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(54) Title: ANTIMICROBIAL COMPOSITIONS COMPRISING DOCUSATE

(57) Abstract: Antimicrobial compositions suitable for treatment of conditions including onychomycosis, poor nail appearance and infected tissue and also suitable for sanitizing surfaces contain a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea. Such compositions do not rely on a separate pharmaceutically active agent for their antimicrobial properties.

WO 2009/054992 A1

ANTIMICROBIAL COMPOSITIONS

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/000,628 filed October 25, 2007 and U.S. Provisional Application No. 61/196,033 filed October 14, 2008, the contents of which are incorporated herein by reference in their entirety.

BACKGROUND

10 The skin is the largest organ in the body and serves important functions that are necessary to life. The skin acts as a barrier to the invasion of various pathogens and toxic substances. Skin is composed of the two layers: the epidermis is the first layer; and the dermis is the layer below the epidermis.

 However, because it must serve as a barrier to the ingress of pathogens and toxic materials, and the egress of physiologic fluids, the skin is highly impermeable. It must be impermeable to preserve its own integrity while at the same time maintaining the delicate dynamic electrolyte balance of the body. The skin must serve a containment function; it must also function as a microbial, chemical, radiation and thermal barrier.

20 A good deal of this impermeability of the skin results from the nature of one very thin layer created by normal developmental and physiological changes in the skin. After cells are formed in the basal layer, they begin to migrate toward the skin surface, until they are eventually sloughed off. As they undergo this migration, they become progressively more dehydrated and keratinized. When they reach the surface, just prior to being discarded, they form a thin layer of dense, metabolically inactive cells approximately ten microns (10-15 cells) thick. This layer is called the stratum corneum or the "cornified layer". As a result of the high degree of keratinization of the cells which comprise the stratum corneum, a formidable barrier is created. Therefore, penetration via the nonpolar route, i.e., across the membrane of these cells, remains most difficult.

30

The problem is even more difficult when trying to deliver an antimicrobial composition through the unguis, the horny cutaneous plates on the dorsal surface of the distal end of the terminal phalanx of a finger or toe (fingernails and toenails).

They are made up of flattened epithelial scales developed from specialized epithelial cells called the matrix. The thick and hardened nature of nails renders access
5 through, and to the area below, nearly impossible with current topical formulations.

Thus, it would be advantageous to have a formulation that is effective when applied to the skin or nails. In particular, the composition should be easy to apply topically in a quantitative amount, rapidly permeate the skin to get where needed,
10 have a pleasant odor and appearance, and not require cleansing to remove the composition.

In addition, it would be advantageous to have a composition that does not rely on a traditional active agent for its antimicrobial activity. For example, traditional active agents are associated with the development of resistant organisms.
15 In addition, certain traditional active agents, particularly antifungals, are associated with a relatively high incidence of side effects.

SUMMARY OF THE INVENTION

In certain embodiments, the invention includes a method for treating or
20 inhibiting a microbial infection in a subject, comprising administering to the subject a therapeutically effective amount of a formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a surfactant wherein the surfactant is a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial
25 agent.

In other embodiments, the invention includes a method for reducing or inhibiting growth of microbes on an inanimate surface, comprising applying an effective amount of a disinfectant formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a surfactant wherein the surfactant is a docusate
30 salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.

In yet other embodiments, the invention includes a method for improving the appearance or health of nails, claws, hooves and other epithelial stratum lucidum, comprising applying to the bed of a nail, claw, hoof or other epithelial stratum lucidum an effective amount of a formulation comprising a mixture of a polar lipid,
5 a biocompatible organic solvent, a surfactant wherein the surfactant is a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.

In further embodiments, the invention includes a method for treating or
10 inhibiting the enlargement of soft tissue wounds or infected external mucosal tissues, comprising applying a therapeutically effective amount of a formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a surfactant wherein the surfactant is a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of
15 an additional antimicrobial agent.

The invention also includes containers containing and articles partially or completely impregnated with an antimicrobial formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a surfactant wherein the surfactant is a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that
20 said formulation does not include an effective amount of an additional antimicrobial agent.

In addition, the invention includes the use of a formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a surfactant, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not
25 include an effective amount of an additional antimicrobial agent, in the manufacture of a medicament or disinfectant for the treatment or inhibition of microbial infection.

The advantages of compositions of the invention include, but are not limited to: avoidance of the risks associated with parenteral treatment; elimination of the inconveniences of parenteral treatment; avoidance of the variable rates of absorption
30 and metabolism inherent in oral treatment; and elimination of gastrointestinal irritation resulting from exposing the gastrointestinal tract to pharmaceutical actives, preservatives, tableting agents, and the like. Most importantly, topical delivery

possesses the potential for effectively treating conditions that are local in nature (or which exhibit local manifestations), systemically as well as locally with the same treatment regimen.

5 DETAILED DESCRIPTION

Compositions of the invention comprise a mixture of a polar lipid, a biocompatible organic solvent, a surfactant, water, and urea, at a pH of between about 5.5 and 8.0 and preferably between 6.0 and 7.0. Such compositions preferably do not include an effective amount of an additional antimicrobial agent. In addition,
10 the composition may optionally include cholesterol or a preservative such as benzyl alcohol.

In certain embodiments, compositions of the invention comprise a polar lipid, such as lecithin or phosphatidylcholine, and two biocompatible organic solvents, one chosen from the group of esters and one chosen from the group of
15 liquid dihydric and polyhydric alcohols, a preservative, water, a thickener and urea, at a pH of between about 5.5 and 7.5 and preferably between 6.0 and 7.0. The compositions may additionally contain other optional components that reduce skin irritation, or enhance their cosmetic appeal or acceptability, e.g, pigments, fragrances, perfumes, and the like. The compositions of the present disclosure
20 typically contain about 10 to 30% by weight of the polar lipid (e.g., 10-15%, 15-20%, 20-25%, or 25-30%).

In certain embodiments, the polar lipid is lecithin or phosphatidylcholine. In certain such embodiments, the lecithin or phosphatidylcholine is of a high quality, pharmaceutical grade. Appropriate lecithin and phosphatidylcholine may be
25 obtained as commercially available soya lecithin or soya phosphatidylcholine. Typically, soya lecithin is used in the composition of this invention.

The biocompatible organic solvent may be any non-toxic solvent in which the polar lipid and urea are soluble. In certain embodiments, the biocompatible organic solvent includes both an ester and a di- or polyhydric alcohol.

30 Typically, the esters are fatty mono esters having a structure, obtainable by replacing the active hydrogen of a fatty acid having 4 to 22 carbon atoms and more typically having 8 to 18 carbon atoms by the alkyl group of a monohydric alcohol,

particular example being 12 carbon atoms. The fatty acid can be saturated or unsaturated and more typically is saturated. The monohydric alcohol typically contains 2 to 8 carbon atoms and more typically 2 to 5 carbon atoms, a particular example being 3 carbon atoms. Acceptable esters for this purpose include, but are not limited to isopropyl esters. Typically, the ester is isopropyl myristate or isopropyl palmitate, with isopropyl myristate being preferred.

The biocompatible organic dihydric and polyhydric alcohol solvents may be any non-toxic di- or polyalcohol in which the polar lipid is soluble. Acceptable dihydric and polyhydric alcohols for this purpose include, but are not limited to di- and tri-alcohol alkanes. Typically, the alcohols contain 3 to 8 carbon atoms and more typically 3 to 5 carbon atoms and are saturated alcohols. Preferably, the polyalcohol is propylene glycol or glycerol, with propylene glycol being particularly preferred.

The compositions of the present disclosure typically contain about 2 to 30% by weight and more typically 4 to 10% by weight of the ester and, when present, about 0.5 to about 20% by weight, more typically 1 to about 20% weight, and even more typically 1 to about 10% weight of the alcohol. Many of the compositions contain about 2 to about 20% by weight or, 2 to about 10% weight of the alcohol. Compositions according to the present disclosure exhibit reduced skin irritation.

In preparing the composition of this invention, the polar lipid is typically dissolved in the organic solvent at mass ratios anywhere from 5:1 to 1:5. Preferably, the polar lipid and organic solvent are mixed in even mass ratios. Thus, in one embodiment of the invention, soya lecithin and isopropyl myristate are mixed in equal mass ratios and mixed until the lecithin is evenly distributed in the isopropyl myristate. This mixture, called lecithin organogel (L.O.), is stable and may be used even after prolonged storage without loss of activity.

In certain embodiments, the polar lipid is dissolved in the organic ester solvent and di- or polyhydric alcohol solvent at mass ratios from about 5:1:1 to about 1:5:5. Preferably, the polar lipid and organic ester solvent and polyalcohol solvent are mixed in equal mass ratios. Thus, in one embodiment of the invention, soya lecithin, isopropyl myristate, and propylene glycol are mixed in equal mass ratios and mixed until the lecithin is evenly distributed.

Depending on the desired characteristics of the final formulation, a surfactant can be included in the formulation at a concentration of between about 0.5 or 1-20% (e.g., 0.5 or 1-5%, 5-10%, 10-15% or 15-20%) of the final composition mass.

Preferably, the surfactant is one which is compatible with administration in vivo without elicitation of undesirable side effects. One preferred surfactant is a docusate salt, such as docusate sodium or docusate calcium, and its more water soluble form, docusate sodium benzoate. Other appropriate ionic or non-ionic surfactants that are optionally present in combination with the docusate salt include polysorbate 80 (e.g., TweenTM 80), tetradecyltrimethylammonium bromide, pentaerythritol glycol monododecyl ether, poloxamer 407 and triethanolamine lauryl sulfate.

Next, an amount of urea, preferably as an aqueous solution, is typically added to the solvent-polar lipid mixture. In certain embodiments, the urea is added so that the urea concentration will be between about 1% and 20% by mass (e.g., 1% to 15% or 5% to 10%) of the final composition mass. Thus, using a 20% aqueous solution of urea, about 10 grams is added to about 100 grams of the solvent-polar lipid mixture.

When a thickener is present, the thickener is advantageously selected from common National Formulary or United States Pharmacopeia thickening agents including, but not limited to appropriate polymer weights of polyethylene glycol, polyvinylpyrrolidone, a polyacrylic acid (e.g., carbomer) and methylcellulose. The amount of thickener is typically about 0.05 to about 5% by weight.

Thus in a specific example, about 5 grams of a 10% aqueous solution of urea, containing 0.7% Carbomer 934, is added to about 100 grams of the surfactant-solvent-polar lipid mixture.

Optionally, one or more preservatives may be included in a composition of the present invention. The preservative protects the composition from microbial contamination and/or oxidation. As such, the preservative can include an antioxidant. Preservatives, such as methyl dibromoglutaronitrile, methylchloroisothiazolinone, phenoxyethanol, diazolidinyl urea, imidazolidinyl urea, iodopropynyl butylcarbamate, chloromethylisothiazolinone, methylisothiazolinone, sodium benzoate, chloracetamide, EDTA, DMDM-hydantoin, quaternium-15, vitamin E and its derivatives including vitamin E acetate,

vitamin C, butylated hydroxytoluene, methylparaben, ethylparaben, propylparaben, butylparaben, essential oils including tea tree, neem seed, and thyme, extracts including grapefruit seed and rosemary, or any mixtures thereof, may be included as a preservative in a composition of the present invention. In one embodiment, a
5 composition of the present invention may have a combination of methylparaben, propylparaben, or butylparaben.

When present, about 0.01 wt. % to about 1 wt. % of preservative may be included in a composition of the present invention. In some embodiments, the present composition has one or more preservatives in an amount that totals about
10 0.05 wt. % to about 0.50 wt. % of the total weight of the composition.

In certain embodiments, the formulation comprises a biocompatible organic solvent, a polar lipid, a docusate salt water, urea, at a pH of about 5.5 to 8.0, wherein the polar lipid is lecithin or phosphatidylcholine, the biocompatible organic solvent is an isopropyl ester selected from the group consisting of isopropyl myristate and
15 isopropyl palmitate, and the urea is present at a concentration of about 5 to 20% by mass of the final composition.

In certain embodiments, the formulation comprises two biocompatible organic solvents, a polar lipid, a docusate salt and optionally one or more additional surfactants, water, urea and thickener; wherein the organic solvents comprise an
20 ester and a dihydric alcohol and/or polyhydric alcohol. In certain such embodiments, the formulation comprises about 2 to about 30% of the ester and about 0.5 to about 20% of the dihydric alcohol and/or polyhydric alcohol. For these embodiments, a preferred ester is isopropyl myristate, a preferred alcohol is propylene glycol, a preferred polar lipid is lecithin and a preferred thickener is methyl cellulose and/or
25 polyacrylic acid (e.g. Carbopol). One or more of these preferred components may be present in a formulation.

In one exemplary embodiment, the formulation consists essentially of two biocompatible organic solvents, a polar lipid, a docusate salt and optionally one or more additional surfactants, water, urea and thickener; wherein the organic solvents
30 comprise an ester and a dihydric alcohol and/or polyhydric alcohol; and wherein the composition comprises about 2 to about 30% of the ester and about 0.5 to about 20%

of the dihydric alcohol and/or polyhydric alcohol. Such formulations optionally comprise a preservative.

In another exemplary embodiment, the formulation comprises about 10 to about 30% by weight of the polar lipid; about 0.5 to about 15% by weight of the docusate salt, about 40 to about 65% by weight of water, about 1 to about 15% by weight of the urea and about 0.05 to about 5% of weight of the thickener.

In yet another exemplary embodiment, the formulation consists essentially of isopropyl myristate, lecithin, docusate sodium, propylene glycol, polysorbate 80, water, urea, methylcellulose, polyacrylic acid and triethanolamine.

Upon formulation of the above described composition with the pharmaceutically active agent, the pH is adjusted to about a pH of 5.5 to 8.0, such as 5.5 to 7.5, 6.0 to 8.0 or 6.0 to 7.0. This is easily accomplished, for example, by addition of aqueous sodium hydroxide, as the compositions initially tend to have an acid pH. However, if the composition is alkaline, addition of acid to reduce the pH would be desirable. This is easily accomplished by addition of aqueous hydrogen chloride, citric acid or a biological buffer such as sodium carbonate or triethanolamine, as in triethanolamine salicylate. Once the composition reaches a pH in the desired range of about 6.0 to 7.0, the formulation thickens and forms a gel for topical administration.

For ease of preparation, it is convenient to prepare a first gel composition, which can be used to add to other components in the formulation of a final composition for topical administration. There are several possible formulations of the speed-gel. For example, a speed-gel may be prepared by mixing lecithin organogel (L.O.), as a 1:1 (m/m) mixture of lecithin and isopropyl myristate, with LID oil (a 1:1 [m/m] mixture of L.O. and docusate sodium), dissolving additional docusate sodium powder into this mixture, and then adding aqueous urea.

In one example, the final concentrations are: L.O.=25%; docusate sodium=15%; urea=10%; and water=50%. These ratios may easily be varied such that the final amounts of each component are as follows: L.O.=20-30%; docusate sodium or another surfactant=10-20%; urea=5-20%; and water=30-60%. The speed-gel may then be added to solubilized active ingredients and other excipients which may be useful in solubilizing the active ingredient, such as DMSO, peppermint oil,

glycerin, and/or polyethylene glycol. An homogenous mixture is then made by carefully blending the various components.

In another embodiment, a composition is prepared by mixing lecithin organogel (L.O.), as a 1:1:1 (m/m/m) mixture of lecithin, isopropyl myristate and propylene glycol, with LID oil (a 1:1 [m/m] mixture of L.O. and docusate sodium),
5 dissolving additional surfactant and/or docusate sodium powder into this mixture, and then adding thickened aqueous urea.

In one example, the final concentrations are: L.O.=30%; docusate sodium=9%; urea=5%; thickener=1%; and water=55%. These ratios may easily be varied such that the final amounts of each component are as follows: L.O.=15-50%;
10 docusate sodium and/or another surfactant=3-15%; urea=1-15%; thickener=0.5-5%; and water=40-65%. Excipients that may be useful include L.O., propylene glycol, isopropyl myristate, peppermint oil, glycerin, and/or polyethylene glycol. A homogenous mixture is then made by carefully blending the various components.

In an additional embodiment, a composition is prepared by mixing lecithin organogel (L.O.), as a mixture of lecithin, isopropyl myristate, and propylene glycol, with docusate sodium and optionally an additional surfactant (e.g., polysorbate 80), and then adding to this mixture a homogenous composition of aqueous urea, thickener (e.g., polyacrylic acid), one or more preservatives (e.g., methylparaben,
15 propylparaben, butylparaben), and optionally additional surfactant (e.g., a polyethylene glycol-polypropylene glycol copolymer such as poloxamer 407). Trolamine is added to this combined mixture to adjust the pH, and a homogenous composition is then made by carefully blending the various components.

It is preferable that the components be compounded in the order: L.O., then
25 surfactant, then aqueous urea, then pH adjustment. Varying the approach to mixing the gel slightly but maintaining the integrity of the appropriate ratios of the components and the order of addition, still allows for the formation of an acceptable gel. Alteration of the ratios beyond the limits described herein, may interfere with product consistency and gel formation.

30 Additional details on preparation of compositions useful in the invention can be found, for example, in U.S. Patent No. 5,654,337 and U.S. Patent Publication

Nos. 2006/0078579, 2006/0078580, 2006/0110342 and 2006/0122279, the contents of which are incorporated herein by reference.

Once the formulations described above have been prepared, use of the formulations is typically a simple matter of applying the formulation to the areas
5 where it is desired.

The compositions of the invention have activity against a wide variety of microbes. In certain embodiments, the microbes are selected from Gram negative bacteria, Gram positive bacteria, anaerobic bacteria, fungi and viruses, particularly fungi or one or more of the types of bacteria listed above. All microbes have the
10 ability to resist or become tolerant to chemotherapeutic agents, antimicrobial agents, or antibiotics. Antimicrobial resistance may be innate to the microorganism, the result of genetic mutation within the microbial genome, or acquired through the lateral or vertical transfer of resistance genes or genetic elements from other organisms. Antibiotic resistance is the ability of a microorganism to survive and/or
15 reproduce in the presence of an antimicrobial agent(s) that was previously effective at killing or retarding reproduction of the microorganism. The compositions of the present invention can have activity against a variety of microorganisms resistant to one or more antimicrobial agents. The microbes may be resistant to one or more antimicrobial (e.g., antibacterial, antifungal, and antiviral) agents. For example,
20 compositions of the invention can have activity against fungi that are resistant to at least one allylamine (e.g., naftifine, terbafine). Microbes can be treated using compositions of the invention on essentially any area of the body, including the scalp, face, axilla, arms, trunk, mucosal membranes, hands, fingernails, groin, legs, toenails and feet. Compositions of the invention are effective against both infections and microbes
25 present on the surface (e.g., those removed by a surgical scrub or other skin disinfectant). In particular, compositions of the invention are effective in reducing the number of microbes or treating a microbial infection on or in epithelial cells, such as stratified squamous epithelial cells and epidermal appendages (e.g., keratinized or non-keratinized), stratified cuboidal cells (e.g., sweat glands,
30 follicles), pilosebaceous glands, and the junction of epithelium and mucous membranes. In certain embodiments, cuboidal cells of the gastrointestinal tract are excluded.

An effective amount of a composition of the invention is an amount sufficient to partially or completely achieve the desired objective. For example, an amount effective to treat or inhibit an infection is an amount that reduces the infection, inhibits the continued growth of an infection, reduces the symptoms
5 resulting from an infection or maintains an infection-free or substantially infection-free (e.g., asymptomatic) state. Similarly, an amount effective to reduce or inhibit growth on a surface is an amount sufficient to reduce the number of microbes or to reduce the rate of growth of microbes. An effective amount of antimicrobial agents is also an amount effective to treat or inhibit an infection is an amount that reduces
10 the infection, inhibits the continued growth of an infection, reduces the symptoms resulting from an infection or maintains an infection-free or substantially infection-free (e.g., asymptomatic) state.

Examples of fungal infections that can be treated by administering a composition of the invention include onychomycosis (also known as tinea unguium)
15 and dermatophytosis (also known as ringworm), which includes tinea pedis, tinea cruris, tinea versicolor, tinea corporis and tinea capitis. Fungal infections include those infections caused by organisms classified generically as yeast (e.g., single celled organisms) and molds (e.g., organisms that grow with hyphae). Such infections may be caused by, for example, one or more fungi selected from
20 *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, *Epidermophyton floccosum*, *Trichophyton violaceum*, *Microsporum gypseum*, *Microsporum canis*, *Microsporum audouinii*, *Trichophyton tonsurans*, *Trichophyton soudanense*, *Trichophyton capitis*, *Scytalidium*, *Scopulariopsis* and *Aspergillus*, particularly for onychomycosis. Fungi that are advantageously treated with a
25 composition of the invention include *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Trichophyton capitis*. Other fungal infections that can be treated using a composition of the invention include diaper dermatitis, thrush and candidal vaginitis.

Other microbial infections (or conditions related to a microbial infection)
30 that can be treated using a composition of the invention include vaginitis, vulvovaginitis, periodontal plaque, gingivitis, acne, rosacea, folliculitis, infected eczema, impetigo, seborrheic dermatitis, intertrigo, ecthyma, angular cheilitis,

paronychia, pitted keratolysis, an infected wound and an infected ulcer. For example, vaginitis and vulvovaginitis can be associated with one or more of *Candida*, chlamydia and human papillomavirus (HPV).

Bacterial infections that can be treated with compositions of the invention includes Streptococcus and Staphylococcus infections, particularly antibiotic-resistant Staphylococcus infections such as methicillin-resistant *S. aureus*.

Viral infections that can be treated with compositions of the invention include warts, HPV, herpes simplex 1 and 2, along with viral lesions.

Compositions of the invention are also useful for preventing superinfection of a wound or lesion caused by or associated with a first microbial infection (e.g., HIV transmission via a herpes lesion).

Compositions of the invention can also be used to sterilize surfaces, such as kitchen, bathroom and hospital floors, walls, cabinets and counter tops, medical devices and other inanimate objects in general. In addition, the compositions can be used as a surgical scrub and skin disinfectant.

For treating infections or otherwise in conjunction with treating a subject, a physician can determine the appropriate amount based on, for example, the condition to be treated, its severity and the age, weight and sex of the subject to be treated. Subjects include humans, companion animals (e.g., cats, dogs), livestock animals (e.g., horses, cows, sheep, goats, deer) and research animals (e.g., mice, rats, monkeys).

Compositions of the invention can be applied to the location where desired, such as topically (e.g., skin or nails) or on a mucosal membrane.

In embodiments where the appearance of a nail is improved, the improvements include one or more of the nail color, the nail clarity, the nail smoothness and the nail integrity. In other embodiments, improving the appearance of a nail involves improving the health of a nail where the nail is broken or damaged. The improvement in the nail includes, for example, decreasing the roughness of the nail surface, reducing any discoloration or opaqueness of the nail or reducing any splitting of a nail.

Wounds that can be treated using compositions of the invention include fungating tumors, bed sores, pressure ulcers, venous ulcers and arterial ulcers.

It is contemplated that the compositions of this invention are administered as frequently as required as long as local reactions or toxicity do not become a problem.

5 Compositions of the invention can be packaged in any appropriate container or impregnated (partially or completely) into an article. For purposes of the present invention, impregnated articles include articles that are coated with a composition as well as those where the composition is present on more than surfaces (e.g., the composition has to some degree penetrated into the article). Suitable containers include an aerosol can, an atomizer, a jar having a pump, a rollette and a tube
10 container. Suitable articles include medical devices, gauze pads, bandages, wound dressings, packages and packaging materials, tissues, towels and towelettes. For example, non-woven substrates such as wet-creped hand towels and spunbonded and meltblown polymeric web commonly used in disposable hospital items such as surgical drapes, gowns, bedsheets, pillow cases and textile materials and the like can
15 be impregnated with compositions of the invention. Hygienic face masks used by persons suffering from respiratory illness or by persons working in a dusty environment where the dust is contaminated with pathogenic fungal spores can be impregnated with an anti-fungally effective amount of compositions of the invention. Further, disposable diapers can be impregnated with compositions of the
20 invention as well as tampons and intravaginal sponges and the like. Compositions of the invention may also be provided in an appropriate carrier as a vaginal douche.

The following non-limiting examples are presented to further illustrate the present disclosure.

EXAMPLES

Example 1

Preparation of Formulations

5

To a clean 16 qt SS beaker (vessel #1) were added 100-120 g of purified water, USP. Stirrer #1 was positioned in the vessel and the speed was set so that a vortex was created while stirring. Next, 20 g of urea, USP was added to vessel #1, followed by 0.1 g of Carbopol 974P, NF, which was added slowly to avoid
10 clumping. The mixture was stirred for 30 min. The mixture was transferred to a clean, tared reaction vessel (vessel #2). Vacuum was applied and the mixture was stirred until a clear solution was obtained. Trolamine, NF (0.15 g) was added to vessel #2 slowly. Stirring was continued until the gel was smooth.

To a clean 6 qt SS beaker (vessel #3) were added 13.0 g of isopropyl
15 myristate, NF. Vessel #3 was placed on a hot plate and a stirrer was added. The speed was adjusted so that a vortex was created while stirring. To vessel #3 was added 14.6-14.7 g of lecithin, NF portionwise. Vessel #3 was heated to 40-45 °C. When the lecithin was dispersed, 1.05 g of Docusate sodium, USP was added to vessel #3. Next, 1.9 g of propylene glycol, USP was added to vessel #3, followed by
20 0.6 g of polysorbate 80, NF. Stirring was continued until all solids were dissolved. Vessel #3 was cooled to 25 °C in a water/ice bath.

The contents of vessel #3 were slowly added to vessel #2 while stirring continued. Once all of the vessel #3 contents had been added, the mixture was stirred for an additional 30 min.

25 To a clean, tared 2 qt SS beaker (vessel #4) was added the combined contents of vessels #2 and #3 with sufficient purified water, USP to bring the total mass in vessel #4 to 200 g. The final formulation contained 0.5% docusate sodium w/w and is referred to below as Formulation A.

Formulations B-I were prepared according to the method described above,
30 but with a weight percentage of docusate sodium of 1%, 1.5%, 3%, 5%, 7.5%, 10%, 15% and 20%, respectively. A control formulation included no docusate sodium.

Example 2

Preparation of Formulations

To a clean SS beaker (vessel #1) were added 344.3 g of purified water, USP.

5 Stirrer #1 was positioned in the vessel and the speed was set so that a vortex was created while stirring. Next, 55 g of urea, USP was added to vessel #1, and the mixture was continuously stirred until all solids were dissolved. Next, 0.275 g of Carbopol 974P, NF was slowly added to the mixture to avoid clumping, and the mixture was continuously stirred until all solid were dissolved. The internal

10 temperature of the mixture was then raised to $60\pm 5^{\circ}\text{C}$. Again, Stirrer #1 was positioned in the vessel and the speed was set so that a vortex was created while stirring. While maintaining the $60\pm 5^{\circ}\text{C}$ temperature, 0.55 g of methylparaben, 0.275 g propylparaben, and 0.11 g of butylparaben were added to the mixture and continuously stirred until all solids were dissolved. With constant stirring, 38.5 g of

15 Poloxamer 407 was added to mixture. The contents of the vessel were allowed to mix for 30 minutes or until the mixture was homogeneous.

To a clean SS beaker (vessel #2) were added 35.915 g of Isopropyl Myristate, NF. Vessel #2 was placed on a hot plate and a stirrer #2 was added. The speed was adjusted so that a vortex was created while stirring. While maintaining a

20 temperature of $60\pm 5^{\circ}\text{C}$, 40.205 g of lecithin, NF was added portionwise to vessel #2. With constant stirring and maintaining temperature, 27.5 g of docusate sodium, USP was added portionwise to the mixture and continuously stirred until all solids were dissolved. Next, 5.39 g of propylene glycol, USP was added to vessel #2, followed by 1.65 g of polysorbate 80, NF. Stirring was continued with the internal

25 temperature being maintained at $60\pm 5^{\circ}\text{C}$ until the mixture was homogeneous.

While continuously stirring, the contents of vessel #2 were slowly added to vessel #1. Once all of the vessel #2 contents had been added, the mixture was stirred for an additional 30 min or until homogeneous while maintaining the temperature at $60\pm 5^{\circ}\text{C}$. Next, 0.385 g of tolamine was added to the mixture. Stirring was continued

30 with the internal temperature being maintained at $60\pm 5^{\circ}\text{C}$ until the mixture was homogeneous. The mixture was cooled to 25°C in a water/ice bath.

The combined contents of vessels #1 and #2 were transferred to a clean SS beaker (vessel #3) and weighed. Purified water, USP was added to the mixture to bring the total mass in vessel #3 to 550 g. The contents were mixed until homogeneous. Finally, the pH of the mixture was determined. If nessessary, the pH of the mixture can be adjusted using a 1N NaOH or 1N HCl solution. After pH adjustment, the contents were mixed for five minutes and then pH was measured again. The procedure was repeated until the content were stably measured at pH 6.5. The final formulation contained 5.0% docusate sodium w/w.

10 Example 3

In Vitro Antimicrobial Activity of Formulations

As shown below in Table 1, the antifungal activity of Formulations A-I was assessed by placing an amount of the formulations on an agar plate inoculated with a dermatophyte. The inoculum was prepared from the 7-day-old cultures of dermatophyte isolates grown on potato dextrose agar slant. Briefly, 3 mL of sterile saline was added on the slant and rubbed gently with the help of sterile swab tip. The inoculum was collected into a sterile tube and kept for 20-30 minutes to settle down the heavy conidia and hyphal fragments. The upper homogenous phase containing conidia and small hyphal fragments was collected into the new sterile glass tube and adjusted to 0.5 McFarland density standards. Saboraud dextrose agar plates (150 mm size) were inoculated by dipping a sterile cotton swab two times into the respective inoculum suspension and evenly streaking the swab in three directions over the entire surface. The inoculated agar surface was allowed to dry for 10-15 min. To determine the zone of inhibition 6 mm well was made into the centre of the inoculated agar using sterile Pasteur pipette (Fisher Scientific, Nepean, Canada) and 100 µl of drug formulation loaded in the well.

Inhibition zone diameter was measured in millimeter (mm) using a dial caliper after 6-days of incubation at 28°C.

30 Formulations containing 5% w/w or more of docusate demonstrated activity against both dermatophytes.

Table 1: Antifungal activity of Formulations A-I against *T. rubrum* and *T. mentagrophytes* isolates using agar diffusion method.

Dermatophyte (# of isolates)	Formulation	Inhibition zone diameter (mm)	
		Range	Arithmetic mean
<i>T. rubrum</i> (6)	Control	00	00
	A	00	00
	B	00	00
	C	00	00
	D	00.00-14.00	6.67
	E	15.00-32.00	21.67
	F	26.00-36.00	31.67
	G	28.00-46.00	36.00
	H	36.00-52.00	44.00
	I	36.00-60.00	43.67
<i>T. mentagrophytes</i> (6)	Control	00	00
	A	00	00
	B	00	00
	C	00	00
	D	00	00
	E	12.00-18.00	15.67
	F	18.00-30.00	25.50
	G	22.00-38.00	27.67
	H	28.00-40.00	31.67
	I	26.00-44.00	35.00

CLAIMS:

1. A method for treating or inhibiting a microbial infection in a subject,
5 comprising administering to the subject a therapeutically effective amount of a formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.
- 10 2. A method for reducing or inhibiting growth of microbes on a surface, comprising applying an effective amount of a disinfectant formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an
15 additional antimicrobial agent.
3. A method for improving the appearance or health of nails, claws, hooves or other epithelial stratum lucidum, comprising applying to the bed of a nail, claw, hoof or other epithelial stratum lucidum an effective amount of a
20 formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.
4. A method for treating or inhibiting the enlargement of soft tissue wounds or infected external mucosal tissues, comprising applying a therapeutically
25 effective amount of a formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.
5. The method of any one of claims 1-4, wherein the polar lipid is lecithin or
30 phosphatidylcholine.

6. The method of any one of claims 1-4, wherein the biocompatible organic solvent is isopropyl palmitate or isopropyl myristate.
7. The method of any one of claims 1-4, wherein the formulation comprises a biocompatible organic solvent, a polar lipid, a docusate salt, water, urea, at a pH of about 5.5 to 8.0, wherein the polar lipid is lecithin or phosphatidylcholine, the biocompatible organic solvent is an isopropyl ester selected from the group consisting of isopropyl myristate and isopropyl palmitate, and the urea is present at a concentration of about 5 to 20% by mass of the final composition.
8. The method of any one of claims 1-4, wherein the formulation comprises two biocompatible organic solvents, a polar lipid, a docusate salt and optionally one or more additional surfactants, water, urea and thickener; wherein the organic solvents comprise an ester and a dihydric alcohol and/or polyhydric alcohol.
9. The method of claim 8, wherein the formulation comprises about 2 to about 30% of the ester and about 0.5 to about 20% of the dihydric alcohol and/or polyhydric alcohol, provided that the formulation does not include an effective amount of an additional antifungal agent.
10. The method of claim 8, wherein the composition further comprises one or more preservatives.
11. The method of claim 10, wherein the preservative is one or more of methylparaben, propylparaben, and butylparaben.
12. The method of claim 8, wherein the surfactant is docusate sodium.
13. The method of any one of claims 8-10 and 12, wherein the ester is isopropyl myristate.
14. The method of any one of claims 8-10 and 12, wherein the alcohol is propylene glycol.

15. The method of any one of claims 8-10 and 12, wherein the polar lipid is lecithin.
16. The method of any one of claims 8-10 and 12, wherein the thickener is one or more of methyl cellulose and a polyacrylic acid.
- 5 17. The method of any one of claims 8-10 and 12, wherein the formulation comprises about 10 to about 30% by weight of the polar lipid; about 0.5 to about 15% by weight of the docusate salt, about 40 to about 65% by weight of water, about 1 to about 15% by weight of the urea, about 0.05 to about 5% of weight of the thickener, and about 0.01 to 1% by weight of the
10 preservative.
18. The method of any one of claims 1-4, wherein the formulation consists essentially of two biocompatible organic solvents, a polar lipid, a docusate salt and optionally one or more additional surfactants, water, urea and thickener; wherein the organic solvents comprise an ester and a dihydric
15 alcohol and/or polyhydric alcohol; and wherein the composition comprises about 2 to about 30% of the ester and about 0.5 to about 20% of the dihydric alcohol and/or polyhydric alcohol.
19. The method of claim 18, wherein the formulation consists essentially of isopropyl myristate, lecithin, docusate sodium, propylene glycol, polysorbate
20 80, water, urea, methylcellulose, polyacrylic acid and triethanolamine.
20. The method of claim 1, wherein the microbial infection is a Gram positive infection, a Gram negative infection, an anaerobic bacterial infection, a fungal infection or a viral infection.
21. The method of claim 20, wherein the microbial infection is a fungal
25 infection.
22. The method of claim 21, wherein the fungal infection is resistant to at least one antifungal agent.

23. The method of claim 22, wherein the fungal infection is resistant to at least one allylamine.
24. The method of claim 20, wherein the fungal infection is onychomycosis.
25. The method of claim 24, wherein the infection is onychomycosis and caused
5 by one or more fungi selected from *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton interdigitale*, *Epidermophyton floccosum*, *Trichophyton violaceum*, *Microsporum gypseum*, *Microsporum canis*, *Microsporum audouinii*, *Trichophyton tonsurans*, *Trichophyton soudanense*, *Trichophyton capitis*, *Scytalidium*, *Scopulariopsis* and *Aspergillus*.
- 10 26. The method of claim 21, wherein the fungal infection is tinea pedis.
27. The method of claim 21, wherein the fungal infection is one or more of tinea cruris, tinea versicolor, tinea corporis and tinea capitis.
28. The method of claim 21, wherein the fungal infection is diaper dermatitis or thrush.
- 15 29. The method of claim 1, wherein the microbial infection is a Gram positive infection, a Gram negative infection or an anaerobic bacterial infection.
30. The method of claim 1, wherein the microbial infection is a viral infection.
31. The method of claim 1, wherein the microbial infection results in vaginitis, vulvovaginitis, periodontal plaque, gingivitis, acne, rosacea, folliculitis,
20 infected eczema, impetigo, seborrheic dermatitis, intertrigo, ecthyma, angular cheilitis, paronychia, pitted keratolysis, an infected wound or an infected ulcer.
32. The method of claim 1, wherein the formulation is applied topically.
33. The method of claim 1, wherein the formulation is applied to a mucosal
25 membrane.

34. The method of claim 2, wherein the microbe is one or more of Gram negative bacteria, Gram positive bacteria, anaerobic bacteria, fungi and viruses.
35. The method of claim 2, wherein the surface is an inanimate surface.
- 5 36. The method of claim 2, wherein the disinfectant formulation is a skin disinfectant or surgical scrub.
37. The method of claim 3, wherein one or more of the nail color, the nail clarity, the nail smoothness and the nail integrity is improved.
38. The method of claim 3, wherein the method is improve the health of a nail
10 and the nail is broken or damaged.
39. The method of claim 4, wherein the wound is a fungating tumor, bed sore, pressure ulcer, venous ulcer or arterial ulcer.
40. A container, selected from the group consisting of an aerosol can, an atomizer, a jar having a pump, a rollette, a medical device and a tube
15 container, containing an antimicrobial formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.
41. The container of claim 40, wherein the polar lipid is lecithin or
20 phosphatidylcholine.
42. The container of claim 40, wherein the biocompatible organic solvent is isopropyl palmitate or isopropyl myristate.
43. The container of claim 40, wherein the formulation comprises a biocompatible organic solvent, a polar lipid, a docusate salt, water, urea, at a
25 pH of about 5.5 to 8.0, wherein the polar lipid is lecithin or phosphatidylcholine, the biocompatible organic solvent is an isopropyl ester selected from the group consisting of isopropyl myristate and isopropyl

palmitate, and the urea is present at a concentration of about 5 to 20% by mass of the final composition.

44. The container of claim 38, wherein the formulation comprises two biocompatible organic solvents, a polar lipid, a docusate salt and optionally one or more additional surfactants, water, urea and thickener; wherein the organic solvents comprise an ester and a dihydric alcohol and/or polyhydric alcohol.
45. The container of claim 40, wherein the formulation comprises about 2 to about 30% of the ester and about 0.5 to about 20% of the dihydric alcohol and/or polyhydric alcohol, provided that the formulation does not include an effective amount of an additional antifungal agent.
46. The container of claim 40, wherein the formulation further comprises a one or more preservatives.
47. The container of claim 44, wherein the surfactant is docusate sodium.
48. The container of any one of claims 43-45 and 47, wherein the ester is isopropyl myristate.
49. The container of any one of claims 43-45 and 47, wherein the alcohol is propylene glycol.
50. The container of any one of claims 44-45 and 47, wherein the polar lipid is lecithin.
51. The container of any one of claims 43-45 and 47, wherein the thickener is one or more of methyl cellulose and a polyacrylic acid.
52. An article, wherein all or part of said article is impregnated or coated with an antimicrobial formulation comprising a mixture of a polar lipid, a biocompatible organic solvent, a docusate salt, water, and urea, at a pH of between about 5.5 and 8.0, provided that said formulation does not include an effective amount of an additional antimicrobial agent.

53. The article of claim 52, wherein the polar lipid is lecithin or phosphatidylcholine.
54. The article of claim 52, wherein the biocompatible organic solvent is isopropyl palmitate or isopropyl myristate.
- 5 55. The article of claim 52, wherein the formulation comprises a biocompatible organic solvent, a polar lipid, a docusate salt, water, urea, at a pH of about 5.5 to 8.0, wherein the polar lipid is lecithin or phosphatidylcholine, the biocompatible organic solvent is an isopropyl ester selected from the group consisting of isopropyl myristate and isopropyl palmitate, and the urea is
10 present at a concentration of about 5 to 20% by mass of the final composition.
56. The article of claim 52, wherein the formulation comprises two biocompatible organic solvents, a polar lipid, a docusate salt and optionally one or more additional surfactants, water, urea and thickener; wherein the
15 organic solvents comprise an ester and a dihydric alcohol and/or polyhydric alcohol.
57. The article of claim 56, wherein the formulation comprises about 2 to about 30% of the ester and about 0.5 to about 20% of the dihydric alcohol and/or polyhydric alcohol, provided that the formulation does not include an
20 effective amount of an additional antifungal agent.
58. The article of claim 52, wherein the formulation further comprises one or more preservatives.
59. The article of claim 57, wherein the surfactant is docusate sodium.
60. The article of any one of claims 55-57 and 59, wherein the ester is isopropyl
25 myristate.
61. The article of any one of claims 55-57 and 59, wherein the alcohol is propylene glycol.

62. The article of any one of claims 55-57 and 59, wherein the polar lipid is lecithin.
63. The article of any one of claims 55-57 and 59, wherein the thickener is one or more of methyl cellulose and a polyacrylic acid.
- 5 64. The article of claim 52, wherein the article is a medical device.
65. The article of claim 52, wherein the article is a gauze pad, bandage or wound dressing.
66. The article of claim 52, wherein the article is a package or packaging material.
- 10 67. The article of claim 52, wherein the article is a tissue, towel or towelette.
68. A method for treating or inhibiting a resistant microbial infection in a subject, comprising administering to the subject a therapeutically effective amount of a formulation comprising a docusate salt, provided the said formulation does not include an effective amount of an additional
15 antimicrobial agent.
69. The method of claim 68, wherein the resistant microbial infection is a resistant fungal infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/012056

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/225 A61K9/06 A61P17/00 A61P31/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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 practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 654 337 A (ROENTSCH ELMER GEORGE [US] ET AL) 5 August 1997 (1997-08-05) example 1, 2, 6, 8	40-43, 47,48,50
Y	US 2006/110342 A1 (DECHOW FREDERICK J [US]) 25 May 2006 (2006-05-25) cited in the application [0012], [0014], [0044], [0062], [0064], examples 6, 10-15	1-69
Y	US 4 885 310 A (KERN GERALD N [US]) 5 December 1989 (1989-12-05) column 1, line 1-15; column 2, line 57 - column 3, line 18; column 4, line 35 - column 5, line 24; examples 1, 10 and 11 -/--	1-69

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"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.

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 717 737 A (KERN GERALD N [US]) 5 January 1988 (1988-01-05) column 1, line 1-13; column 2, line 35-65; column 3, line 11-30; examples 1-3, 8-11 -----	1-69

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/012056

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5654337	A	05-08-1997	AU 5255996 A WO 9629988 A1	16-10-1996 03-10-1996
US 2006110342	A1	25-05-2006	AU 2005294216 A1 BR PI0512583 A CA 2567575 A1 EP 1796632 A1 JP 2008515911 T KR 20070072482 A WO 2006042059 A1	20-04-2006 25-03-2008 20-04-2006 20-06-2007 15-05-2008 04-07-2007 20-04-2006
US 4885310	A	05-12-1989	NONE	
US 4717737	A	05-01-1988	AU 6120186 A EP 0225385 A1 WO 8607258 A1	07-01-1987 16-06-1987 18-12-1986