The present invention relates to new dermatological compositions in the form of a dry spray, which are intended for the pharmaceutical treatment of mycoses and contain an antifungal agent in combination with an uncyclized silicone polymer.

Compositions in dry spray form are known in the pharmaceutical sector, in particular, for the treatment of weeping mycoses. In effect, the powder form is entirely suited to this kind of skin disorders, and its application using an aerosol is practical.

For example, dry powder sprays are on the market which are based on econazole nitrate or on tolnaftate.

However, this type of spray is associated with disadvantages connected to the concentration of active principle which maybe [sic] released after spraying, relative to the concentration of this same active principle inside the canister. Moreover, spraying actions do not release the same amount of active principle over time.

It is therefore one object of the present invention to ensure that the concentration of active principle in the powder spray, after spraying, is identical or close to that in the powder which is present in the aerosol reservoir, that is to say that the spray must release, after spraying, the same percentage of active compound as is contained in the powder in the reservoir.

It is also appropriate to ensure that each successive spraying action releases the same or almost the same amount of active principle, which means that the spraying actions must be perfectly homogeneous over time.

Hitherto the solution to these problems consisted in providing the powder with an excess of active principle before packaging it, so as to obtain at the nozzle outlet the desired concentration. However, this involves an obvious excess production cost.

Moreover, it is often necessary, in order to avoid the technical problems of blocking, for example of the nozzle, to micronize the powder before packaging it as an aerosol, which represents a costly operation, or

else to increase the pressure of the propellent gas within the aerosol, which causes significant cooling of the skin on application.

However, it has now been found in a completely unexpected way that the addition of certain silicone polymers to the powder present in the dry spray makes it possible to obtain a regular dosage of the antifungal active principle and, likewise, a substantially identical dose of this active compound in the powder present in the aerosol canister and in the powder delivered after spraying.

The combination of silicone polymers with dry pharmaceutical sprays has not been described hitherto, although in the cosmetics sector their use in antisudorific aerosols has been described, for example in American Patent No. 4,806,338. However, this patent relates to antiperspirant compositions in which the active compounds are very often hygroscopic compounds. In this type of composition the silicone polymers act as an anti-hygroscopic agent, protecting the solid particles from premature absorption of moisture, and improve the skin adherence qualities of the powder after spraying.

Other cosmetic aerosol compositions which contain silicones include "wet" sprays, i.e. those which additionally contain an organic solvent. In these products, the silicone has a number of functions, for example as a solvent (British Patent No. 1,167,173 and French Patent No. 2,113,920) or else as a solvent evaporation retardant, and it thus improves the quality of the droplets of the "wet" spray (American Patent No. 4,152,416 and European Patent No. 343,843).

In contrast, the present invention relates to a pharmaceutical dry spray composition which contains an antifungal agent of the allylamine family, preferably terbinafine and naftifine and their salts, especially their hydrochloride.

Terbinafine is sold by the company Sandoz under the name Lamisil (trade mark) and is described in European Patent Application No. 024,587.

It possesses antifungal properties insofar as it inhibits the biosynthesis of membrane sterols, by intervening with regard to the enzyme squalene epoxidase, thus preventing the synthesis of ergosterol, which is indispensable to fungi.

It is this feature which makes terbinafine highly effective against dermatophytes such as, for example, Trichophyton rubrum, Epidermophyton floccusum, Trichophyton mentagrophytes, Microsporum canis and Tricophyton tonsurans.

Moreover, both terbinafine and naftifine also intervene in the metabolism of RNA by inhibiting RNA polymerase and intervene in membrane synthesis by inhibiting chitin synthetase in Saccharomyces cerevisiae.

This activity explains the efficacy of terbinafine on different species of Aspergillus, Candida and Fusarium.

The antifungal agents of the allylamine family possess, in particular, no hygroscopic character.

The present invention therefore relates to an antifungal composition in the form of a dry spray, characterized in that it contains, in combination, at least one antifungal agent of the allylamine family, at least one uncyclized silicone polymer, at least one inorganic or organic filler and at least one propellant.

In general, the antifungal composition according to the invention may contain, by weight relative to the total weight of the composition:

- from 0.01 to 0.25 %, and preferably from 0.04 to 0.15 %, of the antifungal agent,
- from 0.01 to 1.25 %, and preferably from 0.04 to 0.6 %, of the uncyclized silicone polymer,
- from 0.01 to 40 %, and preferably from 0.1 to 20 %, of the inorganic or organic filler, and
- from 85 to 95 % of the propellant.

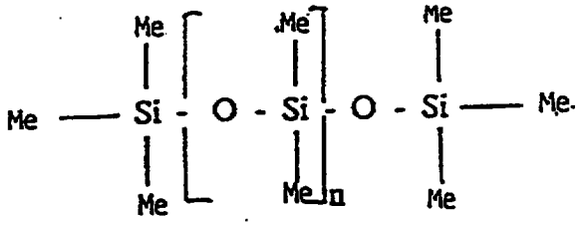
In fact, in studies, it has been noted that the uncyclized silicone polymers provide, in the case of allylamines, a solution to the problem of equivalent dosage between the powder in the aerosol and the powder leaving

the aerosol, without the need to add an excess dosage of active principle to the powder packaged in the aerosol.

Moreover, the uncyclized silicone polymers make it possible to maintain the dose of active principle as the spray is used.

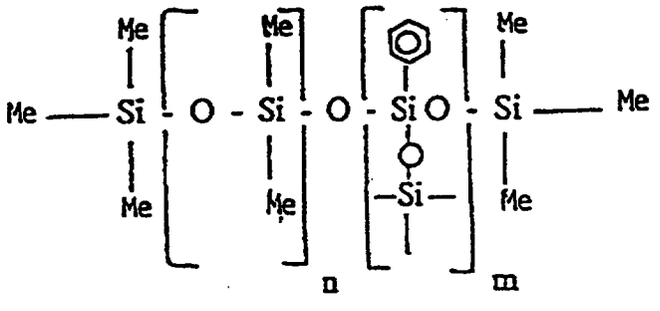
The uncyclized silicone polymers which can be used in accordance with the invention include:

- the dimethicones (DM) of general structure:



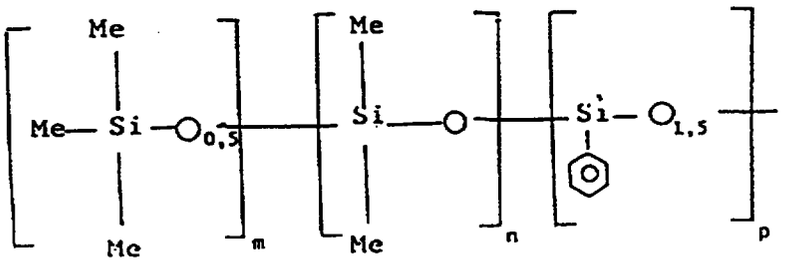
where n is between 3 and 2000, preferably between 20 and 1000, such as the products sold under the names Belsil DM 0,65,35,100 and 350 by the company Wacker;

- the phenyl dimethicones (PDM) of general structure:



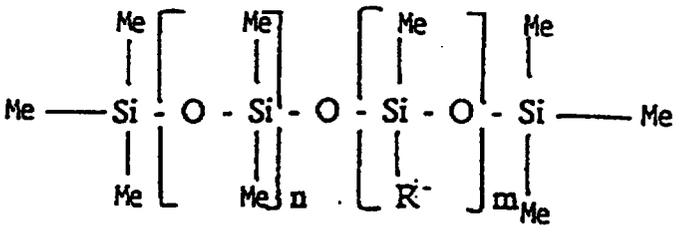
where n and m are between 5 and 2000, preferably between 20 and 1000, such as the products sold under the names Belsil PDM 20, 200 and 1000 by the company Wacker;

- the phenyl trimethicones (PtM) of general structure:

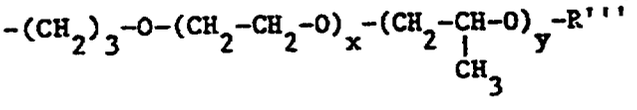


in which m, n and p independently are between 2 and 2000, preferably between 20 and 1000, such as the products sold by the company Goldschmidt under the names Abil AV 20, 200 and 2000.

- the dimethicone copolyols (DMC) of general structure:

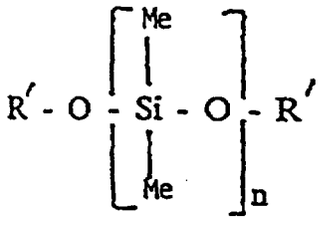


where n and m are between 2 and 2000, preferably between 20 and 1000, and in which R is a branched or non-branched copolyol chain of formula:



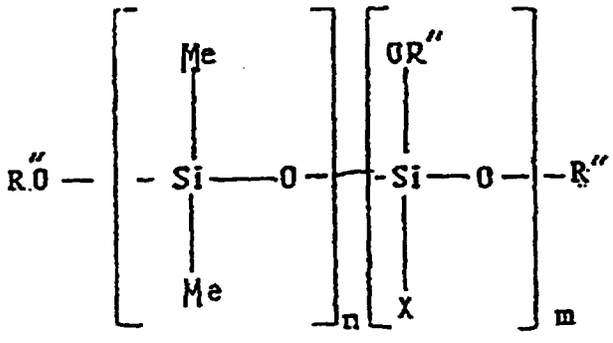
in which:
x and y are between 1 and 20 and R''' is a straight-chain or branched alkyl radical having from 10 to 18 carbon atoms, such as the products sold under the names Belsil DMC 6031, 6032, 6033 and 6035 by the company Wacker;

- the stearoxy dimethicones (SDM) of general structure:



in which R' is a straight or branched C_3 to C_{20} alkyl chain and n is between 3 and 2000, such as the products sold under the names Belsil SDM 6021 and 6022 by the company Wacker; and

- the amino-functional silicones (SAM) of general structure:



in which:

n and m are between 2 and 2000, preferably between 20 and 1000

R" represents independently H, CH_3 or $Si(CH_3)_3$ and

X represents $-(CH_2)_3-NHCH_2CH_2NH_2$.

The amino-functional silicones include the product sold under the name "Amodimethicone" by the company Wacker.

Preference is given to employing nonvolatile silicone polymers in the form of an oil having a viscosity of between 5 and 15,000 centistokes. (5 and 15,000 X $10^{-6}m^2/S$ [sic]). However, the viscosity is not a critical property for the proper implementation of the invention.

The silicone polymers are used in a proportion of

from 0.1 to 10 % by weight, and preferably from 0.5 to 5 %, relative to the weight of the powder phase.

The antifungal agent is present at a concentration of between 0.1 and 2 % by weight, and preferably from 0.5 to 1.5 %, relative to the weight of the powder phase.

The propellants may be liquefiable aliphatic hydrocarbons such as propane, butanes including isobutane, pentane, isopentane, neopentane and mixtures thereof. It is also possible to employ halogenated hydrocarbons such as chlorofluoroalkanes, including monochlorodifluoroethane and monochloridifluoromethane and mixtures thereof.

The ratio by weight of the powder phase to the propellant varies between 1:8 and 1:12.

The inorganic and organic fillers include colloidal silica, zinc oxide, talc, microcrystalline tristearates and zinc stearate.

The inorganic filler preferably used is anhydrous colloidal silica, optionally in combination with at least one other inorganic or organic filler. In particular, the colloidal silica facilitates the suspension of the powder with the liquid propellant before each use. It may be used in a proportion of from 0.1 to 5 % by weight, and preferably from 1 to 2 %, relative to the weight of the powder phase, which is equivalent to from 0.01 to 0.6 %, and preferably from 0.1 to 0.25 %, relative to the total weight of the composition.

Finally, perfumes and/or preservatives such as benzyl alcohol can be introduced into the compositions according to the invention.

The composition in the form of a powder spray according to the invention is indicated in particular for treating areas to which it is difficult to gain access, on the one hand, and macerated mycoses, on the other hand, such as:

genital intertrigo	]	caused by different
submammary intertrigo	]	species of Candida

tinea cruris athlete's foot tineas	}	caused by various species of dermatophytes

The regular use of the composition in the form of a powder spray according to the invention, when it contains 0.1 % of an antifungal agent such as terbinafine, is made by two applications per day until the lesions are completely healed.

The examples of compositions given below illustrate the invention without limiting it.

EXAMPLE 1: DRY SPRAY containing 0.1 % of terbinafine hydrochloride

Micronized talc		8.5 g
Colloidal silica		0.1 g
Microcrystalline glycerol tristearate		0.8 g
Dimethicone such as "Belsil DM 100" from the Company Wacker		0.5 g
Terbinafine HCl		0.1 g
Propellant:	40:60 mixture of dichlorotetrafluoroethane/dichlorodifluoromethane...qs...	100.0 g

The terbinafine hydrochloride, micronized talc, glycerol tristearate and then the silica are introduced into a conventional powder mixer. Mixing is carried out until a homogeneous product is obtained, after which the silicone polymer is added gradually.
After stirring, a powder is obtained which no longer adheres to the walls of the mixer.
This powder is then placed in an aerosol canister which is crimped, and then the propellent mixture is introduced into the canister.

The compositions of Examples 2 and 3 were prepared in the same way as for Example 1.

EXAMPLE 2: DRY SPRAY containing 0.1 % of terbinafine hydrochloride

Zinc oxide	4.0 g
Colloidal silica	0.2 g
Talc	4.7 g
Phenyl dimethicone such as "Belsil PDM 200" from the company Wacker	1.0 g
Terbinafine HCl	0.1 g
Propellant: butane...qs...	100.0 g

EXAMPLE 3: DRY SPRAY containing 0.1 % of naftifine hydrochloride

Zinc oxide	4.3 g
Colloidal silica	0.1 g
Talc	5.0 g
Stearoxy dimethicone such as "Belsil SDM 6021" from the company Wacker	0.6 g
Naftifine HCl	0.1 g
Propellant: 60:40 mixture of monochloro-difluoroethane and monochlorodifluoro-methane...qs...	100.0 g

EXAMPLE 4: DRY SPRAY containing 0.1 % of terbinafine hydrochloride

Zinc oxide	4.1 g
Talc	4.2 g
Colloidal silica	0.2 g
Dimethicone copolyol such as "Belsil DMC 6031" from the company Wacker	0.8 g
Terbinafine HCl	0.1 g
Benzyl alcohol	0.3 g
Propellant: butane...qs...	100.0 g

The procedure for preparing this spray is as follows:

The zinc oxide, talc and colloidal silica are introduced

into a blade-type powder mixer.
After mixing, the terbinafine hydrochloride in solution in the benzyl alcohol is added to the preparation.
Mixing is resumed until a homogeneous product is obtained.
At the time of packaging, the silicone polymer is introduced directly into the canisters, followed by the powder phase containing the terbinafine hydrochloride.
The canisters are then crimped and subsequently pressurized by addition of the propellant.

EXAMPLE 5: DRY SPRAY containing 0.1 % of naftifine hydrochloride

Micronized talc	5.9 g
Zinc stearate	3.1 g
Colloidal silica	0.5 g
Naftifine HCl	0.1 g
Amodimethicone sold by the company Wacker	0.4 g
Propellant: butane...qs...	100.0 g

EXAMPLE 6: DRY SPRAY containing 0.1 % of terbinafine hydrochloride

Micronized talc	9.0 g
Colloidal silica	0.4 g
Phenyl trimethicone sold under the name "Abil AV 20" by the company Goldschmidt	0.5 g
Terbafine HCl	0.1 g
Propellant: isobutane...qs...	100.0 g

CLAIMS

1. Antifungal composition in the form of a dry spray, characterized in that it contains, in combination, at least one antifungal agent of the allylamine family, at least one uncyclized silicone polymer, at least one inorganic or organic filler and at least one propellant.

2. Antifungal composition according to Claim 1, characterized in that it contains, by weight relative to the total weight of the composition:

- from 0.01 to 0.25 %, and preferably from 0.04 to 0.15 %, of the antifungal agent,
- from 0.01 to 1.25 %, and preferably from 0.04 to 0.6 %, of the uncyclized silicone polymer,
- from 0.01 to 40 %, and preferably from 0.1 to 20 %, of the inorganic or organic filler, and
- from 85 to 95 % of the propellant.

3. Composition according to Claim 1 or 2, characterized in that the antifungal agent of the allylamine family is chosen from terbinafine and naftifine and their salts.

4. Composition according to any one of Claims 1 to 3, characterized in that the uncyclized silicone polymer is chosen from dimethicones, phenyl dimethicones, phenyl trimethicones, dimethicone copolyols, stearoxy dimethicones and amino-functional silicones.

5. Composition according to any of the preceding claims, characterized in that the inorganic or organic filler is chosen from colloidal silica, zinc oxide, talc, microcrystalline tristearates and zinc stearate.

6. Composition according to any one of the preceding claims, characterized in that it contains colloidal silica in the proportion of 0.01 to 0.6 %, and preferably 0.1 to 0.25 %, by weight, as inorganic filler.

7. Composition according to Claims 1 to 6, characterized in that the propellant is chosen from liquefiable aliphatic hydrocarbons such as propane, butanes including isobutane, pentane, isopentane, neopentane, halogenated hydrocarbons such as chlorofluoroalkanes including monochlorodifluoroethane and monochlorodifluoromethane, and mixtures thereof.