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(54) Title: TOPICAL COMPOSITION

Figure 1 Effect of the presence of 5% DMSO and/or 5% GLY concentration on IBU permeation


(57) Abstract: A topical composition comprising: from 0.01 to 15% w/v of at least one active agent selected from the group consisting of antifungals and anti-inflammatory actives; from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof.

# TOPICAL COMPOSITION

## Technical Field

[1] The present invention relates to topical compositions and to the use of the topical compositions for the transdermal or topical delivery of an active agent to treat conditions such as bacterial, fungal, yeast and/or mould infections, inflammation and joint pain. The topically applied products and methods are intended to be used to aid in transdermal, transmucosal, subdermal, transmembrane, local and musculoskeletal deliveries of a therapeutically effective amount of an active ingredient to a subject. The invention is particularly directed to topically applied products for delivery of at least one active selected from antifungals and anti-inflammatory agents.

## Background of Invention

[2] Topical compositions have been used to deliver a range of active agents for achieving treatment of the skin and/or localised delivery to underlying tissues tissue such as muscles, bones, ligaments and internal organs covered by the skin. Topical compositions have been used in the delivery of antifungals to the skin and mucosal membranes and anti-inflammatory agents to relieve joint pain.

[3] A range of penetration enhancers have been used to improve transport of actives into and across the skin. Dimethyl sulfoxide (DMSO) has been investigated as a drug and as a penetration enhancer for a number of active agents. A review of penetration enhancers and DMSO are provided by Williams and Barry, (*Advanced Drug Delivery Reviews 56 (2004) 603-618*) and Marren (*Phys Sportsmed. 2011 Sep;39(3):75-82*). Topical compositions with DMSO for administration of a range of actives including Diclofenac are known but generally speaking require a content of at least 60% DMSO for good efficacy. However at these levels DMSO can cause erythema and wheals in the stratum corneum and may denature some proteins. Other side effects associated with the use of high concentration of DMSO include scaling, contact uticaria, stinging and burning sensations. DMSO also is associated with the metabolite dimethyl sulphide which produces a foul odour on the breath and

body odour. Martindale, The Extra Pharmacopoeia, pages 1461-1463, 27th Ed., 1977 details the issues with DMSO including odor and body odor, burning of the skin erythema on skin, reduction of the transparency of crystalline-skin, and tissue necrosis in the animals.

[4] Accordingly, there remains a need for a topical composition that can be used to deliver active agents across the skin to allow effective treatment of conditions such as fungal infections in both the upper and deeper layers of the skin and joint pain.

[5] The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

## Summary of Invention

[6] In one aspect the invention provides topical composition comprising:

from 0.01 to 15% w/v of at least one active agent;
from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate;
from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and
from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof.

[7] The active agent is generally for treatment of conditions selected from conditions of the skin, conditions of mucous membranes and conditions of localised tissues such as muscles, bones, ligaments and internal organs covered by the skin.

[8] Examples of active agents include those selected from the group consisting of antifungal agents, antibiotics, anti-bacterial agents, anti-cancer agents, anti-

rheumatic agents, anti-inflammatory agents, anti-histamine agents, anti-psoriatic agents or combinations thereof. More preferably the active agent is selected from antifungal agents and anti-inflammatory agents.

[9] Preferably the polar aprotic solvent is selected from ethyl acetate, acetone or dimethylsufloxide. Most preferably the polar aprotic solvent is dimethylsulphoxide (DMSO).

[10] Preferably the polyol is selected from linear and branched chain alkyl polyhydroxyl compounds such as, propylene glycol, sorbitol and glycerol. Most preferably the polyol is glycerol.

[11] Accordingly In a preferred set of embodiments the topical composition comprises:

from 0.01 to 15% w/v of at least one active agent selected from the group consisting of antifungals and anti-inflammatory agents;
from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate, preferably DMSO;
from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and
from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof.

[12] The polar aprotic solvent selected from DMSO, acetone and ethyl acetate, preferably DMSO is preferably present in an amount of from 1% to 15.0% w/v of the composition, more preferably from 1% to 10% w/v of the composition.

[13] In some embodiments, the weight ratio of polar aprotic solvent to polyol is between 10:1 to 1:10, preferably 1:5 to 5:1, particularly from1:2 to 2:1 such as about 1:1.In some embodiments, the weight ratio of DMSO to glycerol is between 10:1 to 1:10, preferably 1:5 to 5:1 or about 1:2 to 2:1 such as about 1:1.

[14] In some embodiments of the invention, the active agent is present in an amount of from 0.1% to 10% w/v of the composition, and preferably between 0.1% to 5%, w/v of the composition.

[15] In some embodiments the ratio of polar aprotic solvent to polyol is used to manipulate the permeation of the active. By altering the ratio of polar aprotic solvent to polyol, the rate of delivery of the active agent can be modified.

[16] The composition comprises a lower alkanol selected from ethanol, isopropanol or a mixture thereof.

[17] The total amount of lower alkanol selected from ethanol, isopropanol or a mixture thereof is generally in the range of from 40% to 90%, preferably from 45% to 90% v/v of the composition and still more preferably from 50% to 90% v/v of the composition and most preferably from 55% to 90% v/v of the composition.

[18] In one embodiment, 60% to 90% v/v of the composition is ethanol, isopropanol or a mixture thereof.

[19] In some embodiments the composition comprises water. Typically water is present in an amount of up to 55% v/v of the composition, preferably 1% to 55% v/v of the composition, more preferably from 5% to 55% and in some embodiments from 10% to 55% v/v of the composition.

[20] In some embodiments of the present invention, the composition further comprises a physiologically acceptable surfactant. In some embodiments, the physiologically acceptable surfactant comprises an anionic surfactant, a cationic surfactant, a non-ionic surfactant, an amphoteric surfactant or combinations thereof. In some embodiments, the physiologically acceptable surfactant is an amphoteric surfactant comprising a quaternary ammonium group.

[21] In some embodiments, the composition further comprises a physiologically acceptable acid.

[22] In some embodiments, the acid is selected from the group consisting of citric acid, succinic acid, salicylic acid, salicylates (for example the methyl, ethyl and propyl glycol derivatives), tartaric acid, lactic acid, glycolic acid, phosphoric acid, hyaluronic acid, undecylenic acid, ascorbic acid, formic acid, alpha

Hydroxy acid (AHA), beta hydroxy acid (BHA), trichloracetic acid (TCA) or retinoic acid, and mixtures thereof.

[23] In some embodiments of the present invention, the composition further comprises a preservative. In some embodiments, the preservative is selected from the group consisting of sepicide, tween 80, methylparaben, benzalkonium chloride or other surfactants, benzoic acid, benzyl alcohol, bithional, butyl p-hydroxy benzoate, p-chloro- m-xylenol, dehydro acetia acid, ethyl paraben, methyl-p- hydroxybenzoate, propyl-p- hydroxybenzoate and sorbic acid and mixtures thereof.

[24] In some embodiments of the present invention, the composition further comprises an emollient. In some embodiments the emollient is an ester, a fatty acid, an alcohol, a polyol, a triglyceride, a hydrocarbon or mixtures thereof. In some embodiments the emollient fatty alcohol is $C_{10}$ to $C_{20}$ fatty alcohol such as cetyl, myristyl, palmitic and stearyl alcohols or mixtures thereof. In some embodiments the emollient polyol is polyethylene glycol and propylene glycol or mixtures thereof. In some embodiments the emollient hydrocarbon is $C_{12}$ to $C_{30}$ hydrocarbon such as mineral oil, petroleum jelly, squalene, isoparaffins or mixtures thereof

[25] In some embodiments of the present invention, the composition further comprises a physiologically acceptable cosolvent. In some embodiments, the physiologically acceptable cosolvent is selected from the group consisting of acetone, N-Methyl-2-pyrrolidone, oleyl alcohol, phenylethyl alcohol, propylene glycol, pentylene glycol, polyethylene glycol, liquid paraffin, triglyceride oils, lanolin alcohols, ecamsule, drometrizole trisiloxane, octyldodecanol, octisalate, acetylated lanolin alcohols, benzyl alcohol, cerostearyl alcohol, $C_{10}$ to $C_{26}$ fatty alcohols and salts thereof, liquid mono- or diglycerides and mixtures thereof. In one set of embodiments the total amount of solvent other than the polar aprotic solvent selected from DMSO, acetone and ethyl acetate, polyol selected from glycerol, propylene glycol and mixtures thereof, lower alkanol selected from ethanol, isopropanol and mixtures thereof and water constitutes no more than 5% w/v of the topical composition, preferably no more than 2%

w/v, more preferably no more than 1% and most preferably no more than 0.5% w/v of the topical composition.

[26] In some embodiments, the active agent is an antifungal agent. Examples of classes of antifungals include ciclopirox and salts thereof, imidazole antifungals, triazole antifungals and thiazole antifungals. Preferably, the antifungal agent comprises one or more selected from the group consisting of azoles, echinocandins, polyenes, allylamines, imidazoles, triazoles, thiazoles, allylamines, and others.

[27] In some embodiments, the active agent is an antibiotic. Preferably, the antibiotic comprises carbocephems, ansamycins, aminoglycosides, carbapenems, cephalosporins, glycopeptides, lincosamides, lipopeptides, macrolides, monobactams, nitrofurans, penicillins, flouroquinolones, sulfonamides, tetracyclines, oxazolidonones, penicillins or combinations thereof.

[28] In some embodiments, the active agent is an anti-bacterial agent. Preferably, the anti-bacterial agent comprises quinolones, fluoroquinolones, sulphonamides, tetracyclines, actives against mycobacterial or combinations thereof.

[29] In some embodiments, the active agent is an anti-cancer agent. Preferably, the anti-cancer agent comprises bleomycin, hydroxyurea, doxorubicin, cisplatin, tretinoin, hydroxyurea, 5-fluorouracil, 5-aminolevulinic acid (5-ALA) and its derivatives, imiquimod, resiquimod , ubidecarenone, cis-urocanic acid, indomethacin, disitertide, alitretinoin, ingenol mebutate, diphenylcyclopropenone, their salts or combinations thereof.

[30] In some embodiments, the active agent is an anti-rheumatic agent. Preferably, the anti-rheumatic agent comprises symptom modifying anti-rheumatics, corticosteroids, non-steroidal anti-inflammatory agents, disease modifying anti-rheumatic agents, slow-acting anti-rheumatic agents and immunosuppressive cytotoxic drugs or combinations thereof.

[31] In some embodiments, the active agent is an anti-inflammatory agent. Preferably, the anti-inflammatory agent comprises inhibitors of COX-1, inhibitors of COX-2, naproxen, ibuprofen, ketoprofen, diclofenac, sulindac, etodolac, flubiprofen, piroxicam, ketorolac, indomethacin, meloxicam, mefenamic acid, nabumetone, oxaprozin, meclofenamate, tolmetin or combinations thereof.

[32] In some embodiments, the active agent is an anti-histamine agent. Preferably, the anti-histamine agent comprises fexofenadine, loratadine, phenindamine, dexchlorpheniramine, terfenadine, cetirizine, tripolidine, promethazine, brompheniramine, chlorpheniramine, diphenhydramine, carbinoxamine, cyproheptadine, promethazine, levocetirizine, hydroxyzine, desloratadine, clemastine or combinations thereof.

[33] The preferred active agents are antifungals, anti-inflammatory agents and mixtures of antifungal and anti-inflammatory agents.

[34] In some embodiments, the active agent is an anti-psoriatic agent. Preferably, the anti-psoriatic agent comprises acitretin, methotrexate or combinations thereof.

[35] In some embodiments of the present invention, the composition is in the form of a liquid or semisolid solution, gel, spray, emulsion, suspension, cream, microemulsion or patch.

[36] In some aspects, the present invention provides a method of treating or preventing diseases and conditions affecting the skin of humans and other mammals. In some embodiments, the present invention provides a method of treating skin diseases comprising applying to the skin a therapeutically affective amount of the composition as described herein. The composition will preferably be applied in a dose sufficient to provide an effective amount of the active agent on the skin of the human and other mammal.

In other aspects, the present invention provides use of the composition as described herein for the manufacture of a medicament for the treatment of diseases and conditions affecting the skin of humans and other mammals. In

some embodiments, the present invention provides use of the composition as described herein for the manufacture of a medicament for the treatment or prevention of skin disease.

**Detailed Description**

[37] The term “topical composition” is used to refer to a composition for application to body surfaces such as the skin or mucous membranes to treat ailments. The composition may be in any of a range of forms including but not limited to creams, foams, gels, lotions, patches and ointments. The topical composition may be epicutaneous, meaning that it is applied directly to the skin or mucosa. The effect of the topical composition in the pharmacodynamics sense, may be local and primarily address condition of the skin including either or both of the epidermis and underlying dermal layers and/or tissue such as muscles, bones, ligaments and internal organs covered by the skin rather than systemic, or be systemic or provide both local and systemic effects. Topical compositions can be used for both topical and transdermal administration of substances.

[38] Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

[39] The term "active agent" is used herein to refer to a broad class of useful chemical and therapeutic agents.

[40] The term "active" in describing the agents contemplated herein is used in a broad sense to comprehend not only agents having a direct pharmacological effect on the host, but also those having an indirect or observable effect which is useful in the medical arts. The term physiologically active agent includes prodrugs of the agent which in vivo exerts the physiological effect.

[41] A "prodrug" is an active agent which is administered in an inactive or less active form and is metabolised into an active form. The prodrug itself may have little or none of the desired activity until it interacts with the systems of the

body such as the skin or circulatory systems. Nonetheless a pharmaceutically active agent used in the transdermal delivery system of the invention include agents which are prodrugs which on administration form a more active agent in vivo during or after the process of transdermal administration.

[42] The term “physiologically acceptable” in relation to a component means a component which may be topically applied to a host, particularly to the skin of a host, and is compatible with the skin and preferably suitable for coming into contact with the skin without causing a toxic reaction.

[43] The term “alcohol” is used herein in the broadest sense to refer to compounds in which a hydroxy group, –OH, is attached to a saturated carbon atom.

[44] As used herein the term "polypeptide" means a polymer made up of amino acids linked together by peptide bonds, and includes fragments or analogues thereof. The terms "polypeptide", "protein" and "amino acid" are used interchangeably herein, although for the purposes of the present invention a "polypeptide" may constitute a portion of a full length protein.

[45] The term “antifungal” agent as used herein includes agents that are effective against fungi that cause infections of the skin and/or mucous membranes. Preferably, the “antifungal” agent is effective against the fungi that cause fungal infections of the skin such as one or both of the dermal and epidermal layers of the skin. A listing of antifungal agents, without limitation thereto, may be found, for example, in the Fifteenth Edition of *The Merck Index (2013)* under the classification “Antifungal”.

[46] The term % w/v refers to the percent by weight in the total volume of composition. Generally %w/v refers to the number of grams in 100 mL of composition.

[47] Generally the preferred antifungals are non-plant derived polypeptide antifungal agents, that is, they are preferably not polypeptides which have been both derived from plants and contain antifungal activity.

[48] The term “polar aprotic solvent” as used herein includes solvents with a comparatively high relative permittivity (or dielectric constant), greater

than approximately 15, and a sizable permanent dipole moment, that cannot donate suitably labile hydrogen atoms to form strong hydrogen bonds. The terms polar aprotic solvent and dipolar aprotic solvent are used interchangeably.

[49] The term “polyol” as used herein includes alcohols which contain two or more hydroxyl groups.

[50] The polar aprotic solvent is selected from ethyl acetate, acetone or dimethylsufloxide. Most preferably the polar aprotic solvent is dimethylsulphoxide (DMSO).

[51] Preferably the polyol is selected from linear and branched chain alkyl polyhydroxyl compounds such as, propylene glycol, glycerol, sorbitol and mixtures thereof. Most preferably the polyol is glycerol.

[52] As described above the invention provides topical composition comprising:

from 0.01 to 15% w/v of at least one active agent;

from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate;

from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and

from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof.

[53] In a preferred set of embodiments the topical composition comprises:

from 0.01 to 15% w/v of at least one active agent selected from the group consisting of antifungals and anti-inflammatory agents;

from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate, preferably DMSO;

from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and

from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally water in an amount of from 5% to 55% v/v of the composition, preferably 10% to 55%v/v of the composition and still more preferably from 20% to 55% v/v of the composition.

[54] The composition of the present invention is useful for topical delivery of an active agent, particularly antifungal and anti-inflammatory active agents. The present inventors have found that the topical composition having the combination of components described allow effective administration of the active to the dermal layers of the skin and to the underlying tissue without the deleterious side effects produced by DMSO compositions previously used in topical delivery. Advantageously, the topical composition of the present invention can shorten the treatment period, avoid or eliminate at least some of the disadvantages associated with systemic drugs and improve clinical efficacy as it is applied to the site of the disease.

[55] The topical composition of the present invention is suitable for use for the topical application of active agents to the skin or mucous membrane. The active agent may be a pharmacologically active compound. A "pharmacologically active compound" is a compound that has a therapeutic effect on the human or animal body in the treatment or prevention of a condition.

[56] In some embodiments, the active agent is selected from the group consisting of antifungal agents, antibiotics, anti-bacterial agents, anti-cancer agents, anti-rheumatic agents, anti-inflammatory agents, anti-histamine agents, anti-psoriatic agents or combinations thereof.

[57] In some embodiments, the active agent is an antibiotic. Preferably, the antibiotic comprises at least one selected from the group consisting of carbocephems, ansamycins, aminoglycosides, carbapenems, cephalosporins, glycopeptides, lincosamides, lipopeptides, macrolides, monobactams, nitrofurans, penicillins, flouroquinolones, sulfonamides, tetracyclines, oxazolidonones, penicillins or combinations thereof.

[58] In one set of embodiments, the active agent is an antifungal such as selected from the group consisting of ciclopirox and pharmaceutically acceptable salts

thereof, imidazole antifungals, triazole antifungals, thiazole antifungals, allylamine antifungals and echinocandin antifungals. Examples of imidazole antifungals may be selected from the group consisting of bifonazole, butoconazole, clotrimazole, econazole, fenticonazole, isoconazole, ketoconazole, luliconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole and salts thereof.

[59] Examples of Triazole antifungals may be selected from the group consisting of Albaconazole, efinaconazole, epoxiconazole, fluconazole, isavuconazole, itraconazole, posaconazole, propiconazole, ravuconazole, terconazole, voriconazole and salts thereof.

[60] Examples of Thiazole antifungals include abafungin and salts thereof.

[61] Examples of allylamine antifungals include amorolfine, butenafine, naftifine, terbinafine and salts thereof.

[62] Examples of echinocandin antifungals include anidulafungin, caspofungin, micafungin, and salts or mixtures of these.

[63] Preferred antifungals comprise at least one selected from the group consisting of ciclopirox or its olamine, amorolfine or its salt, amorolafine, bifonazole, tavarole (AN2690), flucytosine, griseofulvin, haloprogin, tolnaftate, terbinafine, intraconazole, fluconazole, clotrimazole, griseofulvin, flucytosine, ketoconazole, voriconazole, naftifine, nystatin, undecylenic acid, econaxzole, miconazole, miconozole nitrate, mycostatin, tolnaftate, oxiconazole, oxiconazole nitrate, sertacanazole, sulconazole, sulconazole nitrate, luliconazole, efinaconazole , butoconazole, fenticonazole, isoconazole, tioconazole, fluconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, and terconazole, abafungin, terbinafine, amorolfine, naftifine, butenafine, anidulafungin, caspofungin, micafungin, amphotericin b, haloprogin, clioquinol, posaconazole,17-AAG, E1210, D75-4590, isavuconazonium sulfate, and micafungin.

[64] In one preferred set of embodiments the active agent comprises ciclopirox, luliconazole or efinaconazole.

[65] In some embodiments the antifungal agent is a lytic peptide, mammalian peptide, insect-derived antimicrobial peptide, amphibian-derived peptide, antifungal peptides produced by bacteria and fungi, chitin synthase inhibitors, peptides affecting glucan synthesis and synthetic peptides.

[66] In some embodiments, the composition comprises an antibiotic. Generally, any antibiotic known to a person skilled in the art may be used. Suitable antibiotics comprise, but are not limited to, carbocephems, ansamycins, aminoglycosides, carbapenems, cephalosporins, glycopeptides, lincosamides, lipopeptides, macrolides, monobactams, nitrofurans, oxazolidonones, penicillins and the like or combinations thereof.

[67] Other suitable antibiotics may include, for example, chloramphenicol, clindamycin, erythromycin, erythromycin ethyl carbonate, erythromycin estolate, erythromycin glucepate, erythromycin ethylsuccinate, erythromycin lactobionate, roxithromycin, lincomycin, natamycin, nitrofurantoin, spectinomycin, vancomycin, aztreonam, colistin IV, metronidazole, tinidazole, fusidic acid and trimethoprim; 2-thiopyridine N-oxide; halogen compounds, particularly iodine and iodine compounds such as iodine-PVP complex and diiodohydroxyquinoline; hexachlorophene; chlorhexidine; chloroamine compounds;benzoylperoxide

[68] In some embodiments, the composition comprises an anti-bacterial agent. Generally, any anti-bacterial agent known to a person skilled in the art may be used. Suitable anti-bacterial agents comprise, but are not limited to, quinolones, fluoroquinolones, sulphonamides, tetracyclines, actives against mycobacterial and the like or combinations thereof.

[69] In some embodiments, the composition comprises an anti-cancer agent. Generally, any anti-cancer agent known to a person skilled in the art may be used. Suitable anti-cancer agents comprise, but are not limited to, bleomycin, hydroxyurea, 5-fluorouracil and others or combinations thereof.

[70] In one set of embodiments the active agent comprises an anti-inflammatory agent. The anti-inflammatory agent may be selected from the group consisting

of steroidal anti-inflammatory agents, particularly corticosteroids, non-steroidal anti-inflammatory agents (NSAIDS) and mixtures thereof.

[71] Examples of non-steroidal anti-inflammatory agents for use in the composition of the present invention include their racemic mixtures or individual enantiomers where applicable, such as ibuprofen, flurbiprofen, ketoprofen, aclofenac, diclofenac, aloxiprin, aproxen, aspirin, diflunisal, fenoprofen, indomethacin, mefenamic acid, naproxen, phenylbutazone, piroxicam,salicylamide, salicylic acid, sulindac, desoxysulindac, tenoxicam, tramadol and ketorolac and the like. Additional non-steroidal anti-inflammatory agents which can be present in the composition of the present invention include salicylamide, salicylic acid, flufenisal, salsalate, triethanolamine salicylate, aminopyrine, antipyrine, oxyphenbutazone, apazone, cintazone, flufenamic acid, clonixeril, clonixin, meclofenamic acid, flunixin, colchicine, demecolcine, allopurinol, oxypurinol, benzydamine hydrochloride, dimefadane, indoxole, intrazole, mimbane hydrochloride, paranylene hydrochloride,tetrydamine, benzindopyrine hydrochloide, fluprofen, ibufenac, naproxol, fenbufen, cinchophen, diflumidone sodium, fenamole, flutiazin, metazamide, letimide hydrochloride, nexeridine hydrochloride, octazamide, molinazole, neocinchophen, nimazole, proxazole citrate, tesicam, tesimide, tolmetin, and triflumidate and the like. The NSAIDS may be present in the form of salts including metal salts such as the sodium salt and organic salts such as the lysine salt. In a preferred example diclofenac is used in a form selected from the acid form, sodium salt form or lysine salt form.

[72] Examples of anti-inflammatory agents include corticosteroids which may comprise at least one selected from the group consisting of betamethasone, betamethasone valerate, betamethasone dipropionate, diflucortolone valerate, cortisone, methylprednisolone aceponate, Clobetasone butyrate, dexamethasone, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, fluocinonide desonide, fluocinolone, fluocinolone acetonide, fluocortolone, halcinonide, halopredone, hydrocortisone, hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate methylprednisolone, prednisolone, prednisolone 21-phosphate, prednisone, triamcinolone, triamcinolone acetonide, alclometasone,

alclometasone dipropionate, clobetasol propionate, clocortolone pivalate, desonide, desoximetasone, diflorasone diacetate, fluticasone, halobetasol propionate, hydrocortisone butyrate, triamcinolone acetonide, , fluocinolone acetonide, mometasone furoate, mometasone, fluticasone propionate and prednicarbate.

[73] Examples of symptom modifying anti-rheumatics for use in the composition of the present invention include aspirin, non-steroidal anti-inflammatory drugs, steroids and the like.

[74] Examples of disease modifying anti-rheumatic agents for use in the compositions of the present invention include cyclosporine, cyclophosphamide, hydroxychloroquine, leflunomide, methotrexate, mycophenolate, sulfasalazine and the like. Additional examples include biological therapies such as abatacept, rituximab, tocilizumab, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and the like.

[75] Examples of slow-acting anti-rheumatic agents for use in the present invention include hydroxychloroquine, aurothioglucose and the like.

[76] Examples of immunosuppressive cytotoxic drugs for use in the present invention include methotrexate, mechlorethamine, cyclophosphamide, chlorambucil, azathioprine and the like.

[77] In some embodiments, the composition comprises an anti-inflammatory agent. Generally, any anti-inflammatory agent known to a person skilled in the art may be used. Suitable anti-inflammatory agents comprise, but are not limited to, inhibitors of COX-1, inhibitors of COX-2, naproxen, ibuprofen, ketoprofen, diclofenac, sulindac, etodolac, flubiprofen, piroxicam, ketorolac, indomethacin, meloxicam, mefenamic acid, nabumetone, oxaprozin, meclofenamate, tolmetin and the like or combinations thereof.

[78] In some embodiments, the composition comprises an anti-histamine agent. Generally, any anti-histamine agent known to a person skilled in the art may be used. Suitable anti-histamine agents comprise, but are not limited to, fexofenadine, loratadine, phenindamine, dexchlorpheniramine, terfenadine,

cetirizine, tripolidine, promethazine, brompheniramine, chlorpheniramine, diphenhydramine, carbinoxamine, cyproheptadine, promethazine, levocetirizine, hydroxyzine, desloratadine, clemastine and the like or combinations thereof.

[79] In some embodiments, the composition comprises anti-psoriatic agents. Generally, any anti-psoriatic agent known to a person skilled in the art may be used. Suitable anti-psoriatic agents comprise, but are not limited to, acitretin, methotrexate and others or mixtures thereof.

[80] The more preferred active agents are antifungals, anti-inflammatory agents and a combination of antifungal and anti-inflammatory agent. The use of a combination is particularly useful in treating fungal infection of the skin and general provides more effective treatment by reducing inflammation to provide improved efficacy in controlling the fungal infection.

[81] The amount of active agent in the composition will differ depending on the nature of the active and the specific identity and composition of the combination which makes up the composition. In some embodiments the amount will be an amount required to achieve an effective concentration of the active at the required treatment site. In some embodiments, the amount of physiologically active agent is in the range between about 0.1 to about 15% by weight of the composition, or in the range between about 0.5 to about 15% by weight of the composition, or in the range between about 0.5 to about 10% by weight of the composition, such as 0.5%, 1.0%, 1.5% 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, by weight, or in the range between about 0.5 to about 5% by weight of the composition.

[82] The optimal ratio of polar aprotic solvent to active will differ depending on the nature of the active and the specific identity and composition of the combination which makes up the polar aprotic solvent. Typically the weight ratio of DMSO to active will be in the range of from 1:10 to 10:1, preferably from 1:5 to 5:1. In some embodiments the ratio of polar aprotic solvent to polyol is used to manipulate the permeation of the active.

[83] In addition to the active agent, the topical composition according to the invention also comprises a combination of from about 0.1% to 20% w/v of a polar aprotic solvent; and from about 0.1% to 20% w/v of a polyol. The polar aprotic solvent is selected from the group consisting of ethyl acetate, acetone and dimethylsufloxide. DMSO and mixtures thereof is particularly preferred. Of the polar aprotic solvents DMSO alone is the most preferred. The polyol is selected from the group consisting of propylene glycol, glycerol, sorbitol and mixtures thereof. The polyol is preferably selected from glycerol, propylene glycol and mixtures thereof. Glycerol alone is the most preferred.

[84] The polar aprotic solvent is present in an amount sufficient to enhance the topical delivery of the active agent. The amount can vary depending on the amount of polyol present in the composition and the desired delivery rate. Generally, the composition comprises from about 0.1% to 20% w/v of polar aprotic solvent. In some embodiments, the composition comprises polar aprotic solvent in an amount in the range of from 1% to 15%, preferably between about 2% to 15.0% w/v, such as from 2% to 10% w/v, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14% and 15% w/v of the composition..

[85] Polyol is present in an amount sufficient to enhance the topical delivery of the active agent. The amount can vary depending on the amount of polar aprotic solvent present in the composition and the desired delivery rate. Generally, the composition comprises from about 0.1% to 20.0% w/v, and preferably between about 1% to 15.0% w/v such as from 2% to 15% w/v, 2% to 10% w/v, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% w/v.

[86] In preferred embodiments, the polar aprotic solvent is DMSO and polyol is glycerol. Without wishing to be bound by theory, it is thought that the combination of polar aprotic solvent, particularly DMSO, and polyol, particularly glycerol, in the above proportions acts to enhance the delivery of the antifungal agent to the site of action.

[87] DMSO is preferably present in an amount sufficient to enhance the topical delivery of the active agent. The amount can vary depending on the amount of glycerol present in the composition and the desired delivery rate. In some embodiments, the composition comprises DMSO in an amount in the range between about 0.1% to 20.0% w/v, and preferably between about 1% to 15.0% w/v, such as 2% to 15% w/v, 2% to 10% w/v, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% w/v.

[88] Glycerol is preferably present in an amount sufficient to enhance the topical delivery of the active agent. The amount can vary depending on the amount of DMSO present in the composition and the desired delivery rate. In some embodiments, the composition comprises glycerol in an amount in the range between about 0.1% to 20.0% w/v, and preferably between about 1% to 15.0% w/v such as 2% to 15% w/v, 2% to 10% w/v, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% w/v.

[89] The ratio of DMSO to glycerol can vary and depends on the desired topical delivery rate of the active agent. The optimal ratio may vary depending on the nature and concentration of the non-plant derived polypeptide antifungal agent and the concentration of polar aprotic solvents, particularly DMSO, and polyol, particularly glycerol, in the composition. Generally, the weight ratio is in the range of from 100:1 to 1:100. In one set of embodiments, the weight ratio of polar aprotic solvent, particularly DMSO, to polyol, particularly glycerol, is in the range of from 1:10 to 10:1, preferably from 1:5 to 5:1 such as 1:10, 1:9, 1:8, 1:7, 1:6, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 and 10:1 In some embodiments, the weight ratio of DMSO to glycerol is from 2:1 to 1:2 such as about 1:1. In some embodiments the ratio of DMSO to glycerol is used to manipulate the permeation of the active. By altering the ratio polar aprotic solvent to polyol, the rate of topical delivery of the active agent can be modified.

[90] The topical composition comprises lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof in an amount in the range of from 40% to 90% v/v, preferably from 50% to 90% w/w and more preferably from 55% to 90% w/w such as 60% to 90% v/v or 70% to 90% v/v.

[91] In a preferred set of embodiments, the topical composition according to the invention further comprises water. Water is preferably present in an amount of from 1% to 55% v/v, preferably 5% to 55% v/v of the composition, more preferably 10% to 55%v/v of the composition. In some embodiments water is present in from 15% to 55% such as 15% to 50%v/v, 15% to 40% v/v or 15% to 30% v/v of the composition. The person skilled in the art would understand that water may have several functions. Water may solubilise the active agent and may also function in combination with the polar aprotic solvent and polyol to enhance transdermal delivery of the active agent.

[92] It will be understood by those skilled in the art that alcohols, DMSO and glycerol, polyols and the like contain a certain amount of water. The composition according to the present invention may, and preferably will also comprise additional water, that is water that is in addition to the water present in the alcohols, DMSO and glycerol.

[93] In some embodiments, the topical composition according to the invention further comprises a thickener. Generally, any thickener known to a person skilled in the art may be used. Suitable thickeners include, but are not limited to, polyacrylic acids; and acrylic acid copolymers, agar, acacia, carrageenan, food starch, gelatins, germ Arabic, guorgem, hydroxyethyl cellulose hydroxypropymethyl cellulose, protein, polyvinyl pyrrolidone; guargum, xanthan gum, gelatin, methylcellulose, methylhydroxypropylcellulose, polypropylcellulose, polypropylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose hypromellose, carboxymethyl cellulose, sodium gluconate, carrageenan, cetyl alcohol, stearyl alcohol, myristal alcohol, octyldodecanol, pectin, polyvinyl alcohol, polyethylene glycol, starches and starch derivatives and mixtures thereof. In one set of embodiments, the preferred thickener is polyvinyl pyrrolidone. The thickener may also serve other functions, such as enhancing topical delivery of the active agent.

[94] The amount of thickener present in the topical composition is sufficient to increase the viscosity of the composition. In some embodiments, the thickener is present in an amount to provide a viscosity of 15 – 1000 cp. In some embodiments, the amount of thickener present in the topical composition is

sufficient to enhance the topical delivery of the active agent. In some embodiments, the thickener is present in an amount of from 0.1 to 10%, by weight of the composition. For example, the thickener may be present in an amount of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.5, 1.7, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5 and 10% by weight of the composition.

[95] In some embodiments, the composition according to the invention further comprises a preservative. Generally, any preservative known to a person skilled in the art may be used. The preservative may be selected from the group consisting of sepicide, tween 80, methylparaben, benzalkonium chloride or other surfactants, benzoic acid, Bithional, butyl p-hydroxy benzoate, p-chloro- m-xylenol, dehydro acetia acid, ethyl paraben, methyl-p-hydroxybenzoate, propyl-p- hydroxybenzoate, sorbic acid and combinations thereof. In some embodiments the preservative is present in an amount from 0.01 to 20%. For example the preservative may be present in an amount of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 007, 0.05, 0.08, 0.09, 0.1, 0.12, 0.15, 0.017, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20% by weight of the composition

[96] In some embodiments, the topical composition according to the invention further comprises a physiologically acceptable cosolvent. Any physiologically acceptable cosolvent known to a person skilled in the art may be used. In some embodiments, the physiologically acceptable cosolvent is selected from the group consisting of acetone, ethyl acetate, butyl acetate or other acetates, oleyl alcohol, phenylethyl alcohol, pentylene glycol, polyethylene glycol, liquid paraffin, triglyceride oils, lanolin alcohols, octyldodecanol, octisalate, acetylated lanolin alcohols, benzyl alcohol, cerostearyl alcohol, $C_6$ to $C_{26}$ fatty alcohols and salts thereof such as $C_{10}$ to $C_{26}$ fatty alcohols, and liquid mono- or diglyceride and the like and combinations thereof. In some embodiments the cosolvent is present in an amount from 2% to 40%. For example the preservative may be present in an amount of 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11, 12, 13, 14, 15, 16, 17,

18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40% by weight of the composition

[97] pH stabilisers including acidifying compounds and their use to lower the pH of a formulation are well known to a practitioner in the art. Examples of such acidifying stabilizers include, but are not limited to compounds selected from the group consisting of hydrochloric acid, citric acid, lactic acid, ascorbic acid, malic acid, isoascorbic acid, cysteine hydrochloride, cysteine dihydrochloride, citric acid fumaric acid, acetic acid, sorbic acid, glycine hydrochloride, arginine hydrochloride, succinic hydrochloride, succinic acid, tartaric acid, phosphoric acid, hydrochloric acid, glucono-delta-lactone, salicylic acid, salicylates (for example the methyl, ethyl and propyl glycol derivatives), glycolic acid, hyaluronic acid, undecylenic acid, formic acid, alpha hydroxy acid (AHA), beta hydroxy acid (BHA), trichloracetic acid (TCA) or retinoic acid and mixtures thereof. Examples of alkali pH stabilizers include, but are not limited to sodium hydroxide, diethylamine, ammonia, ammonia carbonate, diethanolamine, potassium hydroxide, sodium borate, sodium carbonate, trolamine, diisopropanolamine, disodium oleamido monoethanolamine sulfosuccinate, ethylenediamine dihydrochloride, PEG-15 cocamine, rhodamine B, stearamindoethyl diethylamine, triethanolamine lauryl sulfate and tromethamine.

[98] For example the pH stabilising agent may be present in an amount of from 0.01% to 10% w/v of the composition such as , 0.02, 0.03, 0.04, 0.05, 0.06, 007, 0.05, 0.08, 0.09, 0.1, 0.12, 0.15, 0.17, 0.2, 0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10% w/v of the composition.

[99] The topical composition may comprise an antioxidant which may, for example, comprise one or more selected from the group consisting of alpha tocopheral, ascorbic acid, ascobyl palmitate, fumeric acid, malic acid, citric acid, sodium ascorbate, sodium metabisulfate, n-propyl gallate, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), monothioglycerol and the like.

[100] In some embodiments the topical composition according to the invention further comprises a physiologically acceptable emollient. In some embodiments the emollient is an ester, a fatty acid, an alcohol, a polyol, a hydrocarbon or mixtures thereof. In some embodiments the emollient fatty alcohol is C10 to C20 fatty alcohol such as cetyl, myristyl, palmitic and stearyl alcohols or mixtures thereof. In some embodiments the emollient polyol is polyethylene glycol and propylene glycol or mixtures thereof. In some embodiments the emollient hydrocarbon is C12 to C30 hydrocarbon such as mineral oil, petroleum jelly, squalene, isoparaffins or mixtures thereof. In some embodiments, the composition comprises emollient in an amount in the range between about 0.1% to 20.0% w/v, and preferably between about 2% to 15.0% w/v such as 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15% w/v of the composition.

[101] In some embodiments, the topical composition according to the invention further comprises a physiologically acceptable surfactant. Any physiologically acceptable surfactant known to a person skilled in the art may be used. In some embodiments the physiologically acceptable surfactant is selected from the group consisting of an anionic surfactant, a cationic surfactant, a non-ionic surfactant, an amphoteric surfactant and combinations thereof.

[102] Suitable anionic surfactants may include one or more of sodium laurate, sodium lauryl sulfate, and mixtures thereof.

[103] Suitable cationic surfactants may include one or more of etyltrimethylammonium bromide, tetradecyltrimethylammonium bromide, benzalkonium chloride, octadecyltrimethylammonium chloride, cetylpyridinium chloride, dodecyltrimethylammonium chloride, hexadecyltrimethylammonium chloride, and mixtures thereof.

[104] Suitable non-ionic surfactants include one or more of α-hydro-ω-hydroxypoly(oxyethylene)-poly(oxypropyl) poly(oxyethylene) block copolymers, polyoxyethylene ethers, polyoxyethylene sorbitan esters, polyethylene glycol esters of fatty alcohols, and mixtures thereof.

[105] By amphoteric surfactant we mean to include any surfactants having the ability to exhibit both positive and negative functional groups. Suitable amphoteric surfactants may include one or more surfactants referred to as betaines (including sultaines), for example alkyl betaines, alkylamidopropyl betaines, alkyl sulphobetaines, alkylamidopropyl hydroxy sultaines, alkylampho acetates, alkylamphodiacetates, alkylamphopropionates, alkylamphodipropionates, alkyliminodipropionates and alkyliminodiacetates (sulphobetaines) and the like wherein preferably the alkyl and acyl groups have from 8 to 18 carbon atoms. Suitable amphoteric surfactants may also comprise alkyl glycinates, alkyl carboxyglycinates, alkyl amphopropionates, acyl taurates and acyl glutamates and the like wherein preferably the alkyl and acyl groups have from 8 to 18 carbon atoms or other zwitterionic or amphoteric surfactant. Suitable amphoteric surfactants may comprise lauramidopropyl betaine, cocamidopropyl betaine, lauryl betaine, cocobetaine, cocamidopropylhydroxysultaine, aminopropyl laurylglutamide, sodium cocoamphoacetate, sodium lauroamphoacetate, disodium lauroamphodiacetate, disodium cocoamphodiacetate, sodium cocoamphoprqpionate, disodium lauroamphodipropionate, disodium cocoamphodipropionate, sodium lauriminodipropionate, disodium cocoamphocarboxymethylhydroxypropylsulfate, and the like.

[106] Preferably the surfactant is an amphoteric surfactant comprising a quaternary ammonium group.

[107] Optionally, the topical composition according to the invention further comprises a colour pigment. Any colour pigment known to a person skilled in the art may be used.

[108] Optionally, the composition according to the present invention comprises at least one excipient such as, but not limited to, sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water. The compositions encompassed herein will be understood to optionally include one or more other excipients as known to those skilled in the art. A person skilled in the art will know how to identify such an excipient as useful in the present compositions and methods, for example, when such an

excipient enhances the therapeutic effectiveness, stability, or potency of a composition or method.

[109] The person skilled in the art will recognise that one or more of the foregoing ingredients can serve more than one function.

[110] A preferred topical composition according to the invention comprises:

from about 0.01 to 10% w/w active agent (preferably 0.1% to 10% w/v), wherein the active agent is selected from the group consisting of antifungal agents, antibiotics, anti-bacterial agents, anti-cancer agents, anti-rheumatic agents, anti-inflammatory agents, anti-histamine agents, anti-psoriatic agents or combinations thereof, preferably antifungals, anti-inflammatory agents and mixtures thereof;

from about 1% to 10% w/v DMSO;

from about 1% to 15% w/v glycerol;

from about 45% to 90% v/v lower alcohol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally from about 5% to 55% v/v water.

[111] In one set of embodiments the topical composition according to the invention consists of:

from about 0.01 to 10% w/w active agent (preferably 0.1% to 10% w/v), wherein the active agent is selected from the group consisting of antifungal agents, antibiotics, anti-bacterial agents, anti-cancer agents, anti-rheumatic agents, anti-inflammatory agents, anti-histamine agents, anti-psoriatic agents or combinations thereof, preferably antifungals, anti-inflammatory agents and mixtures thereof;

from about 1% to 10% w/v DMSO;

from about 1% to 10% w/v glycerol;

from about 45% to 90% v/v lower alcohol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally from about 5% to 50% v/v water.

[112] In one set of embodiments there is provided a method of treatment of fungal infection of the skin or mucous membrane comprising topically applying the surface of the skin or mucous membrane a topical composition comprising:

from 0.1% to 10% w/v of active agent component comprising at least one antifungal active and optionally and anti-inflammatory in the range of from 0.1% to 10% w/v;

from 1% to 10% w/v (preferably from 1% to 8% w/v) of DMSO;

from 1% to 10% w/v (preferably from 1% to 8% w/v) of glycerol;

from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally from 5% to 55% v/v (preferably from 5% to 40% v/v) water.

[113] A method of treatment of joint pain comprising topically applying to the joint a topical composition comprising:

from 0.1% to 10% w/v of at least one anti-inflammatory active agent;

from 1% to 10% w/v (preferably from 1% to 8% w/v) of DMSO;

from 1% to 10% w/v (preferably from 1% to 8% w/v) of glycerol;

from 40% to 90% v/v (preferably from 55% to 90% v/v) of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally from 5% to 55% v/v (preferably from 5% to 40% v/v) water.

[114] In some embodiments of the invention, the composition is in the form of a liquid or semisolid solution, gel, spray, emulsion, suspension, microemulsion or patch. In some embodiments, the composition may be suitable for application at least once a day, twice daily or as needed. In some embodiments, the composition may be re-applied with or without an intervening water rinse. The composition will preferably be applied to the affected area of skin in a dose and for a period of time sufficient to achieve efficacy.

[115] After application of the topical composition to skin the composition is substantially dry to the touch within a period in the range between 0.5 to 10 minutes, preferably within the range of about 1 to 5 minutes. However, the

person skilled in the art will appreciate the period before the skin is substantially dry to the touch may depend on the specific composition. We have found in this regard that a high proportion of lower alcohol provides rapid drying and also more reliable skin penetration by providing a reservoir of the active agent within the skin layer.

[116] The topical compositions containing antiinflammatory drugs are particularly useful in treatment of joint pain. Joint pains include: shoulder pain, such as AC arthrosis (bursitis, rotator cuff tendonitis); elbow pain, such as medial and lateral Epicondylitis (tennis elbow, golfer's elbow); wrist pain, such as extension and flexor tendonitis; De Quervain's Tenosynovitis (tendonitis); finger problems; hip pain, caused by a “snapping hip;” Trochanteric Bursitis; knee pain; Patellar Athrosis; Post-traumatic patellofemoral pain; Patellar Tendonitis (runner's knee, jumper's knee); Plica; Apophysitis (Osgood-Schlatter) (growing pains); leg pain, such as Gastrocnemius Strain (calf strain); Achilles Tendonitis; ankle pain, such as acute or chronic ankle sprain; foot pain, such as retrocalcaneal Bursitis; Sever's Disease; Plantar Fasciitis; Posterior Tibial Tendonitis (shin splint); Metatarsalgia (toe pain); Turf Toe; Sesamoid Dysfunction; back pain, such as Lumbar Strain; SI pain (sciatica pain); cervical pain and strain; and Trapezius Trigger Points (pinched nerve).

[117] The topical composition, particularly when comprising anti-inflammatory agent, is useful in treatment of arthritis. Pain, particularly of the joints throughout the body, characterizes arthritis. Psoriasis, primarily a skin disorder, can progress to psoriatic arthritis if left untreated. Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis are all examples of degenerative arthritic diseases which may be treated using the topical composition comprising an anti-inflammatory active agent.

[118] In addition to, for example, arthritic causes, normal function of a joint and its movement, and other portions of the body, can be severely impaired as a result of trauma or following orthopaedic and other surgical procedures. This may result in tenderness, aching, pain, and lengthy recovery times, as well as loss of joint mobility or reduced range of motion, tonicity, or elasticity of the joint/articular structures, such as for example, muscle, tendon, capsule, bone,

or ligament. Reduced joint mobility may also involve permanently altered or shortened joint or tissue architecture. Altered or abnormal joint mobility or joint architecture may also be associated with or caused by a variety of injuries and conditions such as, for example, metabolic disorders, ischemia, injury to joint, capsule, bone, cartilage, tendon, ligament or muscle, fractures, subluxation, dislocation, crush injuries, prolonged immobilization (e.g., immobilization of a joint in a cast or splint), and paralysis.

[119] The topical composition for treatment of joint pain may comprise one or more additional active agent selected from the group consisting of glutamine, hyaluronic acid, methylsulfonylmethane and glucosamine.

[120] The topical composition comprising antifungal active agent may be used in treatment of a range of fungal diseases, or mycoses, in both humans and animals. The relevant fungal diseases affecting humans can be divided into four groups based on the level of penetration into the body tissues.

[121] These include:

(i) Superficial mycoses are caused by fungi that grow on the surface of the skin or hair;

(ii) Cutaneous mycoses or dermatomycoses include such infections as athlete's foot and ringworm, where growth occurs only in the superficial layers of skin or hair;

(iii) Subcutaneous mycoses penetrate below the skin to involve the subcutaneous, connective, and bone tissue; and

(iv) Systemic or deep mycoses are able to infect internal organs and become widely disseminated throughout the body. This type is often fatal.

[122] Dermatophytes, including Trichophyton rubrum and Trichophyton mentagrophytes, are responsible for fungal infections of the skin or Dermatophytosis (dermatophytose).

[123] Dermatophytosis (tinea or ringworm) of the scalp and glabrous skin is caused by a by one of the three genera of fungi collectively called dermatophytes—Epidermophyton, Microsporum, and Trichophyton which have the ability to

utilise keratin as a nutrient source, i.e. they have a unique enzymatic capacity [keratinase].

[124] The type and severity of the host response is often related to the species and strain of dermatophyte causing the infection.

[125] The topical composition may be used in treatment of Tinea Pedis, also known as athletes foot, which is a common and contagious dermatophytic fungal infection of the skin that causes scaling, flaking, and itching of the affected areas. Symptoms are caused by fungi such as Epidermophyton floccosum or fungi of the Trichophyton genus such as T. rubrum or T. mentagrophytes. The disease is typically transmitted in moist communal areas where people walk barefoot, such as showers or bathhouses, and requires a warm moist environment, (e.g., the inside of a shoe) to incubate. The condition typically affects the feet, but may infect or spread to other areas of the body such as the groin and tends to spread to areas of skin that are kept hot and moist, such as with insulation, body heat, and sweat.

[126] In another embodiment the topical composition is used in treatment of one or more selected from the group consisting of Tinea Corporis, also known as ringworm, tinea circinata, and tinea glabrosa, is a superficial fungal infection (dermatophytosis) of the arms and legs, especially on glabrous skin; however, it may occur on any part of the body.

[127] The topical composition may be used in treatment of Tinea Cruris, also known as jock itch or ringworm of the groin, which is a dermatophyte fungal infection of the groin region in either sex, though more often seen in males.

[128] Other Tinea which may be treated using the topical composition include Tinea barbae, tinea capitis, Tinea manuum, Tinea imbricate, Tinea Nigra , Tinea blanca and Tinea versicolor.

[129] The topical composition may be used in treatment of Candida, a genus of yeasts and is the most common cause of fungal infections worldwide. Many species are harmless, however, when mucosal barriers are disrupted or the immune system is compromised they can invade and cause

disease. Candida albicans is the most commonly isolated species, and can cause infections (candidiasis or thrush) in humans and other animals. The common sites for candida to cause infection are the vagina (vaginal thrush), the mouth (oral thrush), and the skin. Candida skin infections can occur on almost any area of the body, but are more commonly found in intertriginous regions—where two skin areas may touch or rub together—such as armpits, the groin, skin folds, and the area between the fingers and toes. The fungus thrives in warm, moist, and sweaty conditions.

[130] The compositions of the present invention are useful for treatment of diseases of the skin, diseases of diseases of the skin and/or joint pain. The term "diseases of the skin" is used herein in the broadest sense. The compositions of the present invention may be useful for the treatment of fungal infections of the skin such as psoriasis, paronychia, Tinea pedis, Tinea corporis, Tinea cruris, Tinea capitis, Tinea manuum, Tinea barbae, Tinea facilae, Tinea versicolor, candidiasis, fungal keratitis, or any combination thereof.

[131] In one set of embodiments, the composition of the present invention is useful for the treatment of psoriasis.

[132] In some embodiments, the topical composition is administered on a schedule once a day. In some embodiments, the topical composition is administered twice a day. In some embodiments, the topical composition is administered three times a day, four times a day, five times a day, or more. In some embodiments the topical composition is administered less frequently than once a day. In some embodiments the topical composition is administered once every two days, once every three days, once every four days, once every five days, once every six days, or once every seven days. In some embodiments the topical composition is administered less frequently than once a week. In some embodiments the topical composition is administered once a month. In some embodiments the topical composition is administered twice a month. In some embodiments the topical composition is administered as needed.

[133] In some embodiments, the composition may be re-applied with or without an intervening water rinse. In some embodiments, one application off the

composition is used. In other embodiments, at least two applications of the composition are used depending on the severity and persistence of the condition. In some embodiments, where the active comprises an antifungal the topical composition is applied in a daily regimen for a period sufficient to achieve efficacy. In some embodiment, the method according to the invention is practiced daily until the area of skin is visibly free of the disease. Preferably, the method according to the invention is practiced daily until the condition to be treated is relieved. In some embodiments, a therapeutic dosing regimen is continued for at least one day, at least two days, at least three days, at least four days, at least five days, at least six days, or at least seven days. In some embodiments, a therapeutic dosing regimen is continued for at least one week, at least two weeks, at least three weeks, at least four weeks, at least six weeks, at least eight weeks, at least ten weeks, at least twelve weeks, at least fourteen weeks, or at least sixteen weeks. In some embodiments, a therapeutic dosing regimen is continued for at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, at least nine months, or at least twelve months.

[134] In another aspect, the present invention provides use of the composition as described herein for the manufacture of a medicament for the treatment of at least one of skin diseases and joint pain. In some embodiments, the medicament is for administration on a schedule once a day. In some embodiments, the medicament is for administration twice a day. In some embodiments, the medicament is for administration three times a day, four times a day, five times a day, or more. In some embodiments, the medicament is for administration less frequently than once a day. In some embodiments, the medicament is for administration once every two days, once every three days, once every four days, once every five days, once every six days, or once every seven days. In some embodiments, the medicament is for administration less frequently than once a week. In some embodiments, the medicament is for administration once a month. In some embodiments, the medicament is for administration twice a month. In some embodiments, the medicament is for administration as needed.

[135] In some embodiments, the medicament may be re-applied with or without an intervening water rinse. In some embodiments, one coat of the topical composition comprising an antifungal is applied to the skin. In other embodiments, at least two applications of the medicament are applied. Where more than one application is applied, the first application is substantially touch dry before the subsequent application is applied.

[136] In some embodiments, the medicament is for administration in a daily regimen for a period sufficient to achieve efficacy. In some embodiment, the use according to the invention is practiced daily until the skin is visibly free of disease.

[137] The person skilled in the art will understand, based on the disclosure set forth herein, that specific dosage regimens for compositions encompassed herein may be determined empirically through clinical and/or pharmacokinetic experimentation, and that such dosages may be adjusted according to prespecified effectiveness and/or toxicity criteria. It will also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity and concentration of the specific compounds employed, the characteristics of the patient, drug combination, the judgment of the treating physician and the nature and severity of the particular disease or condition being treated.

[138] The compositions, methods and uses of the present invention provide a regimen suitable for the topical treatment of fungal diseases of the skin of varying levels of severity. The compositions, methods and uses of the present invention are desired to improve the delivery of the active agent and improve the topical bioavailability of the active agent. The compositions, methods and uses of the present invention will allow for more rapid treatment and control of infection relative to conventional topical treatment compositions.

[139] Reference will now be made to experiments that embody the above general principles of the present invention. However, it will be understood that the following description is not to limit the generality of the above description.

## EXAMPLES

### Brief Description of Drawings

[140] The invention is demonstrated in the Examples with reference to the drawings.

[141] In the drawings:
Figure 1 is a column chart relating to Example 3 comparing the diffusion (IBU Q24h mean (µg/cm2)) of a composition of the invention containing DMSO and glycerol ("DMSO/GLY") with corresponding compositions containing only DMSO or only glycerol.

[142] **Example 1**

[143] Compositions 1 to 6 and a comparison composition were prepared by combining the components in the amounts listed below with and without preservative:

- Composition (Comp) 1: 1.0 to 8.0% ciclopirox olamine, 5.0% DMSO, 5% Glycerol, 5%, water, 45% ethyl acetate in aqueous ethanol (95%)
- Comp 2: 1.0 to 8.0% Ciclopirox, 5.0% DMSO, 5% Glycerol, 2% polyvinyl pyrrolidone in 70% aqueous ethanol (95%)
- Comp 3: 0.5 to 5% Ibuprofen, 5.0% DMSO, 1% Glycerol, 50% water, 10% oleyl alcohol in isopropyl alcohol
- Comp 4: 0.1 to 5% Diclofenac, 5.0% DMSO, 1% Glycerol, 50% water, 10% oleyl alcohol in isopropyl alcohol
- Comp 5: 0.5 to 5% Naproxen, 5.0% DMSO, 1% Glycerol, 50% water, 10% oleyl alcohol in isopropyl alcohol
- Comp 6: 0.1 to 5% Ketoprofen, 5.0% DMSO, 1% Glycerol, 50% water, 10% oleyl alcohol in isopropyl alcohol.

[144] Compositions 1 and 2 may be used to treat skin fungal infections by topical to mycoses such as tinea versicolor.

[145] Compositions 3 to 6 may be used in treatment of joint pain by topical application to the joint in which pain if suffered.

[146] **Example 2**

[147] This example demonstrates a number of diclofenac compositions of the invention. Diclofenac can be in acid or salt form including diclofenac, diclofenac sodium, diclofenac potassium and diclofenac diethylamine.

- 2%w/v diclofenac diethylamine, 2.5%w/v DMSO, 2.5% GLY, 10%w/v water in isopropyl alcohol
- 2%w/v diclofenac diethylamine, 1 %w/v acetone, 4% hydroxypropyl cellulose, 10%w/v water in isopropyl alcohol
- 2%w/v diclofenac diethylamine, 2.5% DMSO, 7.5% sorbitol 10%w/v water in isopropyl alcohol
- 2%w/v diclofenac diethylamine, 2.5%w/v DMSO, 2.5% GLY, 10%w/v, 4% hydroxypropyl cellulose water in isopropyl alcohol
- 2%w/v diclofenac sodium, 2.5%w/v DMSO, 2.5% GLY, 10%w/v water in isopropyl alcohol
- 2%w/v diclofenac sodium, 2.5%w/v DMSO, 5 % propylene glycol, 10%w/v water in isopropyl alcohol
- 2%w/v diclofenac sodium, 2.5% acetone, 3.2% hydroxyl propyl cellulose, 10%w/v water, 5 % w/v 95% ethanol in isopropyl alcohol
- 2%w/v diclofenac sodium, 2.5%w/v DMSO, 2.5% GLY, 10%w/v water in isopropyl alcohol
- 1% w/v betamethasone valerate, 2% w/v acetone, 7.5% sorbitol, 10%w/v water in isopropyl alcohol
- 2% ketamine w/v, 2% w/v acetone, 7.5% propylene glycol, 10%w/v water in isopropyl alcohol.

[148] The compositions of Example 2 may be used in treatment of joint pain by topical application to the joint in which pain if suffered.

[149] **Example 3** - Effect of DMSO and Glycerine on NSAID permeation through Human Skin *In Vitro*

[150] ***Methods:*** Finite-dose *in vitro* diffusion studies were undertaken using dermatomed human female abdominal skin (500 µm).

[151] These experiments were performed over 24 hours using stainless steel, flow through diffusion cells based on those described previously (Cooper, E.R. *J. Pharm. Sci.* 1984, *73*, 1153-1156) except that the cell was modified to increase the diffusion area to 1.0cm$^2$. The formulations were applied using a finite dose technique (Franz, T.J. *Curr. Probl. Dermatol.,* 1978, *7,* 58-68) to mimic clinical dosing conditions at an applied dose volume of 3.6 µL /cm$^2$. A piece of stainless steel wire mesh was placed directly below the skin in the receptor chamber of the of the diffusion cell to maintain a turbulent flow of receptor solution below the skin. The diffusion cells were maintained at a flow rate of approximately 0.5 mL/hr by a microcassette peristaltic pump (Watson Marlow 505S UK). The cells were kept at 32 ± 1°C by a heater bar and the samples were collected into appropriately sized glass vials for a period of 24 hr. The receptor solutions (Phosphate Buffered Saline pH7.4) maintained sink conditions below the skin.

[152] The formulations are shown in Table 1

[153] Table 1

| Formulation | IBU (% w/v) | DMSO (% w/v) | Glycerol (% w/v) | MIlliQ water (% v/v) | IPA |
|---|---|---|---|---|---|
| **A** | 5 | 0 | 5 | 34.5 | to volume |
| **B** | 5 | 5 | 5 | 34.5 | to volume |
| **C** | 5 | 5 | 0 | 34.5 | to volume |

[154] ***Results*:** DMSO in combination with Glycerol was found to enhance the permeation of Ibuprofen through human epidermis in vitro. The results are presented in Figure 1 which compares the diffusion of a composition of the invention (B) with corresponding composition comprising only DMSO and not glycerol (C) or glycerol and not DMSO (A) as set out in the table above.

[155] Composition B may be used in treatment of joint pain by topical application to the joint in which pain if suffered.

[156] **Example 4**

[157] Formulations 1 to 6 in Table 2 are prepared by combining the components in the amounts shown.

[158] Table 2

| Formul -ation | Active | Polar Aprotic solvent | Polyol | Water | Other excipients | Volatile solvent |
|---|---|---|---|---|---|---|
| 1 | 5%w/v Ibuprofen | 5%w/v DMSO | 5%w/v Glycerol | 34.5%v/v | n/a | IPA to volume |
| 2 | 0.1 - 5%w/v Diclofenac | 5%w/v DMSO | 1%w/v Glycerol | 45%v/v | 10% Oleyl alcohol | IPA to volume |
| 3 | 0.1 - 5%w/v Naproxen | 5%w/v DMSO | 1%w/v Glycerol | 50%v/v | 10% Oleyl alcohol | IPA to volume |
| 4 | 1.0 - 8.0%w/v ciclopirox olamine | 25% v/v ethyl acetate | 5%w/v Glycerol | n/a | n/a | 95% Ethanol to volume |
| 5 | 1.0 - 8.0%w/v ciclopirox | 5%w/v DMSO | 5%w/v Glycerol | n/a | 2% polyvinyl pyrrolidone | 95% ethanol to volume |
| 6 | 0.1 – 5%w/v Ketoprofen | 1%w/v DMSO | 5%w/v Glycerol | 34%v/v | 10% Oleyl alcohol | IPA to volume |

[159] Compositions 1, 2, 3 and 6 may be used to treat joint pain by topical application to the joint in which pain is suffered.

[160] Compositions 4 and 5 may be used to treat skin fungal infections by topical to mycoses such as tinea versicolor.

**CLAIMS**

1. A topical composition comprising:

from 0.01 to 15% w/v of at least one active agent selected from the group consisting of antifungals and anti-inflammatory actives;

from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate;

from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and

from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof.

2. The topical composition according to claim 1 wherein the active is present in an amount in the range of from 0.01% to 10% w/v of the composition.

3. The topical composition according to claim 1 or claim 2 wherein the polar aprotic solvent is DMSO present in an amount in the range of from 1% to 10% w/v of the composition.

4. The topical composition according to any one of claims 1 to 3 wherein the polyol is present in an amount in the range of from 1% to 15% w/v of the composition.

5. The topical composition according to any one of claims 1 to 4 wherein the composition further comprises water in an amount of up to 55% v/v of the composition.

6. The topical composition of any one of the previous claims, wherein the polyol is glycerol.

7. The topical composition of any one of the previous claims, wherein the weight ratio of polar aprotic solvent to polyol is from 10:1 to 1:10, preferably from 2:1 and 1:2.

8. The topical composition of any one of the previous claims wherein the active agent is present in an amount in the range of from 0.1% to 5% w/v of the composition.

9. The topical composition according to any one of the previous claims wherein the active agent is an antifungal.

10. The topical composition according to any one of the previous claims wherein the active agent is an antifungal selected from the group consisting of azoles, echinocandins, polyenes, allylamines, imidazoles, triazoles, thiazoles, allylamines.

11. The composition of one of the previous claims, wherein the active agent comprises at least one antifungal agent selected from the group consisting of, ciclopirox or its olamine, amorolfine or its salt, amorolafine, bifonazole, tavarole (AN2690), flucytosine, griseofulvin, haloprogin, tolnaftate, terbinafine, intraconazole, fluconazole, clotrimazole, griseofulvin, flucytosine, ketoconazole, voriconazole, naftifine, nystatin, undecylenic acid, econaxzole, miconazole, miconozole nitrate, mycostatin, tolnaftate, oxiconazole, oxiconazole nitrate, sertacanazole, sulconazole, sulconazole nitrate, luliconazole, efinaconazole , butoconazole, fenticonazole, isoconazole, tioconazole, fluconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, and terconazole, abafungin, terbinafine, amorolfine, naftifine, butenafine, anidulafungin, caspofungin, micafungin, amphotericin b, haloprogin, clioquinol, posaconazole,17-AAG, E1210, D75-4590, isavuconazonium sulfate and micafungin.

12. The composition of one of the previous claims, wherein the active agent comprises an anti-inflammatory agent selected from the group consisting of corticosteroids and nonsteroidal anti-inflammatory drugs.

13. The topical composition according to any one of the previous claims wherein the composition comprises atleast one anti-inflammatory corticosteroid selected from the group consisting of betamethasone, betamethasone valerate, betamethasone dipropionate, diflucortolone valerate, cortisone, methylprednisolone aceponate, clobetasone butyrate, dexamethasone, dexamethasone 21-phosphate, fludrocortisone, flumethasone, fluocinonide, fluocinonide desonide, fluocinolone, fluocinolone acetonide, fluocortolone, halcinonide, halopredone, hydrocortisone,

hydrocortisone 17-valerate, hydrocortisone 17-butyrate, hydrocortisone 21-acetate methylprednisolone, prednisolone, prednisolone 21-phosphate, prednisone, triamcinolone, triamcinolone acetonide, alclometasone, alclometasone dipropionate, clobetasol propionate, clocortolone pivalate, desonide, desoximetasone, diflorasone diacetate, fluticasone, halobetasol propionate, hydrocortisone butyrate, triamcinolone acetonide, , fluocinolone acetonide, mometasone furoate, mometasone, fluticasone propionate and prednicarbate.

14. The topical composition according to any one of the previous claims wherein the active agent comprises at least one selected from the group consisting of inhibitors of COX-1, inhibitors of COX-2, naproxen, ibuprofen, ketoprofen, diclofenac, sulindac, etodolac, flubiprofen, piroxicam, ketorolac, indomethacin, meloxicam, mefenamic acid, nabumetone, oxaprozin, meclofenamate, tolmetin and salts thereof thereof.

15. The topical composition according to any one of the previous claims, wherein the active agent is present in an amount between 0.1% to 5%, by weight of the composition.

16. The topical composition of any one of the previous claims, further comprising a thickener in an amount in the range of from 0.1% to 5% w/v of the composition.

17. The composition of claim 16, wherein the thickener is selected from the group consisting of polyacrylic acids; and acylic acid copolymers, agar, acacia, carrageenan, food starch, gelatins, germ Arabic, guorgem, hydroxyethyl cellulose hydroxypropymethyl cellulose, protein, polyvinyl pyrrolidone; guargum, xanthan gum, gelatin, methylcellulose, methylhydroxypropylcellulose, polypropylcellulose, polypropylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hypromellose, carboxymethyl cellulose, sodium gluconate, carrageenan, cetyl alcohol, stearyl alcohol, myristal alcohol, octyldodecanol, pectin, polyvinyl alcohol, polyethylene glycol and starches and starch derivatives.

18. The topical composition according to any one of the previous claims wherein, the viscosity is in the range of from 15cp to 1000 cp.

19. The composition according to any one of the preceding claims, further comprising a physiologically acceptable surfactant.

20. A method of treatment of fungal infection of the skin or mucous membrane comprising topically applying the surface of the skin or mucous membrane a topical composition according to any one of claims 9 to 11.

21. A method of treatment of fungal infection of the skin or mucous membrane comprising topically applying the surface of the skin or mucous membrane a topical composition comprising:

from 0.1% to 10% w/v of at least one antifungal active and optionally an anti-inflammatory agent;

from 1% to 10% w/v of DMSO;

from 1% to 10% w/v of glycerol;

from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally from 5% to 55%w/v water.

22. A method according to claim 21, wherein the anti-inflammatory agent is present in an amount in the range of from 0.1% to 5% w/v of the composition.

23. A method of treatment of joint pain in a subject comprising topically applying the affected joint a topical composition according to any one of claims 12 to 14.

24. A method of treatment of joint pain comprising topically applying to the joint a topical composition comprising:

from 0.1% to 10% w/v of at least one anti-inflammatory active agent;

from 1% to 10% w/v of DMSO;

from 1% to 10% w/v of glycerol;

from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof; and

optionally from 5% to 55%w/v water.

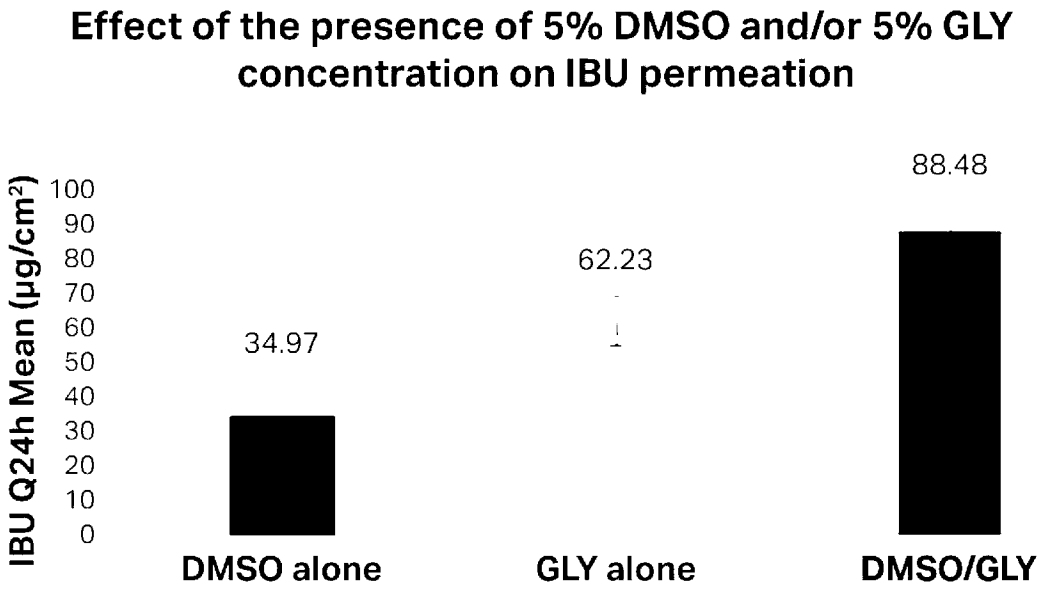
Effect of the presence of 5% DMSO and/or 5% GLY concentration on IBU permeation
IBU Q24h Mean (µg/cm²)
100
90
80
70
60
50
40
30
20
10
0
34.97
62.23
88.48
DMSO alone
GLY alone
DMSO/GLY

Figure 1

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/AU2015/000457**

A. CLASSIFICATION OF SUBJECT MATTER

***A61K 47/20 (2006.01)*** ***A61K 47/08 (2006.01)*** ***A61K 47/10 (2006.01)*** ***A61K 31/192 (2006.01)*** ***A61K 31/573 (2006.01)*** ***A61K 31/57 (2006.01)*** ***A61K 31/135 (2006.01)*** ***A61K 31/4412 (2006.01)*** ***A61K 31/196 (2006.01)*** ***A61P 31/12 (2006.01)*** ***A61P 29/00 (2006.01)***

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)

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)

Databases:WPIAP, EPODOC, Medline, Biosis, CAplus and EMBASE Keywords Used: anti-inflammatory, antifungal, ciclopirox, ibuprofen, diclofenac, naproxen, ketoprofen, betamethasone, topical, mucosa and like terms

Patentscope, Espacenet and AusPat: Applicant and inventor name search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| | Documents are listed in the continuation of Box C | |

[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 |
|---|---|
| 19 October 2015 | 19 October 2015 |
| **Name and mailing address of the ISA/AU** | **Authorised officer** |
| AUSTRALIAN PATENT OFFICE<br>PO BOX 200, WODEN ACT 2606, AUSTRALIA<br>Email address: pct@ipaustralia.gov.au | Arati Sardana<br>AUSTRALIAN PATENT OFFICE<br>(ISO 9001 Quality Certified Service)<br>Telephone No. 0262832905 |

| INTERNATIONAL SEARCH REPORT<br>C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT | | International application No.<br>**PCT/AU2015/000457** |
|---|---|---|
| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | GB 872,893 A (COATES LAURENCE VANN, TATTERSAL KEITH and SIMMONITE DONALD) 12 July 1961<br>page 1, lines 50-63; Example 3 and claims | 1, 2, 4,5, 7-9 and 15-20 |
| X | US 2001/0046526 A1 (GREENFELDER G. P.) 29 November 2001<br>Abstract; [0028]; claims 15-16, page 2, column 2; [0061] to [0063]; Example 4 on page 8 and [0072] to [0082]; [0114] and [0149] | 1-24 |
| X | US 2007/0134232 A1 (STUDIN JOEL and GIULIANO ROBERT) 14 June 2007<br>[0007] to [0009]; [0015] to [0016]; [0020] and Example | 1-5, 7, 8 and 12-19 |
| X | US 6,455,592 B1 (LAUGIER JEAN-PIERRE et al.,) 24 September 2002<br>Abstract; Example 7; column 4, lines 1-30; columns 4 and 7; and claims 4 and 6 | 1-11 and 15-21 |
| X | WO 2001/052897 A2 (PANACEA BIOTEC LIMITED [IN/IN]) 26 July 2001<br>Abstract; page 4, lines 1-5; page 5, last five lines; page 6, third paragraph; page 7, second paragraph; page 10, second paragraph and examples 1 and 2 | 1-8, 12-19, 23 and 24 |
| A | WO 2010/125470 A2 (FOAMIX LTD.) 04 November 2010<br>see whole document in particular Abstract and examples 1-12 | 1-24 |

**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/AU2015/000457**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

**See Supplemental Box for Details**

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

**Supplemental Box**

**Continuation** of: **Box III**

The International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of feature from the prior art. Where different claims have different distinguishing features they define different inventions.

The International Searching Authority has found that there are two different inventions as follows:

Invention 1: Claims 9, 10 & 21 (all completely) and; claims 1-8, 11-20, 22-23 (all partially) are to topical compositions comprising from 0.01 to 15% w/v of an antifungal active agent; from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1 to 20% of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof. Claims of invention 1 are also to topical compositions comprising from 0.01 to 15% w/v of at most more than one active agent including a combination of an antifungal and an anti-inflammatory active agent; from from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1 to 20% of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof. The method of treating fungal infection using the topical compositions above or the topical composition of claim 21.

It is considered that "a topical composition comprising from 0.01 to 15% w/v of an antifungal active agent; from 0.1 to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof" constitutes the first distinguishing feature.

Invention 2: Claim 24 (completely) and; claims 1-8, 11-20, 22-23 (all partially) are to topical compositions comprising from 0.01% to 15% w/v of an anti-inflammatory active agent; from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1 to 20% of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof. Claims of invention 2 are also to topical compositions comprising from 0.01 to 15% w/v of at most more than one active agent including a combination of an anti-inflammatory and an antifungal active agent; from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1 to 20% of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof. The method of treating joint-pain using the above topical compositions or the topical composition of claim 24.

It is considered that "a topical composition comprising from 0.01% to 15% w/v of an anti-inflammatory active agent; from 0.1% to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1 to 20% of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof" constitutes the second distinguishing feature.

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is technical relationship among the claimed inventions involving one or more of the same or corresponding special technical feature. PCT Rule 13.2, second sentence defines a special technical feature as a feature which makes a contribution over the prior art.

When there is no special technical feature common to all the claimed inventions there is no unity of invention.

The only feature common to all of the claimed inventions and which provides a technical relationship among them is "a topical composition comprising from 0.01 to 15% w/v of an active agent; from 0.1 to 20% w/v of polar aprotic solvent selected from the group consisting of DMSO, acetone and ethyl acetate; from 0.1% to 20% w/v of polyol selected from glycerol, propylene glycol, sorbitol and mixtures thereof; and from 40% to 90% v/v of lower alkanol selected from the group consisting of ethanol, isopropanol and mixtures thereof."

However this feature does not make a contribution over the prior art because it is disclosed in D1: GB 872,893 which discloses antifungal compositions suitable for application to human skin for treating mycotic infections, the antifungal composition comprises antimycotic actives 2-alkyloxybenzamide and 2-alkoxyacetophenone within 0.01 to 15% w/v, propylene glycol within 0.1% to 20% w/v, acetone within 0.1 to 20 % w/v, and isopropanol at concentration within 40% to 90% v/v (see page 1, lines 50-63; Example 3 and claims).

## Supplemental Box

This means that the common feature is not a special technical feature within the meaning of PCT Rule 13.2, second sentence, since it is known and therefore makes no contribution over the prior art.

Because the common feature does not satisfy the requirement for being a special technical feature it follows that it cannot provide the necessary technical relationship between the identified inventions. Therefore claims do not satisfy the requirement of unity of invention a posteriori.

| INTERNATIONAL SEARCH REPORT<br>Information on patent family members | International application No.<br>**PCT/AU2015/000457** |
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**End of Annex**

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.