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(54) Title: TOPICAL PHARMACEUTICAL COMPOSITIONS OF TERBINAFINE AND PROCESSES FOR THEIR PREPARATION

(57) Abstract: The present invention relates to topical pharmaceutical compositions of terbinafine,one or more non-ionic surfactants, and one or more fatty acids or fatty alcohols, and processes for their preparation.

Description

TOPICAL PHARMACEUTICAL COMPOSITIONS OF TERBINAFINE AND PROCESSES FOR THEIR PREPARATION

Technical Field of the Invention

The present invention relates to topical pharmaceutical compositions of terbinafine one or more non-ionic surfactants, and one or more fatty acids or fatty alcohols, and processes for their preparation.

Background of the Invention

Terbinafine, a synthetic antimycotic allylamine derivative is known from U.S. 4,755,534 and is commercially marketed by Novartis under the trade name Lamisil®. Lamisil® is available as 250 mg oral tablets for systemic action, and also as 1% topical solution, cream and gel. Lamisil® is indicated for the treatment of onychomycosis of the fingernails and toenails. Onychomycosis is a fungal infection of nail units caused by yeast, dermatophytes, or other molds, and represents approximately 50% of all nail disorders.

Terbinafine acts by inhibiting squalene epoxidase, an enzyme involved in the biosynthesis of ergosterol, which is an essential component of fungal cell membranes. Although onychomycosis may be treated by both systemic and topical therapy, the systemic treatment is less preferred because it requires prolonged dosing which results in increased costs.. Systemic treatment is also associated with a significant number of side effects. Therefore, use of topical compositions of terbinafine is desirable. However, preparing topical compositions of the drugs having poor water solubility, such as terbinafine, can be a significant challenge. Formulators have partially solved this problem through the use of pharmaceutically acceptable salts of terbinafine.

When under storage conditions, terbinafine has a tendency to separate from the carrier medium as the free base, as droplets or even in crystalline form. U.S. 5,681,849, U.S. 5,856,355, U.S. 6,005,001 and U.S. 6,121,314 address the above problems of precipitation of terbinafine, and teach that shelf stable compositions may be prepared using non-ionic surfactants and lower alkanols.

Summary of the Invention

In one general aspect there is provided a topical composition of terbinafine. The composition includes terbinafine, one or more non-ionic surfactants, and one or more fatty acids or fatty alcohols.

Embodiments of the composition may include one or more of the following features. For example, the terbinafine may be present at a concentration from about 0.05% to about 10% w/w of the composition. The terbinafine dose may be from about

0.01 to about 10 μg/cm^2 applied area.

The one or more non-ionic surfactants may include one or more of polyethoxylated fatty acids and their derivatives; alcohol - oil transesterification products; polyglycerized fatty acids; propylene glycol fatty acid esters; sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives; polyethylene glycol alkyl ether or phenols; sugar esters: and polyoxyethylene - polyoxypropylene block copolymer. For example, the non-ionic surfactant may be sorbitan fatty acid esters and their derivatives, or the non-ionic surfactant may be a combination of polysorbate 20 and sorbitan monolaurate.

The one or more non-ionic surfactants may be present at a concentration of from about 0.5% to about 10% w/w of the composition. The non-ionic surfactant may also be present at a concentration of from about 5% to about 10% w/w of the composition.

The one or more fatty acids and fatty alcohols may include a straight or branched chain of at least 5 carbon atoms. For example, the one or more fatty acids or fatty alcohols may be oleic acid or oleyl alcohol. The oleic acid or the oleyl alcohol may be present at a concentration of from about 0.01% to about 20% w/w of the composition.

The topical composition may be in the form of a solution, cream, varnish, lotion, spray, or gel. For example, the topical composition may be an emulsion gel.

The composition may also include one or more pharmaceutically inert excipients. For example, the one or more pharmaceutically inert excipients may include pH adjusters, preservatives, antioxidants, and film-forming agents.

In another general aspect, there is provided a topical emulsion gel of terbinafine. The emulsion gel may include terbinafine, one or more non-ionic surfactants, an oily phase, one or more thickening agents, and one or more fatty acids or fatty alcohols.

Embodiments of the emulsion gel may include one or more of the following features. For example, the oily phase may include one or more of isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate, isopropyl monooleate, propylene glycol diester of caprylic and caprinic acid, propylene glycol dipelagonate and mixtures thereof. The oily phase may include isopropyl myristate. The isopropyl myristate may be present at a concentration of from about 5% to about 40% w/w of the gel.

The one or more thickening agents may include cellulose derivatives, polymethacrylate resins, gums and alginates, gelatins, polyvinyl alcohols, polyvinylpyrrolidones, inorganic materials, polyacrylic acid derivatives and mixtures thereof. For example, the thickening agent may be a polyacrylic acid derivative. The polyacrylic acid derivative may be present at a concentration of from about 0.1% to about 5% w/w of the gel.

In another general aspect there is provided a process for the preparation of a topical

emulsion gel of terbinafine. The process includes dissolving terbinafine and one or more non-ionic surfactants in an oily phase; dissolving one or more fatty acids or one or more fatty alcohols in water to form an aqueous phase; combining the oily phase and the aqueous phase to form an oil-in-water (o/w) emulsion; and adding one or more thickening agents to form a gel.

In another general aspect there is provided a process for the preparation of a topical composition of terbinafine. The process includes combining terbinafine, one or more non-ionic surfactants, one or more fatty acids or fatty alcohols, and one or more pharmaceutically acceptable excipients to form a topical composition.

In yet another general aspect there is provided a method for the treatment of onychomycosis in a mammal in need thereof. The method includes applying to the affected area a topical composition of terbinafine. The topical composition includes terbinafine, one or more non-ionic surfactants, and one or more fatty acids or fatty alcohols.

Embodiments of the method may include one or more of the following features. For example, the topical composition may be an emulsion gel.

Detailed Description of the Invention

The inventors have now developed topical compositions of terbinafine, which do not require the use of lower alkanols. These compositions provide improved spreadability, faster and better drug penetration and are free of the problem of drug precipitation. The topical compositions of terbinafine having the desired solubility and penetration characteristics may be prepared using one or more fatty acids and/or one or more fatty alcohols as penetration enhancing agents.

In one embodiment, there is provided a topical composition that includes terbinafine, one or more non-ionic surfactants, and one or more fatty acids and/or fatty alcohols.

Terbinafine is a lipophilic drug, which remains in the stratum corneum for an extended period of time and does not penetrate into the lower skin layers easily. Topical compositions of terbinafine of the present invention comprise fatty acid and/or alcohol as penetration enhancing agents, which help in the penetration of terbinafine through the hard surface of the nails, and thereby treats onychomycosis. It may be easily spread on the skin, is free of any greasiness, and may be washed with water leaving no residue. The topical composition may be either formulated as a simple solution by dissolving terbinafine, non-ionic surfactant, and fatty acid and/or alcohol, or be further combined with other components to form cream, lotion, varnish, spray, and gels, such as fluid gels or emulsion gels. For example, the topical composition may be formulated as an emulsion gel.

The term 'terbinafine' as used herein includes terbinafine freebase as well as its

pharmaceutically acceptable acid addition salts. For example, the acid addition salt may be terbinafine hydrochloride. Terbinafine may be present at a concentration of from about 0.05% to about 10% w/w of the composition, which would provide a dose of about 0.01 to about 10 $\mu g/cm^2$-applied area.

Suitable non-ionic surfactants include one or more of.polyethoxylated fatty acids and their derivatives, for example polyethylene glycol 400 distearate, polyethylene glycol - 20 dioleate, polyethylene glycol 4 -150 mono dilaurate, polyethylene glycol - 20 glyceryl stearate; alcohol - oil transesterification products, for example polyethylene glycol - 6 corn oil; polyglycerized fatty acids, for example polyglyceryl - 6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol mono-caprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives, for example sitosterol; sorbitan fatty acid esters and their derivatives, for example polyethylene glycol - 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol - 20 cetyl ether, polyethylene glycol - 10 - 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene - polyoxypropylene block copolymers known as 'poloxamer' and mixtures thereof. For example, a combination of sorbitan monolaurate and polysorbate 20 may be used. Non-ionic surfactants may be present at a con-centration of from about 0.5% to about 10% w/w of the composition, or from about 5% to about 10% w/w.

Suitable penetration enhancing agents may include one or more fatty acid and/or alcohols of straight or branched chains with a length of at least 5 carbon atoms. In particular, the chain may comprise eighteen carbon atoms, i.e., oleic acid and/or oleyl alcohol. The one or more fatty acids and/or alcohols may be present at a concentration of from about 0.01% to about 20% w/w of the composition.

The composition may also include one or more additional penetration enhancing agents including glycols, such as propylene glycol, glycerol and butylene glycol; glycol mono- and di-ethers marketed under the trade names Dowanol® and Pyroglydes®; polyoxyethylenated glycerides marketed under the trade name Labrosol®; dimethylsulphoxide, caprolactam, N-methyl-pyrrolidone-2, ethyl lactate and mixtures thereof.

Topical compositions of the desired consistency and physical stability may be obtained by incorporating one or more thickening agents in varying amounts. Suitable thickening agents include one or more of cellulose derivatives, such as methyl cellulose, hydroxypropyl methylcellulose, and ethyl cellulose, propyl cellulose; poly-methacrylate resins marketed under the trade name Eudispert®; gums, such as tragacanth gum, pectin, gum arabica, xantham gum and alginate; gelatin;polyvinylalcohols: polyvinyl-pyrrolidones:inorganic materials such as silica,

bentonite and magnesium aluminium silicate; polyacrylic acid derivatives marketed under the trade name Carbopol® and mixtures. For example, the thickening agent may be Carbopol®. The thickening agents may vary in concentration from about 0.1% to about 5% w/w of the composition.

Topical composition formulated as emulsions may further include one or both of an oily phase and an aqueous phase. The oily phase may include one or more lipophilic substances, such asisopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate and isopropyl monooleate; Miglyol® 840 (Propylene glycol diester of caprylic and caprinic acid); DPPG (propylene glycol dipelagonate).For example, isopropyl myristate may be used. The oily phase may vary in concentration from about 5% to about 40% w/w of the composition. The aqueous phase may include water and other water miscible solvents. Suitable water miscible solvents may include one or morepolyhydric alcohols, such as propylene glycol, butane 1,3-diol, polyethylene glycol, glycerol and mixtures thereof.

The topical composition of terbinafine may also include one or more pharmaceutically inert excipients. Suitable pharmaceutically inert excipients may include one or more of pH adjusters, preservatives, antioxidants, film-forming agents and mixtures thereof.

Suitable pH adjusters may include one or more of acids, bases and buffers. Suitable acids may include one or more of hydrochloric acid, phosphoric acid, and lactic acid. Suitable bases may include one or more of diethanolamine, triethanolamine, and sodium hydroxide. Suitable buffers may include phosphates, such as monobasic sodium phosphate, dibasic sodium phosphate, lactates and citrates. The pH of the topical compositions may be adjusted between from about 3.0 to about 8.0 to provide a non-irritating composition.

Suitable preservatives may include one or more of benzyl alcohol, phenylethyl alcohol, phenoxyethanol, sodium benzoate, methyl paraben, propyl paraben, and mixtures thereof.

Suitable antioxidants may include one or more of butyl hydroxy anisole, butyl hydroxy toluene, palmityl ascorbate, sodium pyrosulfite, tocopherols e.g alpha-tocopherol (vitamin E), and/or its esters.

Film-forming agents aid in retaining the composition on the surface of the nail by forming a film on the surface of the composition exposed to air. Suitable film-forming agents may include any agent which serves the purpose and is compatible with other ingredients in the composition.

Also included in the present invention are methodsfor treating onychomycosis in a mammal in need thereof. The methods include applying to the affected area a topical composition of terbinafine. The compositions may include terbinafine, one or more

non-ionic surfactants, and one or more fatty acids and/or fatty alcohols.

In another embodiment, the treatment of onychomycosis in a mammal in need thereof includes applying to the affected area a topical emulsion gel of terbinafine. The gel includes

terbinafine;

a) one or more non-ionic surfactants;

b) an oily phase;

c) one or more thickening agents; and

d) one or more fatty acids or fatty alcohols.

Also included in the present invention are processes for the preparation of topical formulations of terbinafine. In one of the embodiments, topical compositions of terbinafine may be prepared by mixing terbinafine, non-ionic surfactant, and fatty acid and/or alcohol to form a uniform composition.

The topical emulsion gel of terbinafine may also be prepared by a process that includes the steps of:

a) mixing terbinafine, one or more non-ionic surfactants, and one or more pharmaceutically inert excipients with oily phase, followed by warming the mixture to form a solution;

b) mixing one or more fatty acids and/or alcohols in a portion of a water phase, followed by warming the mixture to form a solution;

c) combining the solutions to form an oily phase/water phase emulsion;

d) dispersing one or more thickening agents in the remaining portion of water phase to form a dispersion, optionally followed by a pH adjustment; and

e) adding the emulsion to the dispersion and stirring to form a homogenous gel.

The invention is further illustrated by the following examples, which should not be construed as limiting the scope of the invention any way.

EXAMPLES 1-4

Terbinafine emulsion gel composition

Ingredient	**Weight (mg/100 mg)**			
	Ex 1	**Ex 2**	**Ex 3**	**Ex 4**
Terbinafine	1.00	1.00	1.00	1.00
Butylated hydroxy toluene	0.02	0.02	0.02	0.02
Sodium hydroxide	0.10	0.10	0.10	0.10
Benzyl alcohol	1.00	1.00	1.00	1.00
Carbopol® 934P	1.00	1.00	1.00	1.00

Sorbitan monolaurate	1.00	1.00	1.00	1.00
Polysorbate 20	5.00	5.00	5.00	5.00
Propylene glycol	-	-	10.00	10.00
Oleyl alcohol	10.00	-	10.00	-
Oleic acid	-	1.00	-	1.00
Isopropyl myristate	10.00	10.00	10.00	10.00
Demineralised water	q.s	q.s	q.s	q.s
Total	100.00	100.00	100.00	100.00

Procedure:

1) Terbinafine, isopropyl myristate, butylated hydroxy toluene, benzyl alcohol, sorbitan monolaurate and polysorbate 20 were mixed together under slight warming to form a solution.

2) Propylene glycol,oleic acid,oleyl alcohol and a half portion of water were heated to about 60°C -70°C and stirred to form a homogenous solution.

3) The solution of step 1 was slowly added to the solution of step 2, followed by stirring and cooling the resultant mixture to form an oil/water emulsion.

4) Carbopol® was mixed with the remaining half portion of water and neutralized with sodium hydroxide to form a dispersion.

5) The emulsion of step 3 was slowly added to the dispersion of step 4 under stirring at room temperature to form a homogenous gel.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

Claims

A topical composition of terbinafine comprising:

a) terbinafine;

b) one or more non-ionic surfactants; and,

c) one or more fatty acids or fatty alcohols.

The topical composition according to claim 1, wherein the terbinafine comprises from about 0.05% to about 10% w/w of the composition.

The topical composition according to claim 2, wherein the composition provides a terbinafine dose of about 0.01 to about 10 $\mu g/cm^2$ applied area.

The topical composition according to claim 1, wherein the non-ionic surfactants comprise one or more of polyethoxylated fatty acids and their derivatives; alcohol - oil transesterification products; polyglycerized fatty acids; propylene glycol fatty acid esters; sterol and sterol derivatives; sorbitan fatty acid esters and their derivatives; polyethylene glycol alkyl ether or phenols; sugar esters: and polyoxyethylene - polyoxypropylene block copolymer.

The topical composition according to claim 4, wherein the non-ionic surfactant comprises sorbitan fatty acid esters and their derivatives.

The topical composition according to claim 5, wherein the non-ionic surfactant comprises a combination of polysorbate 20 and sorbitan monolaurate.

The topical composition according to claim 6, wherein the non-ionic surfactant comprises from about 0.5% to about 10% w/w of the composition.

The topical composition according to claim 7, wherein the non-ionic surfactant comprises from about 5% to about 10% w/w of the composition.

The topical composition according to claim 1, wherein the fatty acids and fatty alcohols comprise a straight or branched chain of at least 5 carbon atoms.

The topical composition according to claim 9, wherein the fatty acids and fatty alcohols comprise oleic acid or oleyl alcohol.

The topical composition according to claim 10, wherein the oleic acid or the oleyl alcohol comprise from about 0.01% to about 20% w/w of the composition.

The topical composition according to claim 1, wherein the topical composition is in the form of one or more of a solution, cream, varnish, lotion, spray, or gel.

The topical composition according to claim 12, wherein the topical composition comprises an emulsion gel.

The topical composition according to claim 1, wherein the composition further comprises one or more pharmaceutically inert excipients.

The topical composition according to claim 14, wherein the one or more pharmaceutically inert excipients comprise one or more of pH adjusters, preservatives,

antioxidants, and film-forming agents.

A topical emulsion gel of terbinafine comprising

a) terbinafine;

b) one or more non-ionic surfactants;

c) an oily phase;

d) one or more thickening agents; and

e) one or more fatty acids or fatty alcohols.

The topical emulsion gel according to claim 16, wherein the oily phase comprises one or more of isopropyl myristate, isopropyl palmitate, isopropyl isostearate, isopropyl linolate, isopropyl monooleate, propylene glycol diester of caprylic and caprinic acid, propylene glycol dipelagonate and mixtures thereof.

The topical emulsion gel according to claim 17, wherein the oily phase comprises isopropyl myristate.

The topical emulsion gel according to claim 18, wherein the isopropyl myristate comprises from about 5% to about 40% w/w of the gel.

The topical emulsion gel according to claim 16, wherein the one or more thickening agents comprise cellulose derivatives, polymethacrylate resins, gums and alginates, gelatins, polyvinylalcohols, polyvinyl-pyrrolidones, inorganic materials, polyacrylic acid derivatives and mixtures thereof.

The topical emulsion gel according to claim 20, wherein the one or more thickening agents comprise a polyacrylic acid derivative.

The topical emulsion gel according to claim 21, wherein the polyacrylic acid derivative comprises from about 0.1% to about 5% w/w of the gel.

A process for the preparation of a topical emulsion gel of terbinafine, the process comprising the steps of:

a) dissolving terbinafine and one or more non-ionic surfactant in an oily phase;

b) dissolving one or more fatty acids or one or more fatty alcohols in water to form an aqueous phase;

c) combining the oily phase and the aqueous phase to form an oil-in-water (o/w) emulsion; and

d) adding one or more thickening agents to form a gel.

A process for the preparation of a topical composition of terbinafine, the process comprising combining terbinafine, one or more non-ionic surfactants, one or more fatty acids or fatty alcohols, and one or more pharmaceutically acceptable excipients to form a topical composition.

A method for the treatment of onychomycosis in a mammal in need thereof, the method comprising applying to the affected area a topical composition of

terbinafine comprising:

a) terbinafine;

b) one or more non-ionic surfactants; and

c) one or more fatty acids or fatty alcohols.

The method for the treatment of onychomycosis in a mammal of claim 24, wherein the topical composition comprises an emulsion gel.