

Description

The present invention is concerned with an antimycotically-active preparation in the form of a nail varnish, which contains at least one antimycotically-active substance and at least one water-insoluble film-former. The invention is also concerned with a process for the manufacture of such a preparation.

Aqueous antimycotic preparations for the treatment of fungal infections of nails and/or of surrounding skin, e.g. for the treatment of the fungal infection onychomycosis which attacks nails, are known from UK Patent Publication 2 202 743 A. These preparations contain miconazole nitrate or econazole nitrate as the active ingredient and, inter alia, a water-soluble solubilizing adjuvant, e.g. ethanol, and can take the form of, inter alia, a nail varnish. In the case of the nail varnish, the solubilizing adjuvant is intended to solubilize a film-former, which is also present, such that a film coating is formed on the nail after evaporation or penetration. Eudragit® E 100, which is a copolymerizate of methacrylic acid dimethylaminoethyl ester and methacrylic acid lower alkyl ester(s), is mentioned among the film-formers which can be used according to this patent publication. No quaternary ammonium groups are present in such copolymerizates.

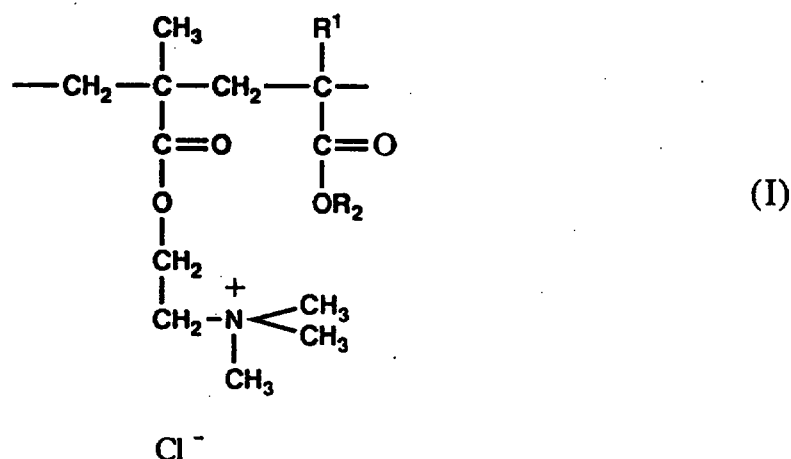
The object of the invention is to improve the quality of preparations of the kind referred to above, especially with respect to the following properties: good rate of penetration, good skin compatibility, good flow behaviour, good spreadability, short drying time, only moderately high gloss, sufficiently great hardness and long durability (about 3-4 days).

This object is achieved in accordance with the invention by using a salt of 4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine or of 4-[3-[p-(1,1-dimethyl-propyl)-phenyl]-2-methyl-propyl]-2,6-dimethylmorpholine as the antimycotically-active substance and a copolymerizate of acrylic acid esters and methacrylic acid esters having a low content of quaternary ammonium groups as the water-insoluble film-former. Such copolymerizates are known e.g. from US Patent Specification 2677679 and DAS 1617751, and such antimycotically-active substances are known from DAS 2752096.

Conveniently, the content of quaternary ammonium groups in the copolymerizate is such that the molar ratio of ammonium groups to the remaining neutral acrylic acid esters and,

respectively, methacrylic acid esters ($-\text{COOR}^2$ in formula I below) lies between about 1:20 and about 1:40.

The average molecular weight of such a copolymerizate amounts to about 150,000. Such copolymerizates can be characterized by the following partial formula in which R_1 signifies hydrogen or methyl and R_2 signifies methyl or ethyl



Such substances are commercially available as 12.5% varnish solutions and as solvent-free solids under the brand EUDRAGIT® RL and RS (see Römpp's Chemielexikon, 8th edition, p. 1211).

Such substances can also be mixed with one another according to the particular requirements.

Because of their swelling capacity and porosity, the use of such copolymerizates guarantees a high rate of diffusion and a high rate of permeability for the active substance.

Further, the use of such copolymerizates guarantees, in addition to the aforementioned properties, a high resistance of the coating of varnish against mechanical damage and against washing-off in the entire pH range. This makes it possible for the film of varnish containing the antimycotically-active substance to remain on the nail for several days and therefore the period between two applications of the varnish solution amounts to several days.

Conveniently, in the preparation in accordance with the invention the copolymerizate and the antimycotically-active substance and any further additives such as plasticizers, evaporation retarders and/or evaporation accelerators are dissolved in an inert organic solvent, especially in ethanol or methylene chloride.

As plasticizers there can be named: glycerol acetates such as triacetin, phthalates or plasticizers based on camphor. In addition to the preferred solvents, namely ethanol and methylene chloride, there can also be used, for example, acetone and isopropanol.

Toluene, butanol, butyl acetate, amyl alcohol and amyl acetate are examples of evaporation retarders and ethyl acetate can be named as an example of an evaporation accelerator.

The antimycotically-active substance present in the preparation in accordance with the invention is 4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine or 4-[3-[p-(1,1-dimethylpropyl)-phenyl]-2-methyl-propyl]-2,6-dimethylmorpholine, in each case in salt form, especially in the form of the hydrochloride or of the nitrate. The cis isomers of these compounds are preferably used. These cis isomers are known from European Patent Publication No. 24 334, the second-named compound being known under the name 4-[3-(p-tert.amyl-phenyl)-2-methylpropyl]-2,6-dimethyl-morpholine. The use of the cis isomer of this compound, especially in the form of the hydrochloride, is especially preferred.

An especially preferred embodiment of the preparation in accordance with the invention contains the antimycotically-active substance, namely the aforementioned morpholine derivative, in an amount of about 0.25 to about 10 wt.%, especially in an amount of about 5 wt.%, based on the base.

In accordance with a convenient embodiment of the preparation in accordance with the invention, this contains the water-insoluble copolymerizate in an amount of about 2-30 wt.%, preferably 10-20 wt.%, especially about 12.5 wt.%.

The process in accordance with the invention for the manufacture of the preparation comprises mixing the copolymerizate in dissolved form with the active substance and any additives such as plasticizers, evaporation accelerators, evaporation retarders and the like.

Example 1

A preparation in accordance with the invention, which contains methylene chloride as the solvent, has the following composition:

Active substance	5.574 g
EUDRAGIT® RL 100	12.5 g
Triacetin	2.5 g
Butyl acetate	15.0 g
Methylene chloride	ad 100.0 ml

Example 2

A preparation in accordance with the invention, which contains ethanol as the solvent, has the following composition:

Active substance	5.574 g
EUDRAGIT® RL 100	12.5 g
Butyl acetate	5.0 g
Ethyl acetate	15.0 g
Ethanol	ad 100.0 ml

The active substance used in the above Examples is cis-4-[3-[p-(1,1-dimethylpropyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride or cis-4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride, and EUDRAGIT® RL 100 is a copolymerizate of acrylic acid esters and methacrylic acid esters which contains ammonium groups in a molar ratio of 1:20 (see the company prospectus Röhm Pharma GMBH, Weiterstadt, Federal Republic of Germany: "EUDRAGIT" RL und RS Anwendung in der Arzneimittelherstellung" 1982). Instead of this particular copolymerizate, structurally similar copolymerizates can be used, e.g. a copolymerizate of trimethyl-methacryloxyethylammonium chloride, methyl methacrylate and ethyl acrylate having a low content of ammonium groups.

Claims

1. A nail varnish containing at least one antimycotically-active substance and at least one water-insoluble film-former, characterized in that the antimycotically-active substance is a salt of 4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine or of 4-[3-[p-(1,1-



Example 1

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A preparation in accordance with the invention, which contains ethanol as the solvent, has the following composition:

Active substance	5.574 g
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Butyl acetate	5.0 g
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The active substance used in the above Examples is cis-4-[3-[p-(1,1-dimethylpropyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride or cis-4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride, and EUDRAGIT® RL 100 is a copolymerizate of acrylic acid esters and methacrylic acid esters which contains ammonium groups in a molar ratio of 1:20 (see the company prospectus Röhm Pharma GMBH, Weiterstadt, Federal Republic of Germany: "EUDRAGIT" RL und RS Anwendung in der Arzneimittelherstellung" 1982). Instead of this particular copolymerizate, structurally similar copolymerizates can be used, e.g. a copolymerizate of trimethyl-methacryloxyethylammonium chloride, methyl methacrylate and ethyl acrylate having a low content of ammonium groups.

Claims

1. A nail varnish containing at least one antimycotically-active substance and at least one water-insoluble film-former, characterized in that the antimycotically-active substance is a salt of 4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine or of 4-[3-[p-(1,1-



dimethylpropyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine and the water-insoluble film-former is a copolymerizate of acrylic acid esters and methacrylic acid esters having a low content of quaternary ammonium groups.

2. A nail varnish according to claim 1, characterized in that the molar ratio of ammonium groups to the remaining neutral acrylic acid esters and, respectively, methacrylic acid esters in the copolymerizate lies between about 1:20 and about 1:40.

3. A nail varnish according to claim 1 or 2, characterized in that the average molecular weight of the copolymerizate amounts to about 150,000.

4. A nail varnish according to claim 1, 2 or 3, characterized in that the copolymerizate and the antimycotically-active substance and any further additives such as plasticizers, evaporation retarders and/or evaporation accelerators are dissolved in an inert organic solvent, especially in ethanol or methylene chloride.

5. A nail varnish according to any one of claims 1-4, characterized in that it contains cis-4-[3-[p-(α,α -dimethylbenzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride as the antimycotically-active substance.

6. A nail varnish according to any one of claims 1-4, characterized in that it contains cis-4-[3-[p-(1,1-dimethylpropyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride as the antimycotically-active substance.

7. A nail varnish according to any one of claims 1-6, characterized in that it contains the antimycotically-active substance in an amount of about 0.25 to about 10 wt.%, especially 5 wt.%, based on the base.

8. A nail varnish according to any one of claims 1-7, characterized in that it contains the water-insoluble copolymerizate in an amount of about 2-30 wt.%, preferably 10-20 wt.%, especially about 12.5 wt.%.

9. A process for the manufacture of a nail varnish according to any one of claims 1-8, characterized by mixing the copolymerizate in dissolved form with the active substance and any additives such as plasticizers, evaporation accelerators, evaporation retarders and the like.



10. A process according to claim 9, characterized in that there is used a copolymerizate in which the molar ratio of ammonium groups to the remaining neutral acrylic acid esters and, respectively, methacrylic acid esters in the copolymerizate lies between about 1:20 and about 1:40.

11. A process according to claim 9 or 10, characterized in that the average molecular weight of the copolymerizate used amounts to about 150,000.

12. A process according to claim 9, 10 or 11, characterized in that cis-4-[3-[p-(α,α -dimethyl-benzyl)-phenyl]-2-methyl-propyl]-2,6-dimethyl-morpholine hydrochloride is used as the antimycotically-active substance.

13. A process according to claim 9, 10 or 11, characterized in that cis-4-[3-[p-(1,1-dimethylpropyl)-phenyl]-2-methyl-propyl]-2,6-dimethylmorpholine hydrochloride is used as the antimycotically-active substance.

14. A process according to any one of claims 9-13, characterized in that the antimycotically-active substance is used in an amount of about 0.25 to about 10 wt.%, especially 5 wt.%, based on the base.

15. A process according to any one of claims 9-14, characterized in that the copolymerizate is used in an amount of about 2-30 wt.%, preferably 10-20 wt.%, especially about 12.5 wt.%.