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Samour et al.

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(54) **ANTIFUNGAL NAIL LACQUER AND METHOD USING SAME**

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Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61K 6/00**; A61K 7/00; A61K 7/04; A01N 25/34

(52) **U.S. Cl.** **424/401**; 424/61; 424/404

(58) **Field of Search** 424/61, 401, 404

(56) **References Cited**

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4,636,520		1/1987	Umio et al.	514/399
4,957,730		9/1990	Bohn et al.	424/61
5,002,938		3/1991	Wang et al.	514/171
5,110,809		5/1992	Wang et al.	514/171
5,120,530		6/1992	Ferro et al.	424/61
5,219,877		6/1993	Shah et al.	514/399
5,264,206	*	11/1993	Bohn et al.	424/61
5,346,692		9/1994	Wohlrab et al.	424/61
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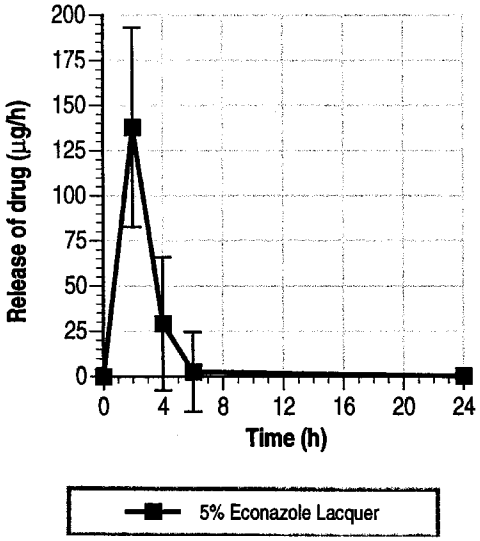
(57) **ABSTRACT**

A nail lacquer effective for the treatment or prevention of fungal infections, such as, onychomycosis, includes fungicidally effective amount of ciclopirox, econazole, or other antifungal agent in a clear, stable, film-forming lacquer vehicle which includes a water-insoluble film-forming polymer; 2-n-nonyl-1,3-dioxolane or similar penetration enhancer; and volatile solvent. A plasticizer for the film-forming polymer which is also compatible with the other components may be included although the preferred penetration enhancers may also function as plasticizer. The composition, when applied to the nails provides a hard, clear, water-resistant film containing the antifungal agent. The film is resistant to multiple washings and is effective in the treatment of onychomycosis.

40 Claims, 2 Drawing Sheets



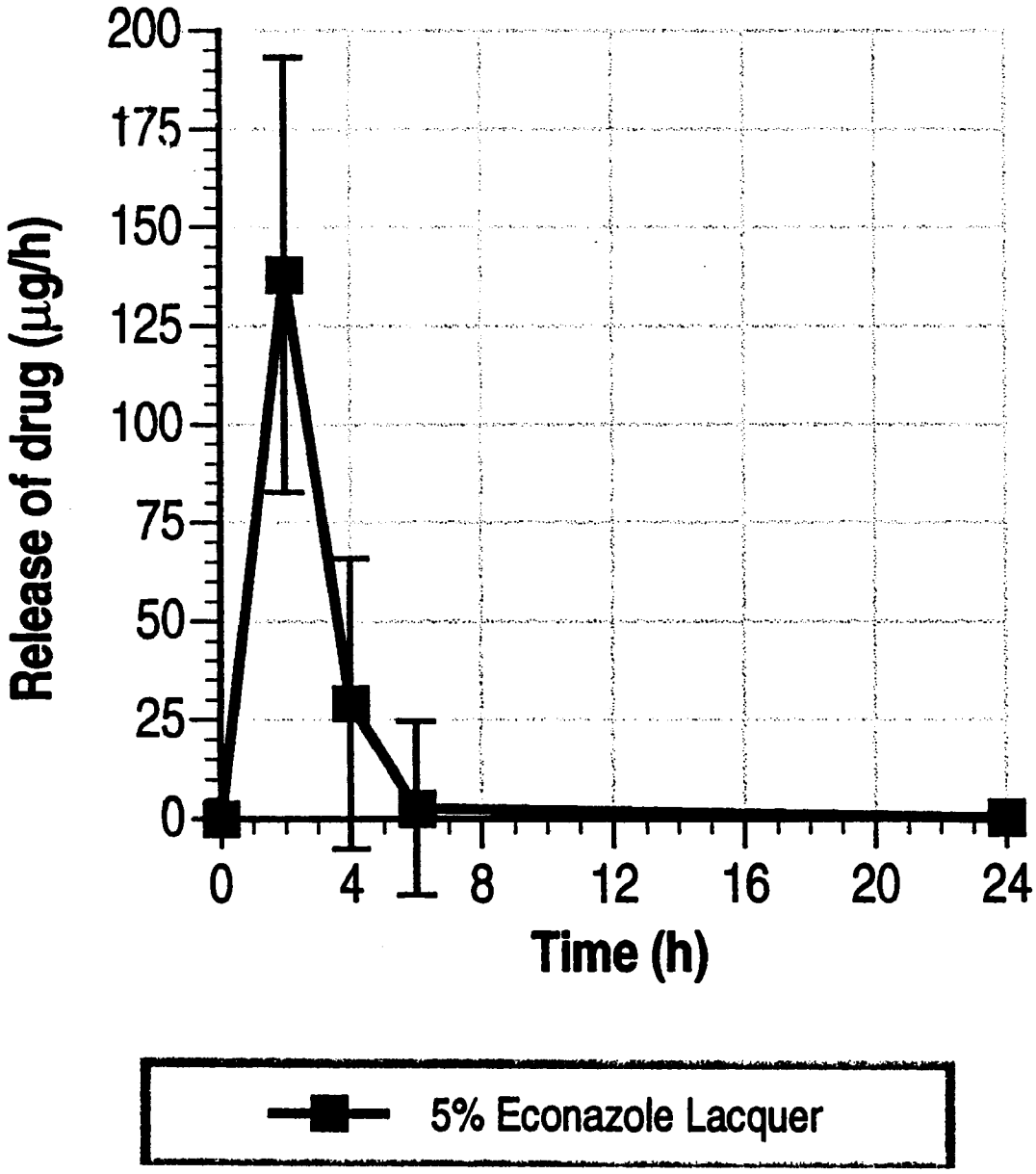


FIGURE 1

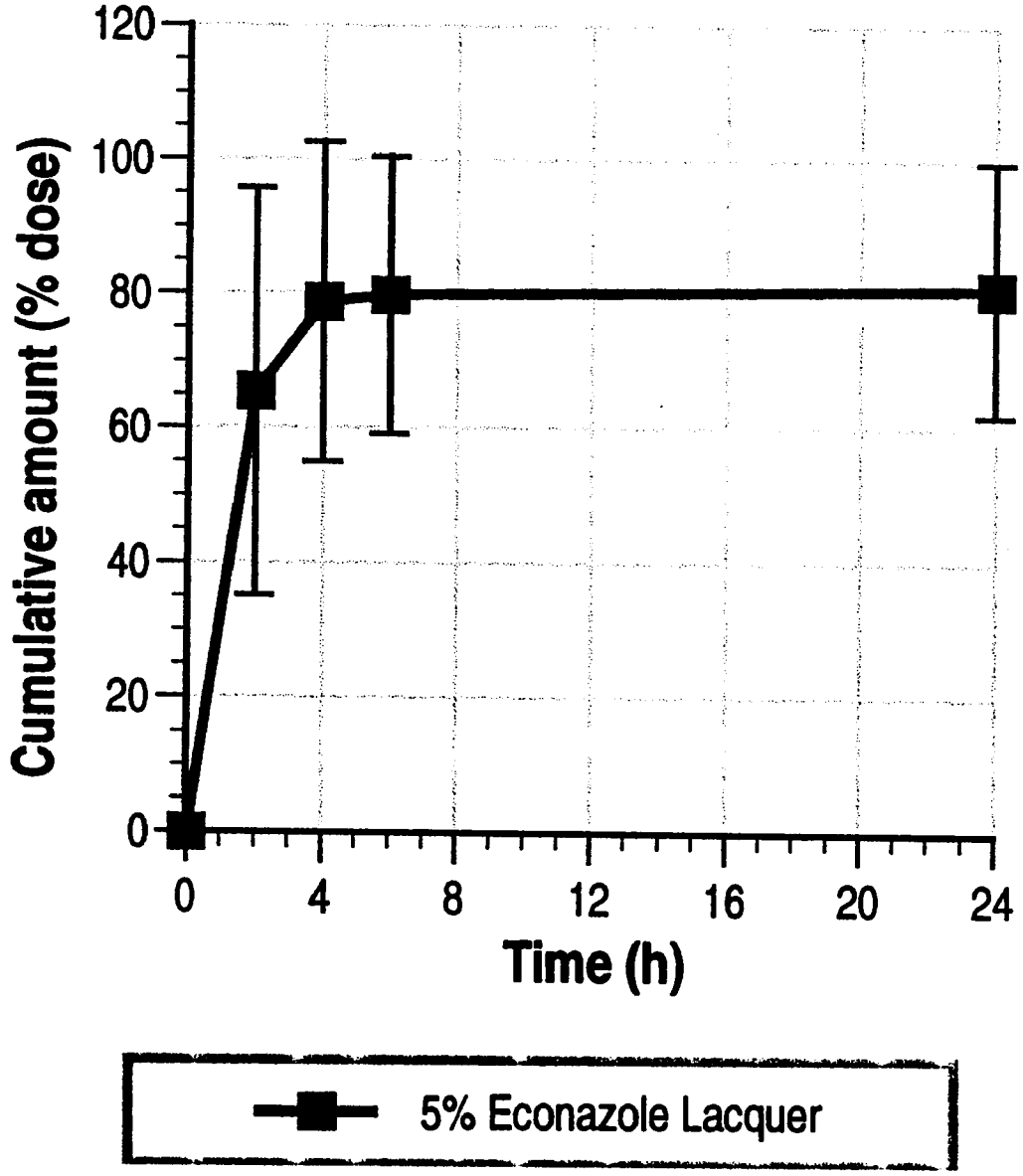


FIGURE 2

ANTIFUNGAL NAIL LACQUER AND METHOD USING SAME

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional application Ser. No. 60/074,025, filed Feb. 9, 1998.

BACKGROUND OF THE INVENTION

(1). Field of Invention

This invention relates to antifungal nail lacquer compositions and to the treatment of onychomycoses or other fungal infestations affecting toe nails or finger nails using the nail lacquer composition. More particularly, the invention relates to antifungal nail lacquers which when applied to nails form strongly adherent, water-resistant, clear films; and to the method for treating or preventing fungal infestations of animal nails by applying the antifungal composition to the infected nail or to the fungal susceptible nail.

(2). State of the Prior Art

Fungal infection of the nails, commonly referred to as onychomycosis, is most frequently caused by dermatophytes but also can be caused by molds and Candida. Mixed infections also occur. Onychomycosis includes dermatophyte infection of the nail plate and includes infection of nails by any fungus, including yeast or molds. Thus, for example, onychomycosis serves as a reservoir for dermatophytes and contributes to treatment failure and recurrence of tinea pedis.

Most common causes of tinea unguium are *Trichophyton rubrum* (most frequent), *T. mentagrophytes*, and *Epidermophyton floccusum*. Onychomycosis due to nondermatophytes is usually caused by Candida species.

Nail lacquers for the treatment of onychomycoses and similar fungal infections affecting nails (toe nails and/or finger nails) of humans, in particular, or other animals, are known. Representative examples are described in the patent literature, of which the following U.S. Pat. Nos. can be mentioned: 4,957,730 (1-hydroxy-2-pyridone in water-insoluble film-former); 5,120,530 (amorolfine in quaternary ammonium acrylic copolymer); 5,264,206 (tioconazole, econazole, oxiconazole, miconazole, tolnaftate, naftifine hydrochloride, in water-insoluble film-former); 5,346,692 (with urea and dibutyl phthalate plasticizer); 5,487,776 (griseofulvin as colloidal suspension).

Other U.S. Pat. Nos. which relate to antifungal products include, for example, 4,636,520 (combination of imidazole and pyrrolnitrin); 5,002,938 (gel, combination of imidazole and 17-ester corticosteroid antiinflammatory agent); 5,110,809 (antifungal gel plus steroid); 5,219,877 (gel product with imidazole antifungal optionally with steroidal antiinflammatory, in a vehicle system that includes lauryl alcohol); 5,391,367 (aqueous alcoholic gel with tioconazole); 5,464,610 (salicylic acid plaster); 5,696,105 (mometasone furoate).

Effectiveness of nail lacquers as a delivery vehicle for topically administering the antifungal agent amorolfine is described by Jean-Paul L. Marty, J. of the European Academy of Dermatology and Venereology, 4(Suppl. 1), pp.S17–S21 (1995). As described by the author, the film-generating solution as the lacquer base for the active principle basically consists of volatile solvent (ethanol, ethyl/butyl/methyl acetate, methylene chloride, methyl ethyl ketone, isopropanol), and a non-water-soluble polymer (methacrylic acid copolymers, vinyl polymers) which leaves a thin continuous film following evaporation of the solvent. Plasticizers (triacetin, dibutyl phthalate) impart sufficient mechanical flexibility to prevent flaking and removal. Marty further notes the similarity of the film-generating solution to the nail lacquers used in cosmetics.

It is further explained that the specific aims addressed in formulating the film-generating solution of the anti-fungal nail lacquer include obtaining maximal affinity of the active principle to the nail keratin and obtaining the highest possible thermodynamic activity compatible with maintaining the active principle in true or supersaturated solution.

Differences in diffusion characteristics between nail and skin are also discussed in the Marty article. The nail structure is characterized as a water-gel in which water facilitates diffusion of at least polar compounds. In contrast, the skin tends to more readily facilitate diffusion of lipophilic, non-polar molecules, through the extracellular lipids of the stratum corneum. Thus, since the absolute transmission of water vapor through nails is about 10 times that through skin, and since nails are approximately 100 times as thick as stratum corneum, the permeability of nails to water vapor is about 1000 times greater.

Therefore, Marty reports that "excipients developed for use on skin are thus inappropriate for releasing active principles on the nail, as shown by the inefficacy of diffusion promoters such as DMSO" (citing Walters K A, Penetration of chemicals into, and through, the nail plate. Pharm Int. 1985; April, p. 85–89).

It has also been suggested in the literature (Mast, "Nail Products". . .) that "[a]s a working hypothesis, it should be assumed that nails are, in general, quite permeable to polar and semipolar low molecular weight chemicals." See also, Walters K A and Flynn G L, "Permeability characteristics of the human nail plate" Intl J. of Cosmetic Science, 5, 231–246 (1983) for a review of the structure and characteristics of the nail and a discussion of permeation through the nail plate of various chemicals and permeation coefficients of C_1–C_{12}-alcohols.

These authors conclude, on the basis of the accumulated data that in connection with the successful formulation of drugs used in the treatment of nail infections, "that solvents with proven efficacy as skin 'penetration enhancers' show little promise as enhancers of nail plate permeability" (citing to Walters, K A and Flynn G L, J. Pharm. Pharmac. 33 6P (1981) and Kligman, A M J. Amm. Med. Ass. 193 796–804 (1965).

Nevertheless, there remains a need for more effective and more durable (longer lasting) nail lacquer formulations which incorporate an antifungal agent.

There also remains a need for an antifungal nail lacquer formulation which provides clear and glossy films which are capable of resisting multiple washings.

It is also known in the art, as indicated by several of the patent documents discussed above, that the overall effectiveness of antimycotic products for treating fungal infections of the skin may often be improved by combining the antifungal agent with a steroidal antiinflammatory agent. To date however such combination products have not been formulated into a lacquer type product for the treatment of onychomycosis but, rather, have been limited to gels, lotions, creams and other topically applied solutions.

DESCRIPTION OF THE DRAWING

FIG. **1** is a graphical presentation of release rate (μg/h) of econazole as a function of time from the invention lacquer of Example 2; and

FIG. **2** is a graphical presentation of the release rate (% dose) of econazole as a function of time from the invention lacquer of Example 2.

SUMMARY OF INVENTION

The present invention aims to solving the above needs. Thus, according to the present invention there is provided a stable, nail lacquer formulation incorporating an antifungal agent, which formulation, when applied to nails yields a hard, durable, substantially clear, long lasting film, effective in the treatment or prevention of fungal infestations or infections on or associated with nails.

In particular, the present invention provides a composition effective for the treatment or prevention of fungal infections of nails, comprising:

(a) at least one antifungal agent effective in the treatment or prevention of onychomycoses;

(b) penetration enhancing agent selected from the group consisting of C_7–C_4-hydrocarbyl substituted 1,3-dioxolane, C_7-C_{14}-hydrocarbyl substituted 1,3-dioxane and C_7-C_{14}-substituted acetal;

(c) water-insoluble, film-forming polymer; and,

(d) volatile solvent, the composition, when applied to nails, forming, upon evaporation of the volatile solvent, a hard, water-resistant film from which the antifungal agent is releasable and becomes available to treat or prevent fungal infection.

In a particular embodiment of the invention a nail lacquer composition is provided which includes a combination of an antifungal or antimycotic agent and a steroidal antiinflammatory agent in a solution of film-forming polymer in at least one volatile solvent; the composition may also include at least one penetration enhancing agent selected from the group consisting of C_7–C_{14}-hydrocarbyl substituted 1,3-dioxolane, C_7–C_{14}-hydrocarbyl substituted 1,3-dioxane and C_7–C_{14}-substituted acetal. A plasticizer for the film-forming polymer may also be included.

The invention also provides lacquer compositions effective for providing long-lasting, water-resistant adherent films on animal (e.g., human) skin and nails comprising a substantially non-aqueous solution of water-resistant, film-forming polymer, and plasticizing effective amount of at least one compound selected from the group consisting of C_7–C_{14}-hydrocarbyl substituted 1,3-dioxolane, C_7–C_{14}-hydrocarbyl substituted 1,3-dioxane and C_7–C_{14}-substituted acetal in volatile solvent.

The resulting water-resistant, adherent films provide novel products especially suitable as a delivery matrix for drugs, including the antifungal agents and others. When such film with drug incorporated therein, is deposited on animal, especially human or other mammal, skin or nail, the drug will leach from the film and will be capable of being absorbed by or transported into and through the skin or nail.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

The present invention provides still further improvements in the physical properties (e.g., durability, water-resistance, flexibility) of water-insoluble adherent films provided upon evaporation of the volatile solvent from the film-generating solution of nail lacquer composition, as well as improved diffusion characteristics of active principle(s) included in the lacquer composition from the resulting film.

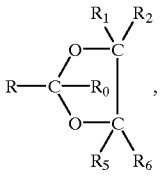
The present invention makes it possible to effectively incorporate two, generally chemically dissimilar active principles: an antifungal agent and a steroidal antiinflammatory agent in a nail lacquer effective in treatment of onychomycosis.

The improvement in nail lacquer products according to the present invention is, in part, made possible by the incorporation into the film-generating solution of a specific class of penetration enhancing agent, namely, C_7–C_{14}-hydrocarbyl substituted 1,3-dioxolanes, 1,3-dioxanes and acetals, which have previously been described as enhancers for penetration of various pharmacologically active principles through the skin, and commercially available from MacroChem Corporation, Lexington, Mass., under the SEPA® trademark. The SEPA® skin penetration enhancers (hereinafter may be referred to as SPE's) are the subject matter of several issued U.S. Pat. Nos., including, 4,861,764, 5,391,567, 4,910,020, and 5,620,980, issued to one or more of the current inventors, and the disclosures of which are incorporated herein by reference thereto.

The preferred SPE's for use in the present invention may be represented by the following general formulas:

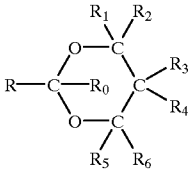
2-substituted 1,3-dioxolanes of the formula (I):

(I)



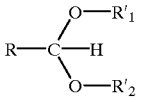
2-substituted 1,3-dioxanes of the formula (II):

(II)



substituted-acetals of the formula (III):

(III)



In the above formulas (I), (II) and (III) R preferably represents a C_7 to C_{14} hydrocarbyl group,

R_0, R_1, R_2, R_3, R_4, R_5, and R_6, each, independently, represent hydrogen or a C_1 to C_4 alkyl group.

R'_1 and R'_2, each, independently, represent C_1 to C_4 alkyl group.

The hydrocarbyl group for R may be a straight or branched chain alkyl, alkenyl or alkynyl group, especially alkyl or alkenyl. Preferably, R represents a C_7 to C_{12} aliphatic group; especially C_7 to C_{10} aliphatic group. Examples of suitable alkyl groups include, for example, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, 2-methyl-octyl, 4-ethyl-decyl, 8-methyl-decyl, and the like. The straight chain alkyl groups, such as n-heptyl, n-octyl, n-nonyl and n-decyl, are especially preferred. Examples of alkenyl groups include, for example, 2-hexenyl, 2-heptenyl,

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