，6.0、12.1、14.1和15.4峰是与克瑞沙硼相关。具体而言，峰6.0和15.4是优选的相关峰。

[0516] 表1：形式1API的PXRD峰列表。加星号的峰位置代表特征峰。

角度	相对强度
6.1*	100
12.2	14
14.2	9
15.4*	31

[0517]

16.1	6
17.7	2
18.2	46
21.5	11
23.1	5
24.3	8
24.9	12
26.2	61
26.5	7
28.5	12
29.1	3
31.6	7
31.4	17
31.7	7
32.8	2
33.8	3
37.0	2

[0518]

[0519] 表2：形式2API的PXRD峰列表

[0520]

角度	相对强度
2θ°	**%**
7.1	6
12.3	12
14.3	18
14.9	4
15.5	2
16.4	13
16.7	75
17.7	43
17.9	7
18.4	10
20.0	8
20.9	100
21.4	29
21.8	36
22.2	5
22.7	59
23.2	30
23.5	8
24.2	4
24.9	31
24.9	26
26.1	11
26.4	7
26.5	7
27.1	8
27.5	9
27.8	15
28.0	32
28.8	6
29.1	3
30.1	10
31.0	3
31.5	5
32.1	3
33.7	3
34.4	2
34.9	5
37.4	7
38.9	2
39.9	2
43.1	4
45.6	2
46.5	3

[0521]

[0522] 表3:克瑞沙硼形式3API的PXRD峰列表

[0523]

角度 2-θ°	相对强度 %
13.8	2
14.3	2
15.8	5
16.4	6
16.6	13
16.7	13
16.8	7
17.7	8
18.4	9
18.4	8
18.8	15
19.7	12
20.8	100
21.4	13
21.9	9
22.7	16
23.2	4
23.5	4
23.9	17
24.9	4
26.4	3
26.2	8
26.5	3
27.1	3
27.6	6
27.9	33
28.8	5
29.1	3
31.4	6
32.3	2
34.9	2
37.3	6

[0524] 表4:克瑞沙硼形式1药品的PXRD峰列表

[0525]

角度 2-θ°	相对强度 %
6.0	89
12.1	11
14.1	33
15.4	100
16.0	17

	17.7	6
	18.2	40
	18.6	2
	21.5	33
	23.1	6
	24.9	37
	26.2	87
	26.5	14
	27.6	2
[0526]	28.5	33
	28.5	27
	29.1	7
	31.0	6
	31.4	11
	31.7	9
	31.8	8
	32.8	3
	33.8	7
	37.1	3
	39.3	2

[0527] 2.生产形式1的方法

[0528] 在70℃下将克瑞沙硼溶解于乙酸(约3.5体积)中,随后添加约0.75体积水。将混合物冷却至约61℃(范围:58℃至63℃),使用克瑞沙硼加晶种(1%晶种±1%)且在该温度下维持约15分钟。然后将反应混合物经45分钟至60分钟时间冷却至50℃(±3℃)且通过拉曼光谱监测直至达到适当终点。然后将反应混合物经3小时至5小时(目标:4小时)进一步冷却至20℃(±5℃)且通过拉曼光谱监测直至达到适当终点。过滤固体且使用3×2体积的水洗涤且在45℃(±10℃)下干燥。参见表1和图2:形式1的PXRD光谱和图4:克瑞沙硼药品安慰剂批次与形式1叠加的PXRD。

[0529] 3.生产形式2的方法

[0530] 在70℃下将克瑞沙硼溶解于乙腈中且将约2体积的水添加至溶液中,使得形式2立即沈淀。参见表2和图3:形式1、形式2和形式3的PXRD光谱。

[0531] 4.生产形式3的方法

[0532] 通常,仅在使用从溶剂(诸如乙酸乙酯、甲基乙基酮和甲基叔丁基醚)的快速蒸发研究的多晶型筛选期间发现多晶型3。在75℃下将约1g克瑞沙硼溶解于乙腈中,随后过滤。在75℃下将水添加至滤液中作为反溶剂。所得混合物是澄清溶液,且将其使用约2mg形式III晶种来种晶。然后将混合物在20℃/h下冷却至环境温度并搅拌过夜。将固体通过过滤分离且使用约2mL水洗涤。在真空下在环境温度下将固体干燥20小时,然后经XRPD分析以确认形式III的形成。参见图2:形式1、形式2和形式3的PXRD光谱。

[0533] 溶剂选择

[0534] 再配制克瑞沙硼中遇到的关键方面中之一是活性剂完全溶解于其溶剂内。大于10%w/w克瑞沙硼溶解度的选择标准用于选择能够在最终药品制剂中携载至少1%克瑞沙硼的溶剂,假定药品含有10%溶剂。评估克瑞沙硼在10种溶剂中的溶解度以通过目测评价来鉴别具有大于10%w/w的克瑞沙硼溶解度的那些溶剂。最佳溶剂的平衡溶解度随后经HPLC验证。参见表5。

[0535] 表5:克瑞沙硼形式II的溶解度研究

[0536]

溶剂	目视溶解度[a] (% w/w)	溶解度，HPLC[b] (mg/mL)
Transcutol® P, NF	28.6%	21.2
己二醇，NF	25.9%	356
丙二醇，USP	24.0%	274
聚乙二醇(PEG) 400，USP	15.0%	164
碳酸丙烯酯，NF	9.9%	96
己二酸二异丙酯	7.7%	--
油醇，NF	2.3%	33
羟基硬脂酸乙基己酯	1.6%	21
[0537]		
肉豆蔻酸异丙酯，NF	0.6%	--
油酸，NF	<0.1%	--

[0538] --未测试

[0539] a.克瑞沙硼多晶型2

[0540] b.Transcutol P等同于二乙二醇单乙醚

[0541] 还通过评价在80％饱和度下在50℃和40℃/75％RH下储存7天后克瑞沙硼溶液中的降解物形成来评估满足大于10％w/w溶解度要求的溶剂的克瑞沙硼相容性。

[0542] 7种经评估溶剂中的三种(丙二醇、碳酸丙烯酯和PEG400)的克瑞沙硼溶液展现两种主要降解物，包括杂质1。这三种溶液中的丙二醇溶液具有最低总降解和最高克瑞沙硼溶解度。4种剩余溶剂的克瑞沙硼溶液均展现其他降解物且因此从研发排除。(参见表6)

[0543] 表6：克瑞沙硼与各种溶剂的相容性

[0544]

溶剂	条件	降解物(峰面积%) 杂质2	杂质1	杂质3	总量
丙二醇，USP	T_0	—	—	—	—
	7天，40℃/75% RH	0.0	0.0	—	0.15
	7天，50℃	0.11	0.15	—	0.26
碳酸丙烯酯，NF	T_0	—	—	—	—
	7天，40℃/75% RH	—	1.3	—	1.37
	7天，50℃	0.07	2.01	—	2.08
PEG 400，USP	T_0	0.2	—	—	0.27
	7天，40℃/75% RH	0.7	0.0	—	0.82
	7天，50℃	0.99	0.10	—	1.09
己二醇，NF	T_0	—	—	—	—
	7天，40℃/75% RH	0.1	0.0	0.1	0.30
	7天，50℃	0.27	0.15	0.32	0.74
Transcutol P, NF[a]	T_0	0.1	—	—	0.12
	7天，40℃/75% RH	0.2	—	—	0.22
	7天，50℃	0.28	0.06	0.13	0.47
油醇，NF	T_0	0.4	—	0.0	0.53
	7天，40℃/75% RH	5.9	—	0.1	6.02
	7天，50℃	9.18	0.10	0.20	9.48
羟基硬脂酸乙基己酯	T_0	0.1	—	7.8	7.97
	7天，40℃/75% RH	0.2	—	11.	11.78
	7天，50℃	0.41	—	13.4	13.81

[0545] RRT，相对保留时间；—未检测。

[0546] a Transcutol P等同于二乙二醇单乙醚。

[0547] 乳化剂选择

[0548] 为形成含有分散于矿脂基内的丙二醇相的软膏剂，实施研究以鉴别具有适当亲水-亲油平衡(HLB)值、可接受克瑞沙硼相容性且显示乳化能力的乳化剂。期望HLB值为4-6的乳化剂用于油包水型乳剂，且评估以下4种潜在乳化剂的克瑞沙硼相容性：HLB值分别为3.8、3.7、4.3和3.8的甘油单酯和甘油二酯(MDG)、失水山梨醇倍半油酸酯、失水山梨醇单油酸酯和单油酸甘油酯。

[0549] 将克瑞沙硼溶解于丙二醇中，向其中添加各乳化剂，从而形成溶液或部分悬浮液。每一种的水平约等同于含有10％丙二醇、2％克瑞沙硼和5％乳化剂的软膏剂制剂中的水平。将样品在50℃下储存7天，然后对其分析克瑞沙硼的降解。相容性结果概述于表7中。

[0550] 表7：克瑞沙硼与各种乳化剂的相容性

[0551]

乳化剂	条件	降解物(峰面积%)	
		杂质X	杂质1
甘油单酯和甘油二酯[a]	7天，50℃	—	1.2
失水山梨醇倍半油酸酯，NF	7天，50℃	—	13.2
失水山梨醇单油酸酯，NF	7天，50℃	0.45	8.4
单油酸甘油酯，NF	7天，50℃	.15	18.9

[0552] —，未检测。

[0553] a鉴别为纯化单硬脂酸甘油酯。

[0554] 初始对克瑞沙硼相容性评估的MDG等级是非药典的且鉴别为经纯化单硬脂酸甘油酯。然而，测试展示相较于单硬脂酸甘油酯(NF(GMS)药典规范)，该材料更紧密符合甘油单酯和甘油二酯(NF药典规范)。因此，本文将其描述为MDG。在尝试改善制剂中，非药典的MDG替换为药典等级的单硬脂酸甘油酯NF(Sasol Imwitor®491)。然而，可能由于MDG与GMS之间固有的甘油单酯和甘油二酯的不同比例，SasolImwitor®491展现差的乳化性质。

[0555] 随后评估各种药典及非药典的MDG和GMS等级的克瑞沙硼相容性。用于乳化剂评估：

[0556] (a)制备软膏剂活性相的溶液：2g克瑞沙硼、8.91g丙二醇、0.09g水和0.1g硼酸；

[0557] (b)将1克活性相与0.6克乳化剂混合，且

[0558] (c)将样品在50℃下储存7天。

[0559] 克瑞沙硼相容性结果呈现于表8中。

[0560] 表8：克瑞沙硼与潜在乳化剂等级的相容性

[0561]

源(材料)	等级	药典状态	甘油单酯含量(%)	降解物(峰面积%)	
				杂质	杂质1
对照A[a]	—	—	—	0.	0.
Gattefosse (Geleol™)	MDG	NF	5	0.	0.
Alfa Aesar (单硬脂酸甘油酯)	MDG	无	4	0.	0.
Sasol (Imwitor® 491)	GMS	NF	9	0.	0.
Sasol (Imwitor® 900K)	MDG	NF	4	0.	1.
Caravan (BFP® 74K)	MDG	无	4	0.	1.
Caravan (BFP® 74E)	MDG	无	4	0.	3.
Abitec (Capmul® MCM NF)	MDG	NF	5	0.	2.
对照B[a]	—	—	—	0.	0.
Cognis (Cutina® GMS V PH)	MDG	NF	5	0.	0.

[0562] GMS，单硬脂酸甘油酯；MDG，甘油单酯和甘油二酯；RRT，相对保留时间；

[0563] —，不适用。

[0564] a对照A是与除Cutina之外的所有乳化剂同时实施，Cutina是与对照B同时实施。

[0565] 多种甘油单酯和甘油二酯源在这些稳定性条件下展现与克瑞沙硼的可接受相容性。示例性源包括Gattefosse(Geleol™)、Alfa Aesar(单硬脂酸甘油酯)、Sasol(Imwitor® 491)、Sasol(Imwitor®900K)、Caravan(BFP®74K)、Caravan(BFP®74E)、Abitec(Capmul®MCM NF)、Cognis(Cutina®GMS V PH)。基于药典状态、HLB值、化学相容性和经确定的乳化能力，甘油单酯和甘油二酯NF经选择为2％克瑞沙硼局部软膏剂的乳化剂。

[0566] 稳定剂选择

[0567] 在约1％的丙二醇溶剂被水替代时，早期原型制剂展示改善的稳定性，尤其关于质子去硼化(protodeboronation)。在将少量硼酸添加至制剂中时，发现稳定性的进一步改善。因此，克瑞沙硼软膏剂Z6制剂，包括少量的水和硼酸二者。然而，未充分理解水和硼酸降低质子去硼化率的机制。

[0568] 然而，在放大程序期间，丙二醇中水的存在降低克瑞沙硼形式I(商业多晶型)的溶解度，呈现潜在制剂挑战。此外，水和硼酸组合不能充分稳定克瑞沙硼且因此寻求替代稳定剂。

[0569] 在各种水平下在药品制剂内使用用于2％克瑞沙硼局部软膏剂中的相同赋形剂，经评估依地酸钙二钠(EDTA)作为稳定剂。于多种候选管(包括等同于市售初级容器封闭系统(除了不具有孔口密封)的60-g层压管)中在25℃/60％RH和40℃/75％RH二者下评估药品制剂。

[0570] 所评估的制剂仅在所用稳定剂上不同于2％克瑞沙硼局部软膏剂：0ppm EDTA(Z10)、24ppmEDTA(软膏剂Z7)、90ppm EDTA、450ppm EDTA和0.09％水与0.10％硼酸(等同于软膏剂Z6，但使用MDG而非GMS)。在60-g层压管中的评估结果呈现于表5和6中。在6个月后，不具有稳定剂的制剂在40℃/75％RH条件下展现最大总克瑞沙硼降解及最低含量测定，其次为软膏剂Z6制剂(水和硼酸作为稳定剂)。在24ppm EDTA和90ppm EDTA水平下观察到最大稳定效应。24ppm EDTA制剂(软膏剂Z7)随后用于临床研究中。

实施例

[0571] 实施例1

[0572] 本发明局部药物制剂的制造

[0573] a)具有活性剂的局部药物制剂

[0574] 步骤1：油相的制备

[0575] 在主混合容器中，在持续螺旋桨混合下添加白矿脂、石蜡和甘油单酯和甘油二酯，同时加热至70-80℃。将此混合物的温度维持在70-80℃下，使混合物视觉上看起来熔融且均匀。在螺旋桨搅拌下，添加丁基化羟基甲苯并混合以溶解，同时将温度维持至70-80℃。在搅拌的同时，将混合物冷却降至40-46℃并维持直至添加药物溶液相。

[0576] 步骤2：药物溶液相的制备

[0577] 在副混合容器中，在持续螺旋桨混合下将依地酸钙二钠添加至丙二醇中，同时加热至40-46℃。将此混合物的温度维持在40-46℃下，使混合物视觉上看起来溶解且均匀。在持续混合下，添加克瑞沙硼以溶解，同时将温度维持在40-46℃下。

[0578] 步骤3：乳化

[0579] 将药物溶液相通过80目过滤器过滤并添加至油相中。然后将其均化10分钟，同时将温度维持在40-46℃下。将最终组合物在螺旋桨混合下冷却至25℃直至获得均匀软膏剂。

[0580] 所有组分均是药典级的。2％软膏剂制剂Z是根据以上程序生产且具有以下组分：

[0581]

组分	Z％w/w
克瑞沙硼	2.000
丙二醇	9.000
丁基化羟基甲苯	0.100
甘油单酯和甘油二酯	7.000
石蜡	5.000
白矿脂	76.8965
依地酸钙二钠	0.0035

[0582] b)不具有活性剂的局部药物制剂

[0583] 步骤1：油相的制备

[0584] 在主混合容器中，在持续螺旋桨混合下添加白矿脂、石蜡和甘油单酯和甘油二酯，同时加热至70-80℃。将此混合物的温度维持在70-80℃下，使混合物目测看起来熔融且均匀。在螺旋桨搅拌下，添加丁基化羟基甲苯并混合以溶解，同时将温度维持至70-80℃。在搅拌的同时，将混合物冷却降至40-46℃并维持直至添加药物溶液相。

[0585] 步骤2：溶剂相的制备

[0586] 在副混合容器中，在持续螺旋桨混合下将依地酸钙二钠添加至丙二醇中，同时加热至40-46℃。将此混合物的温度维持在40-46℃下，使混合物目测看起来溶解且均匀。

[0587] 步骤3：乳化

[0588] 将溶剂相通过80目过滤器过滤并添加至油相中。然后将其均化10分钟，同时将温度维持在40-46℃下。将最终组合物在螺旋桨混合下冷却至25℃直至获得均匀软膏剂。

[0589] 所有组分均是药典级的。2％软膏剂制剂Y是根据以上程序生产且具有以下组分：

[0590]

组分	Y％w/w
丙二醇	9.000
丁基化羟基甲苯	0.100
甘油单酯和甘油二酯	7.000
石蜡	5.000
白矿脂	78.8965
依地酸钙二钠	0.0035

[0591] 实施例2

[0592] 2％和5％克瑞沙硼乳膏的通量(Flux)测试—

[0593] 测量乳膏制剂中克瑞沙硼穿过人类离体尸体皮肤的体外渗透。2％克瑞沙硼乳膏制剂Z1和5％克瑞沙硼乳膏制剂Z2的组成提供于下文中。Z1和Z2二者都公开于美国专利申请第12/399,015号(美国专利公开第US2009/0291917号)和国际专利申请第PCT/US09/036250号(国际专利公开第WO2009/111676号)中。

[0594]

组分	Z1%w/w	Z2%w/w
克瑞沙硼	2.0	5.0
对羟基苯甲酸甲酯	0.15	0.15
对羟基苯甲酸丙酯	0.03	0.03
单硬脂酸甘油酯SE	8.0	8.0
丁基化羟基甲苯	0.02	0.02
依地酸二钠	0.05	0.05
Pemulen TR-2	0.25	0.25
Carbopol Ultrez 10	0.20	0.20
25%三乙醇胺	0.84	0.84
丙二醇	5.0	5.0
辛基十二烷醇	10.0	10.0
油醇	10.0	10.0
苄醇	2.0	2.0
己二酸二异丙酯	10.0	10.0
纯化水	QS 100	QS 100

[0595] 25%三乙醇胺溶液

[0596]

组分	%w/w
三乙醇胺	25.0
纯化水	75.0

[0597] 根据以下方案来实施测试。

[0598] 研究皮肤制备

[0599] 使用体外尸体皮肤有限剂量技术测量经皮渗透。此研究中使用在1年内收集无明显皮肤疾病迹象的人类离体躯干部皮肤。将其经皮刀切离，制备用于冷冻保存，密封于不透水塑料袋中并在≤-70℃下储存直至实验之日。在使用前将其在约37℃水中解冻，然后在水中冲洗以自表面移除任何黏附血液或其他材料。

[0600] 将来自单一供体的皮肤切成多个足够大以装配于静态1.0cm^2弗兰兹扩散池(Franz diffusion cell)上的较小切片。填充真皮室以容纳磷酸盐缓冲等渗盐水(PBS)的储存溶液(pH 7.4±0.1)且使表皮室(烟囱状物(chimney))开放置于环境实验室条件。所有池均装于扩散装置中，其中将真皮浸泡溶液以约600RPM磁力搅拌且将皮肤表面温度维持在32.0±1.0℃。

[0601] 为确保各皮肤切片的完整性，在施用测试产物之前，测定其对氚化水的渗透性。Franz TJ等人，Abst.J Invest Dermatol 1990,94:525。在短暂(0.5-1小时)平衡期后，通过滴管将^3H_2O(NEN,Boston,MA,sp.Act.，约0.5μCi/mL)成层于整个皮肤上面，以使得整个暴露表面被覆盖(约250-500μL)。在5分钟后，移除^3H_2O含水层。在30分钟收集接受溶液并通过液体闪烁计数来分析放射性含量。其中^3H_2O的吸收小于1.56μL-equ/cm^2的皮肤样本视为可接受。

[0602] 在水测试后，将室按制剂组来排列，以使得在各制剂的各组内存在具有相关水渗透的室的均匀倾斜分布。

[0603] 给药和样品收集

[0604] 即将给药之前，获得给药前的样品并使用具有0.1％Volpo的0.1×PBS新鲜溶液替换储存溶液。从弗兰兹池移除烟囱状物以允许完全接近皮肤的表皮表面。然后使用设定为递送5μL制剂/cm^2的容积式移液管(positive displacement pipette)将所有制剂施用至皮肤切片。使用移液管的特氟龙(Teflon)尖端使剂量在整个表面延展开。施用后5分钟至10分钟，将弗兰兹池的烟囱状物部分放回。注意在不使用时保持给药溶液的容器盖盖子且在给药期间尽可能少地使其开放以最小化蒸发。

[0605] 在给药后的预选时间(4小时、8小时、12小时、24小时和48小时)，将储存溶液整体移除，替换为新鲜储存溶液，且保存预定的体积等分样品以供随后分析。将所有样品收集于2mL耐煮微管(Boil-Proof Microtubes)(Axygen Scientific MCT-200-C)中。

[0606] 可获得备用池，其未经给药但用于评估可能干扰分析方法的扩散出皮肤的物质的出现。

[0607] 在收集最后样品后，将表面使用乙腈洗涤两次(每次0.5mL体积)以从皮肤表面收集未吸收的制剂。在洗涤后，将皮肤用胶带剥离(Transpore®胶带，3M)不超过10次以移除角质层。将胶带条于乙腈中提取过夜。然后将皮肤从室移除，分离为表皮和真皮。将每一个于乙腈中提取过夜。另外，在研究结束时，将室部分(给药烟囱状物和储存室)单独使用乙腈冲洗并将样品保留以供分析。

[0608] 结果：

[0609] 对于Z1和Z2，经48小时穿过人类尸体皮肤的总经皮渗透提供于以下：

[0610] 经48小时穿过人类尸体皮肤的克瑞沙硼的平均累积量(μg/cm^2)(乳膏)

[0611]

	Z1	Z2
平均值± SD N=3个供体，每个供体3次重复。	1.13 ±0.67 μg/cm^2	4.57± 3.51 μg/cm^2

[0612] 实施例3

[0613] 2％克瑞沙硼软膏剂Z3和5％克瑞沙硼软膏剂Z4的通量测试—

[0614] 测量两种软膏剂制剂中的克瑞沙硼穿过人类离体尸体皮肤的体外渗透。2％克瑞沙硼软膏剂制剂Z3和5％克瑞沙硼软膏剂制剂Z4的组成提供于下文中。Z3和Z4二者都公开于美国专利申请第12/399,015号(美国专利公开第US2009/0291917号)和国际专利申请第PCT/US09/036250号(国际专利公开第WO2009/111676号)中。

[0615]

组分	Z3％w/w	Z4％w/w
克瑞沙硼	2.0	5.0
羟基硬脂酸乙基己酯	10.0	10.0
油醇	10.0	10.0
白矿脂	78.0	75.0

[0616] 根据实施例2的方案来实施测试。

[0617] 结果：

[0618] 对于Z3和Z4,经48小时穿过人类尸体皮肤的总经皮渗透提供于以下:

[0619] 历经48小时穿过人类尸体皮肤的克瑞沙硼的平均累积量(μg/cm^2)(软膏剂)

[0620]

	Z3	Z4
平均值± SD N=3个供体，每个供体3次重复。	3.89 ± 0.87 μg/cm^2	4.43±1.81 μg/cm^2

[0621] 实施例4

[0622] 2％克瑞沙硼乳膏Z1和2％克瑞沙硼软膏剂Z的通量测试—

[0623] 测量2％乳膏制剂Z1和软膏剂制剂Z中的克瑞沙硼穿过人类离体尸体皮肤的体外渗透。

[0624] 2％克瑞沙硼乳膏Z1的组成描述于实施例2中。2％克瑞沙硼软膏剂Z的组成描述于实施例1中。皮肤样品和供体人口统计

[0625] 人类离体尸体皮肤是由Allosource(6278South Troy Circle,Centennial,CO)供应并在-80℃下储存直至使用。经皮刀分离的皮肤厚度为约500μm。在研究期间使用来自3个供体的不具有明显皮肤疾病迹象的人类尸体皮肤。

[0626] 测试程序

[0627] 将人类离体尸体皮肤在-80℃下储存直至研究的早晨。通过浸没于预温热的磷酸盐缓冲盐水(PBS)(37℃)中来将皮肤解冻并对任何可见洞或损伤进行检查。仔细地使用解剖刀将皮肤切分为适当大小以用于置于垂直扩散池上。

[0628] 将预温热至37℃的接收介质(水:丙二醇v/v,90:10)和搅拌棒添加至每一扩散池中并允许平衡最少30分钟。将皮肤切片置于各池顶部,且将池使用夹子组装以确保皮肤位置适当。移除池的组装期间引入的任何气泡。在池组装后,使皮肤和介质平衡最少30分钟。

[0629] 收集400μL给药前接受介质样品用于分析且使用预温热新鲜介质来替换等体积。将制剂加温至31±1℃并平衡约1小时,然后给药。在即将给药前使用移液管尖端将制剂简单混合。以1分钟间隔,将各池使用容积式移液管使用约5μL/cm^{2}的分别的制剂给药1次。玻璃杆用于使制剂均匀地扩展,从而覆盖皮肤的整个表面区域。将取样口用石蜡封口膜(parafilm)封闭以防止研究期间接受介质的蒸发。将各玻璃杆保存且将尖端于400μL提取溶液(0.1％乙腈中的甲酸)中提取过夜。

[0630] 在剂量给药后3小时、6小时、12小时、24小时和48小时,使用移液管通过各池的取样柄来移除400μL等分的接收介质。在移除介质后,添加等体积的预温热新鲜接收介质以替换在取样期间所移除的体积。注意避免在取样期间产生任何气泡,且(若需要)仔细地移除任何气泡。

[0631] 在研究结束时,将池拆卸并从各池仔细地移除皮肤。使用0.5mL的提取溶液(0.1％乙腈中的甲酸)将各皮肤切片洗涤两次以从皮肤表面收集未吸收的制剂。使用实验纸巾将皮肤表面轻柔地清洁以移除来自洗涤液的任何残余液体。使用3M Transpore胶带将组织经胶带剥除1-2次以收集角质层。收集胶带条,合并,并于1mL提取溶剂(0.1％乙腈中的甲酸)中提取。

[0632] 在胶带剥除后,使用镊子将皮肤仔细地分离为表皮及真皮。将各切片添加至经称皮重的小瓶中并收集重量。向各表皮小瓶中,以10×组织重量的比率添加均化溶液(0.1％水/丙二醇[10:90v/v]中的甲酸)。以4×组织重量的比率向各真皮小瓶中添加均化溶液。使

用珠均化器(Omni BeadRuptor,具有含有2.8mm陶瓷珠的2mL微型管)在以下设置下将组织均化:

[0633] 速度:7.45m/秒;循环时间:15秒;循环次数:2;留置时间:1min

[0634] 样品分析

[0635] 将从扩散池组件所收集的接收介质等分至96孔板中并在-20℃下冷冻。还将在实验结束时所制备的表皮和真皮均化物和角质层的胶带条提取物在-20℃下冷冻。

[0636] 结果

[0637] 将从扩散池组件所收集的接收介质等分至96孔板中并在-20℃下冷冻。

[0638] 经48小时渗透穿过人类尸体皮肤至接收介质中的克瑞沙硼的平均累积量(μg/cm^2)

[0639]

	Z	Z1
平均值 ±SD N=3个供体，每个供体2个重复，	35.04 ± 10.81 μg/cm^2	20.60±10.18 μg/cm^2

[0640] Z进入并穿过人类皮肤的渗透大于Z1的渗透。

[0641] 实施例5

[0642] 具有油醇的2%克瑞沙硼软膏剂Z3和具有丙二醇的2%克瑞沙硼软膏剂Z6的通量测试—

[0643] 测量两种软膏剂制剂中的克瑞沙硼穿过人类离体尸体皮肤的体外渗透。具有油醇的2%克瑞沙硼软膏剂制剂Z3和具有丙二醇的2%克瑞沙硼软膏剂制剂Z6的组成提供于以下。

[0644]

组分	Z3% w/w

[0645]

克瑞沙硼	2.0
羟基硬脂酸乙基己酯	10.0
油醇	10.0
白矿脂	78.0

[0646]

组分	Z6% w/w
克瑞沙硼	2.00
丙二醇	8.91
硼酸	0.10
纯化水	0.09
丁基化羟基甲苯	0.10
甘油单酯和甘油二酯，40-55%甘油单酯	7.00
石蜡	5.00
白矿脂	76.80

[0647] 皮肤样品和供体人口统计:

[0648] 不具有明显皮肤疾病迹象的人类离体尸体皮肤用于研究中。将其储存在约-70℃下直至使用。将其经皮刀分离,制备用于冷冻保存,密封于不透水塑料袋中并在约-70℃下储存直至实验之日。

[0649] 测试程序:

[0650] 将人类离体尸体皮肤在约-70℃下储存直至研究的早晨。将皮肤通过浸没于预温

热的水(37℃)中解冻,并对任何可见洞或损伤进行检查。将来自单一供体的皮肤切成多个足够大以装配于标称1.0cm^2静态弗兰兹扩散池上的较小切片。

[0651] 将来自单一供体的皮肤切成多个足够大以装配于标称1.0cm^2静态弗兰兹扩散池上的较小切片。填充真皮室以容纳磷酸盐缓冲等渗盐水(PBS)的储存溶液(pH 7.4±0.1)且将表皮室(烟囱状物)开放置于环境实验室条件。所有池均装于扩散装置中,其中将真皮浸泡溶液以约600RPM磁力搅拌且将皮肤表面温度维持在32.0±1.0℃。

[0652] 测定水完整性测试,然后施用测试产物。在短暂(0.5-1小时)平衡期后,将^3H_2O(Perkin Elmer,sp.Act.,约0.5μCi/mL)成层于整个皮肤上面,以使得整个暴露表面被覆盖(约250-500μL)。在5分钟后,移除^3H_2O含水层。在30分钟收集接受溶液并通过液体闪烁计数来分析放射性含量。其中^3H_2O的吸收小于1.56μL-equ/cm^2的皮肤样本视为可接受。

[0653] 即将给药之前,使用具有80μg/mL庆大霉素的蒸馏去离子水(ddH_2O)的新鲜溶液来替换储存溶液。从弗兰兹池移除烟囱状物以允许完全接近皮肤的表皮表面。将测试制剂在30±2℃的受控温度下轻微加温并在所维持的温度下平衡约2小时,然后给药。

[0654] 将产物施用至相同供体皮肤的5个重复切片。使用容积式移液管来实施给药,该移液管设定为递送5μL制剂/cm^2或(若对移液管的黏度不足)以重量计(5mg/cm^2)。

[0655] 结果:

[0656] 对于Z3和Z6,经48小时穿过人类尸体皮肤的总经皮渗透提供于以下:

[0657] 经48小时渗透穿过人类尸体皮肤至接收介质中的克瑞沙硼的平均累积量(μg/cm^2)

[0658]

	Z3	**Z6**
平均值± SD N=2个供体,每个供体5个重复。	68.047± 8.15 μg/cm^2	82.212± 5.18 μg/cm^2

[0659] Z6的穿过皮肤的克瑞沙硼的通量令人惊讶地大于Z3。

[0660] 实施例6

[0661] 物理稳定性离心应力测试

[0662] 药物制剂Z5含有以下成分:

[0663]

组分	**Z5% w/w**
克瑞沙硼	2.00
丙二醇	8.91

[0664]

硼酸	0.10
纯化水	0.09
丁基化羟基甲苯	0.10
甘油单酯和甘油二酯,90%甘油单酯	7.00
石蜡	5.00
白矿脂	76.80

[0665] 且如以上实施例1中所述来制备，但其中在步骤2A中添加硼酸和水而非EDTA。

[0666] 药物制剂Z6含有以下成分：

[0667]

组分	Z6% w/w
克瑞沙硼	2.00
丙二醇	8.91
硼酸	0.10
纯化水	0.09
丁基化羟基甲苯	0.10
甘油单酯和甘油二酯，40-55%甘油单酯	7.00
石蜡	5.00
白矿脂	76.80

[0668] 且如上文对Z5所述来制备。

[0669] 通过离心来测试Z5和Z6的物理稳定性。将各软膏剂的样品置于15mL低密度聚乙烯离心管中。样品大小是约10mL/离心管。将样品在25℃/60％RH烘箱中平衡约1小时，然后离心。将管置于Beckman Coulter Allegra 6R Series Centrifuge中并在2890rpm下旋转。在旋转1.5小时后，测量内部体积分离的百分比。

[0670] 通过测量分离相高度来测定物理分离的材料体积且使用图1中所提供方程来计算体积。然后通过将分离相体积除以总软膏剂体积来计算分离的总样品百分比。

[0671] Z6测得0％内部体积分离，而Z5测得1.4％内部体积分离。然后再将软膏剂旋转1.5小时(总共3.0小时)，且再次测量内部体积分离的百分比。Z6测得0％内部体积分离，而Z5测得1.5％内部体积分离。

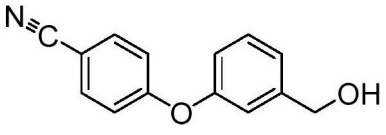
[0672] 使用其中甘油单酯百分比在40-55％的甘油单酯和甘油二酯(MDG)的软膏剂制剂的物理稳定性高于使用其中甘油单酯百分比是至少90％的甘油单酯和甘油二酯(MDG)的软膏剂制剂。

[0673] 实施例7

[0674] 降解物减少测试：

[0675] 已观察并监测稳定性批次中的杂质，包括杂质1，据信其为克瑞沙硼的稳定性质子去硼化产物。

[0676] 杂质1：

[0677] 

[0678] 使用核磁共振光谱(NMR)、质谱(MS)来表征杂质1且针对标准品确认高效液相(HPLC)的保留时间。基于NMR数据的杂质1的H和C位置指定列示于表2中。

[0679] 表2：杂质1的^{1}H NMR及^{13}C NMR指定

[0680]

位置[a]	$\delta^{1}H$ (ppm)	多重性 J_{HH} (Hz)	$\delta^{13}C$ (ppm)
1	—	—	105.02
2	7.84	d,	134.63
3	7.08	m	118.04
4	—	—	161.16
5	7.08	m	118.04

[0681]

6	7.84	d,	134.63
7	7.00	dd, 7.9, 2.4	118.37
8	7.41	明显t，7.8	130.08
9	7.21	d,	122.96
10	—	—	145.57
11	7.08	m	117.79
12	—	—	154.44
13	4.52	d,	69.26
14	5.28	t, 5.8	—
15	—	—	118.73

[0682] d,双重峰;dd,双组双重峰;m,多重峰;t,三重峰。

[0683] a,通过扩展NMR(gCOSY、NOESY 1D、gHSQC和gHMBC)来确认位置指定。

[0684] 基于稳定性数据,FDA对于杂质1的建议的接受标准是不多于2.0％克瑞沙硼标记强度。观察到杂质1水平随时间增加,对于主要和支持稳定性批次(primary and supporting stability lots)在长期(25℃,60％相对湿度)和加速(40℃,75％相对湿度)储存条件下分别高达1.2％标记强度和1.4％标记强度。

[0685] 因此,最小化克瑞沙硼的降解量是制剂的目标。

[0686] 具有不同类型和量的稳定剂的药物制剂(Z、Z6、Z7、Z8、Z9和Z10)对于其减少杂质1的量的能力进行测试。

[0687] 本文描述Z和Z6的组成。2％软膏剂制剂Z7、Z8、Z9和Z10具有以下组分且是根据本文所述方法生产:

[0688]

组分	Z7％w/w	Z8％w/w	Z9％w/w	Z10％w/w
克瑞沙硼	2.000	2.000	2.000	2.000
丙二醇	9.000	9.000	9.000	9.000
丁基化羟基甲苯	0.100	0.100	0.100	0.100
甘油单酯和甘油二酯	7.000	7.000	7.000	7.000
石蜡	5.000	5.000	5.000	5.000
白矿脂	76.8976	76.9810	76.855	76.900
依地酸钙二钠	0.0024	0.0090	0.0450	0.0000

[0689] 总而言之,这些制剂含有以下类型和量的稳定剂。

[0690] Z6:稳定剂:硼酸;水 量:0.1％w/w;0.09％w/w

[0691] Z7:稳定剂:依地酸钙二钠 量:0.0024％w/w

[0692] Z8:稳定剂:依地酸钙二钠 量:0.0090％w/w

[0693] Z9:稳定剂:依地酸钙二钠 量:0.0450％w/w

[0694] Z10:稳定剂:无

[0695] Z:稳定剂:依地酸钙二钠 量:0.0035％w/w

[0696] 分析杂质1的分析方法:

[0697] 使用反相HPLC方法使用BDS Hypersil C18柱(150×4.6mm,5微米)和1.0mL/min流速,10μL注射体积,在254nm下使用UV检测来分析含克瑞沙硼的软膏剂。流动相(梯度)描述于以下:

[0698] 流动相A:0.1％磷酸溶液/乙腈95％/5％(v/v)

[0699] 流动相B:0.1%磷酸溶液/乙腈5%/95%(v/v)

[0700] 对局部药物制剂进行化学稳定性测试,具有下表5中的结果:

[0701] 表5:在各种条件下稳定剂对软膏剂中杂质1形成的效果

[0702] 杂质1(%)

[0703] 时间

[0704]

(月)	Z6	Z7	Z8	Z9	Z10
0	0.07	0.12			ND
40℃/75% RH					
1	0.31	0.16	0.18	0.27	0.35
3	0.88	0.53	0.64	0.88	1.13
6	1.73	1.07	1.25	1.63	2.08

[0705] 25℃/60%RH

[0706]

1	0.07	0.03	0.04	0.06	0.08
3	0.14	0.09	0.10	0.15	0.17
6	0.25	0.18	0.20	0.29	0.30

[0707] ND,未检测;RH,相对湿度。

[0708] 表5表明在这些所列举制剂中,不具有稳定剂的制剂Z10展现最高杂质1水平。在24ppm EDTA(Z7)和90ppm EDTA(Z8)水平下观察到最大稳定效果。

[0709] 另外对Z6、Z7和Z进行稳定性测试并呈现于表6中:

[0710] 表6:在各种条件下稳定剂对软膏剂中杂质1形成的效果

[0711] 杂质1(%)

[0712] 时间

[0713]

(月)	Z6	Z7	Z
0	0.12	0.12	ND
40℃/75% RH			
1	0.69	0.49	0.21
3	1.6	1.0	0.62
6	2.5	1.6	1.2
25℃/60% RH			
1	0.22	0.19	0.07
3	0.46	0.35	0.12
6	0.66	0.54	0.25
9	0.82	0.74	0.29
12	1.1	0.89	0.37
18	1.7	1.2	0.54
24	2.0	1.6	0.73

[0714] ND,未检测;RH,相对湿度。

[0715] 这些测试表明使用药物制剂Z可出现比制剂Z6和Z7更低量的杂质1。

[0716] 实施例8

[0717] 在轻度至中度特应性皮炎(AD)的治疗中Z和Y的安全性和效力

[0718] 试验的目的是测定在儿童、青少年和成人(2岁及以上)的轻度至中度特应性皮炎(AD)治疗中,每天施用两次(BID)的Z相比于Y的安全性及效力。Z的组成是:

[0719]

组分	Z%w/w
克瑞沙硼	2.000

丙二醇	9.000
丁基化羟基甲苯	0.100
甘油单酯和甘油二酯	7.000
石蜡	5.000
白矿脂	76.8965
依地酸钙二钠	0.0035

[0720] Y的组成是：

[0721]

组分	Y％w/w
丙二醇	9.000
丁基化羟基甲苯	0.100
甘油单酯和甘油二酯	7.000
石蜡	5.000
白矿脂	78.8965
依地酸钙二钠	0.0035

[0722] 在美国实施两个多中心双盲赋形剂对照研究，每一研究入组超过750名患者。入组的患者为2岁及以上，患有轻度至中度特应性皮炎，患处>5％体表面积。患者以2:1(Z:Y)随机化且每天治疗两次持续28天。

[0723] 主要效力终点是定义为在第29天根据研究者静态总体评价(Investigator's Static Global Assessment,ISGA)实现“完全(Clear)”(0)或“几乎完全”(1)状态且从基线改善2级或更多级。

[0724] 次要效力终点是定义为在第29天根据研究者静态总体评价(ISGA)实现“完全”(0)或“几乎完全”(1)状态，不考虑从基线的改善。

[0725] 在一个试验中，503名患者接收Z而256名接收Y。那些接收Z的平均年龄是12岁，且在2岁至65岁范围内。那些接收Y的平均年龄是12.4岁，且在2岁至63岁范围内。39.0％的那些接收Z的具有“轻度”(2)的基线ISGA，而61.0％的那些接收Z的具有“中度”(3)的基线ISGA。36.3％的那些接收Y的具有“轻度”(2)的基线ISGA，而63.7％的那些接收Y的具有“中度”(3)的基线ISGA。那些接收Z的患有特应性皮炎的体表面积的平均值％是18.8％，且是5％至95％。那些接收Y的患有特应性皮炎的体表面积的平均值％是18.6％，且是5％至90％。

[0726] 从此试验，32.8％的那些接收Z的实现主要终点，而25.4％的那些接收Y的实现主要终点。51.7％的那些接收Z的实现次要终点，而40.6％的那些接收Y的实现次要终点。

[0727] 在另一试验中，513名患者接收Z而250名接收Y。那些接收Z的平均年龄是12.6岁，且在2岁至79岁范围内。那些接收Y的平均年龄是11.8岁，且在2岁至79岁范围内。38.4％的那些接收Z的具有“轻度”(2)的基线ISGA，而61.6％的那些接收Z的具有“中度”(3)的基线ISGA。40.0％的那些接收Y的具有“中度”(2)的基线ISGA，而60.0％的那些接收Y的具有“中度”(3)的基线ISGA。那些接收Z的患有特应性皮炎的体表面积的平均值％是17.9％，且是5％至95％。那些接收Y的患有特应性皮炎的体表面积的平均值％是17.7％，且是5％至90％。

[0728] 从此试验，31.4％的那些接收Z的实现主要终点，而18.0％的那些接收Y的实现主要终点。48.5％的那些接收Z的实现次要终点，而29.7％的那些接收Y的实现次要终点。

[0729] 应理解，本文所述实施例和实施方案仅用于说明性目的，且本领域技术人员会提出根据其的各种修改或改变且各种修改或改变应包括在本申请的精神和范围和所附权利要求的范围内。出于所有目的，本文所引用的所有出版物、专利和专利申请的全部内容援引加入本文。

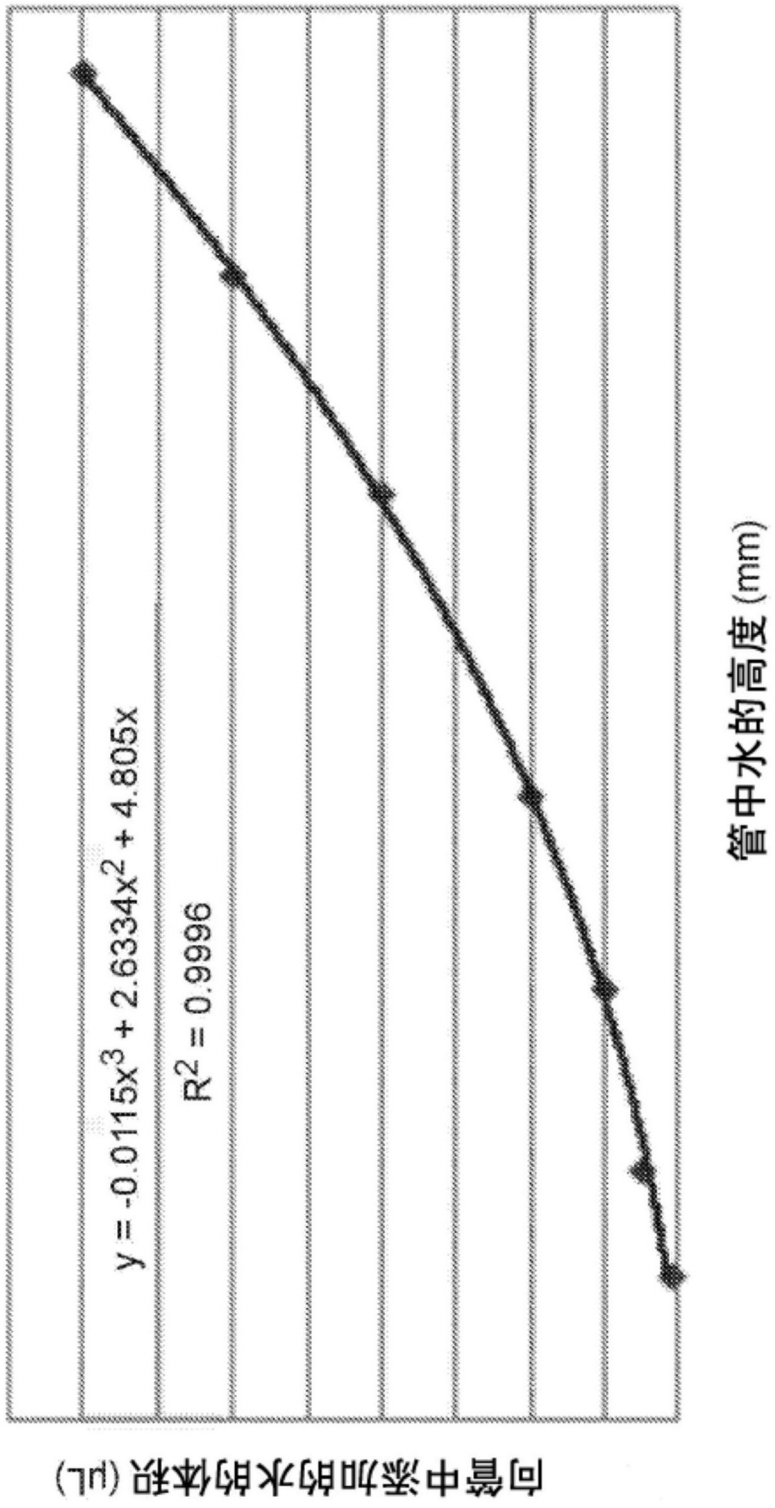


图1

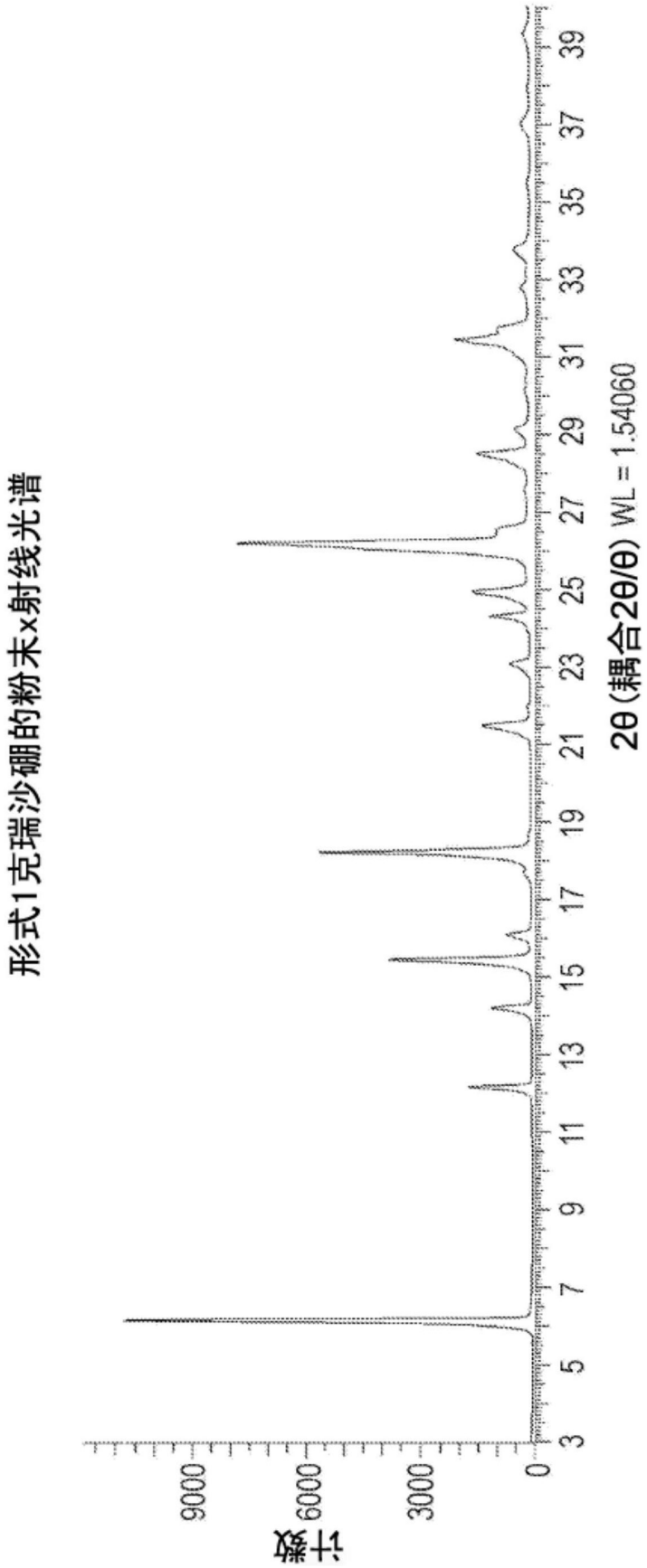

形式1克瑞沙硼的粉末x射线光谱
计数
9000
6000
3000
0
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2θ(耦合2θ/θ) WL = 1.54060

图2

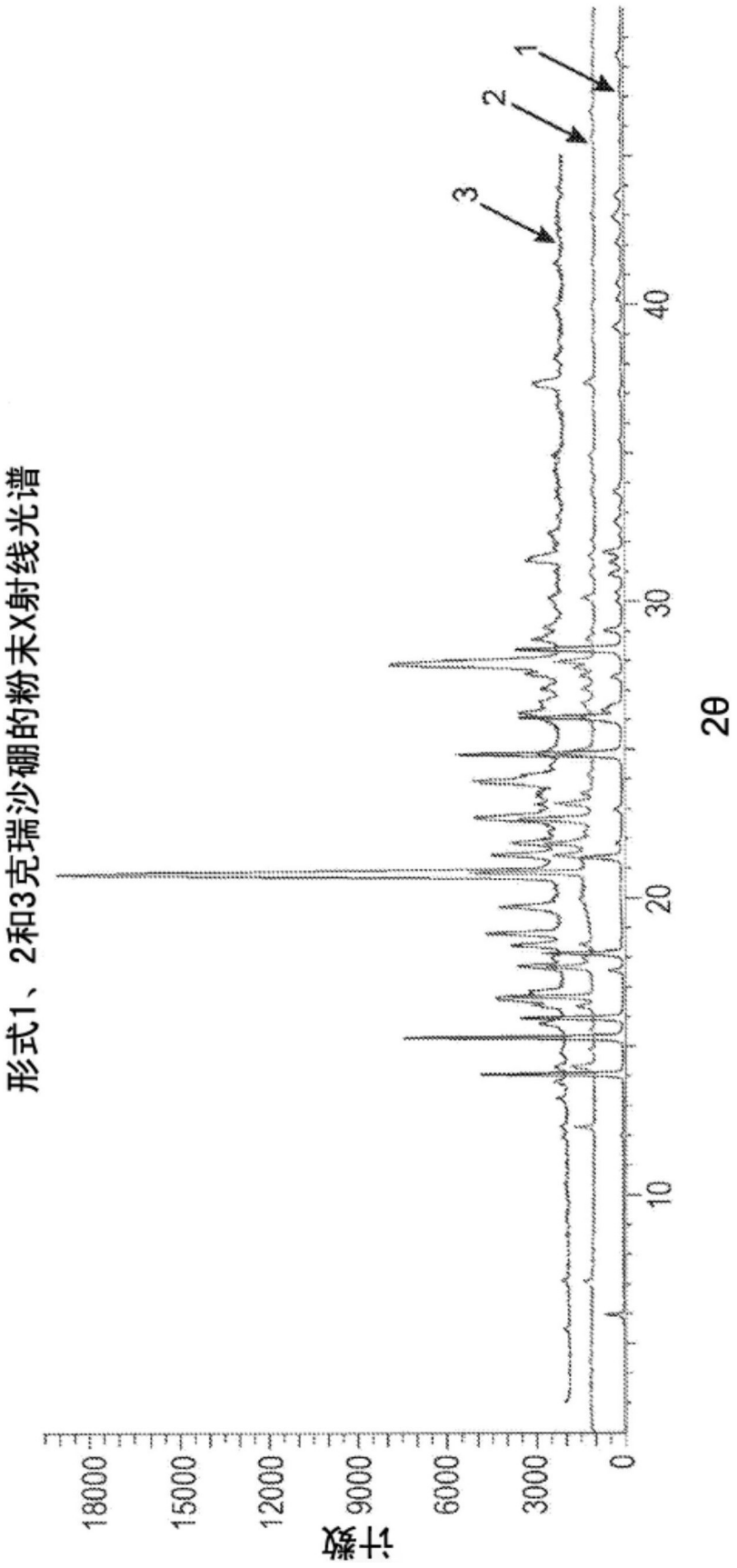

形式1、2和3克瑞沙硼的粉末X射线光谱
计数
18000
15000
12000
9000
6000
3000
0
10
20
30
40
2θ
1
2
3

图3

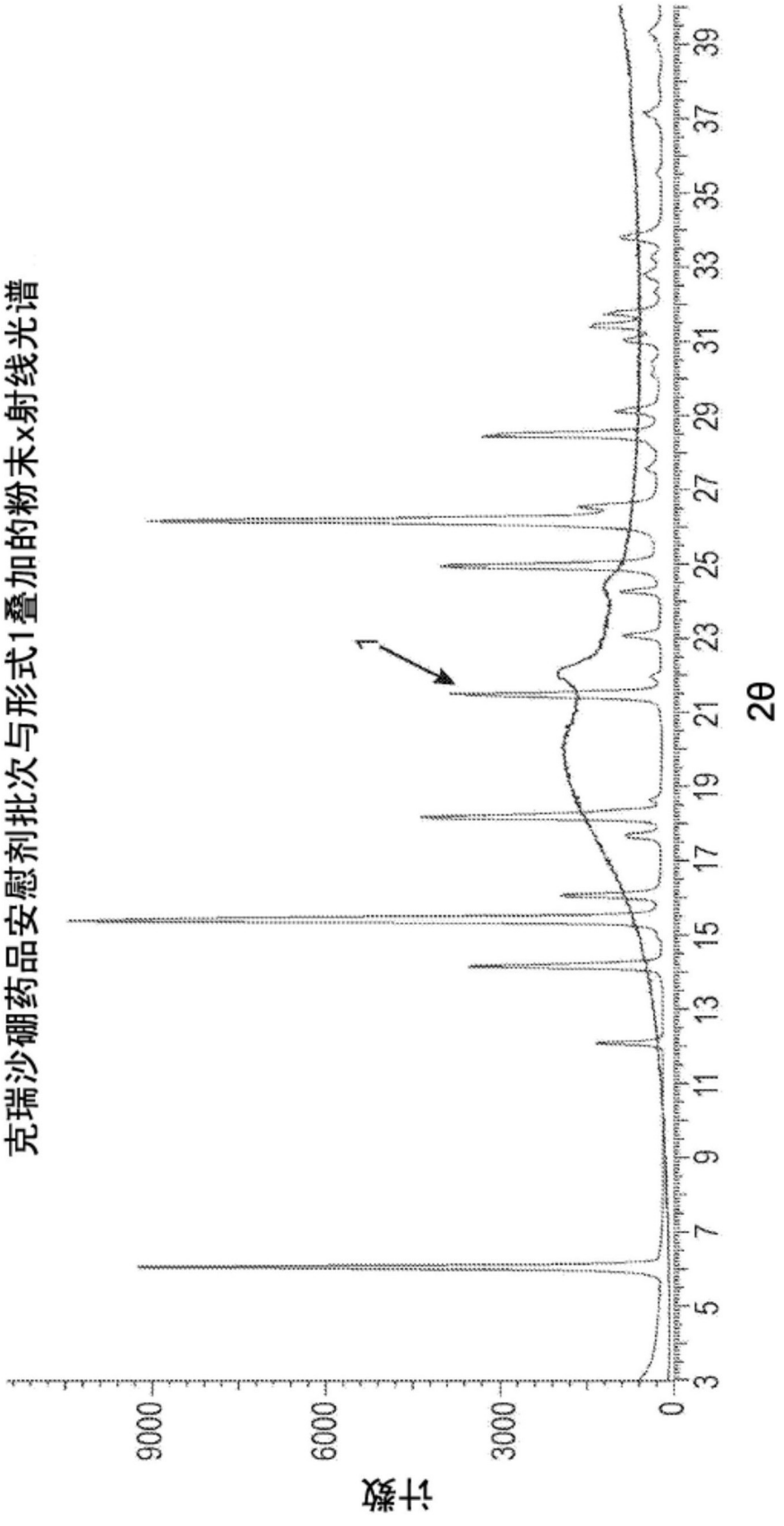

克瑞沙硼药品安慰剂批次与形式1叠加的粉末x射线光谱
计数
9000
6000
3000
0
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
2θ
1

图4