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(54) Title: UREA-BASED FILM-FORMING SOLUTION FOR TREATING NAIL PSORIASIS

(57) Abstract: The invention relates to a film-forming solution comprising: - 10 to 20 % of urea, - 5 to 15 % of film- forming polymer, 45 to 65 % of a polar solvent, 1 to 20 % of a co-solvent, 0.01 to 5% of a plasticizer selected from the list consisting of diethyl phthalate, triethyl citrate, dibutyl sebacate, diethyl sebacate, dibutyl phthalate, acetyltriethyl citrate, and polyethylene glycols, and - water up to 100% intended for treating ungual fungic infections and nail psoriasis.

UREA-BASED FILM-FORMING SOLUTION FOR TREATING NAIL PSORIASIS

The present invention relates to the treatment of hyperkeratosis of pathological nails.

Many diseases affect nails and bother many individuals.

Among them, mention may be made of nail psoriasis and onychomycoses.

Psoriasis is a chronic disease which causes significant suffering and morbidity. The nail is affected in 10 to 50% of the cases (Scher, 1985; van Laborde and Scher, 2000), and it is estimated that 80 to 90% of psoriatic patients have nails affected at a moment of their life (De Berker, 2000). Ungual psoriasis in the absence of skin disease accounts for 1 to 5% of the patients (van Laborde and Scher, 2000).

Ungual psoriasis is painful and invalidating. More than 50% of the patients suffer from nail changes due to ungual psoriasis, about 60% estimate that ungual psoriasis limits their daily activities and 93% consider ungual psoriasis as a cosmetic handicap (De Jong *et al.*, 1996).

Fingernails are more frequently affected than toenails.

Treatment of ungual psoriasis is focused on improving functional and psychosocial aspects of the disease since no curative treatment exists today.

In spite of recent advances in the treatment of skin psoriasis, the treatment options for ungual psoriasis are much more limited. Depending on the disease, a distinction is made between topic, systemic and intralesional injection corticotherapies, or even PUVA therapy. Systemic therapy has the drawbacks of systemic secondary effects and drug interactions (Murdan, 2002). Intralesional injections of corticosteroids, have shown their effectiveness in certain cases of ungual matrix psoriasis but are extremely painful and have local secondary effects. Topical therapy is the primary therapy for skin psoriasis. However its use on nails is not very documented and proof of its effectiveness on nail dystrophies is an extrapolation of the considered advantages for treating lesions of the skin. In order to be effective, the drug should penetrate through the plate of the nail in order to reach the bed of the nail and the matrix target. Unfortunately, topical drugs formulated for treating skin

diseases are not adapted for optimizing the penetration of drugs in and through the plate of the nail, and diffusion in the strongly keratinized plate of the nail of available formulations, regardless of the active substance (for example corticosteroids, calcipotriol, 5-fluorouracil), is very low. Topical treatment of ungual psoriasis by using commercial available formulations is therefore disappointing.

An onychomycosis is defined as a fungic infection of the ungual system, i.e. of the matrix, the bed or the plate of the nail caused by dermatophytes (of the genus *Trichophyton*, *Epidermophyton* or *Microsporum*), yeasts (*Candida* or *Malassezia*) or fungi (*Fusarium*). At the fingers, these are most often yeasts (*Candida*).

Onychomycosis is the most frequent of ungual pathologies. It concerns 6 to 9% of the general population.

This is especially a disease of adults; it is rare in children. Its prevalence increases with age; it is 30% after 70 years of age.

90% of the onychomycoses affect the toes and in 9 cases out of 10, these are dermatophytes.

Onychomycosis never cures spontaneously and is known as being difficult to treat.

Ungual hyperkeratosis is one of the symptoms of ungual psoriasis and of onychomycoses. This is an excessive proliferation of the bed of the nail which may lead to onycholysis. It results from the deposition of cells under the plate of the nail which have not been eliminated by desquamation. As this is a symptom which only affects the bed of the nail, it may be treated with a topical product such as varnish. Hyperkeratosis may be painful, may reduce the penetration of topical drugs and is not aesthetic.

As compared with creams and ointments, curative nail varnishes are relatively new formulations, known as transungual release devices (Murdan, 2002). The varnish forms a film which adheres to the plate of the nail and does not flake off during daily activities. The film acts as a drug reservoir from where the drug is released, penetrating and acting in the nail during the whole duration of the application. Further, the formation of a film on the plate of the nail reduces

the water loss of the surface of the nail, resulting in hyperhydration of the upper layers of the nail, which may also contribute to diffusion of the drug.

Urea has been used for long time in dermatology for its keratolytic properties.

There is a significant need for a nail varnish comprising a high proportion of urea intended for treating ungual hyperkeratosis providing the patient with improved comfort by reducing the thickness of the plate of the nail and by improving the aesthetic aspect of the nail as well as better compliance with the treatment, considering its ease of application.

The problem however is the following: for significant amounts of urea the solution precipitates before and/or after application.

There is a need for a film-forming transparent solution containing a high proportion of urea and intended for treating ungual hyperkeratosis.

Surprisingly, the inventors have developed a nail varnish, the composition of which provides urea amounts of 15% and transparence in the flask and after application.

The object of the present invention is thus a film-forming solution comprising:

- 10 to 20 % of urea,
- 5 to 15 % of film-forming polymer,
- 45 to 65 % of a polar solvent,
- 1 to 20 % of a co-solvent,
- 0.01 to 5%, for example 0.01% to 1%, for example 0.5 to 5%, for example from 0.5 to 1% of a plasticizer or a second co-solvent and
- water up to 100%.

Preferentially, the film-forming solution according to the invention comprises 13-17% of urea. More preferably, the film-forming solution according to the invention comprises 17% of urea.

Preferentially, the film-forming solution according to the invention comprises 8 to 12% of a film-forming polymer. More preferably, the film-forming solution according to the invention comprises 10% of a film-forming polymer.

Preferentially, the film-forming solution according to the invention comprises 45 to 50% of a polar solvent. More preferably, the film-forming solution according to the invention comprises 48 to 49% of a polar solvent.

Preferentially, the film-forming solution according to the invention comprises 1 to 5% of a co-solvent. More preferably, the film-forming solution according to the invention comprises 4 to 5% of a co-solvent.

Preferentially, the film-forming solution according to the invention comprises 0.5 to 1% of a plasticizer. More preferably, the film-forming solution according to the invention comprises 0.6 to 0.7% of a plasticizer.

Advantageously, the film-forming polymer of the film-forming solution according to the invention is a Eudragit. Preferably, the film-forming polymer of the film-forming solution according to the invention is a Eudragit E, RL, RS, L or S. More preferably, the film-forming polymer of the film-forming solution according to the invention is Eudragit E100, Eudragit RL/RS, Eudragit L100, Eudragit S100 and Eudragit L100-55.

In the sense of the present invention, a polymer of methacrylates and/or acrylates is called a «Eudragit ».

Eudragit E100 is a copolymer of methyl methacrylate and of butyl methacrylate.

Eudragit RL/RS is a copolymer of trimethyl ammonioethyl methacrylate chloride.

Eudragit L are copolymers of methacrylic acid and of ethyl acrylates.

Eudragit S are copolymers of methacrylic acid and of methacrylates.

Advantageously, the polar solvent of the film-forming solution according to the invention is ethyl alcohol, preferably 96% ethyl alcohol.

Advantageously, the co-solvent of the film-forming solution according to the invention is selected from the list consisting of propylene glycol, glycerin, sorbitol, ethoxyglycol, ethyl acetate, isopropanol, butyl alcohol, and polyethylene glycol 200, for example from the list consisting of propylene glycol, glycerin, sorbitol and polyethylene glycol 200. Indeed, these co-solvents have sufficient volatility in order to achieve rapid drying of the varnish while improving the solubility of the urea in the

presence of the film-forming polymer. Preferably, the co-solvent of the film-forming solution according to the invention is propylene glycol which has proved to be the best co-solvent for solubilizing urea in the presence of the film-forming polymer.

Advantageously, the plasticizer or the second co-solvent of the film-forming solution according to the invention is selected from the list consisting of diethyl phthalate, triethyl citrate, triacetine, dibutyl sebacate, diethyl sebacate, dibutyl phthalate, acetyltriethyl citrate, and polyethylene glycols. Indeed, with these plasticizers and co-solvents it is possible to obtain the sought transparency. For example, the plasticizer or the second co-solvent of the film-forming solution according to the invention is selected from the group consisting of diethyl phthalate, triethyl citrate, dibutyl sebacate, diethyl sebacate, dibutyl phthalate, acetyltriethyl citrate, and polyethylene glycols. Diethyl phthalate further has an interesting potential as a bitterness agent which may be prove to be useful in a nail varnish for nail-biting patients. According to an embodiment of the invention, the mentioned plasticizers are used as an additional co-solvent, for example the solution according to the invention comprises from 0.01 to 5%, for example from 0.01% to 1%, for example from 0.5 to 5%, for example from 0.5 to 1% of said agents in addition to the co-solvents mentioned earlier.

In an embodiment of the invention, the film-forming solution comprises 10 to 20% of urea, 45 to 65% of a polar solvent, 5 to 15% of a co-solvent, 5 to 15% of a film-forming agent, 0.5 to 5%, for example 0.5 to 1% of a second so-solvent and water up to 100%.

In an embodiment of the invention, the film-forming solution comprises 10 to 20% of urea, 45 to 65% of 96% ethyl alcohol, 5 to 15% of propylene glycol, 5 to 15% of Eudragit E100, 0.5 to 5% for example 0.5 to 1% of diethyl phthalate and water up to 100%.

A preferred film-forming solution of the invention comprises:

- 15 % of urea,
- 48.69 % of 96% ethyl alcohol,
- 4.4 % of propylene glycol,

- 10 % of Eudragit E100,
- 0.63 % of diethyl phthalate and
- 21.28 % of water.

Advantageously, the film-forming solution according to the invention is used for treating nails having hyperkeratosis. This hyperkeratosis may be related to another pathology, for example a hyperkeratosis related to lupus. .

Another object of the invention is a film-forming solution according to the invention for a use intended to remove abnormal ungual keratinous material, in particular abnormal ungual keratinous material resulting from psoriasis or onychomycosis.

Another object of the invention is the use of a film-forming solution according to the invention for making a drug intended for removing abnormal ungual keratinous material.

Preferably, this abnormal ungual keratinous material results from onychomycosis or psoriasis.

The following examples illustrate the invention without limiting the scope thereof.

Example 1: Formulation according to the invention

Formula SR2852

Material designation	Amounts g/100 g
Urea	15.00
96% ethyl alcohol	48.69
Propylene glycol	4.40
Eudragit E100	10.00
Diethyl phthalate	0.63
Purified water	21.28

After applying the formula SR2852, a transparent film is formed on the nail. The urea does not crystallize after drying of the varnish on the nail.

Example 2: Formulation without any plasticizer (comparative test)

Formula SR2893

Material designation	Amounts g/100 g
Urea	15.00
96% ethyl alcohol	49.32
Propylene glycol	4.40
Eudragit E100	10.00
Purified water	21.28

After applying the formula SR2893, an opaque film is formed on the nail. The film is the result of recrystallization of urea after drying the varnish on the nail

Example 3: Method for preparing a formulation according to the invention

The operating procedure for making the formula or Example 1 for a batch of 500 g is the following:

In a beaker 106.4 g of water and 75 g of urea are introduced with stirring. To the solution are added 22 g of propylene glycol, 243.45 g of ethyl alcohol, and 3.15 g of diethyl phthalate and 50 g of Eudragit E100. Stirring is performed until the solution becomes limpid.

Example 4: Effectiveness and tolerance of the medical device with 15% urea nail varnish in the treatment of hyperkeratosis of psoriatic nails of the hand: an exploratory study.

1- Main goal: evaluate the effectiveness of a nail varnish with 15% of urea for treating hyperkeratosis of psoriatic nails of the hand after 6 months of daily application.

2- Secondary goals:

evaluation of the success of the treatment after 6 months

global self-evaluation of the treatment by the patient after 6 months

evaluate local and general tolerance of the product

evaluation of the life quality of the patient

3- Composition of the medical device: urea 15%, ethanol, propylene glycol, Eudragit E100, diethyl phthalate, purified water.

Administration: the product is applied once daily just before going to bed for 6 months.

4 – Inclusion criteria

- man or woman of more than 18 years of age
- patient with a history of skin psoriasis
- patient having at least two nails with hyperkeratosis with a thickness of more than 2 mm

5 – Evaluation criterion:

5.1- Main criterion:

Effectiveness of the nail varnish with 15% of urea for treating hyperkeratosis of psoriatic nails after 6 months.

For each patient, the thickness of the treated nail is measured in millimeters with a vernier caliper. At each visit, the measurement is made at the same nail area (defined as the initial condition), where the thickness is the largest at the moment of the inclusion.

5.2 – Intermediate secondary criteria:

- measurement of hyperkeratosis after 1.5 and 3 months.
- the investigator determines a global dynamic score (dynamic Investigator Physician Global Assessment) which assesses global improvement after 1.5, 3 and 6 months as compared with the initial condition. At each visit, a global clinical assessment is carried out by comparison with photographs taken at the inclusion.
- the investigator determines a global statistic score (static Investigator Physician Global Assessment, sIPGA) at each visit (inclusion, after 1.5, 3 and 6 months) without any comparison with the initial condition. The severity of psoriasis, i.e. the ungual surface having psoriatic lesions, is assessed according to the scale detailed below. The

affected nails are not assessed separately, but a global score is assigned for the whole of the affected nails.

6 - Conclusion

The provided results correspond to intermediate results after 3 months of application.

28 patients were analyzed for these intermediate results, 4 patients were withdrawn from the study.

As regards effectiveness, a significant reduction in hyperkeratosis was observed after 3 months of treatment. This reduction is of -25% after 3 months and was -10 % after 1.5 months of treatment. A daily application of 15% nail varnish containing 15% of urea for treating psoriasis of the nail shows a significant effect in the reduction of hyperkeratosis, and trends in favor of the effectiveness for the other criteria (global dynamic score, global static score). Good tolerance is observed.

CLAIMS

1- A film-forming solution comprising:

- 10 to 20 % of urea,
- 5 to 15 % of a film-forming polymer,
- 45 to 65 % of a polar solvent,
- 1 to 20 % of a co-solvent,
- 0.01 to 5% of a plasticizer selected from the list consisting of diethyl phthalate, triethyl citrate, dibutyl sebacate, diethyl sebacate, dibutyl phthalate, acetyltriethyl citrate, and polyethylene glycols, and
- water up to 100%.

2- The film-forming solution according to claim 1, comprising 13 to 17% of urea.

3- The film-forming solution according to claim 1 or 2, comprising 15% of urea.

4- The film-forming solution according to any of the preceding claims, comprising :

- 8 to 12 % of a film-forming polymer,
- 45 to 50 % of a polar solvent,
- 1 to 5 % of a co-solvent,
- 0.5 to 1% of a plasticizer and
- water up to 100%.

5- The film-forming solution according to any of the preceding claims, the film-forming polymer being a Eudragit.

6- The film-forming solution according to claim 5, the film-forming polymer being selected from the list consisting of Eudragit E100, Eudragit RL/RS, Eudragit L100, Eudragit S100 and Eudragit L100-55.

7- The film-forming solution according to any of the preceding claims, the polar solvent being ethyl alcohol.

8- The film-forming solution according to any of the preceding claims, the co-solvent being selected from the list consisting of propylene glycol, glycerin, sorbitol and polyethylene glycol 200.

9- The film-forming solution according to claim 1, comprising 10 to 20% of urea, 45 to 65% of 96% ethyl alcohol, 5 to 15% of propylene glycol, 5 to 15% of Eudragit E100, 0.5 to 1% of diethyl phthalate and water up to 100%.

10- The film-forming solution according to any of claims 1 to 8, comprising:

- 15 % of urea,
- 48.69 % of 96% ethyl alcohol,
- 4.4 % of propylene glycol,
- 10 % of Eudragit E100,
- 0.63 % of diethyl phthalate and
- 21.28 % of water.

11- The film-forming solution according to any of the preceding claims, for a use intended for removing abnormal ungual keratinous material.

12- The film-forming solution according to claim 11, the abnormal ungual keratinous material resulting from psoriasis or onychomycosis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/063771

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/155 A61P17/00 A61K47/10

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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	FR 2 613 227 A1 (OREAL [FR]) 7 October 1988 (1988-10-07) page 2, lines 34-35; example 4 page 3, lines 34-37	1-12
A	KRÜGER N ET AL: "Effect of urea nail lacquer on nail quality; Clinical evaluation and biophysical measurements" DER HAUTARZT ; ZEITSCHRIFT FÜR DERMATOLOGIE, VENEROLOGIE UND VERWANDTE GEBIETE, SPRINGER, BERLIN, DE, vol. 57, no. 12, 1 December 2006 (2006-12-01), pages 1089-1094, XP019446849 ISSN: 1432-1173 paragraph 2 - column 2, paragraph 3; table 1 abstract	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
23 December 2009	05/01/2010

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/063771

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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