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(54) **Title**: TERBINAFINE COMPOSITIONS FOR ONYCHOMYCOSIS TREATMENT

(57) **Abstract**: Novel terbinafine topical compositions for the treatment of nail onychomycosis comprising terbinafine or a terbinafine salt, up to 60% (w/w) of at least one volatile solvent selected from ethanol, isopropanol, n-propanol, butanol, and combinations thereof, water, at least one film-forming ingredient and at least one phospholipid, forming an ethosome lipid system, processes for their preparation and methods for treating onychomycosis, wherein after the application of the compositions on the treated nail surface and evaporation of volatile solvents, the film formed exhibits web-like structures containing the terbinafine or salt thereof.

TERBINAFINE COMPOSITIONS FOR ONYCHOMYCOSIS TREATMENT

BACKGROUND OF THE INVENTION

[0001] Nail fungal infections are a widespread and hard to cure affliction. While several systemic and topical treatments are commercially available, none is completely satisfactory, as evidenced by the continuous effort to find new therapeutic methods. The nail fungal infection known as onychomycosis, caused mainly by the dermatophyte trichphyton rubrum, is particularly difficult to treat, and while some treatments prove effective, there are significant side-effects and the infection is recurrent.

[0002] The most prominent drugs for nail fungal infections are terbinafine and ciclopirox. Other antifungal drugs in use or development include griseofulvin, posaconazole, amorolfine, itraconazole, econazole and butenafine.

[0003] Terbinafine (Lamisil®), a very effective drug for the treatment of onychomycosis (tinea unguium), is mainly administered systemically, despite the known side-effects like liver toxicity. Terbinafine is commercially available also as the 1% Lamisil® OTC topical cream, but the indications for the cream are different.

[0004] The significant side-effects are the main reason why topical treatments, likely to diminish the systemic effects, are being coveted, and attempts are being made to develop efficient topical drugs, with minimal side-effects.

[0005] The FDA www.ClinicalTrials.gov site lists 15 clinical studies with terbinafine, mostly topical treatments against onychomycosis, including terbinafine nail lacquer. Higher concentrations of terbinafine and alternative actives, like posaconazole and 5% amorolfine nail lacquer are being investigated as possible treatment for nail fungal infections, which evidences the fact that there is still an unmet medical need for safe and effective topical treatments of nail fungal infections. Only four clinical studies are listed on this site for ciclopirox, out of which none for onychomycosis or other nail infections, which shows that ciclopirox is not considered a preferred treatment, while terbinafine is.

[0006] Another antifungal drug, ciclopirox, of limited antifungal activity, is administered only topically. The commercial product Penlac® nail lacquer is a 8% ciclopirox topical solution which is applied once daily and repeatedly to the nail and to the skin beneath it to

form a lacquer layer. Another commercial nail lacquer is 5% amorolfine, commercially available as OTC in the UK as Loceryl or Curanail.

[0007] The nail application of Penlac® results in formation of a dry film, after evaporation of the liquid components of the composition. Penlac® composition includes the following ingredients: each gram of PENLAC® NAIL LACQUER (ciclopirox) Topical Solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, NF; isopropyl alcohol, USP; and butyl monoester of poly[methylvinyl ether/maleic acid] in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application.

[0008] The activity of the topical lacquers like Penlac® depends in large measure on the composition of the film that forms on the nail after the evaporation of the solvents. In the Penlac® case, after the evaporation of the solvents, the film is formed by ciclopirox in butyl monoester of poly[methylvinyl ether/maleic acid (Gantrez® ES-435), a copolymer.

[0009] Conventional antifungal compositions, however, exhibit poor to marginal efficacy against nail fungal infections, and there is clearly an unmet need for antifungal compositions with improved efficacy in the treatment of nail fungal infections.

SUMMARY OF THE INVENTION

[0010] The present invention successfully addresses unmet medical needs, providing an innovative ethosomal drug delivery system for terbinafine and salts thereof. The formulation of the present invention produces structured films having as main elements terbinafine or a salt thereof, phospholipids and a film-forming ingredient. The compositions of the present invention preferably are liquid ethosomal compositions comprising terbinafine or a salt thereof, up to 60% (w/w) of at least one volatile solvent selected from ethanol, isopropanol, n-propanol, butanol, and combinations thereof (hereinafter "alcohol" or "alcohols"), at least one phospholipid, and water, forming a lipid vesicular system known as "ethosomes," at least one film-forming ingredient and, optionally, other inactive pharmaceutically acceptable ingredients.

[0011] Ethosomes are known lipid vesicular systems containing one or more phospholipids, one or more alcohols, optionally in combination with one or more glycols, and water, in sufficient concentrations and ratios to form "soft" vesicles. Ethosomes and methods for preparing ethosomes are described in U.S. Patent No. 5,716,638.

[0012] The compositions of the invention preferably are applied to the nail surfaces as solutions that are in the form of a lacquer. After the compositions of the invention are applied, the drying of volatiles results in a film on the treated surface, which film exhibits a web-like structure containing the terbinafine and/or salt(s) thereof, the phospholipid(s) and other inactive pharmaceutically acceptable ingredients, which may include residual solvents. These structured arrangements exhibit sustained and improved delivery of the terbinafine and/or salt(s) thereof to the treated nail. While we do not wish to be bound by any specific theory, we believe that the improved delivery is due to the reservoir effect of the web-like structures.

[0013] The film formed adheres to the nail surface, is substantive to it, and contains the drug incorporated mainly in the web-structure which probably acts as a reservoir for the terbinafine and/or salt(s) thereof. The compositions of this invention contain sufficient concentration of volatile solvent(s) to afford a rapid formation of a continuous, cohesive film on the treated nail surface. The structures in the film are formed in the presence of phospholipids and film-forming ingredient in the composition. In the absence of phospholipids, no such web-like structure are observed. The presence of volatile solvents in the composition allows for quick formation of stable and continuous films.

[0014] After evaporation of solvents, a thin and continuous film containing structures resembling a web is formed on the treated surface.

[0015] Microscopy study of the films obtained from the compositions of the present invention show that a unique structure is formed and maintained in the film. Light Microscopy (Figure 1) shows web-like arrangement structures, dispersed throughout the film.

[0016] This system allows for improved and sustained drug delivery and drug retention into the tissue, thanks to the reservoir effect and the phospholipid's presence and effect.

[0017] The composition may be applied once to multiple times per day and repeated until complete remission. The effectiveness of said compositions enables a shortened period of treatment with superior results.

[0018] These and other aspects of the invention will become apparent from the description of the invention, which follows below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 depicts a light micrograph of the film formed by formulation no. II - Axioscope Zeiss light microscope, connected by a C-mount to a video camera, a TV screen and a PC.

[0020] Figure 2 depicts a light micrograph of the film formed by formulation no. III - Axioscope Zeiss light microscope, connected by a C-mount to a video camera, a TV screen and a PC.

DETAILED DESCRIPTION OF THE INVENTION

[0021] This invention provides compositions for topical application of terbinafine and salts thereof resulting in structured continuous, cohesive films following evaporation of volatiles in the composition, said films containing web-like structures serving as drug reservoirs.

[0022] In one embodiment of this invention, liquid compositions are provided, that can be applied on the nail, to form a structured webbed film after application. We have surprisingly found that compositions comprising a phospholipid, a film-forming ingredient, and volatile solvents result in films exhibiting novel and hitherto unknown web-like structures. When the compositions comprise terbinafine or a salt thereof, the terbinafine and/or salt(s) thereof become part of the web, which is acting like a reservoir for the terbinafine and/or salt(s) thereof.

[0023] In an embodiment of this invention, there are provided compositions comprising terbinafine or a salt thereof, a phospholipid, up to 60% (w/w) of at least one volatile solvent selected from ethanol, isopropanol, n-propanol, butanol, and combinations thereof (hereinafter "alcohol" or "alcohols"), water and optionally a glycol and at least one film-forming ingredient, wherein the composition is ethosomal and forms a cohesive film exhibiting a web-like structure on application on the treated nail following rapid subsequent evaporation of the volatiles.

[0024] The film-forming ingredient, the phospholipid, terbinafine and/or one or more salts thereof, other inactive ingredients, and residual solvent(s) are part of the novel webbed structures.

[0025] The compositions of this invention are preferably liquid, in the form of solution, lotion, low viscosity gel, spray, lacquer, foam, emulsion, patch, drug reservoir, suspension or cream.

[0026] The compositions of the present invention comprise a therapeutically effective amount of terbinafine or a terbinafine salt and pharmaceutically/cosmetically acceptable inactive ingredients.

[0027] The nail fungal infection includes onychomycosis in its various forms.

[0028] The antifungal agent includes terbinafine or a terbinafine salt.

[0029] In a further embodiment, the compositions of this invention comprise:

a. 0.01-20% of terbinafine and/or one or more terbinafine salts,

b. 0.2-15 % w/w of at least one film-forming ingredient,

c. 0.2-20% w/w of at least one phospholipid,

d. 50-60% w/w of at least one volatile solvent selected from ethanol, isopropanol, n-propanol, butanol, and combinations thereof,

e. 15-40% w/w water

f. 0-10% of an alkaline (basic) molecule,

g. 0-30% of a hydrophilic agent such as glycols, trehalose, PCA, NaPCA,

h. 0-10% of a base, selected from pharmaceutically acceptable bases, including but not limited to sodium hydroxide, potassium hydroxide, triethanolamine, tromethamine and ammonia.

i. 0-5% of other pharmaceutically acceptable excipients, including but not limited to, plasticizers, emollients, sunscreens, pigments, antioxidants, stabilizers, perfumes, etc. according to need.

[0030] The phospholipid is selected from soy lecithin, egg lecithin, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, synthetic phospholipids, PEG-ylated phospholipids, phosphorylated lipids, phosphorylated vitamin E and mixtures thereof.

[0031] The concentration of the phospholipid in the compositions ranges between 0.2-10%.

[0032] The film-forming ingredient is selected from, ethyl cellulose, esters of poly[methylvinyl ether/maleic acid copolymer, PVP, PVA, PVP/PVA combinations, cationic cellulose polymers, chitosan , chitosan derivatives, polyacrylates, Eudragits, other pharmaceutically acceptable polymers or combinations thereof.

[0033] The film-forming ingredient in the compositions is ranged between 0.2-15%, preferably between 0.5-5%, and more preferably between 0.5-2%.

[0034] In one embodiment the composition comprises a hydrophilic film-forming ingredient selected from cellulose derivatives, hydroxypropylcellulose, hydroxyethylcellulose, PVP and others. In some embodiments, the film-forming ingredient includes a non-ionic, water-soluble cellulose ether such as, for example, hydroxypropylcellulose, an example of which includes Klucel®, e.g., Klucel® HF, a hydroxypropylcellulose that is sold in the United States by Hercules Inc., Wilmington, DE.

[0035] The volatile solvents preferably are selected from, C2-C4 alcohols, ethanol, isopropanol, n-propanol and butanol, and combinations thereof (hereinafter "alcohol" or "alcohols").

[0036] The glycol, which can be used in the compositions of the invention, is preferably selected from ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol, tetraglycol, butylene glycol, hexylene glycol and glycol esters or ethers like ethylene glycol monomethyl ether, diethylene glycol monoethyl ether, or other pharmaceutically acceptable glycols (hereinafter "glycol" or "glycols") and combinations thereof. Propylene glycol is among the preferred glycols. The glycol concentration (e.g., the propylene glycol concentration) is preferably from about 5 wt% to about 20 wt%, e.g., from about 5 wt% to about 15 wt% (e.g., about 13 wt%).

[0037] In another embodiment, the ethosomal compositions comprise a phospholipid, ethanol, and water, a film forming ingredient, terbinafine or a terbinafine salt and optionally sodium hydroxide or potassium hydroxide.

[0038] In another preferred embodiment, the compositions comprise a phospholipid, ethanol, glycol, and water forming an ethosome lipid system, terbinafine or a terbinafine salt, a film forming ingredient and optionally sodium hydroxide or potassium hydroxide.

[0039] In another preferred embodiment, the compositions comprise a phospholipid, ethanol, and water forming an ethosome lipid system, a hydrophilic film forming polymer, terbinafine or a salt of terbinafine and optionally a base such as sodium hydroxide or potassium hydroxide.

[0040] In another preferred embodiment, the compositions comprise a phospholipid, ethanol, and water forming an ethosome lipid system, a hydrophilic film forming polymer, terbinafine

or a salt of terbinafine, optionally glycol and optionally sodium hydroxide or potassium hydroxide.

[0041] In a preferred embodiment, the concentration of the terbinafine and/or salt(s) thereof in the composition ranges from 0.01 % to 20%.

[0042] In a preferred embodiment of this invention, there are provided nail lacquers, providing a film containing phospholipid web-like structures over the treated nail area, thus improving the usefulness of the treatment.

[0043] The nail fungal infections suitable for treatment are selected from the group comprising onychomycosis in its various forms.

[0044] The active in the instant compositions includes terbinafine, in the form of a salt such as the hydrochloride, or the free base.

[0045] A preferred terbinafine topical solution comprises 10% terbinafine HCl, 5% phospholipid, 0.5-1.5% Klucel HF, 50% ethanol 96 forming an ethosome lipid system, 7% sodium hydroxide solution (1N), and water to 100%

[0046] A preferred terbinafine topical solution comprises 10% terbinafine HCl, 5% phospholipid, 0.5-1.5% Klucel HF, 50-60% ethanol 96 forming an ethosome lipid system, 7% sodium hydroxide solution (1N), 0-13% propylene glycol and water to 100%.

[0047] In an additional embodiment of this invention, there are provided methods of treatment of nail fungal infections by topical administration of the compositions of the present invention to the afflicted area of the nail as a solution, lotion, gel, foam, cream, spray or spray lacquer, whereby after the application a film is formed on the nail exhibiting phospholipid-polymer structures, generating a drug reservoir in the film.

[0048] In a preferred embodiment of this invention, the compositions are topical solutions, to be applied evenly on the nail with a brush, spatula, pipette, applicator, metered spray or mist, sponge or patch.

[0049] The volatiles in the composition preferably evaporate rapidly after application, leaving on the nail a thin cohesive film substantive to the applied surface containing phospholipid structured reservoirs that release terbinafine to the site of application.

[0050] The application may be done once to multiple times daily and repeated as per physician's instructions. If possible, it should be applied to the nail bed, and the under surface of the nail plate when it is free of the nail bed. The next day, an additional application is done on the previous coat or on the cleaned nail plate.

[0051] Removal of the unattached, infected nail, as frequently as monthly, by a healthcare professional may be needed. The effectiveness of said compositions could enable a shortened period of treatment with superior results.

[0052] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

[0053] Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.

EXAMPLES

[0054] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1

Table No. 1

	Formulation No. I
Ingredients	**% w/w**
Ethanol (96%)	55.56
Terbinafine HCl	7
Phospholipid	5.56
Hydroxy propylcellulose	1.5
Water	To 100

EXAMPLE 2

[0055] Comparison between Formulation no. II (Figure 1 light microscopy) that contains terbinafine HCl, phospholipid and hydroxypropylcellulose (Klucel HF) and Formulation No. III (Figure 2 light microscopy) that does not contain phospholipid. It can be seen that only

Formulation No. II provided a film containing phospholipid web-like structures while Formulation No. III did not.

[0056] The compositions of Formulation No. II and comparison Formulation No. III are detailed in Table No. 2 below:

Table No. 2

	Formulation No. II	**Formulation No. III (phospholipid-free formulation for comparison – drug precipitation, unstable)**
Ingredients	**% w/w**	**% w/w**
Ethanol (96%)	50	50
Propylene Glycol	13.3	13.3
Phospholipid	5	-
Hydroxypropyl cellulose	1.5	1.5
NaOH aq. Solution (1N)	7	7
Terbinafine HCl	10	10
Vitamin E acetate	0.2	0.2
Water	13	13

Method of preparation of Formulation No. II

[0057] The phospholipid was dissolved in ethanol, and vitamin E and glycol were added thereto. Terbinafine HCl was dissolved in the above ethanolic solution. The solution was mixed with a mechanical mixer until the drug was dissolved. Sodium hydroxide solution was added with continuous mixing. Hydroxypropyl cellulose was dispersed speedily on the surface of the above composition with continuous mixing. The composition was left for at least 12 hours for the dispersion of the polymer then mixed again until a homogenous liquid was obtained.

[0058] A drop from the above formulation was applied and spread on a slide glass and left at room temperature for 10 to 60 minutes to allow evaporation of the solvents and film formation. The slides were observed under a Zeiss light microscope connected by a C-mount to a video camera, a TV screen and a PC.

EXAMPLE 3

Table No. 3

	Formulation No. IV
Ingredients	**% w/w**
Ethanol (96%)	60
Terbinafine HCl	10
Phospholipid	3
Polyvinylpyrolydone (PVP) 90K	10
Vitamin E	0.2
Water	to 100

EXAMPLE 4

[0059] Evaluation of the drug amount retained by the nail after application of 10% terbinafine HCl formulations on clipped nails.

Protocol of experiment

1. Weigh 4 samples of about 10 mg nail pieces (clipped from a healthy adult male).
2. Place each nails sample on a microscope glass slide and add on the nails about 30 mg of each formulation tested.
3. Leave the slide uncovered for about 24h at Room Temperature.
4. By using tweezers, introduce the nail samples in an Eppendorf and wash the nails with 1.5 ml 50% ethanol by vortexing than remove and wash again in 1.5 ml distilled water by vortexing.
5. Remove the nail pieces, using tweezers, place them on filter paper and wipe with Kimwipes until they look dry.
6. Insert each sample to 0.5 ml safe-lock Eppendorf by using tweezers and add 0.5 ml ACN: MeOH: Water mixture.
7. Shake for 24 h for extraction.
8. Withdraw the nails by using tweezers and centrifuge the extract at 5000 rpm for 15 min. Remove 400 µl of supernatant and place it in a 0.5 ml Eppendorf.
9. Filtrate through Acrodisk GHP 0.45µ into a safe-lock Eppendorf.
10. Inject samples to HPLC.

Results

[0060] The concentration of Terbinafine retained in the nails and measured by HPLC in nail extracts were:

- 57.20 ± 12.18 mcg/mg nail - for formulation No. II from example No. 2 above.
- 62.30 ± 8.56 mcg/mg nail - for formulation No. II from example No. 2 but were propylene glycol was replaced by water.

[0061] The results indicate that high amounts of terbinafine HCl were retained by the nail after 24 hours application.

[0062] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein. In addition, the citation or identification of any reference in this application shall not be construed as an admission that such reference qualifies as prior art with respect to the present invention.

[0063] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0064] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred

embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIMS:

1. A topical composition for the treatment of onychomycosis in a human or animal, comprising 0.01-20% terbinafine or a pharmaceutically acceptable terbinafine salt, 0.2-20% of one or more phospholipids, 50-60% of volatile solvents selected from C2-C4 alcohols or combinations thereof, 15-40% water, 0-30% of a glycol 0.2-15% of a film-forming ingredient and optionally 0-5% other pharmaceutically acceptable inactive ingredients, forming an ethosome lipid vesicular system, wherein following the evaporation of volatiles, a continuous film is formed on the nail surface treated, said film exhibiting a web-like structure comprising the terbinafine or terbinafine salt.

2. The composition of claim 1, wherein the said glycol is selected from ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol, tetraglycol, butylene glycol, hexylene glycol and glycol esters or ethers like ethylene glycol monomethyl ether, diethylene glycol monoethyl ether, or other pharmaceutically acceptable glycols and combinations thereof.

3. The composition of claim 1, wherein the terbinafine or salt thereof is terbinafine, terbinafine hydrochloride or a combination thereof.

4. The topical composition of claim 1, exhibiting improved nail healing activity due to its web-like structure.

5. The composition of claim 1, wherein the phospholipid is selected from soy lecithin, egg lecithin, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, synthetic phospholipids, PEG-ylated phospholipids, phosphorylated lipids, phosphorylated vitamin E and mixtures thereof.

6. The composition of claim 1, wherein the optional other pharmaceutically acceptable inactive ingredients are selected from glycols, trehalose, PCA, NaPCA, a base, selected from pharmaceutically acceptable bases, like but not limited to sodium hydroxide, potassium hydroxide, triethanolamine and ammonia, borax, plasticizers, emollients, sunscreens, pigments, antioxidants, stabilizers, perfumes and combinations thereof.

7. The composition of claim 1, wherein the film structure is as exemplified in Fig. 1.

8. The composition of claim 1, wherein the film-forming ingredient is selected from cellulose derivatives, hydroxypropylcellulose, hydroxyethylcellulose, PVP, others and combinations thereof.

9. The composition of claim 1, wherein the film-forming ingredient is selected from ethyl cellulose, esters of poly[methylvinyl ether/maleic acid copolymer, PVA, PVP/PVA combinations, cationic cellulose polymers, chitosan, chitosan derivatives, polyacrylates, Eudragits, other pharmaceutically acceptable polymers and combinations thereof.

10. The composition of claim 1, in the form of a pharmaceutically acceptable form of administration, selected from a solution, a lotion, a gel, a foam, a patch, a cream, a spray and a spray lacquer.

11. The composition of claim 1, comprising the following components:

a. 0.01-20% of terbinafine or terbinafine salts,

b. 0.2-15% of a film-forming ingredient selected from cellulose derivatives, butyl monoesters of poly[methylvinyl ether/maleic acid] copolymer, PVP, PVA, Eudragits, other pharmaceutically acceptable polymers and combinations thereof,

c. 0.2-20% w/w of one or more phospholipids,

d. 50-60% of a volatile solvent selected from ethanol, isopropanol, n-propanol, butanol, and combinations thereof,

e. 15-40% water,

f. 0-10% of a 0.5N to 1.0N aqueous solution of a base selected from sodium hydroxide, potassium hydroxide, ammonia borax and combinations thereof,

g. 0-30% of a glycol selected from ethylene glycol, diethylene glycol, propylene glycol, dipropylene glycol, tetraglycol, butylene glycol, hexylene glycol and glycol esters or

ethers like ethylene glycol monomethyl ether, diethylene glycol monoethyl ether or other pharmaceutically acceptable glycols and combinations thereof, and

h. 0-5% of other inactive pharmaceutically acceptable excipients, selected from plasticizers, emollients, sunscreens, pigments, antioxidants, stabilizers, perfumes, etc according to need.

12. The composition of claim 1, wherein in the form of a topical solution, whereby said solution or spray is applied to the nail with a brush, a spray or a metered dose device and allowed to dry, forming a film.

13. A method of treatment of a nail onychomycosis in a human in need thereof, by application to the nail of a therapeutically effective dose of the compositions of claim 1, and allowing the composition to dry, forming a film.

14. A method of treatment of onychomycosis by treating the afflicted area with the compositions of claim 1, forming an occlusive film over the nail areas of a patient in need thereof, thus improving the treatment of said onychomycosis.

15. An article of manufacture comprising a dispensing device and the composition of any one of claims 1-12 contained therein.

Fig. 1

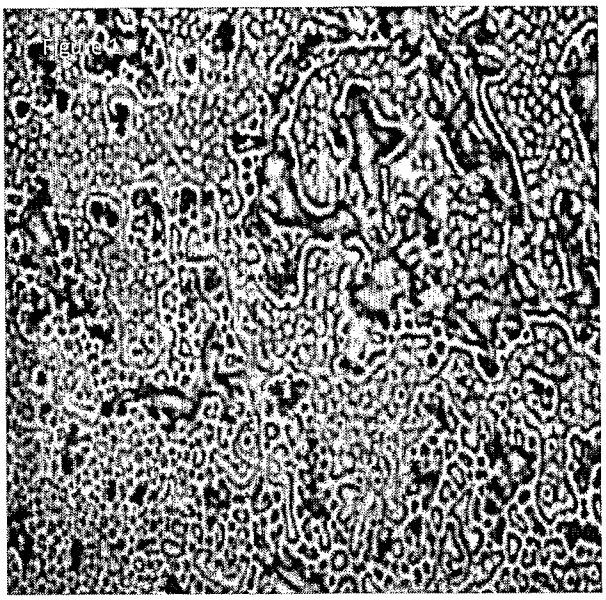

Figure 1: Light micrograph of the film formed by formulation no. II - Axioscope Zeiss light microscope, connected by a C-mount to a video camera, a TV screen and a PC.

The formulation contains terbinafine HCL and both phospholipid and polymer.

The web-like structure clearly appears in the figure.

Fig. 2

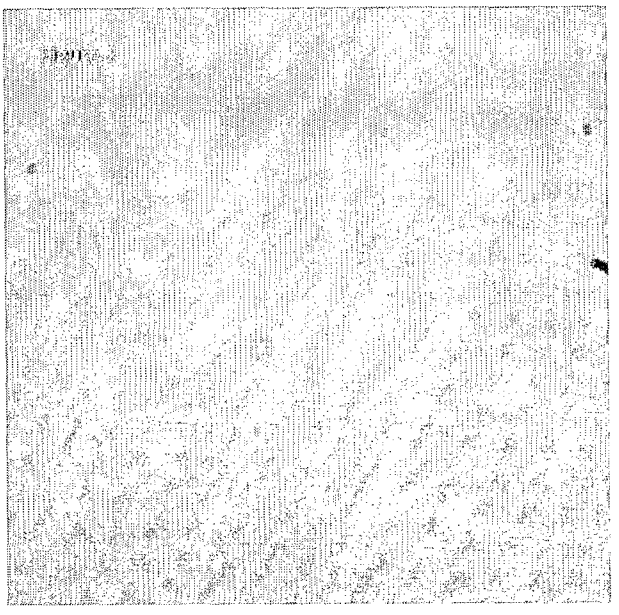

Figure 2: Light micrograph of the film formed by formulation no. III - Axioscope Zeiss light microscope, connected by a C-mount to a video camera, a TV screen and a PC.

The formulation contains terbinafine HCL and polymer but not phospholipid.

The web-like structure is absent here.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 10/00168

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 33/02; A61K 31/135 (2010.01)
USPC - 514/649
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)
USPC: 514/649

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/450, 465, 469; 514/655; 564/384 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, EPAB, JPAB)
topical, nail, nails, skin, composition, lotion, spray, liquid, ointment, solution, gel, foam, patch, cream, spray lacquer, onychomycosis, human, animal, mammal, animal, terbinafine, terbinafme hydrochloride, phospholipids, soy lecithin, egg lecithin,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0261986 A1 (FRIDEN et al.) 23 October 2008 (23.10.2003) para [0006]-[0008], [0012]-[0015], [0039], [0041], [0043]-[0046], [0048], [0050]-[0052], [0056]-[0058], [0060]-[0061], [0063]-[0067], [0069]-[0071], [0073], [0077]-[0078], [0089], [0094]-[0096], [0099]-[0101], [0105], [0109], [0117], [0123], [0132], [0137], [0142], [0144], [0147]	1-15
Y	US 2007/0299043 A1 (HUNTER et al.) 27 December 2007 (27.12.2007) para [2113], [2117]-[2118]	1-15
Y	US 5,540,934 A (TOUITOU) 30 July 1996 (30.07.1996) col 2, ln 1-54; col 3, ln 1-7; col 4, ln 23-45	1-15

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

* 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
28 May 2010 (28.05.2010)	15 JUN 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)