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ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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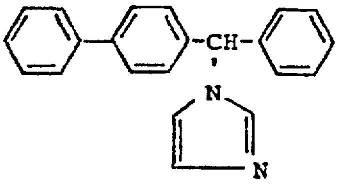
(54) Antimycotic Agent With a High Release of Active Compounds, in the Form of a Cream

(57) The invention relates to antimycotic cream compositions containing bifonazole as an antimycotic compound and including 5—25% by weight of a spreading agent, which is preferably selected from silicone oils, fatty acids, fatty acid esters, fatty alcohols and triglycerides.

SPECIFICATION

Antimycotic Agent with a High Release of Active Compounds, in the Form of a Cream

The present invention relates to a novel formulation of the known antimycotic compound bifonazole of the formula



which has a relatively high release of the active compound and thereby permits short-term therapy.

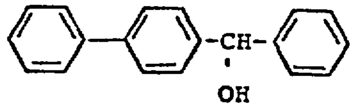
Formulations of antimycotic derivatives have already been disclosed for the treatment of mycoses in humans, above all mycoses of the skin and cutaneous appendages. A therapy time of 14 to 21 days has been required for complete cure with these formulations.

In order to shorten the duration of therapy, for example in the case of vaginal or bucall mycoses or dermatomycoses, higher release of the active compounds in an aqueous medium is necessary, in particular to eliminate the germs and to achieve a mycologically reliable cure. The known formulations are of only limited suitability for this, because only a small amount of the active compound available dissolves in the volume of liquid at the infection site. Thus, if a shortening in the duration of therapy, for example to a few days with a single daily administration, it is to be achieved, with or without a further increase in the concentration of active compound, optimum bioavailability of the active compound must be ensured.

It has now been found that formulations of bifonazole which contain 5—25% of a spreading agent, in addition to the conventional formulation substances and solvents, release a greater amount of the active compound and thereby permit a shortening of the duration of therapy to a few days. This effect of higher release of active compound can achieve an increase up to a power of ten.

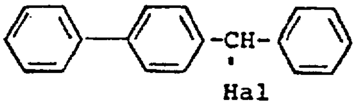
The formulations according to the invention are prepared by a process in which, in a manner which is known per se, either

(a) the carbinol of the formula



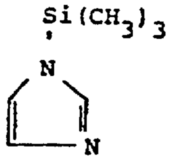
is reacted with thionyl-bis-imidazole, if appropriate in the presence of a diluent, or

(b) the halogeno-methane of the formula



is either

1) reacted with imidazole, if appropriate in the presence of an acid-binding agent and if appropriate in the presence of a diluent, or
2) reacted with the silver salt or alkali metal salts of the imidazole, if appropriate in the presence of a diluent, or
3) reacted with trimethylsilylimidazole of the formula



if appropriate in the presence of a diluent, and, if appropriate, the azol-1-yl-methane thereby obtained is reacted with physiologically acceptable acids, and the product thereby obtained is mixed with 5—25% of a spreading agent, conventional formulation auxiliaries and a solvent.

The agents according to the invention contain bifonazole in amounts of 0.05%—1.5%, preferably of 0.1—1% and very particularly preferably 1%.

Spreading agents are understood as meaning oily liquids which distribute themselves particularly readily on the skin [R. Keymer, Pharm. Ind. 32 [1970], 577—581]. The following compounds are particularly suitable spreading agents for the agents according to the invention:

Silicone oils of various viscosities.

Fatty acid esters, such as ethyl stearate, di-n-butyl adipate, hexyl laurate, dipropylene glycol pelargonate, esters of a branched fatty acid of medium chain lengths with saturated C_{16}—C_{18}-fatty alcohols, isopropyl myristate, isopropyl palmitate, caprylic/capric acid esters of saturated fatty alcohols of C_{12}—C_{18} chain lengths, iso-propyl stearate, oleyl oleate, decyl oleate, ethyl oleate, ethyl lactate, waxy fatty acid esters, such as synthetic duck uropygial gland fat, dibutyl phthalate, diisopropyl adipate, ester mixtures related to the latter and the like.

Triglycerides, such as caprylic/capric acid triglyceride, triglyceride mixtures with vegetable fatty acids of C_8—C_{12} chain lengths or other specially selected naturally occurring fatty acids, partial glyceride mixtures of saturated or unsaturated fatty acids, optionally containing hydroxyl groups, monoglycerides of the C_8/C_{10}-fatty acids and the like.

Fatty alcohols, such as isotridecyl alcohol, 2-octyl-dodecanol, cetylstearyl alcohol and oleyl alcohol.

Fatty acids, such as, for example, oleic acid.

The following spreading oils are particularly suitable; isopropyl myristate, isopropyl palmitate, caprylic/capric acid esters of saturated fatty alcohols of C_{12}—C_{18} chain lengths, waxy fatty acid esters, such as synthetic duck uropygial gland fat, silicone oils and a mixture of isopropyl myristate/isopropyl stearate/isopropyl palmitate.

The following auxiliairies and/or formulation base auxiliaries can be used in the preparation of the agents according to the invention.

"Glyceryl stearates", a mixture of monoglycerides and diglycerides of palmitic acid and stearic acid	Oil-in-water cream base, not self-emulsifying
Colloidally disperse mixture of cetyl-stearyl alcohol and sodium cetyl-stearyl sulphate	Oil-in-water emulsion base, self-emulsifying
Esters of a branched fatty acid with saturated C_{16}—C_{18}-fatty alcohols	Oil component with a marked hydrophobic effect for skin protection products
Cetyl palmitate	Synthetic spermaceti, consistency for creams, ointments, emulsions
Polyethylene stearate	Nonionic hydrophylic emulsifier
Cetyl-stearyl alcohol oxy-ethylated with about 12 moles of ethylene oxide	Nonionic oil-in-water emulsifier
Cetyl-stearyl alcohol oxy-ethylated with about 30 moles of ethylene oxide	Nonionic oil-in-water emulsifier
Sorbitan and glycerol fatty acid esters	Nonionic emulsifier

Suitable formulation auxiliaries are:

a. substances which, for example, can stabilise a suspension, for example colloidal silicic acid, montmorillonites and the like.

b. Surfactants (includes emulsifiers and wetting agents), for example

1. anionic, such as Na lauryl-sulphate, fatty alcohol ether-sulphates and monoethanolamine salts of mono/dialkyl polyglycol ether orthophosphates;
2. cationic, such as cetyltrimethylammonium chloride;
3. ampholytic, such as di-Na-N-lauryl-β-iminodipropionate or lecithin; and
4. nonionic, for example polyoxyethylated castor oil, polyoxyethylated sorbitan monooleate, sorbitan monostearate, cetyl alcohol, glycerol monostearate, polyoxyethylene stearate and alkylphenol polyglycol ethers.

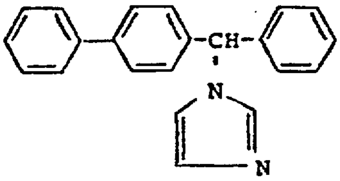
c. Stabilisers for preventing the chemical degradation which occurs to some active compounds, such as antioxidants, for example tocopherols or butylhydroxyanisole.

d. Softeners, for example propylene glycol, glycerol, di- and tri-propylene glycol, triethanolamine, waxes and the like.

Suitable solvents are water and all water-miscible solvents. Examples of solvents which can be used are alkanols, such as ethanol and isopropyl alcohol, propylene glycol, Methylcellosolve, Cellosolve, esters, morpholines, dioxane, dimethylsulphoxide, dimethylformamide, tetrahydrofuran and cyclohexanone.

One or more solvents can be used in the preparation of the formulations according to the invention.

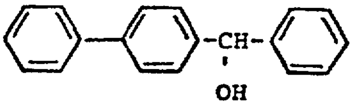
Preparation of the Active Compound Bifonazole



Process Variant (a)

13.6 g (0.2 mole) of imidazole are dissolved in 150 ml of acetonitrile, and 3.5 ml of thionyl chloride are added at 10°C. 13 g (0.05 mole) of diphenyl-phenyl-carbinol are added to the solution of thionyl-bis-imidazole thus obtained. After the mixture has been left to stand at room temperature for 15 hours, the solvent is removed by distillation in vacuo. The residue is taken up in chloroform and the mixture is washed with water. The organic phase is separated off, dried over sodium sulphate and filtered and the solvent is distilled off in vacuo. The oily residue is dissolved in ethyl acetate and the solution is freed from insoluble, resinous constituents by filtration. The solvent is distilled off again in vacuo and the residue is purified by recrystallisation from acetonitrile. 8.7 g (56% of theory) of diphenyl-imidazole-1-phenyl-methane (bifonazole) of melting point 142°C are obtained.

Starting Substance



38.8 g (0.15 mole) of 4-phenyl-benzophenone are dissolved in 200 ml of ethanol, and 3 g (0.075 mole) of sodium borohydride are added. After the mixture has been heated under reflux for 15 hours, the cooled reaction mixture is hydrolysed with water containing a small amount of hydrochloric acid. The solid thereby formed is purified by recrystallisation from ethanol. 36 g (89% of theory) of diphenyl-phenyl-carbinol of melting point 72—73°C are obtained.

Process Variant (b/3.)

167 g (0.6 mole) of diphenyl-phenyl-chloromethane and 92 g (0.66 mole) of trimethylsilylimidazole, dissolved in 500 ml of acetonitrile, are heated under reflux for 15 hours. After the solvent has been distilled off, the crystalline residue is purified by recrystallisation from ethyl acetate. 97 g (52% of theory) of diphenyl-imidazol-1-yl-phenyl-methane (bifonazole) of melting point 142°C are obtained.

EXAMPLE 1
Cream, Oil-in-Water

Phase I

Sorbitan monostearate	2.0 g
Polyoxyethylene (20)-sorbitan monostearate	1.5 g
Synthetic spermaceti	3.0 g
Cetyl-stearyl alcohol	10.0 g
2-Octyldodecanol	13.5 g

Warm to 75°C, stir, mix.

Phase II

Bifonazole	1.0 g

Add to phase I, stir, dissolve.

Phase III

Benzyl alcohol	1.0 g
Water, demineralised	68.0 g

Warm to 75°C and add to phase II. Mix intensively, cool slowly to room temperature, with further stirring. Homogenise.

EXAMPLE 2
Cream, Oil-in-Water

Phase I

Sorbitan monostearate	1—3 g
Polyoxyethylene (20)-sorbitan monostearate	0.5—2.5 g
Synthetic spermaceti	2—4 g
Cetyl-stearyl alcohol	5—15 g
2-Octyldodecanol	5—25 g

Warm to 75°C, stir, mix.

Phase II

Bifonazole	0.5—1.5 g

Add to phase I, stir, dissolve.

Phase III

Benzyl alcohol	0.5—1.5 g
Water demineralised	quant. sat.

Warm to 75°C and add to phase II, mix intensively, cool slowly to room temperature, with further stirring. Homogenise.

Testing of the Activity of the Agents According to the Invention on Guinea Pigs Infected with Trichophyton

Trichophyton-infected Pirbright white guinea pigs weighing on average 600 g were used as the test model for comparative testing of the activity of the formulations according to the invention. The backs of the animals were shaved with electric clippers such that stubble about 1/10 mm long remained.

The animals were infected with Trichophyton mentagrophytes by gently rubbing a spore suspension, which had been germinated in Sabouraud nutrient solution for 24 hours, of the pathogen on an approximately 2x2 cm area of their shaved backs. 0.5 ml of germ suspension containing 1—3×10^5 infectious fungal particles, was applied per animal.

With this mode of infection, the first symptoms of dermatophytosis manifest themselves as reddening and scaling of the skin 2—3 days after infection. In the case of untreated animals, the dermatophytosis is of maximum severity about 14 days after infection: areas of hair loss and bloody integumentary defects within a scaly edge zone changed by inflammation.

The formulations to be tested were applied locally to the reddened infection site of the animals once, on the 2nd day after infection, and were gently rubbed in with a horn spatula. In each case 0.5 ml of the formulations=5 mg of active compound (1% strength formulation) was applied. The progress of the infection was evaluated daily up to the 20th day after infection.

The formulations according to the invention exhibit a very good action in this test.

If formulation which, besides bifonazole, contain no spreading agent are used for comparison, an effect corresponding to that of the formulations according to the invention is achieved only after three applications.

It will of course be understood that the present invention has been described above purely by way of example, and modifications of detail can be made within the scope and spirit of the invention.

CLAIMS

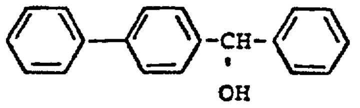
1. Antimycotic agents with a higher release of the active compounds and containing bifonazole, a solvent and conventional formulation auxiliaries, characterised in that they contain 5—25% by weight of a spreading agent.

2. Antimycotic agents according to Claim 1, characterised in that they contain 0.05—1.5%, preferably 0.1—1%, of bifonazole.

3. Antimycotic agents according to Claim 1, characterised in that they contain 1.0% of bifonazole.

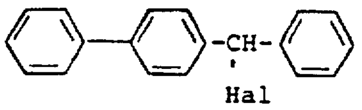
4. Process for the preparation of formulations of bifonazole, characterised in that, in a manner which is known per se, either

(a) the carbinol of the formula



is reacted with thionyl-bis-imidazole, if appropriate in the presence of a diluent, or

(b) the halogeno-methane of the formula

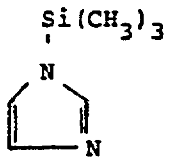


is either

1) reacted with imidazole, if appropriate in the presence of an acid-binding agent and if appropriate in the presence of a diluent, or

2) reacted with the silver salt or alkali metal salts of the imidazole, if appropriate in the presence of a diluent, or

3) reacted with trimethylsilylimidazole of the formula



if appropriate in the presence of a diluent, and, if appropriate, the azol-1-yl-methanes thereby obtained is reacted with physiologically acceptable acids, and the product thereby obtained is mixed with 5—25% of a spreading agent, conventional formulation auxiliaries and a solvent.

5. Antimycotic agent according to Claim 1, substantially as described in Example 1 or Example 2.

6. Process according to Claim 4, substantially as hereinbefore described under "Process variant (a)" or "Process variant (b/3)".

7. Composition as defined in Claim 1 for use in combating mycoses.

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