(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2017 (05.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/004319 A1

(51) International Patent Classification:
A61K 31/192 (2006.01) *A61K 31/235* (2006.01)

(21) International Application Number:
PCT/US2016/040287

(22) International Filing Date:
30 June 2016 (30.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/187,743 1 July 2015 (01.07.2015) US

(71) Applicant: **TWI BIOTECHNOLOGY, INC.**; 8F, No.41, Lane 221, Kang Chien Rd., Nei Hu Dist., Taipei, 114 (TW).

(72) Inventor; and
(71) Applicant *(for US only)*: **BROWN, III, Carl, Oscar** [US/US]; 13034 Alora Point, San Diego, CA 92130 (US).

(72) Inventors: **CHEN, Chih-Kuang**; 8F, No.41, Lane 221, Kang Chien Rd., Nei Hu Dist., Taipei, 114 (TW). **LEE, Jing-Yi**; 8F, No.41, Lane 221, Kang Chien Rd., Nei Hu Dist., Taipei, 114 (TW). **LU, Wei-Shu**; 8F, No.41, Lane 221, Kang Chien Rd., Nei Hu Dist., Taipei, 114 (TW).

(74) Agents: **KATZ, Martin, L.** et al.; Wood, Phillips, Katz, Clark & Mortimer, 500 West Madison Street, Suite 1130, Chicago, IL 60661 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: DIACEREIN OR RHEIN TOPICAL FORMULATIONS AND USES THEREOF

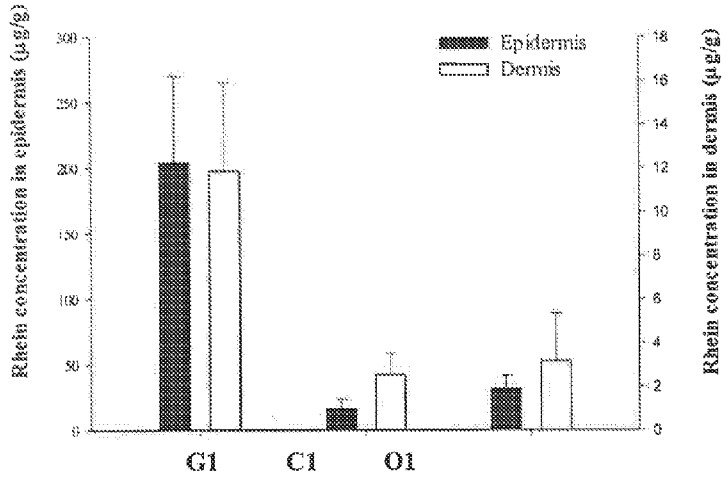


FIG. 1

(57) **Abstract**: A topical pharmaceutical composition containing diacerein and/or its analogs is provided. Also provided is a method for treating various diseases using this topical pharmaceutical composition.

WO 2017/004319 A1

DIACEREIN OR RHEIN TOPICAL FORMULATIONS AND USES THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Serial No. 62/187,743, filed July 1, 2015, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

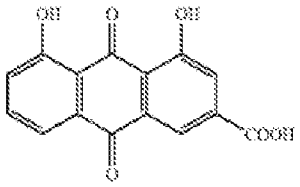
Field of the Invention

[0002] The present invention relates to a topical pharmaceutical composition containing diacerein and/or its analogs, and also relates to uses of this topical pharmaceutical composition in treatment of various diseases or conditions.

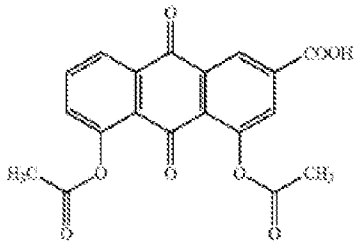
Descriptions of the Related Art

[0003] Chemically, rhein is 9, 10-dihydro-4, 5-dihydroxy-9, 10-dioxo-2-anthracene carboxylic acid having a structure of Formula (I), and one of its prodrugs, diacerein, is 4, 5-bis (acetyloxy) 9, 10-dihydro-4, 5-dihydroxy-9, 10-dioxo-2-anthracenecarboxylic acid having a structure of Formula (II). Diacerein is entirely converted into rhein before reaching the systemic circulation, and exerts its physiological function in form of rhein within the body.

Formula (I)



Formula (II)



[0004] Diacerein is an anti-inflammatory agent widely used in the treatment of osteoarthritis, which has been demonstrated to inhibit interleukin-1 (IL-1) signaling. Presently, diacerein capsules are available in 50 mg strength and are marketed under various trade names in different countries, including Art 50®, Artrodar®, etc. As disclosed in US Patent Nos. 8,536,152 and 8,865,689, diacerein can be used as an adjunctive treatment for type II diabetes mellitus, and was also found to be effective in reducing blood uric acid levels and can accordingly be used for treating hyperuricemia or a metabolic disorder associated with hyperuricemia. In addition, it has been reported that diacerein has a potential effect in the treatment of epidermolysis bullosa (Wally et al., Orphanet Journal of Rare Diseases, 2013, vol. 8, issue 69).

[0005] Although diacerein can be administered by the oral route, it cannot be completely absorbed by the digestive tract, and the oral bioavailability of diacerein has been estimated to be approximately 40% to 60%. The incomplete absorption of diacerein may result in

undesirable side effects such as diarrhea or soft stools. In vitro and in vivo studies have showed that non-absorbed diacerein is metabolized to rhein in the colon, which then induces a laxative effect.

[0006] Since such side effects may occur due to oral administration, non-oral diacerein compositions have been proposed to overcome these problems.

[0007] PCT International Application No. WO 2009/133430 discloses topical compositions containing diacerein or rhein, which can be in various forms, such as a lotion, cream, ointment, paste, gel, etc. However, these compositions are not intended for any specific disease, and thus one cannot know which form would be most suitable for a certain kind of disease to be treated from the context of this article.

[0008] Wally et al. disclosed a cream diacerein formulation for epidermolysis bullosa (Wally et al., Orphanet Journal of Rare Diseases, 2013, vol. 8, issue 69). However, it is unclear whether or how the properties of the formulation affect the treatment efficacy on epidermolysis bullosa from this article.

[0009] It appears that precise properties of diacerein formulations are very important for its treatment efficacy for different diseases.

[00010] Considering that the literature provides little information about the relationship between physicochemical properties of a diacerein/rhein topical formulation and its treatment effect, the present invention provides topical formulations adapted to different diseases accordingly.

SUMMARY OF THE INVENTION

[00011] This invention provides a topical composition comprising a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is in the form of ointment, cream, or gel, and at least about 90% by volume of the compound has a particle size of about 0.5 to 35 μm.

[00012] This invention also provides a topical composition comprising a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is in the form of gel, and at least about 90% by volume of the compound has a particle size of less than about 1 μm.

[00013] This invention also provides a method of treating inflammatory and/or hyperproliferative and pruritic skin diseases, and diseases with epithelial barrier dysfunction including aged skin and epidermolysis bullosa, comprising administering to a subject in need thereof an effective amount of the composition of the present invention.

[00014] This invention also provides a method of treating hyperuricemia, a metabolic disorder associated with hyperuricemia, osteoarthritis or type 2 diabetes mellitus, comprising administering to a subject in need thereof an effective amount of the composition of the present invention.

[00015] In some embodiments, the treatment methods of the invention specifically exclude administration of any other active agents to treat the diseases treatable by the compositions of

the present invention. In some embodiments, however, the methods allow for administration of other active agents.

[00016] Preferably, the treatment methods of the invention result in effective treatment of the relevant disease in at least one treated subject, and preferably, in the substantial number of the treated subjects, and more preferably, in the majority of the treated subjects.

[00017] The detailed technology and preferred embodiments implemented for the subject invention are described in the following paragraphs accompanying the appended drawings for people skilled in this field to well appreciate the features of the claimed invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[00018] **FIG. 1** is a statistical bar graph showing rhein concentrations in dermis and epidermis post 8 hours treatment with three tested diacerein formulations (G1, C1 and O1, n=4);

[00019] **FIGs. 2A and 2B** is a plot of cumulative rhein penetration (ng/cm^2) from the skin tissue into the receiver solution vs time for three tested diacerein formulations (G1, C1, and O1, n=4);

[00020] **FIG. 3** is a statistical bar graph showing rhein concentrations in dermis and epidermis 8 hours post treatment with two tested diacerein ointment formulations (O2 and O3, n=3);

[00021] **FIG. 4** is a plot of cumulative rhein penetration (ng/cm^2) from the skin tissue into the receiver solution vs time for two tested diacerein ointment formulations (O2 and O3, n=3),

[00022] **FIG. 5** is a statistical bar graph showing rhein concentrations in dermis and epidermis 8 hours post treatment with the tested diacerein ointment formulation (O3, n=3) or a comparative formulation (n=3); and

[00023] **FIG. 6** is a plot of cumulative rhein penetration (ng/cm^2) from the skin tissue into the receiver solution vs time for the tested diacerein ointment formulation (O3, n=3) and the comparative formulation (n=3).

DETAILED DESCRIPTION OF THE INVENTION

[00024] The term "therapeutically effective amount," as used herein, refers to an amount that alleviates or reduces one or more symptoms of a disease.

[00025] The term "diacerein or its analogs," as used herein, refers to diacerein, rhein, monoacetylrhein, or a pharmaceutically acceptable salt or ester or a prodrug thereof.

[00026] Unless otherwise stated herein, the terms "a (an)", "the" or the like used in this specification (especially in the Claims hereinafter) shall be understood to encompass both the singular form and the plural form.

[00027] As stated above, topical administration of diacerein may prevent undesired side effects of oral administration since it bypasses the gastrointestinal route which has tolerability limitations, and reduces the amount of diacerein entering into systemic circulation, as compared to oral administration. Besides, when diacerein is used to treat skin diseases, it is advantageous that diacerein may penetrate through the stratum corneum easily to reach the target site (e.g., dermis or epidermis, where skin disorders may occur). Meanwhile, it is also desired that diacerein is retained in the skin as long as possible to exert its function

sufficiently. Therefore, a delicate balance needs to be achieved so as to, on the one hand, allow diacerein or rhein to penetrate into the target site quickly, but on the other hand, retain it in the target site for extended exposure.

[00028] The inventors of the present invention discovered that the form of a topical diacerein/rhein composition and/or the particle size of an active component contained therein play key roles in penetrability (or diffusivity) and the retention rate in the skin.

[00029] The present invention thus provides a topical diacerein/rhein pharmaceutical composition that is suitable for skin diseases and meets the above requirement. The topical pharmaceutical composition comprises a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is in the form of ointment, cream, or gel, and at least about 90% by volume of the compound has a particle size of about 0.5 to 35 μm.

[00030] The particle size distribution in the context of this application is based on volume D values (i.e., Dv values, such as Dv10, Dv50 and Dv90), which are commonly used to represent a range of the particle sizes of a given sample.

[00031] Preferably, the composition is provided as an ointment or cream, and more preferably as an ointment. It was unexpectedly found that an ointment or cream formulation provides higher retention rate and longer retention time in the skin as compared to a gel formulation.

[00032] In one embodiment, at least about 90% by volume of the compound in the composition has a particle size of about 1 to about 15 μm, preferably about 2 to about 5 μm. Preferably, the composition containing the compound with this particle size is in form of an ointment or cream, and when it is administered to the skin of a subject, greater than 90% of the compound (by number), preferably substantially all of the compound is retained in the skin for at least about 2 hours, more preferably about 4 hours, even more preferably about 6 hours, and most preferably about 8 hours after the administration. The retention rate and time of the compound in the skin can be measured through, for example, a diffusion cell study. In this study, a diffusion cell setup consisting essentially of a piece of skin clamped between two clamps is mounted, and a formulation containing the compound is applied on one side of the skin (top) and compound concentration is measured at certain time-intervals in a receiver portion (bottom) of the setup (which can be a container filled with buffer that is in contact with the skin).

[00033] Besides, when it is administered to the skin of a subject, the concentration of the compound can be, for example, about 8 to about 20 μg in per gram epidermis tissue, and/or about 1 to about 3 μg in per gram dermis tissue, after 8 hours from the administration.

[00034] In another embodiment, at least about 90% by volume of the compound in the composition has a particle size of about 10 to about 30 μm, preferably about 12 to about 25 μm. Preferably, the composition containing the compound with this particle size is in form of an ointment or cream, more preferably an ointment, and when it is administered to the skin of a subject, greater than 90% of the compound (by number), preferably substantially all of

the compound is retained in the skin for at least preferably about 4 hours, more preferably about 6 hours, and most preferably about 8 hours after the administration.

[00035] Besides, when it is administered to the skin of a subject, the concentration of the compound can be, for example, about 3 to about 6 μg in per gram epidermis tissue, and/or about 0.2 to about 2 μg in per gram dermis tissue, after 8 hours from the administration.

[00036] The topical pharmaceutical composition having the above properties provides good balance between penetration and retention, and thus is useful in treatment of skin diseases, such as inflammatory and/or hyperpoliferative and pruritic skin diseases selected from atopic dermatitis, psoriasis, pustular psoriasis, rosacea, keloids, hypertrophic scars, acne, Netherton's syndrome or other pruritic dermatoses including prurigo nodularis, unspecified itch of the elderly, and diseases with epithelial barrier dysfunction including aged skin, and epidermolysis bullosa. Preferably, it is useful in treatment of epidermolysis bullosa.

[00037] The present invention also relates to a method of treating inflammatory and/or hyperpoliferative and pruritic skin diseases, and diseases with epithelial barrier dysfunction including aged skin and epidermolysis bullosa, comprising administering to a subject in need thereof an effective amount of the composition of the present invention.

[00038] The present invention further provides a topical diacerein/rhein pharmaceutical composition useful in treatment of hyperuricemia, a disorder associated with hyperuricemia (e.g., acute gout, chronic gout, gout flares, uric acid nephrolithiasis, gouty nephropathy, etc.), osteoarthritis and type 2 diabetes mellitus. In difference with those compositions used for treatment of skin diseases, the composition herein allows the active compound to penetrate

easily into the skin and enter into the body relatively quicker, so as to reach systemic circulation and exert its function in the body. The topical composition comprises a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is in the form of gel, and at least about 90% by volume of the compound has a particle size of less than about 1 μm, and preferably greater than about 0.1 um.

[00039] Preferably, when the composition is administered to the skin of a subject, the compound is released from the skin into the body within about 6 hours, more preferably about 4 hours, and most preferably about 2 hours after the administration.

[00040] The present invention also provides a method of treating hyperuricemia, a disorder associated with hyperuricemia (e.g., acute gout, chronic gout, gout flares, uric acid nephrolithiasis, gouty nephropathy, etc.), osteoarthritis and type 2 diabetes mellitus, comprising administering to a subject in need thereof an effective amount of the composition of the present invention.

[00041] In some embodiments, the treatment methods of the invention specifically exclude administration of any other active agents to treat the diseases treatable by the compositions of the present invention. In some embodiments, however, the methods allow for administration of other active agents.

[00042] Preferably, the treatment methods of the invention result in effective treatment of the relevant disease in at least one treated subject, and preferably, in the substantial number of

the treated subjects, and more preferably, in the majority of the treated subjects.

[00043] The topical pharmaceutical composition of the present invention may comprise preferably about 0.1% to about 10% w/w, more preferably about 0.1% to 5%, and most preferably about 0.5% to about 2% w/w of the compound based on the total weight of the composition.

[00044] The pharmaceutically acceptable excipients in the composition may include antioxidants, gelling agents/hydrogel bases, pH adjusting agents/buffers, penetration enhancers, preservatives, chelating agents, humectants, surfactants, emulsifiers, thickeners, solvents, stabilizers, etc. Herein, excipients/ingredients in the present invention may have multiple functions, e.g., one excipient can be used as surfactant and/or stabilizer and/or emulsifier, etc.

[00045] Examples of antioxidants include, but not limited to, one or more of vitamin C, vitamin A and alpha-lipoic acid, ascorbyl palmitate, sodium pyrosulfite, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT), and the like.

[00046] Suitable gelling agents/hydrogel base may include, but not limited to, one or more of guar, xanthan, and carregeenan gums, anionic, nonionic, cationic and lipophilically modified guar gums, polyacrylic acids (e.g., carbomer), polymethacrylic acids, cellulose resins, polyethylene glycols, hydroxy alkyl celluloses, carboxy alkyl celluloses, polyalkylene amines, and the like.

[00047] Examples of pH adjusting agents/buffers include, but not limited to, one or more of sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate,

magnesium gluconate, aluminum hydroxide, aluminum hydroxide/sodium bicarbonate co precipitate, amino acids, aluminum glycinate, sodium citrate, sodium tartrate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate, tripotassium phosphate, sodium phosphate, sodium acetate, potassium metaphosphate, magnesium oxide, magnesium hydroxide, magnesium carbonate, magnesium silicate, calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, citric acid, and the like.

[00048] Examples of penetration enhancers includes, but not limited to, one or more of diethylene glycol monoethyl ether, dimethyl sulfoxide, propylene glycol, isopropyl myristate (IPM), cal- cipotriene, detergents, emollients, Ethoxy diglycol, Triacetin, Propylene Glycol, Benzyl Alcohol, Sodium Laureth Sulfate, Dimethyl Isosorbide, Isopropyl Myristate, Medium Chain Triglyceride Oil (MCT Oil), Menthol, Isopropyl Palmitate, Isopropyl Isostearate, Propylene Glycol Monostearate, Lecithin, Diisopropyl Adipate, Diethyl Sebacate, Oleic Acid, Ethyl Oleate, Urea, Glyceryl Oleate, Caprylic/Capric Triglyceride, Propylene Glycol Dicaprylate/Dicaprate, Laureth 4, Oleth-2, Oleth-20, Propylene Carbonate, Nonoxynol-9, 2-n-nonyl-l,3-dioxolane, C7 to C14-hydrocarbyl substituted 1,3-dioxolane, 1,3-dioxane, or acetal, and Nonoxynol-15, and the like.

[00049] Preservatives can be, for instance, one or more of sodium benzoate, butylated hydroxy toluene, butylated hydroxyanisole, ethylenediamine tetraacetic acid (EDTA), paraoxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenylethyl alcohol,

dehydroacetic acid, sorbic acid, benzalkonium chloride, benzethonium chloride, phenol, phenylmercuric nitrate, thimerosal, methyl-, ethyl-, and/or propyl-paraben.

[00050] Examples of suitable solvents include, but not limited to, one or more of alcohol, castor oil, diisopropyl adipate, ethoxylated alcohol, ethyl alcohol, fatty alcohol citrate, glycerin, 1,2,6-hexanetriol, hexylene glycol, isopropyl alcohol, isopropyl myristate, isopropyl palmitate, mineral oil, phosphoric acid, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 1450, polyethylene glycol 8000, polyethylene glycol 1000 monocetyl ether, polyethylene glycol monostearate, polyethylene glycol 400 monostearate, polyethylene glycols, polyoxyl 20 cetostearyl ether, polyoxypropylene 15-stearyl ether, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbates, propylene carbonate, propylene glycol, purified water, SD alcohol 40, triglycerides of saturated fatty acids, and the like.

[00051] Suitable stabilizers or surfactants can be, for example, one or more of ionic polysorbate surfactant, Tween 20, Tween 40, Tween 60, Tween 80, nonylphenol polyethylene glycol ethers, (alkylphenol-hydroxypolyoxyethylene), Poly(oxy-1,2-ethanediyl), alpha-(4-nonylphenol)- omega-hydroxy-, branched (i.e., Tergitol® NP-40 Surfactant), nonylphenol polyethylene glycol ether mixtures (i.e., Tergitol® NP-70 (70% AQ) Surfactant), phenoxypolyethoxyethanols and polymers thereof such as Triton®, Poloxamer®, Spans®, Tyloxapol®, different grades of Brij, sodium dodecyl sulfate, cetyl alcohol, stearic acid, polyoxyl stearate, and the like.

[00052] Examples of chelating agents include, but not limited to, antioxidants, citric acid, disodium edetate (EDTA), edetate calcium disodium, edetic acid, malic acid, maltol, pentetic acid, sodium edetate, trisodium edetate, and the like.

[00053] Examples of humectants include, but not limited to, glycerine, propylene glycol, sorbitol, polyethylene glycol, polysaccharides (such as fructose, glucose, maltose, etc.), corn syrup, polyols, urea and derivatives and natural honey. Preferred humectants are propylene glycol and glycerine.

[00054] Examples of thickeners include, but not limited to, stearic acid, cellulose polymer, a carbomer polymer, a carbomer derivative, a cellulose derivative, polyvinyl alcohol, poloxamers, polysaccharides, and the like.

[00055] Examples of oil base for cream include, but not limited to, vegetable oils (e.g., castor oil), white petrolatum, mineral oil, and the like.

[00056] Examples of ointment base include, but not limited to, petrolatum, fatty oil, lanolin, Vaseline, glycerine, paraffin, poloxamer, polyethylene glycol, stearic acid, bee wax, and the like. Examples of ointment base modifiers include, but not limited to, mineral oil, liquid paraffin, and the like.

[00057] In one embodiment, the topical pharmaceutical composition of the present invention is in form of a gel, and comprises about 0.1% to about 10% w/w of diacerein or its analogs, about 0.1% to about 5% w/w of a hydrogel base, about 2% to about 50% w/w of a humectant, and about 0.1% to about 2.5% w/w of a stabilizer/surfactant.

[00058] In one embodiment, the topical pharmaceutical composition of the present invention is in form of a cream, and comprises about 0.1% to about 10% w/w of diacerein or its analogs, about 0.5% to about 25% w/w of a surfactant, about 0.5 to about 25% w/w of an oil base, about 2% to about 50% w/w of a humectant, and water.

[00059] In one embodiment, the topical pharmaceutical composition of the present invention is in form of a cream, and comprises a part A and a part B; wherein the part A comprises about 0.1% to about 10% w/w of diacerein or its analogs, about 1.5% to about 40% w/w of a thickener, about 1% to about 40% of an oil base, and about 0.4% to about 10% w/w of a surfactant; and the part B comprises about 0.2% to about 5% w/w of a stabilizer, about 0.6% to about 15% w/w of a humectant, and water.

[00060] In one embodiment, the topical pharmaceutical composition of the present invention is in form of an ointment, and comprises 0.1% to about 10% w/w of diacerein or its analogs, about 15% to about 99% w/w of an ointment base, about 0% to about 60% w/w of a base modifier, and about 0% to about 10% w/w of a surfactant.

[00061] Preferably, the topical pharmaceutical composition of the present invention is a once or twice-daily composition. That is, it is suitable to allow once or twice daily administration in order to achieve a desired therapeutic effect.

[00062] The topical pharmaceutical compositions of the present invention have the following advantages. First, they can be administered directly to the sites affected by dermatological subdermal conditions, bypassing the gastrointestinal route and having greatly reduced systemic exposure. Second, they are easy to apply and thus are more convenient

for patients. Third, these topical formulations are also more preferred than oral ones for patients who suffer from dysphagia or are averse to the taste of the medicine. Fourth, they are easier to achieve sustained exposure to the targeted sites.

[00063] The present invention also relates to a method of treating inflammatory and/or hyperpoliferative and pruritic skin diseases, and diseases with epithelial barrier dysfunction including aged skin and epidermolysis bullosa, comprising administering to a subject in need thereof an effective amount of a topical pharmaceutical composition, wherein the composition comprises a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients; wherein when the composition is administered to the skin of the subject, greater than 90% (by number) of the compound is retained in the skin for at least about 2 hours, preferably at least about 4 hours, even more preferably about 6 hours, and most preferably about 8 hours after administration.

[00064] The present invention also relates to a method of treating inflammatory and/or hyperpoliferative and pruritic skin diseases, and diseases with epithelial barrier dysfunction including aged skin and epidermolysis bullosa, comprising administering to a subject in need thereof an effective amount of a topical pharmaceutical composition, wherein the composition comprises a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients; wherein when the composition is administered to the skin of the subject, the concentration of the compound can be, for

example, about 8 to about 20 μg in per gram epidermis tissue, and/or about 1 to about 3 μg in per gram dermis tissue, after 8 hours from administration.

[00065] The present invention also relates to a method of treating inflammatory and/or hyperpoliferative and pruritic skin diseases, and diseases with epithelial barrier dysfunction including aged skin and epidermolysis bullosa, comprising administering to a subject in need thereof an effective amount of a topical pharmaceutical composition, wherein the composition comprises a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients; wherein when the composition is administered to the skin of the subject, the concentration of the compound can be, for example, about 3 to about 6 μg in per gram epidermis tissue, and/or about 0.2 to about 2 μg per gram dermis tissue, after 8 hours from administration.

[00066] The present invention further relates to a method of treating hyperuricemia, a disorder associated with hyperuricemia, osteoarthritis and type 2 diabetes mellitus, comprising administering to a subject in need thereof an effective amount of a topical pharmaceutical composition, wherein the composition comprises a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients; wherein when the composition is administered to the skin of the subject, the compound is released from the skin into the body within about 6 hours, more preferably about 4 hours, and most preferably about 2 hours after administration.

[00067] Hereinafter, the present invention will be further illustrated with reference to the following examples. However, these examples are only provided for illustrative purposes, but not to limit the scope of the present invention.

[Preparation Example] Preparation of Diacerein Topical Compositions

[00068] Seven diacerein topical compositions (G1, C1, C2, and O1 to O4) with three different forms (gel, cream and ointment) were prepared according to following Tables 1 to 4. The particle size (Dv90) of the compound in each composition was measured by Mastersizer 2000 Ver. 5.60. Excipients/ingredients listed in the following tables may have multiple functions, e.g., one excipient is used as surfactant and/or stabilizer and/or emulsifier, etc.

Table 1.

Gel		
Formulation	Gx (Preferred Range)	G1
Ingredients (function)	% (w/w)	% (w/w)
Micronized Diacerein (active ingredient)	0.1 to 10	1.00
Carbomer (hydrogel base)	0.1 to 5	1.00
Methylparaben (preservative)	0.01 to 0.25	0.10
Propylparaben (preservative)		0.02
EDTA (chelating agent)	0.004 to 0.1	0.02
Glycerin (humectant)	2 to 50	10.00
Tween 80 (stabilizer/surfactant)	0.1 to 2.5	0.50
Citric acid monohydrate (pH adjusting agents/buffers)	0.025 to 0.7	0.13

Sodium citrate dihydrate (pH adjusting agents/buffers)		0.14
Total	100.00	100.00

Table 2.

Cream		
Formulation	Cx (Preferred Range)	C1
Ingredients (function)	% (w/w)	% (w/w)
Part A		
Micronized Diacerein (active ingredient)	0.1 to 10	1
Stearic acid (thickener)	1.5 to 40	7.5
Castor oil (oil base)	1 to 40	8
White petrolatum (oil base)		6
SPAN 60 (surfactant)	0.4 to 10	2
Part B		
Tween 60 (stabilizer)	0.2 to 5	1
EDTA (chelating agent)	0.004 to 0.1	0.02
Glycerin (humectant)	0.6 to 15	3
Methylparaben (preservative)	0.01 to 0.25	0.1
Propylparaben (preservative)		0.02
Citric acid monohydrate (pH adjusting agents/buffers)	0.025 to 0.7	0.13
Sodium citrate dihydrate (pH adjusting agents/buffers)		0.14
Purified water	q.s.	q.s. 100
Diacerein Particle Size (Dv90, before mixed with other excipients)	0.5 to 35 μm	2.66 μm

Table 3.

Cream		
Formulation	Cy (Preferred Range)	C2
Ingredients	% (w/w)	% (w/w)
Micronized Diacerein (active ingredient)	0.1 to 10	1
Stearic acid (surfactant)	0.5 to 25	9.75
cetyl alcohol (surfactant)		3.25
Polyoxyl 40 stearate (surfactant)		5
Minerol oil (oil base)	0.5 to 25	2.6
Ethylparaben (preservative)	0.1 to 2.5	0.5
Purified water	q.s.	67.7
Propylene Glycerol (humectant)	2 to 50	10.2
Total	100	100
Diacerein Particle Size (Dv90, before mixed with other excipients)	0.5 to 35 μm	2.66 μm

Table 4.

Ointment					
Formulation	Ox (Preferred Range)	O1	O2	O3	O4
Ingredients (function)	% (w/w)	% (w/w)	% (w/w)	% (w/w)	% (w/w)
Micronized Diacerein (active ingredient)	0 to 10	-	1.00	-	1.00
Diacerein (active ingredient)	0 to 10	1.00	-	1.00	-
White Petrolatum (ointment base)	15 to 99	74.00	82.00	82.00	84.5
Mineral oil (ointment base modifier)	0 to 60	25.00	16.00	16.00	12.00
Cetyl Alcohol (surfactant)	0 to 10	-	0.50	0.50	2.00
Ethylparaben (preservative)	0 to 2.5	-	0.50	0.50	0.50
Total	100.00	100.00	100.00	100.00	100.00
Diacerein Particle size (Dv90)	0.5 to 35 µm	N/A	Before mixing: 2.66 µm After mixing: 4.2 µm	Before mixing: 14.15 µm After mixing: 20 µm	N/A

[EXAMPLE 1] Diffusion Cell Study of Topical Diacerein Compositions

[00069] Procedure**:** Mice were sacrificed by cervical dislocation. The full-thickness flank skin was removed and placed on the diffusion cell in contact with receptor phase, which was PBS (pH 5.4) with 30% PEG 300 (at 37°C). Buffer was pumped through the receiver compartment at a flow rate of 3 to 4 mL/h. A dose of 20 µl of 1% diacerein gel (Formulation G1), 1% diacerein cream (Formulations C1 and C2), or 1% diacerein ointment (Formulations O1, O2 and O3) were added onto the skin surface in the donor compartment. Receiver solutions were collected at hours 0, 1, 2, 4, 6 and 8. At the end of 8 hours of treatment with

the formulations, skin was dismounted from the diffusion cell, and the skin surface was cleaned carefully with three alcohol swabs (without tape-stripping). Epidermis was separated from dermis using scalpel blade. Both the separated epidermis and dermis were weighed and minced, and extracted twice with 0.5 ml acetonitrile: acetic acid: water (60:0.1:40) by vigorous shaking for 1 hour. The skin extracts were then centrifuged at 14,500 rpm for 20 minutes. All procedures were performed under reduced light. Both skin extracts and receiver solutions were stored at -20°C until submitted for analyses of diacerein and rhein concentrations by HPLC (diacerein is easily converted into rhein during the experiment). Skin flux was calculated from the slope of the linear part of the cumulative penetration of rhein concentration versus time curve. The results are summarized as follows.

[The Influence of forms on Penetrability and Retention]

Penetrability

[00070] As shown in Fig. 1, the gel diacerein formulation (G1) penetrates the stratum corneum better than the cream and ointment formulations (C1 and O1). After 8 hours from administration, rhein concentration in per gram epidermis is 204.0 μg for G1, 16.1 μg for C1, and 31.2 μg for O1; and rhein concentration in per gram dermis is 11.9 μg for G1, 2.53 μg for C1, and 3.14 μg for O1.

Retention

[00071] As shown in Figs. 2A and 2B, rhein penetrated the skin tissue and was released into the receiver solution after 1 hour for the gel formulation (G1) and after 2 hours for the cream formulation (C1), but for the ointment formulation (O1), rhein did not penetrate the skin tissue and enter into the receiver solution until 4 hours, indicating that an ointment formulation has higher retention rate and longer retention time than gel and cream formulations.

[00072] The results indicate that diacerein/rhein would have a higher penetrability to the stratum corneum in a gel formulation as compared with a cream or ointment formulation, and would have a longer retention time in the skin target site in an ointment formulation as compared with a cream or gel formulation. The gel formulation has the shortest retention time in the skin target site among the three formulations.

[The Influence of particle size on Penetrability and Retention]

[00073] Fig. 3 shows that the ointment formulation having smaller particle size (O2) penetrated faster than that having larger particle size (O3). After 8 hours from administration, rhein concentration in per gram epidermis is 10.7 μg for O2, and 4.8 μg for O3; and rhein concentration in per gram dermis is 1.6 μg for O2, and 0.7 μg for O3.

[00074] Fig. 4 shows that the ointment formulation O2 released rhein after 4 hours, and the ointment formulation O3 did not release rhein until 8 hours or even longer. Ointment formulation O3 demonstrated similar compound concentration in skin layer, but has longer retention time compared to O2.

[EXAMPLE 2] Comparative Example

[00075] Wally et al. discloses a cream formulation containing 1% diacerein in a commonly used care cream ultraphil® (Wally et al., Orphanet Journal of Rare Diseases, 2013, vol. 8, issue 69). A comparison study was conducted between this cream formulation (the comparative formulation) and the ointment formulation O3 of the present invention. The results are shown in Figs. 5 and 6.

[00076] As shown in Fig. 5, the ointment formulation O3 penetrated the stratum corneum more than the comparative formulation and reveals higher retention in the skin layer. Furthermore, as shown in Fig. 6, rhein in the comparative formulation penetrated the skin tissue and was detectable in the receiver solution after 4 hours, but rhein in the O3 formulation did not penetrate the skin tissue into the receiver solution until 6 hours.

[00077] The results demonstrated that the O3 formulation has a higher penetrability to the stratum corneum, a higher retention rate, and longer retention duration than the comparative formulation, indicating a higher drug concentration maintained in the skin layer with the O3 formulation.

[00078] The above disclosure is related to the detailed technical contents and inventive features thereof. People skilled in this field may proceed with a variety of modifications and replacements based on the disclosures and suggestions of the invention as described without departing from the characteristics thereof. Nevertheless, although such modifications and replacements are not fully disclosed in the above descriptions, they have substantially been covered in the following claims as appended.

What is claimed is:

1. A topical pharmaceutical composition comprising a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is in the form of ointment, cream, or gel, and at least about 90% by volume of the compound has a particle size of about 0.5 to about 35 μm.

2. The composition of claim 1, which is in the form of ointment or cream.

3. The composition of claim 1, which is in the form of ointment.

4. The composition of claim 3, wherein at least about 90% by volume of the compound has a particle size of about 10 to about 30 μm.

5. The composition of claim 4, wherein at least about 90% by volume of the compound has a particle size of about 12 to about 25 μm.

6. The composition of claim 3, wherein when the composition is administered to the skin of a subject, greater than 90% (by number) of the compound is retained in the skin for at least about 4 hours after administration.

7. The composition of claim 6, wherein when the composition is administered to the skin of a subject, greater than 90% (by number) of the compound is retained in the skin for at least about 6 hours after administration.

8. The composition of claim 7, wherein when the composition is administered to the skin of a subject, greater than 90% (by number) of the compound is retained in the skin for at least about 8 hours after administration.

9. The composition of claim 1, for use in treatment of inflammatory and/or hyperpoliferative and pruritic skin diseases selected from atopic dermatitis, psoriasis, pustular psoriasis, rosacea, keloids, hypertrophic scars, acne, Netherton's syndrome or other pruritic dermatoses including prurigo nodularis, unspecified itch of the elderly, and diseases with epithelial barrier dysfunction including aged skin, and epidermolysis bullosa.

10. The composition of claim 9, for use in treatment of epidermolysis bullosa.

11. The composition of claim 1, wherein the compound is present in an amount between about 0.1% to about 10.0% w/w of the total composition.

12. The composition of claim 11, wherein the compound is present in an amount between about 0.1% to 5.0% w/w of the total composition.

13. The composition of claim 12, wherein the compound is present in an amount between about 0.5% to about 2.0% w/w of the total composition.

14. The composition of claim 1, which is a once or twice-daily composition.

15. A topical composition comprising a therapeutically effective amount of a compound selected from the group consisting of diacerein, rhein, monoacetylrhein, and salts or esters or prodrugs thereof, and one or more pharmaceutically acceptable excipients, wherein the composition is in the form of gel, and at least about 90% by volume of the compound has a particle size of less than about 1 μm.

16. The composition of claim 15, wherein when the composition is administered to the skin of a subject, the compound is released from the skin into the body within about 6 hours after administration.

17. The composition of claim 15, which for use in treatment of osteoarthritis, hyperuricemia, a disorder associated with hyperuricemia, and type 2 diabetes mellitus.

18. The composition of claim 15, which for use in treatment of osteoarthritis.

19. A method of treating inflammatory and/or hyperpoliferative and pruritic skin diseases, and diseases with epithelial barrier dysfunction, comprising administering to a subject in need thereof an effective amount of the composition of claim 3.

20. The method of claim 19, wherein the diseases with epithelial barrier dysfunction includes aged skin and epidermolysis bullosa.

21. A method of treating hyperuricemia, a disorder associated with hyperuricemia, osteoarthritis and type 2 diabetes mellitus, comprising administering to a subject in need thereof an effective amount of the composition of claim 15.

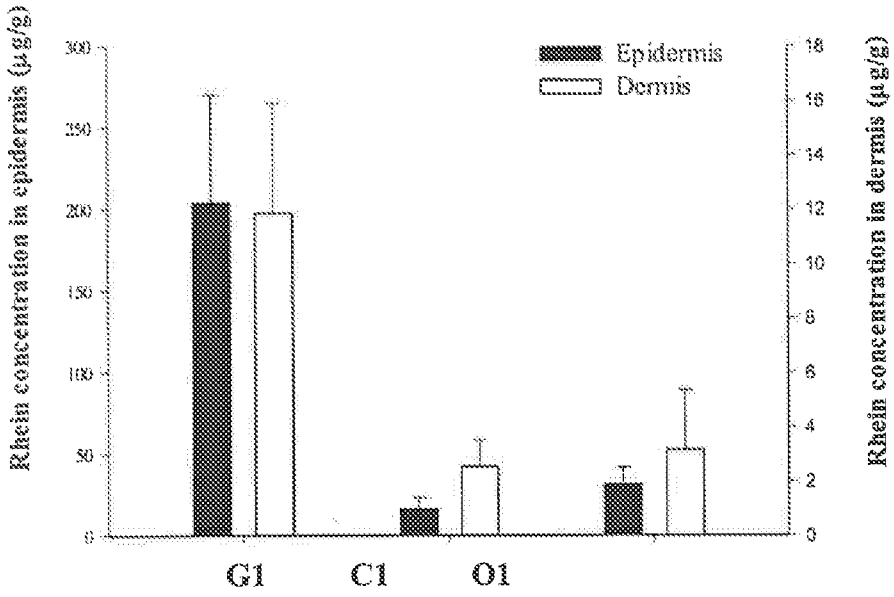

Rhein concentration in epidermis (μg/g)
Rhein concentration in dermis (μg/g)
Epidermis
Dermis
300
250
200
150
100
50
0
18
16
14
12
10
8
6
4
2
0
G1
C1
O1

FIG. 1

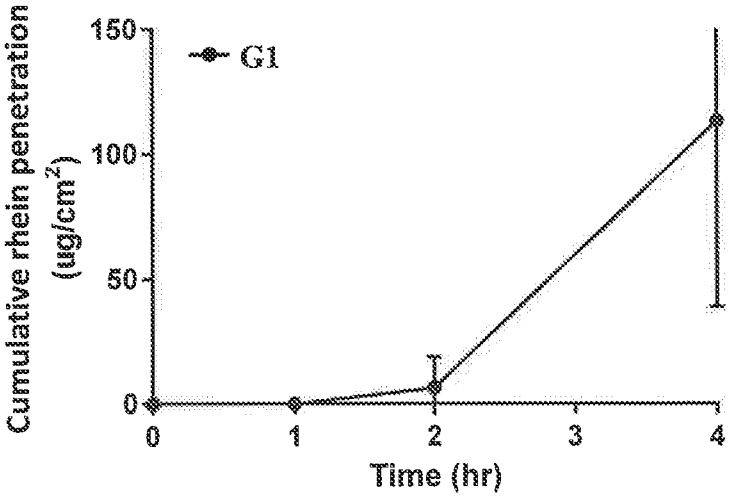

Cumulative rhein penetration
(ug/cm2)
150
100
50
0
G1
0
1
2
3
4
Time (hr)

FIG. 2A

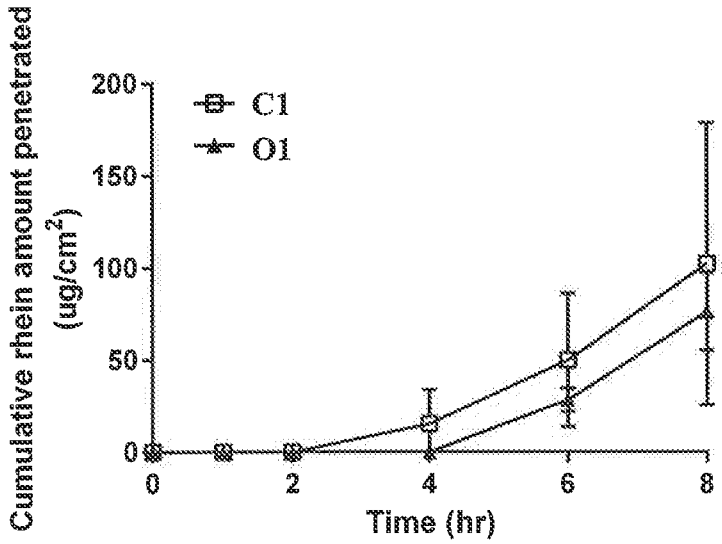

Cumulative rhein amount penetrated
(ug/cm2)
200
150
100
50
0
C1
O1
0
2
4
6
8
Time (hr)

FIG. 2B

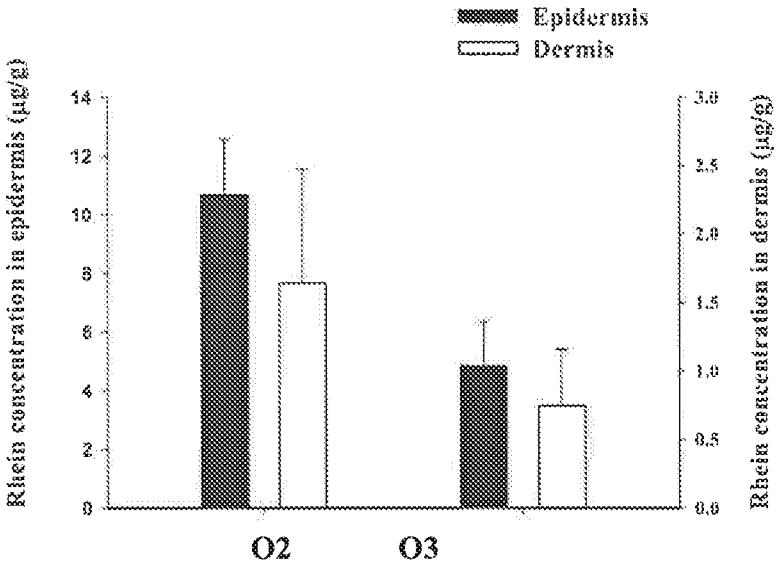

Epidermis
Dermis
Rhein concentration in epidermis (μg/g)
Rhein concentration in dermis (μg/g)
14
12
10
8
6
4
2
0
3.0
2.5
2.0
1.5
1.0
0.5
0.0
O2
O3

FIG. 3

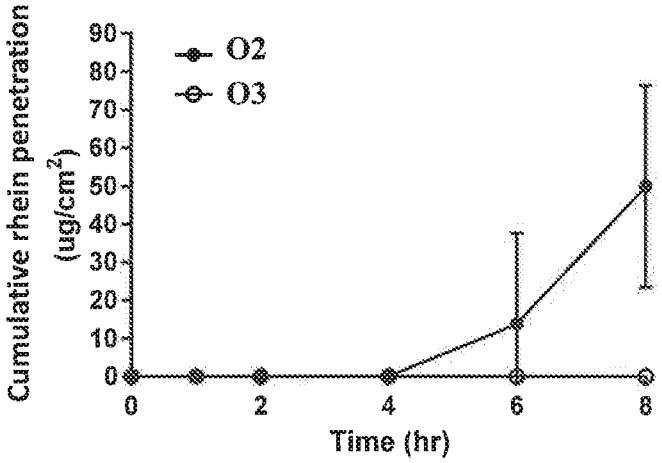

Cumulative rhein penetration
(ug/cm2)
O2
O3
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
Time (hr)

FIG. 4

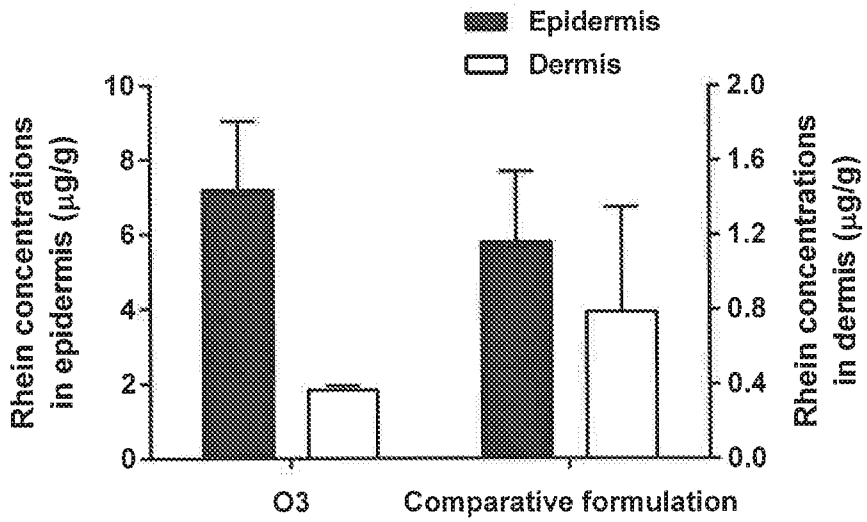

Epidermis
Dermis
Rhein concentrations in epidermis (μg/g)
Rhein concentrations in dermis (μg/g)
10
8
6
4
2
0
2.0
1.6
1.2
0.8
0.4
0.0
O3
Comparative formulation

FIG. 5

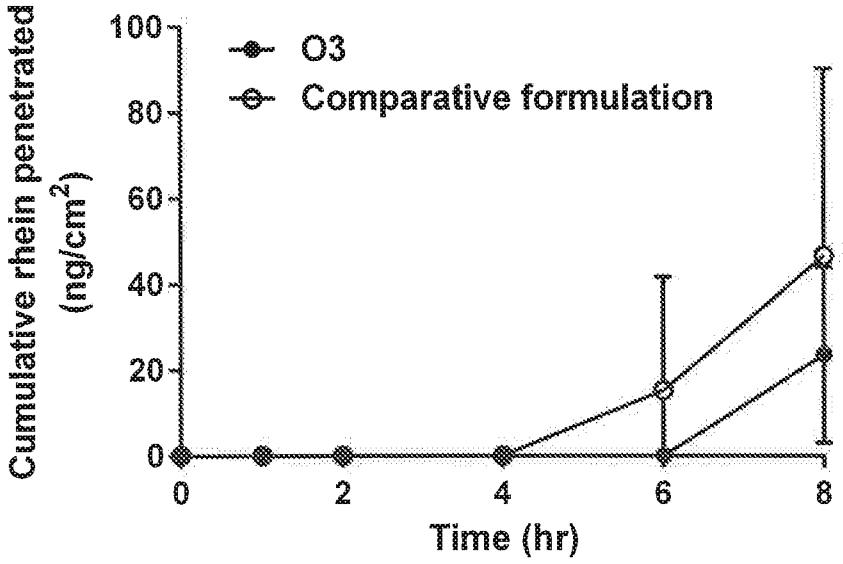

Cumulative rhein penetrated (ng/cm²)
100
80
60
40
20
0
O3
Comparative formulation
0
2
4
6
8
Time (hr)

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/40287

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/192, 31/235 (2016.01)
CPC - A61K 31/192, 9/06
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)
IPC(8): A61K 31/192, 31/235 (2016.01)
CPC: A61K 31/192, 9/06

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); EBSCO; PubMed; Google/Google Scholar; topical, diacerein, rhein, monoacetylrhein, ointment, gel, particle, size, skin, retain, epidermolysis, bullosa, osteoarthritis, diabetes

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/133430 A1 (WOCKHARDT RESEARCH CENTRE) 05 November 2009; abstract; paragraphs [14], [18]-[20], [41]-[42]	1-21
Y	US 2010/0285114 A1 (DABRE, R et al.) 11 November 2010; paragraphs [0029], [0040], [0094], [0107], [0111]	1-21
Y	WO 2006/029189 A2 (MORGAN, C) 16 March 2006; abstract; page 6, lines 14-19	6-8
Y	US 2013/0156857 A1 (TWI BIOTECHNOLOGY, INC.) 20 June 2013; paragraphs [0006], [0037]-[0038]	9-10, 19-21
A	US 2009/0093509 A1 (NAZIR, T et al.) 09 April 2009; paragraphs [0010], [0017]	6-8

☐ Further documents are listed in the continuation of Box C. ☐ 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
31 August 2016 (31.08.2016)	14 SEP 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 107921013 A
(43)申请公布日 2018.04.17

(21)申请号 201680050004.8

(22)申请日 2016.06.30

(30)优先权数据
62/187,743 2015.07.01 US

(85)PCT国际申请进入国家阶段日
2018.02.27

(86)PCT国际申请的申请数据
PCT/US2016/040287 2016.06.30

(87)PCT国际申请的公布数据
WO2017/004319 EN 2017.01.05

(71)申请人 安成生物科技股份有限公司
地址 中国台湾台北市

(72)发明人 卡尔·奥斯卡·布朗三世 陈志光
李静宜 卢威书

(74)专利代理机构 北京品源专利代理有限公司 11332
代理人 刘明海 周瑞

(51)Int.Cl.
A61K 31/192(2006.01)
A61K 31/235(2006.01)

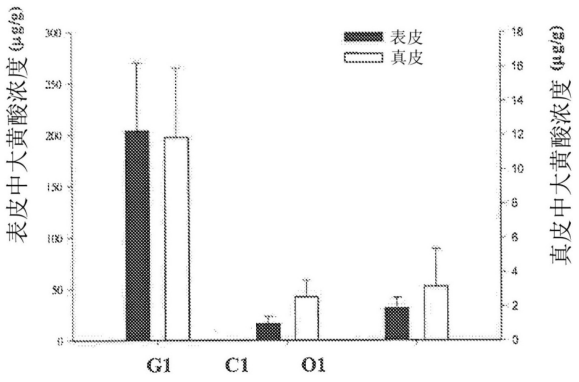
权利要求书2页 说明书11页 附图4页

(54)发明名称

双醋瑞因或大黄酸局部用制剂及其用途

(57)摘要

提供了一种含有双醋瑞因和/或其类似物的局部用药物组合物。还提供了使用该局部用药物组合物来治疗多种疾病的方法。



CN 107921013 A

1.一种局部用药物组合物，其包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂，其中所述组合物是软膏、乳膏或凝胶的形式，并且，至少约90％体积的化合物具有约0.5至约35μm的粒度。

2.根据权利要求1所述的组合物，其是软膏或乳膏的形式。

3.根据权利要求1所述的组合物，其是软膏的形式。

4.根据权利要求3所述的组合物，其中，至少约90％体积的化合物具有约10至约30μm的粒度。

5.根据权利要求4所述的组合物，其中，至少约90％体积的化合物具有约12至约25μm的粒度。

6.根据权利要求3所述的组合物，其中，将所述组合物施用于受试者的皮肤时，在施用后大于90％(以数量计)的化合物在皮肤中保留至少约4小时。

7.根据权利要求6所述的组合物，其中，将所述组合物施用于受试者的皮肤时，在施用后大于90％(以数量计)的化合物在皮肤中保留至少约6小时。

8.根据权利要求7所述的组合物，其中，将所述组合物施用于受试者的皮肤时，在施用后大于90％(以数量计)的化合物在皮肤中保留至少约8小时。

9.根据权利要求1所述的组合物，其用于治疗炎性和/或过度增殖性和瘙痒性皮肤疾病，所述皮肤疾病选自特应性皮炎、银屑病、脓疱性银屑病、红斑痤疮、瘢痕瘤、增生性疤痕、痤疮、内塞顿综合征或其他瘙痒性皮肤病，包括结节性痒疹、老年人不明确瘙痒以及包括皮肤老化和大疱性表皮松解症在内的具有上皮屏障功能障碍的疾病。

10.根据权利要求9所述的组合物，其用于治疗大疱性表皮松解症。

11.根据权利要求1所述的组合物，其中所述化合物以总组合物的约0.1％至约10.0％w/w的量存在。

12.根据权利要求11所述的组合物，其中所述化合物以总组合物的约0.1％至5.0％w/w的量存在。

13.根据权利要求12所述的组合物，其中所述化合物以总组合物的约0.5％至约2.0％w/w的量存在。

14.根据权利要求1所述的组合物，其是每日一次或每日两次的组合物。

15.一种局部用组合物，其包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂，其中所述组合物是凝胶的形式，并且，至少约90％体积的化合物具有小于约1μm的粒度。

16.根据权利要求15所述的组合物，其中，当将所述组合物施用于受试者的皮肤时，所述化合物在施用后约6小时内从皮肤释放至体内。

17.根据权利要求15所述的组合物，其用于治疗骨关节炎、高尿酸血症、与高尿酸血症相关的病症和2型糖尿病。

18.根据权利要求15所述的组合物，其用于治疗骨关节炎。

19.一种治疗炎性和/或过度增殖性和瘙痒性皮肤疾病以及具有上皮屏障功能障碍的疾病的方法，其包括向需要其的受试者施用有效量的权利要求3的组合物。

20.根据权利要求19所述的方法，其中，所述具有上皮屏障功能障碍的疾病包括皮肤老

化和大疱性表皮松解症。

21.一种治疗高尿酸血症、与高尿酸血症相关的病症、骨关节炎和2型糖尿病的方法，其包括向需要其的受试者施用有效量的权利要求15的组合物。

双醋瑞因或大黄酸局部用制剂及其用途

[0001] 相关申请的交叉引用

[0002] 本申请要求于2015年7月1日提交的美国临时申请号62/187,743的优先权,其全部内容通过引用并入本文。

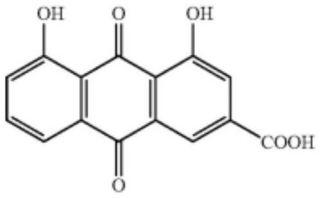
技术领域

[0003] 本发明涉及含有双醋瑞因(diacerein)和/或其类似物的局部用药物组合物,并且还涉及该局部用药物组合物在治疗多种疾病或病况中的用途。

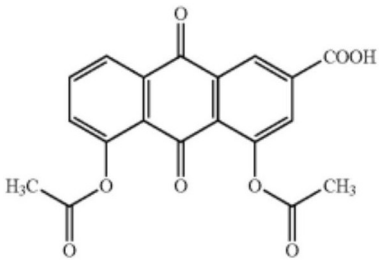
背景技术

[0004] 在化学上,大黄酸(rhein)是9,10-二氢-4,5-二羟基-9,10-二氧代-2-蒽甲酸,具有式(I)的结构,其前药之一,双醋瑞因,是4,5-双(乙酰氧基)9,10-二氢-4,5-二羟基-9,10-二氧代-2-蒽甲酸,具有式(II)的结构。双醋瑞因在到达体循环之前完全转化为大黄酸,并在体内以大黄酸的形式发挥其生理功能。

[0005] 式(I)

[0006] 

[0007] 式(II)

[0008] 

[0009] 双醋瑞因是在治疗骨关节炎中广泛使用的一种抗炎剂,其已被证实能抑制白细胞介素-1(IL-1)信号传导。目前,双醋瑞因胶囊有50mg的规格并且在不同国家以多种商品名称销售,包括Art50®、Artrodar®等。如美国专利号8,536,152和8,865,689中所公开的,双醋瑞因可以用作II型糖尿病的辅助治疗,还被发现能有效降低血尿酸水平,并因此可用于治疗高尿酸血症或与高尿酸血症相关的代谢病症。此外,据报道,双醋瑞因在治疗大疱性表皮松解症(epidermolysis bullosa)中具有潜在的效果(Wally等人,Orphanet Journal of Rare Diseases,2013,第69期,第8卷)。

[0010] 尽管双醋瑞因可以口服施用,但其不能被消化道完全吸收,而且据估计双醋瑞因的口服生物利用度为约40%至60%。双醋瑞因的不完全吸收可能导致不良副作用如腹泻或软便。体外和体内研究显示,未吸收的双醋瑞因在结肠中被代谢为大黄酸,其然后引起通便效果。

[0011] 由于这种副作用可能由于口服施用而发生,所以已经提出非口服双醋瑞因组合物来克服这些问题。

[0012] PCT国际申请号WO2009/133430公开了含有双醋瑞因或大黄酸的局部用组合物,其可以是多种形式,例如洗剂、乳膏、软膏、糊剂、凝胶等。然而,这些组合物不旨在用于任意具体的疾病,因此不能从该文的上下文中得知哪种形式最适合某种疾病。

[0013] Wally等人公开了一种用于大疱性表皮松解症的双醋瑞因乳膏制剂(Wally等人,Orphanet Journal of Rare Diseases,2013,第69期,第8卷)。然而,从该文中不清楚该制剂的性质是否以及如何影响对大疱性表皮松解症的治疗功效。

[0014] 似乎双醋瑞因制剂的精确性质对于其针对不同疾病的治疗功效是非常重要的。

[0015] 考虑到文献很少提供关于双醋瑞因/大黄酸局部用制剂的理化性质与其治疗效果之间的关系的信息,因此,本发明提供了适于不同疾病的局部用制剂。

发明内容

[0016] 本发明提供了一种局部用组合物,其包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物,以及一种或多种药学上可接受的赋形剂,其中所述组合物是软膏、乳膏或凝胶的形式,并且,至少约90%体积的化合物具有约0.5至35μm的粒度。

[0017] 本发明还提供了一种局部用组合物,其包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物,以及一种或多种药学上可接受的赋形剂,其中所述组合物是凝胶的形式,并且,至少约90%体积的化合物具有小于约1μm的粒度。

[0018] 本发明还提供了治疗炎性和/或过度增殖性和瘙痒性皮肤疾病以及具有上皮屏障功能障碍的疾病包括老化的皮肤和大疱性表皮松解症的方法,所述方法包括向需要其的受试者施用有效量的本发明的组合物。

[0019] 本发明还提供了治疗高尿酸血症、与高尿酸血症相关的代谢病症、骨关节炎或2型糖尿病的方法,所述方法包括向需要其的受试者施用有效量的本发明的组合物。

[0020] 在一些实施方案中,本发明的治疗方法明确排除施用任何其他活性剂来治疗可由本发明的组合物治疗的疾病。然而,在一些实施方案中,所述方法允许施用其他活性剂。

[0021] 优选地,本发明的治疗方法在至少一个所治疗的受试者中,优选地,在相当数量的所治疗的受试者中,更优选地,在大部分所治疗的受试者中产生相关疾病的有效治疗。

[0022] 为了使本领域的技术人员较好地领会所要求保护的本发明的特征,在下面的段落及附图中描述了用于实施本发明的详细技术和优选实施方案。

附图说明

[0023] 图1是显示用三种测试的双醋瑞因制剂(G1、C1和O1,n=4)处理8小时后,真皮和表皮中大黄酸浓度的统计柱状图;

[0024] 图2A和2B是三种测试的双醋瑞因制剂(G1、C1和O1,n=4)从皮肤组织至接收器溶液中的大黄酸累积渗透(ng/cm^2)-时间的绘图。

[0025] 图3是显示用两种测试的双醋瑞因软膏制剂(O2和O3,n=3)处理8小时后,真皮和

表皮中大黄酸浓度的统计柱状图；

[0026] 图4是两种测试的双醋瑞因软膏制剂(02和03，n＝3)从皮肤组织至接收器溶液中的大黄酸累积渗透(ng/cm^2)-时间的绘图。

[0027] 图5是显示用测试的双醋瑞因软膏制剂(03，n＝3)或对比制剂(n＝3)处理8小时后，真皮和表皮中大黄酸浓度的统计柱状图；以及

[0028] 图6是测试的双醋瑞因软膏制剂(03，n＝3)和对比制剂(n＝3)从皮肤组织至接收器溶液中的大黄酸累积渗透(ng/cm^2)-时间的绘图。

具体实施方式

[0029] 如本文所用，术语“治疗有效量”指缓和或减轻疾病的一种或多种症状的量。

[0030] 如本文所用，术语“双醋瑞因或其类似物”指双醋瑞因、大黄酸、单乙酰大黄酸或其药学上可接受的盐或酯或前药。

[0031] 除本文另有说明外，本说明书(特别是权利要求书)中使用的术语“一种(a(an))”、“所述(the)”等应理解为包括单数形式和复数形式。

[0032] 如上所述，局部施用双醋瑞因可以防止口服施用的不期望的副作用，因为与口服施用相比，局部施用绕过了具有耐受性限制的胃肠道途径，并且降低了进入体循环的双醋瑞因的量。此外，当双醋瑞因用于治疗皮肤疾病时，有利的是，双醋瑞因可以很容易地渗透穿过角质层以到达靶部位(例如，可能发生皮肤病症的真皮或表皮)。同时，还期望双醋瑞因尽可能长时间地保留在皮肤中以充分发挥其功能。因此，需要实现一个微妙的平衡，以便一方面使双醋瑞因或大黄酸能够快速渗透至靶部位，另一方面使其保留在靶部位以延长暴露时间。

[0033] 本发明的发明人发现，双醋瑞因/大黄酸局部用组合物的形式和/或其中含有的活性成分的粒度在渗透性(或扩散性)和在皮肤中的保留率方面起关键作用。

[0034] 因此，本发明提供了适用于皮肤疾病并满足上述要求的双醋瑞因/大黄酸局部用药物组合物。所述局部用药物组合物包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂，其中所述组合物是软膏、乳膏或凝胶的形式，并且，至少约90％体积的化合物具有约0.5至35μm的粒度。

[0035] 在本申请的上下文中描述的粒度分布是基于体积D值(即，Dv值，诸如Dv10、Dv50和Dv90)的，其通常用于表示给定样品的粒度范围

[0036] 优选地，所述组合物作为软膏或乳膏提供，更优选地作为软膏提供。出乎意料地发现，与凝胶制剂相比，软膏或乳膏制剂提供在皮肤中更高的保留率和更长的保留时间。

[0037] 在一个实施方案中，组合物中，至少约90％体积的化合物具有约1至约15μm，优选约2至约5μm的粒度。优选地，含有具有这种粒度的化合物的组合物是软膏或乳膏形式，并且将其施用于受试者的皮肤时，在施用后大于90％(以数量计)的化合物，优选基本上全部的化合物在皮肤中保留至少约2小时，更优选约4小时，甚至更优选约6小时，最优选约8小时。化合物在皮肤中的保留率和时间可以通过例如扩散池研究来测量。在该研究中，安装了基本上由夹在两个夹具之间的一片皮肤组成的扩散池装置，并且将含有该化合物的制剂应用在皮肤的一侧(顶部)，并且在装置的接收器部分(底部)(其可以是填充有与皮肤接触的缓

冲液的容器)以一定的时间间隔测量化合物浓度。

[0038] 此外,当将其施用于受试者的皮肤时,自施用8小时后,化合物的浓度可以为例如约8至约20μg/克表皮组织,和/或约1至约3μg/克真皮组织。

[0039] 在另一个实施方案中,组合物中,至少约90%体积的化合物具有约10至约30μm,优选约12至约25μm的粒度。优选地含有具有这种粒度的化合物的组合物为软膏或乳膏形式,更优选为软膏形式,并且将其施用于受试者的皮肤时,在施用后大于90%(以数量计)的化合物,优选基本上全部的化合物在皮肤中保留至少优选约4小时,更优选约6小时,最优选约8小时。

[0040] 此外,当将其施用于受试者的皮肤时,自施用8小时后,化合物的浓度可以为例如约3至约6μg/克表皮组织,和/或约0.2至约2μg/克真皮组织。

[0041] 具有上述性质的局部用药物组合物提供了渗透和保留之间的良好平衡,因此可用于治疗皮肤疾病,例如炎性和/或过度增殖性和瘙痒性皮肤疾病,所述皮肤疾病选自特应性皮炎、银屑病、脓疱性银屑病、红斑痤疮、瘢痕瘤、增生性疤痕、痤疮、内塞顿综合征(Netherton's syndrome)或其他瘙痒性皮肤病,包括结节性痒疹、老年人不明确瘙痒以及包括皮肤老化和大疱性表皮松解症在内的具有上皮屏障功能障碍的疾病。优选地,其在治疗大疱性表皮松解症中是有用的。

[0042] 本发明还涉及治疗炎性和/或过度增殖性和瘙痒性皮肤疾病以及具有上皮屏障功能障碍的疾病包括老化的皮肤和大疱性表皮松解症的方法,所述方法包括向需要其的受试者施用有效量的本发明的组合物。

[0043] 本发明还提供了可用于治疗高尿酸血症、与高尿酸血症相关的病症(例如,急性痛风、慢性痛风、痛风发作、尿酸肾结石、痛风性肾病等)、骨关节炎和2型糖尿病的双醋瑞因/大黄酸局部用药物组合物。与用于治疗皮肤疾病的那些组合物不同,本文的组合物使活性化合物能够很容易地并相对较快地渗透至皮肤中并进入体内,从而到达体循环并在体内发挥其功能。所述局部用组合物包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物,以及一种或多种药学上可接受的赋形剂,其中所述组合物是凝胶的形式,并且,至少约90%体积的化合物具有小于约1μm,并优选大于约0.1μm的粒度。

[0044] 优选地,当将组合物施用于受试者的皮肤时,化合物在施用后约6小时内,更优选约4小时,最优选约2小时内从皮肤释放到体内。

[0045] 本发明还提供了治疗高尿酸血症、与高尿酸血症相关的病症(例如,急性痛风、慢性痛风、痛风发作、尿酸肾结石、痛风性肾病等)、骨关节炎和2型糖尿病的方法,其包括向需要其的受试者施用有效量的本发明的组合物。

[0046] 在一些实施方案中,本发明的治疗方法明确排除施用任何其他活性剂以治疗可由本发明的组合物治疗的疾病。然而,在一些实施方案中,所述方法允许施用其他活性剂。

[0047] 优选地,本发明的治疗方法在至少一个所治疗的受试者中,优选地,在相当数量的所治疗的受试者中,更优选地,在大部分所治疗的受试者中产生相关疾病的有效治疗。

[0048] 基于组合物的总重量,本发明的局部用药物组合物可包含优选约0.1%至约10%w/w,更优选约0.1%至5%,最优选约0.5%至约2%w/w的化合物。

[0049] 组合物中的药学上可接受的赋形剂可以包括抗氧化剂、胶凝剂/水凝胶基质、pH调

节剂/缓冲剂、渗透促进剂、防腐剂、螯合剂、湿润剂(humectant)、表面活性剂、乳化剂、增稠剂、溶剂、稳定剂等。本文中，本发明中的赋形剂/成分可以具有多种功能，例如，赋形剂可以用作表面活性剂和/或稳定剂和/或乳化剂等。

[0050] 抗氧化剂的实例包括但不限于维生素C、维生素A和α-硫辛酸、抗坏血酸棕榈酸酯、焦亚硫酸钠、丁基羟基茴香醚(BHA)、丁基羟基甲苯(BHT)等中的一种或多种。

[0051] 合适的胶凝剂/水凝胶基质可以包括但不限于瓜尔胶，黄原胶和卡拉胶，阴离子、非离子、阳离子和亲脂改性的瓜尔胶，聚丙烯酸(例如，卡波姆)，聚甲基丙烯酸，纤维素树脂，聚乙二醇，羟烷基纤维素，羧烷基纤维素，聚亚烷基胺等中的一种或多种。

[0052] pH调节剂/缓冲剂的实例包括但不限于碳酸氢钠、碳酸氢钾、氢氧化镁、乳酸镁、葡萄糖酸镁、氢氧化铝、氢氧化铝/碳酸氢钠共沉淀物、氨基酸、甘氨酸铝、柠檬酸钠、酒石酸钠、醋酸钠、碳酸钠、多磷酸钠、多磷酸钾、焦磷酸钠、焦磷酸钾、磷酸氢二钠、磷酸氢二钾、磷酸三钠、磷酸三钾、磷酸钠、醋酸钠、偏磷酸钾、氧化镁、氢氧化镁、碳酸镁、硅酸镁、醋酸钙、甘油磷酸钙、氯化钙、氢氧化钙、乳酸钙、碳酸钙、碳酸氢钙、柠檬酸等中的一种或多种。

[0053] 渗透促进剂的实例包括但不限于二乙二醇单乙醚，二甲基亚砜，丙二醇，肉豆蔻酸异丙酯(IPM)，卡泊三烯(cal-cipotriene)，去垢剂，软化剂，乙氧基二甘醇(Ethoxy diglycol)，三醋精，丙二醇，苄醇，月桂醇聚醚硫酸钠，二甲基异山梨醇，肉豆蔻酸异丙酯，中链甘油三酯油(MCT油)，薄荷醇，棕榈酸异丙酯，异硬脂酸异丙酯，单硬脂酸丙二醇酯，卵磷脂，己二酸二异丙酯，癸二酸二乙酯，油酸，油酸乙酯，尿素，油酸甘油酯，辛酸/癸酸甘油三酯，丙二醇二辛酸酯/二癸酸酯，月桂醇聚醚4(Laureth 4)，油醇聚醚-2(Oleth-2)，油醇聚醚-20，碳酸丙烯酯，壬苯醇醚-9，2-正-壬基-1,3-二氧戊环，C7至C14烃基取代的1,3-二氧戊环、1,3-二氧杂环已烷或缩醛，以及壬苯醇醚-15等中的一种或多种。

[0054] 防腐剂可以是例如苯甲酸钠，丁基化羟基甲苯，丁基化羟基茴香醚，乙二胺四乙酸(EDTA)，对羟基苯甲酸酯，氯丁醇，苯甲醇，苯乙醇，脱氢乙酸，山梨酸，苯扎氯铵，苄索氯铵，苯酚，硝酸苯汞，硫汞撒(thimerosal)，对羟基苯甲酸甲酯、对羟基苯甲酸乙酯和/或对羟基苯甲酸丙酯中的一种或多种。

[0055] 合适的溶剂的实例包括但不限于醇，蓖麻油，己二酸二异丙酯，乙氧基化醇，乙醇，柠檬酸脂肪醇酯，甘油，1,2,6-己三醇，己二醇，异丙醇，肉豆蔻酸异丙酯，棕榈酸异丙酯，矿物油，磷酸，聚乙二醇300，聚乙二醇400，聚乙二醇1450，聚乙二醇8000，聚乙二醇1000单鲸蜡基醚，聚乙二醇单硬脂酸酯，聚乙二醇400单硬脂酸酯，聚乙二醇，聚氧乙烯20鲸蜡硬脂基醚，聚氧丙烯15-硬脂基醚，聚山梨醇酯20，聚山梨醇酯40，聚山梨醇酯60，聚山梨醇酯80，聚山梨醇酯，碳酸丙烯酯，丙二醇，纯化水，SD醇40，饱和脂肪酸的甘油三酯等中的一种或多种。

[0056] 合适的稳定剂或表面活性剂可以是例如离子型聚山梨醇酯表面活性剂、吐温20、吐温40、吐温60、吐温80，壬基酚聚乙二醇醚，(烷基酚-羟基聚氧乙烯)，聚(氧-1,2-乙二烷基)，α-(4-壬基酚)-ω-羟基-，支链(即Tergitol®NP-40表面活性剂)，壬基酚聚乙二醇醚混合物(即Tergitol® NP-70(70％AQ)表面活性剂)，苯氧基聚乙氧基乙醇及其聚合物如Triton®、泊洛沙姆®、Spans®、Tyloxapol®，不同等级的苄泽(Brij)，十二烷基硫酸钠，鲸蜡醇，硬脂酸，聚氧乙烯硬脂酸酯(polyoxyl stearate)等中的一种或多种。

[0057] 螯合剂的实例包括但不限于抗氧化剂，柠檬酸，依地酸二钠(EDTA)，依地酸钙二钠，依地酸，苹果酸，麦芽酚，三胺五乙酸(pentetic acid)，依地酸钠，依地酸三钠等。

[0058] 湿润剂的实例包括但不限于甘油，丙二醇，山梨糖醇，聚乙二醇，多糖(如果糖、葡萄糖、麦芽糖等)，玉米糖浆，多元醇，尿素和衍生物以及天然蜂蜜。优选的湿润剂是丙二醇和甘油。

[0059] 增稠剂的实例包括但不限于硬脂酸，纤维素聚合物，卡波姆聚合物，卡波姆衍生物，纤维素衍生物，聚乙烯醇，泊洛沙姆，多糖等。

[0060] 用于乳膏的油性基质的实例包括但不限于植物油(例如，蓖麻油)、白矿脂、矿物油等。

[0061] 软膏基质的实例包括但不限于矿脂，脂肪油，羊毛脂，凡士林，甘油，石蜡，泊洛沙姆，聚乙二醇，硬脂酸，蜂蜡等。软膏基质改性剂的实例包括但不限于矿物油、液体石蜡等。

[0062] 在一个实施方案中，本发明的局部用药物组合物为凝胶形式，并且包含约0.1％至约10％w/w的双醋瑞因或其类似物，约0.1％至约5％w/w的水凝胶基质，约2％至约50％w/w的湿润剂，以及约0.1％至约2.5％w/w的稳定剂/表面活性剂。

[0063] 在一个实施方案中，本发明的局部用药物组合物为乳膏形式，并且包含约0.1％至约10％w/w的双醋瑞因或其类似物，约0.5％至约25％w/w的表面活性剂，约0.5至约25％w/w的油性基质，约2％至约50％w/w的湿润剂，以及水。

[0064] 在一个实施方案中，本发明的局部用药物组合物为乳膏形式，并且包含部分A和部分B；其中部分A包含约0.1％至约10％w/w的双醋瑞因或其类似物，约1.5％至约40％w/w的增稠剂，约1％至约40％的油性基质，以及约0.4％至约10％w/w的表面活性剂；并且部分B包含约0.2％至约5％w/w的稳定剂，约0.6％至约15％w/w的湿润剂，以及水。

[0065] 在一个实施方案中，本发明的局部用药物组合物为软膏形式，并且包含0.1％至约10％w/w的双醋瑞因或其类似物，约15％至约99％w/w的软膏基质，约0％至约60％w/w的基质改性剂，以及约0％至约10％w/w的表面活性剂。

[0066] 优选地，本发明的局部用药物组合物为每日一次或每日两次的组合物。也就是说，为了达到所需的治疗效果，适宜每日施用一次或两次。

[0067] 本发明的局部用药物组合物具有以下优点。首先，它们可以直接施用于受皮肤皮下病况影响的部位，绕过胃肠道途径并大大降低全身暴露。其次，它们易于应用，并因此对于患者更方便。第三，对于患有吞咽困难或不喜欢药物味道的患者，这些局部用制剂也比口服制剂更优选。第四，它们更容易实现持续暴露于靶部位。

[0068] 本发明还涉及治疗炎性和/或过度增殖性和瘙痒性皮肤疾病以及具有上皮屏障功能障碍的疾病包括老化的皮肤和大疱性表皮松解症的方法，所述方法包括向需要其的受试者施用有效量的局部用药物组合物，其中所述组合物包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂；其中，当将组合物施用于受试者的皮肤时，在施用后大于90％(以数量计)的化合物在皮肤中保留至少约2小时，优选约4小时，甚至更优选约6小时，最优选约8小时。

[0069] 本发明还涉及治疗炎性和/或过度增殖性和瘙痒性皮肤疾病以及具有上皮屏障功能障碍的疾病包括老化的皮肤和大疱性表皮松解症的方法，所述方法包括向需要其的受试者施用有效量的局部用药物组合物，其中所述组合物包含治疗有效量的、选自由双醋瑞因、

大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂；其中，当将组合物施用于受试者的皮肤时，自施用8小时后，化合物的浓度可以为例如约8至约20μg/克表皮组织，和/或约1至约3μg/克真皮组织。

[0070] 本发明还涉及治疗炎性和/或过度增殖性和瘙痒性皮肤疾病以及具有上皮屏障功能障碍的疾病包括老化的皮肤和大疱性表皮松解症的方法，所述方法包括向需要其的受试者施用有效量的局部用药物组合物，其中所述组合物包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂；其中，当将组合物施用于受试者的皮肤时，自施用8小时后，化合物的浓度可以为例如约3至约6μg/克表皮组织，和/或约0.2至约2μg/克真皮组织。

[0071] 本发明还涉及治疗高尿酸血症、与高尿酸血症相关的病症、骨关节炎和2型糖尿病的方法，所述方法包括向需要其的受试者施用有效量的局部用药物组合物，其中所述组合物包含治疗有效量的、选自由双醋瑞因、大黄酸、单乙酰大黄酸及其盐或酯或前药组成的组的化合物，以及一种或多种药学上可接受的赋形剂；其中，当将组合物施用于受试者的皮肤时，化合物在施用后约6小时内，更优选约4小时，最优选约2小时内从皮肤释放到体内。

[0072] 在下文中，将参考以下实施例进一步说明本发明。然而，这些实施例仅用于说明的目的，而不是限制本发明的范围。

[0073] [制备实施例]双醋瑞因局部用组合物的制备

[0074] 根据下表1至4制备三种不同形式(凝胶、乳膏和软膏)的七种双醋瑞因局部用组合物(G1、C1、C2和O1至O4)。通过Mastersizer 2000版本5.60测量各组合物中化合物的粒度(Dv90)。下表中列出的赋形剂/成分可具有多种功能，例如，一种赋形剂用作表面活性剂和/或稳定剂和/或乳化剂等。

[0075] 表1.

[0076]

凝胶		
制剂	Gx（优选范围）	G1
成分 （功能）	%（w/w）	%（w/w）
微粒化的双醋瑞因 （活性成分）	0.1 至 10	1.00
卡波姆	0.1 至 5	1.00

[0077]

（水性基质）		
对羟基苯甲酸甲酯（防腐剂）	0.01 至 0.25	0.10
对羟基苯甲酸丙酯（防腐剂）		0.02
EDTA（螯合剂）	0.004 至 0.1	0.02
甘油（湿润剂）	2 至 50	10.00
吐温 80（稳定剂/表面活性剂）	0.1 至 2.5	0.50
柠檬酸一水合物（pH 调节剂/缓冲剂）	0.025 至 0.7	0.13
柠檬酸二水合物（pH 调节剂/缓冲剂）		0.14
总计	100.00	100.00

[0078] 表2.

[0079]

乳膏		
制剂	Cx（优选范围）	C1
成分（功能）	%（w/w）	%（w/w）
部分 A		
微粒化的双醋瑞因（活性成分）	0.1 至 10	1
硬脂酸（增稠剂）	1.5 至 40	7.5
蓖麻油（油性基质）	1 至 40	8
白矿脂（油性基质）		6
SPAN 60（表面活性剂）	0.4 至 10	2
部分 B		
吐温 60（稳定剂）	0.2 至 5	1
EDTA（螯合剂）	0.004 至 0.1	0.02
甘油（湿润剂）	0.6 至 15	3
对羟基苯甲酸甲酯（防腐剂）	0.01 至 0.25	0.1
对羟基苯甲酸丙酯（防腐剂）		0.02

[0080]

柠檬酸一水合物（pH 调节剂/缓冲剂）	0.025 至 0.7	0.13
柠檬酸二水合物（pH 调节剂/缓冲剂）		0.14
纯化水	足量	足量 100
双醋瑞因粒度（Dv90，在与其他赋形剂混合之前）	0.5 至 35 μm	2.66 μm

[0081] 表3.

[0082]

乳膏		
制剂	Cy（优选范围）	C2
成分	%（w/w）	%（w/w）
微粒化的双醋瑞因（活性成分）	0.1 至 10	1
硬脂酸（表面活性剂）	0.5 至 25	9.75
鲸蜡醇（表面活性剂）		3.25
聚氧乙烯 40 硬脂酸酯（表面活性剂）		5
矿物油（油性基质）	0.5 至 25	2.6
对羟基苯甲酸乙酯（防腐剂）	0.1 至 2.5	0.5
纯化水	足量	67.7
丙二醇（湿润剂）	2 至 50	10.2
总计	100	100
双醋瑞因粒度（Dv90，在与其他赋形剂混合之前）	0.5 至 35 μm	2.66 μm

[0083] 表4.

[0084]

软膏					
制剂	Ox（优选范围）	O1	O2	O3	O4
成分（功能）	%（w/w）	%(w/w)	%（w/w）	%（w/w）	%（w/w）
微粒化的双醋瑞因（活性成分）	0 至 10	-	1.00	-	1.00
双醋瑞因（活性成分）	0 至 10	1.00	-	1.00	-

[0085]

白矿脂（软膏基质）	15 至 99	74.00	82.00	82.00	84.5
矿物油（软膏基质改性剂）	0 至 60	25.00	16.00	16.00	12.00
鲸蜡醇（表面活性剂）	0 至 10	-	0.50	0.50	2.00
对羟基苯甲酸乙酯（防腐剂）	0 至 2.5	-	0.50	0.50	0.50
总计	100.00	100.00	100.00	100.00	100.00
双醋瑞因粒度（Dv90）	0.5 至 35 μm	N/A	混合前：2.66 μm 混合后：4.2 μm	混合前：14.15 μm 混合后：20 μm	N/A

[0086] [实施例1]双醋瑞因局部用组合物的扩散池研究

[0087] 步骤:通过颈椎脱臼处死小鼠。去除全厚侧翼皮肤,并将其置于与受体相接触的扩散池中,所述受体相是具有30％PGE300的PBS(pH 5.4)(在37℃下)。将缓冲液以3至4mL/h的流速泵送穿过接收器隔室。将20μl的1％双醋瑞因凝胶(制剂G1)、1％双醋瑞因乳膏(制剂C1和C2)或1％双醋瑞因软膏(制剂O1、O2和O3)的剂量加入到供体隔室中的皮肤表面上。在0、1、2、4、6和8小时时收集接收器溶液。在用制剂处理8小时结束时,从扩散池取下皮肤,并用三个酒精棉签小心地清洁皮肤表面(无胶带剥离(tape-stripping))。使用手术刀片将表皮与真皮分离。将分离的表皮和真皮称重并切碎,并用0.5ml乙腈:乙酸:水(60:0.1:40)剧烈摇动1小时,提取两次。然后将皮肤提取物以14,500rpm离心20分钟。所有程序均在减光下进行。将皮肤提取物和接收器溶液储存在-20℃,直到用于通过HPLC分析双醋瑞因和大黄酸浓度(在实验期间双醋瑞因很容易转化为大黄酸)。从大黄酸累积渗透浓度-时间曲线的线性部分的斜率计算皮肤通量。结果总结如下。

[0088] [形式对渗透性和保留的影响]

[0089] 渗透性

[0090] 如图1所示,双醋瑞因凝胶制剂(G1)比乳膏和软膏制剂(C1和O1)更好地渗透角质层。自施用8小时后,每克表皮中大黄酸浓度为:G1为204.0μg,C1为16.1μg,O1为31.2μg;每克真皮中大黄酸浓度为:G1为11.9μg,C1为2.53μg,O1为3.14μg。

[0091] 保留

[0092] 如图2A和2B所示，对于凝胶制剂(G1)，大黄酸在1小时后渗透皮肤组织并释放到接收器溶液中，对于乳膏制剂(C1)，为2小时后，但对于软膏制剂(O1)，大黄酸没有渗透皮肤组织并进入到接收器溶液中直至4小时，表明软膏制剂比凝胶和乳膏制剂具有更高的保留率和更长的保留时间。

[0093] 结果表明，与乳膏或软膏制剂相比，凝胶制剂中的双醋瑞因/大黄酸对角质层具有更高的渗透性，并且与乳膏或凝胶制剂相比，软膏制剂中的双醋瑞因/大黄酸在皮肤靶部位的保留时间更长。在三种制剂中，凝胶制剂在皮肤靶部位的保留时间最短。

[0094] [粒度对渗透性和保留的影响]

[0095] 图3显示，具有较小粒度的软膏制剂(O2)比具有较大粒度的软膏制剂(O3)渗透得更快。自施用8小时后，每克表皮中大黄酸浓度为：O2为10.7μg，O3为4.8μg；并且每克真皮中大黄酸浓度为：O2为1.6μg，O3为0.7μg。

[0096] 图4显示，软膏制剂O2在4小时后释放大黄酸，软膏制剂O3直到8小时甚至更长时间才释放大黄酸。与O2相比，软膏制剂O3在皮肤层中表现出类似的化合物浓度，但具有更长的保留时间。

[0097] [实施例2]对比例

[0098] Wally等人公开了在常用的护理乳膏ultraphil®中含有1％双醋瑞因的乳膏制剂(Wally等人，Orphanet Journal of Rare Diseases，2013，第69期，第8卷)。在该乳膏制剂(对比制剂)和本发明的软膏制剂O3之间进行比较研究。结果如图5和6所示。

[0099] 如图5所示，软膏制剂O3比对比制剂渗透角质层更多，并且在皮肤层中显示出更高的保留。此外，如图6所示，在4小时后，对比制剂中的大黄酸渗透皮肤组织并在接收器溶液中可检测到，但O3制剂中的大黄酸直到6小时才渗透皮肤组织进入到接收器溶液中。

[0100] 结果表明，O3制剂比对比制剂具有更高的角质层渗透性、更高的保留率和更长的保留持续时间，表明使用O3制剂在皮肤层中能保持较高的药物浓度。

[0101] 以上公开内容涉及详细的技术内容及其特征。本领域的技术人员可以基于所描述的本发明的公开和建议进行各种修改和替换，而不背离其特征。尽管如此，尽管在以上描述中没有充分公开这样的修改和替换，但是在所附的权利要求中基本上已经涵盖了它们。

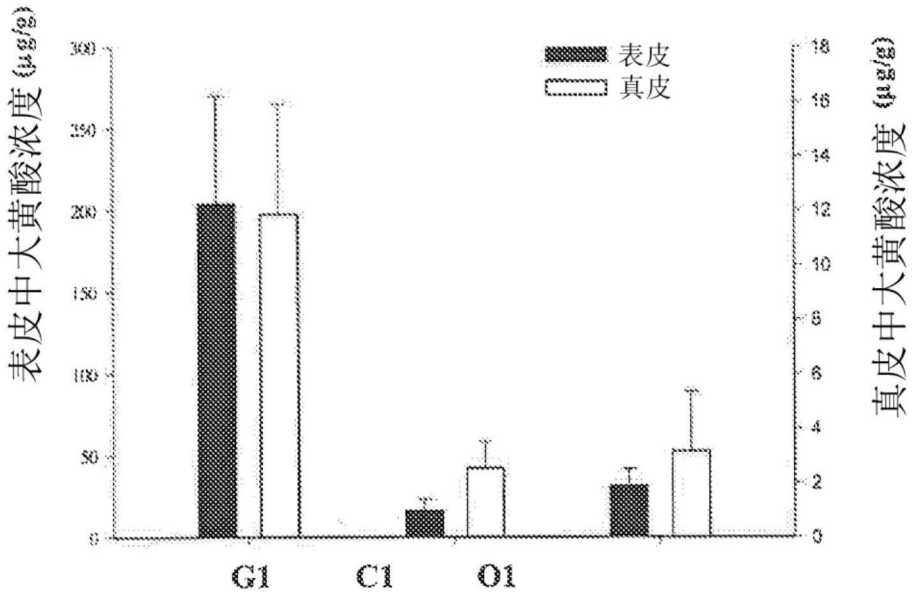

表皮中大黄酸浓度 (μg/g)
真皮中大黄酸浓度 (μg/g)
表皮
真皮
G1
C1
O1

图1

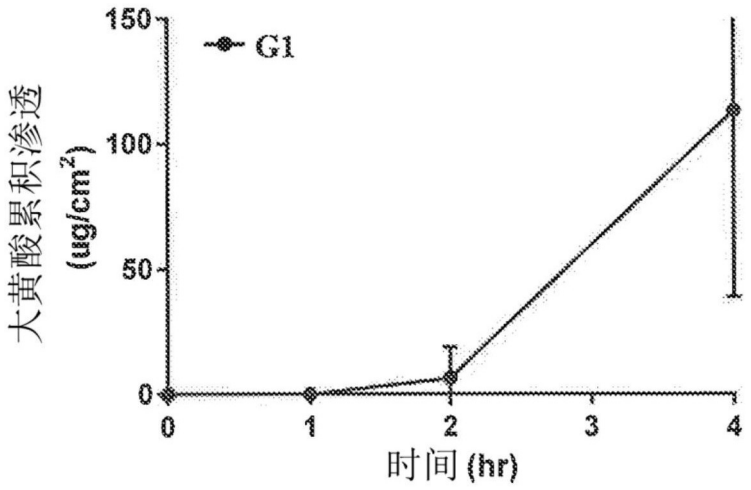

G1
大黄酸累积渗透 (ug/cm²)
时间 (hr)

图2A

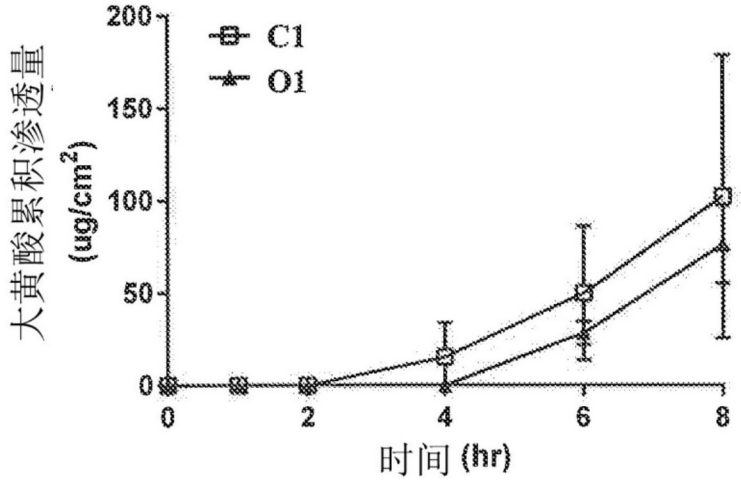

大黄酸累积渗透量
(ug/cm²)
200
150
100
50
0
C1
O1
0
2
4
6
8
时间 (hr)

图2B

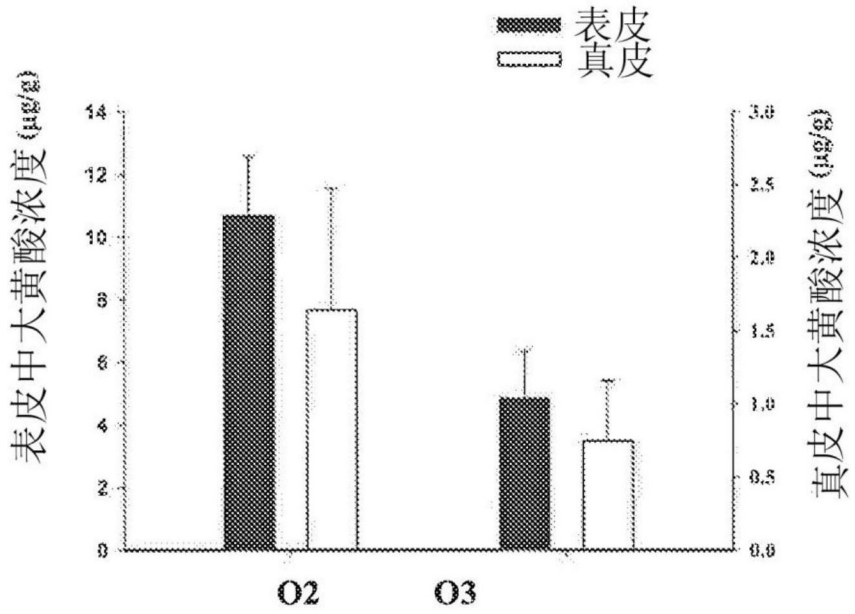

表皮
真皮
表皮中大黄酸浓度 (μg/g)
真皮中大黄酸浓度 (μg/g)
O2
O3

图3

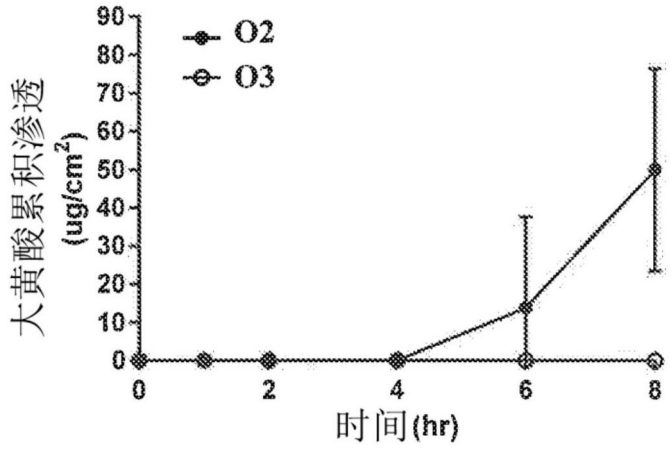

O2
O3
大黄酸累积渗透 (ug/cm²)
时间(hr)
0
10
20
30
40
50
60
70
80
90
0
2
4
6
8

图4

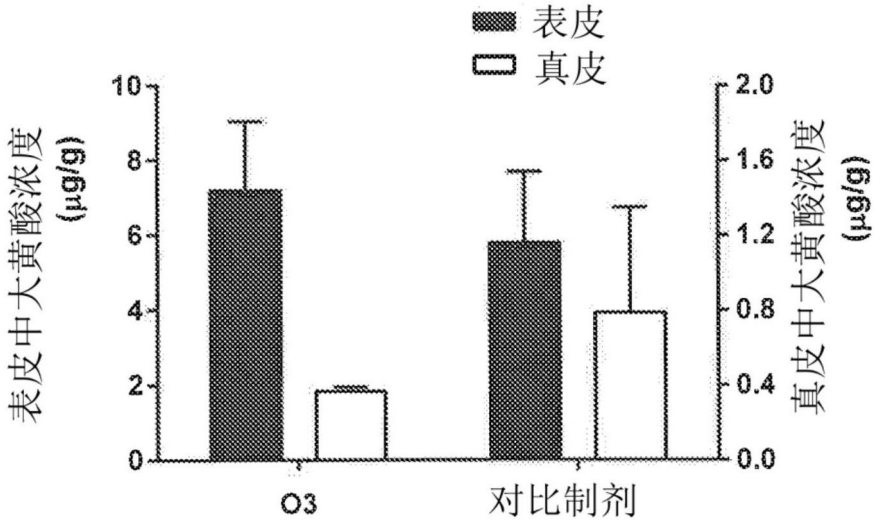

表皮
真皮
表皮中大黄酸浓度 (μg/g)
真皮中大黄酸浓度 (μg/g)
0
2
4
6
8
10
0.0
0.4
0.8
1.2
1.6
2.0
O3
对比制剂

图5

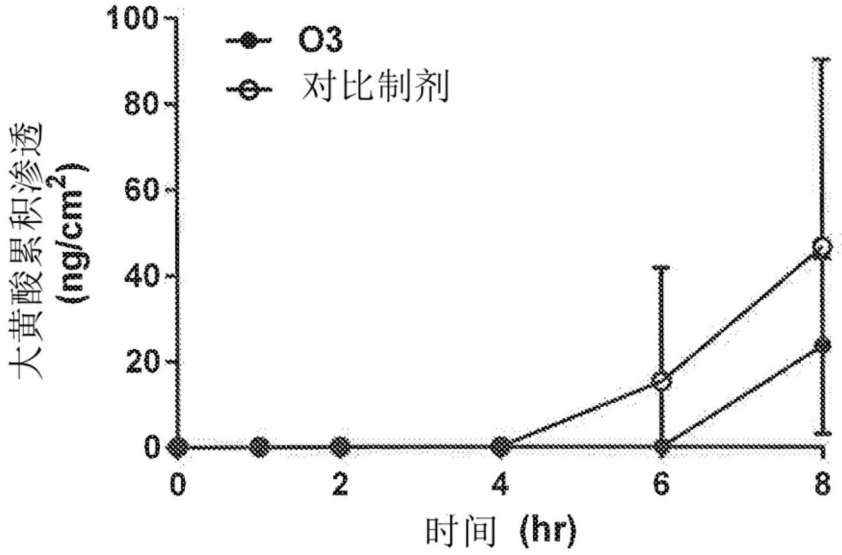


图6