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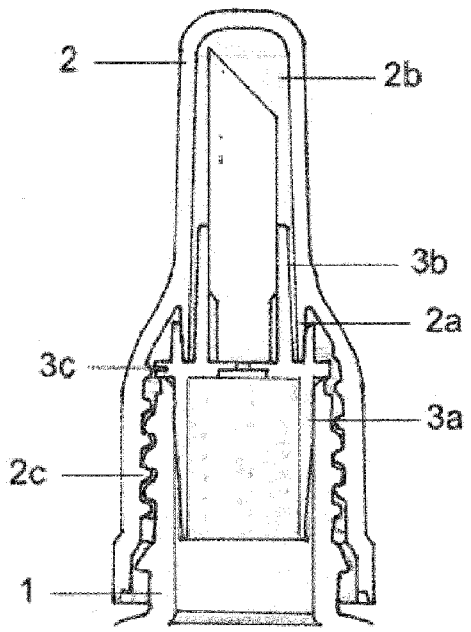

FIG. 3

(57) Abstract: The present invention relates to a tip part (4) for use in a container part (1) for liquid compositions, wherein the tip part (4) has a columnar shape and the top of the tip part forms an angle (a) between 15° and 85° with the horizontal plane. It also relates to a device for topically applying a liquid composition comprising a container part (1) having an opening; a tip part (4), wherein the tip part (4) has a columnar shape and the top of the tip part forms an angle (a) between 15° and 85° with the horizontal plane; and a tip holder (3) wherein the tip part (4) is inserted, disposed at the opening of the container part (1).

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Pharmaceutical device

The present invention relates to a pharmaceutical device for topically applying a liquid composition.

STATE OF THE ART

Nails infected with fungi, such as *Trichophyton*, present onychomycosis, also known as *tinea ungium*. This condition may affect both toenails and fingernails, toenail infections being more common. Visible signs of a fungal nail infection include scaling under the nail, white or yellow streaks on the nail and even loss of the nail.

Both systemic and topical medications are used to treat the infection, however topical application of pharmaceutical compositions is preferred.

EP2730310 discloses an applicator for an antifungal composition comprising a columnar brush member made of synthetic fibers wherein the tip portion of the brush has a fan shape expanding in a perpendicular lateral direction. However, the shape of the brush is lost with use. Moreover, the high volume of the columnar brush is wetted during application and subsequently evaporated when stored, leading to product loss.

Topical treatments for antifungal infection are lengthy and it is required that the device holding the liquid composition provides a homogeneous application of the liquid composition on the treated area for the duration of the treatment. It is also highly desirable, to improve the durability of the tip part of the device to ensure the adequate application of the composition for the whole length of the treatment. In addition, it is also required that once the device is first used, the loss of the liquid composition, either because of leaks or because of evaporation, is minimized.

DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical device for topically applying a liquid composition and the tip part thereof. More specifically, for topically applying an antifungal liquid composition, preferably to the nail.

In a first aspect, the present invention relates to a tip part (4) for use in a container part (1) for liquid compositions, wherein the tip part (4) has a columnar shape and the top of the tip part forms an angle (a) between 15º and 85º with the horizontal plane, preferably, between 30º and 55º with the horizontal plane, most preferably between 35º and 50º with the horizontal plane. A tip part (4) with the shape provides a surface which can be easily in contact with a nail when tipping a container. The columnar shape provides sturdiness to the tip and provides a volume that soaks with the liquid composition when in use.

Columnar shape means that the tip has a tridimensional shape wherein one of the dimensions is longer than the other two, for instance, a column with circular, square, rectangular, triangular, rhombohedral or any other shape base. In a first embodiment of the first aspect, the tip part (4) has a circular section. That it is to say, the tip part has a cylindrical shape with a section in angle on the top part. This shape provides a sturdy tip part which minimizes deformation when in use and therefore extends the durability of the tip, as well as a homogenous application of the liquid composition. Treatments involving topical administration of a composition are usually lengthy and it is desired that the device will maintain its shape and function for the duration of the treatment.

In another embodiment of the first aspect, the tip part (4) as previously described is made of a bundle of fibers or of a foam, preferably of a bundle of fibers. A tip part made of a bundles of fibers is manufactured by providing fibers and compacting the fibers into the desired shape. A tip part made of a bundle of fibers improves the transport of the liquid composition to be applied thereof to the treated areas.

In another embodiment of the first aspect, tip part (4) as previously described is made of materials comprising polypropylene, polyethylene, polyamide, polyethylene terephthalate, polybutylene terephthalate or mixtures thereof, preferably polypropylene, polyethylene or mixtures thereof. A tip part (4) comprising said materials have shown low reactivity and good chemical stability as well as good mechanical properties which extends the durability of the tip. Best results have been obtained when the tip part is made of materials comprising a mixture of polypropylene and polyethylene, especially when the mixture of polypropylene and polyethylene 50:50.

In another embodiment of the first aspect, the density of the tip part (4) as previously described is between 0.05 g/m^3 to 0.5 g/cm^3, preferably between 0.15 g/cm^3 to 0.37 g/cm^3. In another embodiment of the first aspect, the porosity of the tip part (4) is between 30% and 90%, preferably between 50% and 85%. A tip part (4) having said density allows a suitable and homogeneous application of the liquid composition as well as a sturdy tip that will minimize deformation and durability when in use. A tip part (4) having said density and porosity provides good mechanical properties as well as a soft touch in a manner than when the tip part is put into contact with the nail it does not feel hard and the liquid composition to be applied can flow onto the treatment area.

Porosity in the context of the invention is defined as the percentage of pore space in a unit of volume of the material of the tip part (4). By pore is understood a hollow part, empty of the material which forms the tip part (4).

In another embodiment of the first aspect, tip part (4) as previously described is made of materials comprising polypropylene, polyethylene or mixtures thereof, preferably of materials comprising a mixture of polypropylene and polyethylene;
the density of the tip part (4) is between 0.15 g/cm^3 to 0.37 g/cm^3; and
the porosity of the tip part (4) is between 50% and 85%.

In a second aspect, the present invention relates to a tip holder (3) for holding a tip part (4) wherein the tip holder has two tubular portions (3a, 3b) in opposite directions from a bottom part; wherein the bottom part of the tip holder (3) comprises at least one pore (3d), preferably, the pore has a diameter (d) between 0.1 mm and 2 mm, more preferably between 0.5 mm and 1.5 mm. The pore (3d) allows a good flow of the liquid composition from the interior of the container to the tip part. The pore diameter can be adjusted in order to regulate the flow and the amount of the liquid compositions provided.

In one embodiment of the second aspect, the tip holder (3) as previously described further comprises an edge (3c) for sitting on an opening of a container part. This edge (3c) holds the tip holder on the opening of the container part. This maintains the tip holder in place. It can be seen in fig. 3, the tubular portion (3a) can be inserted in a container part (1) and the edge (3c) sits on the container opening.

In another embodiment of the second aspect, the tip holder (3) as previously described further comprises a concave portion (3e) defined by the space between one of the tubular portions (3b) and a rim (3d) in at least a portion around the tubular portion (3b). This concave portion provides a space where a protruding portion (2a) of a lid part (2) can fit tightly. This disposition minimizes water loss of the liquid composition in the container part. It also prevents leaks of the liquid composition if the device is not placed vertically. A sealed space (2b) is created when the lid (2) is screwed on. Preferably, the rim goes all around the tubular portion (3b).

In another embodiment of the second aspect, the tip holder (3) as previously described is made of materials comprising (3) polyethylene, preferably high density polyethylene (HDPE). These materials are inert and are compatible with the vast majority of pharmaceutical ingredients. Moreover, a tip holder of these materials is hard-wearing and resistant in order to work as required during the lengthy treatment. HDPE is preferred as it has an improved moisture and oxygen barrier and provides an improved stability of the liquid compositions contained in the container part (1).

In another embodiment of the second aspect, the tip holder (3) as previously described comprises the tip part (4) as described previously inserted in one of the tubular portions (3b). Preferably, between 30% and 70% of the length with respect to the total length of the tip part is inserted in one of the tubular portions, more preferably between 40% and 60% of the length with respect to the total length of the tip part.

A third aspect of the present invention relates to a device for topically applying a liquid composition comprising the tip part (4) as previously described and/or the tip holder (3) as previously described.

A fourth and fifth aspect of the present invention relate to the use of the tip part (4) as previously described, or the tip holder (3) as previously described in a device for topically applying liquid composition.

A sixth aspect of the present invention relates to a device for topically applying a liquid composition comprising:

i) a container part (1) having an opening;

ii) a tip part (4), wherein the tip part (4) has a columnar shape and the top of the

tip part forms an angle (a) between 15º and 85º with the horizontal plane; and
iii) a tip holder (3) wherein the tip part (4) is inserted, disposed at the opening of the container part (1).

The container part (1) contains the liquid composition which is applied topically preferably on the nail with the tip part (4), which is hold in the opening of the container part (1) by the tip holder (3).

In one embodiment of the fifth aspect, the top of the tip part (4) forms and angle (a) between 30º and 55º, preferably between 35º and 50º with the horizontal plane. The advantages of the tip part (4) shape have been explained previously.

In another embodiment of the sixth aspect, the tip part (4) has a circular section. That it is to say, the tip part has a cylindrical shape with a section in angle on the top part. This shape provides a sturdy tip part which minimizes deformation when in use and therefore extends the durability of the tip, as well as a homogenous application of the liquid composition. Treatments involving topical administration of a composition are usually lengthy and it is desired that the device will maintain its shape and function for the duration of the treatment.

In another embodiment of the sixth aspect, the tip holder (3) has two tubular portions (3a, 3b) in opposite directions from a bottom part;
wherein the tip part (4) is inserted in one of the tubular portions (3b) of the tip holder (3) and the other tubular portion (3a) of the tip holder (3) is inserted in the opening of the container part (1); and
wherein the bottom part of the tip holder (3) comprises at least one pore (3d).

A schematic view of the tip holder can be seen in fig. 2. The tip part (4) is inserted in the tip holder (3) in one part of the tip holder (3a). The bottom part of the tip holder (3b) is introduced in the opening of the container part (1). The pore (3d) allows a good flow of the liquid composition from the interior of the container to the tip part. The pore diameter can be adjusted in order to regulate the flow and the amount of the liquid compositions provided. Preferably, the diameter (d) of the pore is between 0.1 mm and 2 mm, more preferably, between 0.5 mm and 1.5 mm.

In another embodiment of the sixth aspect, the tip holder (3) comprises an edge (3c) that sits on opening of the container part. As stated previously, this edge (3c) holds the tip holder on the opening of the container part. This maintains the tip holder in place. It can be seen in fig. 3, the tubular portion (3a) can be inserted in a container part (1) and the edge (3c) sits on the container opening.

In another embodiment of the sixth aspect, the device as previously described further comprises a lid part (2). The lid part protects the tip part (4) from the environment and minimizes the evaporation of the liquid composition of the container part (1) or impregnating the tip part (4).

In another embodiment of the sixth aspect, the tip holder (3) comprises a concave portion (3e) defined by the space between the tubular portion wherein the tip part is inserted (3b) and a rim (3d) in at least a portion around the tubular portion (3b); and wherein the lid part (2) comprises a protruding portion (2a) that fits tightly in said concave portion (3e) of the tip holder, preferably the rim goes all around the tubular portion (3b). As stated above, this disposition minimizes water loss of the liquid composition in the container part. It also prevents leaks of the liquid composition if the device is not placed vertically. A sealed space (2b) is created when the lid (2) is screwed on.

A preferred embodiment of the sixth aspect relates to a device for topically applying a liquid composition comprising:

i) a container part (1) having an opening;

ii) a tip part (4), wherein the tip part (4) has a columnar shape and the top of the tip part forms an angle (a) between 15º and 85º with the horizontal plane; and

iii) a tip holder (3) wherein the tip part (4) is inserted, disposed at the opening of the container part (1);

iv) a lid part (2); and

wherein tip part (4) is made of materials comprising a mixture of polypropylene and polyethylene;

the density of the tip part (4) is between 0.15 g/cm^3 to 0.37 g/cm^3; and

the porosity of the tip part (4) is between 50% and 85%;

wherein the tip holder (3) comprises a concave portion (3e) defined by the space

between the tubular portion wherein the tip part is inserted (3b) and a rim (3d) in at least a portion around the tubular portion (3b); and

wherein the lid part (2) comprises a protruding portion (2a) that fits tightly in said concave portion (3e) of the tip holder, preferably the rim goes all around the tubular portion (3b).

In another embodiment of the sixth aspect, the lid part (2) and the container part (1) comprise a thread (2c) that seals the lid (2) with the container part (1). This, together with the protruding and concave portions described above seal tightly the contents of the container part (1) and the tip part (4) minimizing the evaporation of the liquid compositions.

In another embodiment of the sixth aspect, the tip part (4) is made of a bundle of fibers or a foam, preferably of a bundle of fibers. A tip part made of a bundles is manufactured by compacting the fibers into the desired shape. A tip part formed by bundle of fibers improves the transport of the liquid composition to be applied thereof to the treated areas.

In another embodiment of the sixth aspect, the tip part (4) is made of materials comprising polypropylene, polyethylene, polyamide, polyethylene terephthalate, polybutylene terephthalate or mixtures thereof, preferably the tip part (4) is made of materials comprising polypropylene, polyethylene or mixtures thereof. A tip part (4) comprising said materials have shown low reactivity and good chemical stability as well as good mechanical properties which extends the durability of the tip. Best results have been obtained when the tip part is made of materials comprising a mixture of polypropylene and polyethylene, especially when the mixture of polypropylene and polyethylene 50:50.

In another embodiment of the sixth aspect, the density of the tip part (4) is between 0.05 g/m^3 to 0.5 g/cm^3, preferably between 0.15 g/cm^3 to 0.37 g/cm^3. In another embodiment of the sixth aspect, the porosity of the tip part (4) is between 30% and 90%, preferably between 50% and 85%. A tip part (4) having said density allows a suitable and homogeneous application of the liquid composition as well as a sturdy tip that will minimize deformation and durability when in use. A tip part (4) having said density and porosity provides good mechanical properties as well as a soft touch in a

manner than when the tip part is put into contact with the nail it does not feel hard and the liquid composition to be applied can flow onto the treatment area.

In another embodiment of the sixth aspect, the container part (1) and/or the tip holder (3) and/or the lid part (2) is/are made of materials comprising polyethylene, preferably high density polyethylene (HDPE). These materials are inert and are compatible with the vast majority of pharmaceutical ingredients. Moreover, a tip holder, lid part and/or container part of these materials is hard-wearing and resistant in order to work as required during the lengthy treatment. HDPE is preferred as it has an improved moisture and oxygen barrier and provides an improved stability of the liquid compositions contained in the container part (1).

A tip holder made of a material which comprises polyethylene, preferably high density polyethylene has enough resistance to hold the tip in place.

A lid part made of a material which comprises polyethylene, preferably high density polyethylene minimizes the loss of composition by leak or evaporation while having enough resistance and durability to be used in multiple occasions to open and close the container.

In another embodiment of the sixth aspect, the container part (1) contains a liquid composition comprising an antifungal compound, preferably an azole antifungal compound, more preferably the antifungal compound is selected from efinaconazole, itraconazole, posaconazole, fluconazole, ketoconazole, clotrimazole, miconazole, voriconazole and mixtures thereof.

A seventh aspect of the present invention relates to the use of the tip part as previously described, the tip holder as previously described and/or the device as previously described for topically applying a liquid composition, preferably for topically applying on a nail, more preferably on a toe nail.

In one embodiment of the seventh aspect of the present invention, the liquid composition comprises an antifungal compound, preferably an azole antifungal, more preferably the antifungal compound is selected from efinaconazole, itraconazole, posaconazole, fluconazole, ketoconazole, clotrimazole, miconazole, voriconazole and

mixtures thereof, most preferably the antifungal compound is efinaconazole.

An eighth aspect of the present invention relates to a pharmaceutical batch comprising at least 2000 units of the device as previously described, preferably the batch comprises at least 5000 units.

A ninth aspect of the present invention relates to a cardboard box with a patient information leaflet comprising at least one unit of the device as previously described containing a liquid composition comprising an antifungal compound, preferably an azole antifungal, more preferably efinaconazole, itraconazole, posaconazole, fluconazole, ketoconazole, clotrimazole, miconazole, voriconazole and mixtures thereof, most preferably the antifungal compound is efinaconazole. Preferably, the pharmaceutical composition comprises efinaconazole, a solvent which may be an alcohol selected form the group consisting of C1-C5 linear or branched alcohols and/or water, polyethylene glycol, pH regulator and a preservative. Preferably all pharmaceutical compositions described herein comprise between 8-15 % of efinaconazole.

Most preferably, the composition comprises efinaconazole; a solvent which may be an alcohol selected form the group consisting of C1-C5 linear or branched alcohols and/or water; a pH regulator, such as citric acid; a preservative selected form Vitamin E (alfa-tocoferol), BTA, EDTA or Disodium edetate; and polyethylene glycol. The formulation may also contain wetting agents such as diisopropyl adipate and C12-C15 alkyl lactate. Suitable Polyethylene glycol (also referred as PEG) can be selected from, PEG 200, PEG 400, PEG 600, PEG 1000, PEG 2000, being the numeric figure after the name PEG the number average molecular weight.

In a preferred embodiment, the preservative is selected form Vitamin E (alfa-tocoferol), BTA, EDTA or Disodium edetate or mixture thereof. In a most preferred embodiment the preservative Vitamin E, BTA or mixtures thereof. In another preferred embodiment the pH regulator is citric acid. Most preferably pharmaceutical compositions comprise efinaconazole, a preservative selected form Vitamin E, BTA or mixtures thereof and citric acid pH regulator, whereby the stability of the compositions is improved.

In a preferred embodiment, the pharmaceutical composition comprises efinaconazole,

ethanol or aqueous ethanol, Vitamin E (alfa-tocoferol), citric acid and polyethylene glycol. In another preferred embodiment, the pharmaceutical composition comprises efinaconazole, ethanol or aqueous ethanol, citric acid, BHA and polyethylene glycol. In a more preferred embodiment, the two previous preferred pharmaceutical compositions may also contain wetting agents such as diisopropyl adipate and C12-C15 alkyl lactate.

A tenth aspect of the present invention relates to a method for preparing a pharmaceutical dossier to obtain the marketing authorization of the device as previously described comprising the following steps:

i) manufacturing at least one pharmaceutical batch as previously described;

ii) performing stability tests of the batches of step (i);

iii) compiling the results obtained in steps (i) to (iii); and

iv) providing the compiled results of step (iii) in a data carrier.

An eleventh aspect of the present invention relates to a data carrier comprising the compiled results of a pharmaceutical dossier obtained by the method for preparing a pharmaceutical dossier as previously described, preferably said data carrier is selected from the group consisting of a digital data carrier such as CD, DVD, USB, hard drive; and paper.

The twelfth aspect of the present invention relates to pharmaceutical composition of the azole antifungal, efinaconazole, which shows good stability in the device of the invention and in glass vials, particularly the device of the 3rd and 6th aspects, the pharmaceutical composition comprises efinaconazole, a solvent which may be an alcohol selected form the group consisting of C1-C5 linear or branched alcohols and/or water, polyethylene glycol, pH regulator and a preservative. Preferably all pharmaceutical compositions described herein comprise between 8-15 % of efinaconazole. Suitable Polyethylene glycol (also referred as PEG) can be selected from, PEG 200, PEG 400, PEG 600, PEG 1000, PEG 2000, being the numeric figure after the name PEG, the number average molecular weight.

In a preferred embodiment of the twelfth aspect, the preservative is selected form Vitamin E (alfa-tocoferol), BTA, EDTA or Disodium edetate or mixture thereof. In a most preferred embodiment the preservative Vitamin E, BTA or mixtures thereof. In another preferred embodiment the pH regulator is citric acid. Most preferably

pharmaceutical compositions comprise efinaconazole, a preservative selected form Vitamin E, BTA or mixtures thereof and citric acid pH regulator, whereby the stability of the compositions is improved. Stability of the compositions is improved in glass containers as well as in the device of the invention.

In a preferred embodiment of the twelfth aspect, the pharmaceutical composition comprises efinaconazole, ethanol or aqueous ethanol, Vitamin E (alfa-tocoferol), citric acid and polyethylene glycol. In another preferred embodiment, the pharmaceutical composition comprises efinaconazole, ethanol or aqueous ethanol, citric acid, BHA and polyethylene glycol. In a more preferred embodiment, the two previous preferred pharmaceutical compositions may also contain wetting agents such as diisopropyl adipate and C12-C15 alkyl lactate.

The term “stable” as used herein refers to a pharmaceutical composition comprising an antifungal compound wherein the total content of impurities is below 5 % (w/w), preferably 3 % (w/w), more preferably 2 % (w/w), and most preferably 1 % (w/w), as determined by liquid chromatography (HPLC) at 210 nm if such a composition is stored for 2 months at 40°C and 75 % relative humidity (RH).

All percentages, parts, and ratios herein are by weight unless specifically noted otherwise. As used herein, the term "about" refers preferably to a range that is ±10 %, preferably ±5 %, or more preferably ±1 % of a value with which the term is associated. Unless otherwise indicated, all the analysis methods are carried out according to the European Pharmacopoeia 7th edition.

DESCRIPTION OF THE FIGURES

FIG. 1. Perspective view of the device. 1: container part; 2: lid part; 3: tip holder; 4: tip part.

FIG. 2. Section view of the tip holder (3) with the inserted tip part (4). a: Angle formed by the top of the tip part the horizontal plane; (d): diameter of the pore of the bottom part; (3a): tubular portion wherein the tip part is (3d): rim around the tubular portion; (3e): concave portion defined by the space between the tubular portion (3b) and the rim (3d); (4): tip part; (4a): total length of the tip part; (4b): length of the tip part which is not inserted in the tip holder.

FIG.3. Section view of the tip holder (3) inserted in the opening of the container part (1) and the lid part (2). 2a: protruding part of the lid part; 2b: sealed space created when the lid is screwed on; 2c: thread.

EXAMPLES

Compositions of efinaconazole

	Composition A		Composition B		Composition C	
Components	**(mg/g)***	**Amount (g)**	**(mg/g)***	**Amount (g)**	**(mg/g)***	**Amount (g)**
Efinaconazole	100.0	12.00	100.0	12.00	100.00	12.00
Citric acid anhydrous	1.00	0.120	1.00	0.120	1.00	0.120
BHT	1.00	0.12				
BHA			0.2	0.024		
Vitamin E					0.50	0.060
C12-C15 alkyl lactate	100.0	12.00	100.0	12.00	100.0	12.00
Diisopropyl adipate	120.0	14.40	120.0	14.400	120.0	14.400
Disodium edetate	0.0025	0.0003	0.0025	0.0003	0.0025	0.0000
Purified water	10.0	1.20	10.0	1.20	10.00	1.200
Ethanol (96%)	668.00	80.16	668.80	80.256	668.50	80.220
TOTAL	1000.00	120.00	1000.00	120.00	1000.00	120.00

Table 1: Efinaconazole compositions
*: mg of substance/ gr of solution.

Composition D **Components**	**(mg/g)***	**Amount (g)**	**(mg/g)***	**Amount (g)**
Efinaconazole	100.00	12.00	100.00	12.000
Citric acid anhydrous	1.00	0.120	1.00	0.120
BHA	0.20	0.024		
Vitamin E			0.50	0.0600
C12-C15 alkyl lactate	100.00	12.000	100.00	12.000
PEG 400	130.00	15.600	130.00	15.600
Diisopropyl adipate	120.00	14.400	120.00	14.400
Disodium edetate	0.0025	0.00030	0.0025	0.00030
Purified water	10.00	1.200	10.00	1.200
Ethanol (96%)	538.80	64.656	538.50	64.620
TOTAL	1000.00	120.00	1000.00	120.000

Table 2: Efinaconazole compositions
*: mg of substance/ gr of solution.

Example 1: Stability

8 ml of a composition comprising an alcohol as a solvent, 10% w/w of efinaconazole, a wetting agent and 1-5% w/w of suitable preservative was placed in the device of the invention of the embodiment illustrated in the figures 1, 2 and 3. The diameter of the pore is 1 mm, the tip part measures in total 20 mm (4a) and the part of the tip part which is not covered by the tip holder is of 10 mm. The container part (1), tip holder (3) and lip part (2) were made of HDPE. The tip part (4) was made of a mixture 50:50 of polypropylene and polyethylene, with a density of 0.250 g /cm^3.

The devices were kept unopened for 1 month, at 40ºC and 75% RH.
The devices were kept unopened for 1 month, at 25ºC and 60% RH.

In all cases the total content of total impurities of the antifungal compound does not exceed 5 % (w/w).

Example 2: Stability

8 ml of a composition comprising an alcohol as a solvent, 10% w/w of efinaconazole and 1-5% w/w of suitable preservative was placed in the device of the invention of the embodiment illustrated in the figures 1, 2 and 3. The diameter of the pore is 1 mm, the tip part measures in total 20 mm (4a) and the part of the tip part which is not covered by the tip holder is of 10 mm. The container part (1), tip holder (3) and lip part (2) were made of HDPE. The tip part (4) was made of a mixture 50:50 of polypropylene and polyethylene, with a density of 0.250 g /cm^3.

The devices were kept unopened for 1 month, at 40ºC and 75% RH
The devices were kept unopened for 1 month, at 25ºC and 60% RH.

In all cases the total content of total impurities of the antifungal compound does not exceed 5 % (w/w).

Example 3: Stability

Each of the compositions A, B, C, D and E was placed in a device of the invention of

the embodiment illustrated in the figures 1, 2 and 3. The diameter of the pore is 1 mm, the tip part measures in total 20 mm (4a) and the part of the tip part which is not covered by the tip holder is of 10 mm. The container part (1), tip holder (3) and lip part (2) were made of HDPE. The tip part (4) was made of a mixture 50:50 of polypropylene and polyethylene, with a density of 0.250 g /cm^3.

The devices were kept unopened for 1 month, at 40ºC and 75% RH.
The devices were kept unopened for 1 month, at 25ºC and 60% RH.

In all cases the stability results were very good and total content of total impurities of the antifungal compound does not exceed 5 % (w/w).

Example 4: Stability

Each of the compositions A, B, C, D and E was packed in a glass amber vial and subjected to stability testing at 40°C and 75% relative humidity (RH) and 25°C and 60% relative humidity (RH) for one month and 3 months.

	A	B	C	D	E
	% impurities	% impurities	% impurities	% impurities	% impurities
T0	0.04	0.04	0.02	0.03	0.03
40°C 75% RH 3 month	1.05	0.34	0.41	0.41	0.43
25°C 60% RH 3 month	0.07	0.11	0.12	0.09	0.11

Table 3: Stability results in glass amber vials at 3 months.

Example 5: stability

Devices like the ones described for example 1, 2 and 3 were kept for 1 month at 40ºC and 75% RH, but once daily they were opened, a dose from each device was

administered over a clean glass and the device was closed again by screwing the lid part (2) on the container part (1).

In all cases the total content of total impurities of the antifungal compound does not exceed 5 % (w/w).

CLAIMS

1. A tip part (4) for use in a container part (1) for liquid compositions, wherein the tip part (4) has a columnar shape and the top of the tip part forms an angle (a) between 15º and 85º with the horizontal plane, preferably, between 30º and 55º with the horizontal plane, most preferably between 35º and 50º with the horizontal plane.

2. The tip part (4) according to the preceding claim, wherein the tip part (4) has a circular section.

3. The tip part (4) according to any of the preceding claims wherein the tip part (4) is made of a bundle of fibers or a foam, preferably of a bundle of fibers.

4. The tip part (4) according to any of the preceding claims wherein the density of the tip part (4) is between 0.05 g/m^3 to 0.5 g/cm^3, preferably between 0.15 g/cm^3 to 0.37 g/cm^3.

5. The tip part (4) according to any of the preceding claims wherein the porosity of the tip part (4) is between 30% and 90%, preferably between 50% and 85%.

6. The tip part (4) according to any of the preceding claims wherein the tip part (4) is made of materials comprising polypropylene, polyethylene, polyamide, polyethylene terephthalate, polybutylene terephthalate or mixtures thereof, preferably polypropylene, polyethylene or mixtures thereof, more preferably a mixture of polypropylene and polyethylene.

7. A tip holder (3) for holding a tip part (4) according to any of the preceding claims, wherein the tip holder has two tubular portions (3a, 3b) in opposite directions from a bottom part; wherein the bottom part of the tip holder (3) comprises at least one pore (3d).

8. The tip holder (3) according to any of the preceding claims claim wherein the pore has a diameter (d) between 0.1 mm and 2 mm, preferably between 0.5 mm and 1.5 mm.

9. The tip holder (3) according to any of claims 7 or 8, further comprising an edge (3c) for sitting on an opening of a container part.

10. The tip holder (3) according to any of claims 7 to 9, further comprising a concave portion (3e) defined by the space between one of the tubular portions (3b) and a rim (3d) in at least a portion around the tubular portion (3b).

11. The tip holder (3) according to any of claims 7 to 10, wherein the tip holder (3) is made of materials comprising polyethylene, preferably high density polyethylene.

12. The tip holder (3) according to any of claims 7 or 11, comprising the tip part (4) according to any of claims 1 to 7 inserted in one of the tubular portions (3b).

13. A device for topically applying a liquid composition comprising the tip part (4) according to any of claims 1 to 6 and/or the tip holder (3) according to any of claims 7 to 12.

14. Use of the tip part (4) according to any of claims 1 to 6 or the tip holder (3) according to any of claims 7 to 12 in a device for topically applying a liquid composition.

15. A device for topically applying a liquid composition comprising:

i) a container part (1) having an opening;

ii) a tip part (4), wherein the tip part (4) has a columnar shape and the top of the tip part forms an angle (a) between 15º and 85º with the horizontal plane; and

iii) a tip holder (3) wherein the tip part (4) is inserted, disposed at the opening of the container part (1).

16. The device according to the previous claim, wherein the top of the tip part (4) forms and angle (a) between 30º and 55º, preferably between 35º and 50º with the horizontal plane.

17. The device according to any of claims 15 or 16, wherein the tip part (4) has a circular section.

18. The device according to any of claims 15 to 17, wherein the tip holder (3) has two

tubular portions (3a, 3b) in opposite directions from a bottom part;
wherein the tip part (4) is inserted in one of the tubular portions (3b) of the tip holder (3) and the other tubular portion (3a) of the tip holder (3) is inserted in the opening of the container part (1); and
wherein the bottom part of the tip holder (3) comprises at least one pore (3d).

19. The device according to the previous claim wherein the pore has a diameter (d) between 0.1 mm and 2 mm, preferably between 0.5 and 1.5 mm.

20. The device according to any of claims 15 to 19, wherein the tip holder (3) comprises an edge (3c) that sits on opening of the container part.

21. The device according to any of claims 15 to 20, wherein it further comprises a lid part (2).

22. The device according to the previous claim,
wherein the tip holder (3) comprises a concave portion (3e) defined by the space between the tubular portion wherein the tip part is inserted (3b) and a rim (3d) in at least a portion around the tubular portion (3b); and
wherein the lid part (2) comprises a protruding portion (2a) that fits in said concave portion (3e) of the tip holder.

23. The device according to the previous claim, wherein the lid part (2) and the container part (1) comprise a thread (2c) that seals the lid (2) with the container part (1).

24. The device according to any of claims 15 to 23, wherein the tip part (4) is made of a bundle of fibers or a foam, preferably of a bundle of fibers.

25. The device according to any of claims 15 to 24, wherein the density of the tip part (4) is between 0.05 g/m^3 to 0.5 g/cm^3, preferably between 0.15 g/cm^3 to 0.37 g/cm^3.

26. The device according to any of claims 15 to 25, wherein the porosity of the tip part (4) is between 30% and 90%, preferably between 50% and 85%.

27. The device according to any of claims 15 to 26, wherein the tip part (4) is made of materials comprising polypropylene, polyethylene, polyamide, polyethylene terephthalate, polybutylene terephthalate or mixtures thereof.

28. The device according to any of claims 15 to 27, wherein the tip part (4) is made of materials comprising polypropylene, polyethylene or mixtures thereof, preferably of a mixture of polypropylene and polyethylene.

29. The device according to any of claims 15 to 28, wherein the container part (1) is made of materials comprising polyethylene, preferably high density polyethylene.

30. The device according to any of claims 15 to 29, wherein the tip holder (3) is made of materials comprising polyethylene, preferably high density polyethylene.

31. The device according to any of claims 15 to 30, wherein the lid part (2) is made of materials comprising polyethylene, preferably high density polyethylene.

32. The device according to any of claims 15 to 31, wherein the container part (1) contains a liquid composition comprising an antifungal compound, preferably an azole antifungal compound, more preferably the antifungal compound is selected from efinaconazole, itraconazole, posaconazole, fluconazole, ketoconazole, clotrimazole, miconazole, voriconazole and mixtures thereof.

33. Use of the tip part according to any of claims 1 to 6, the tip holder according to any of claims 7 to 12 and/or the device according to any of claims 13 to 32 for topically applying a liquid composition, preferably for topically applying on a nail.

34. Use according to the previous claim, wherein the liquid composition comprises an antifungal compound, preferably an azole antifungal compound.

35. Use according to the previous claim, wherein the antifungal compound is selected from efinaconazole, itraconazole, posaconazole, fluconazole, ketoconazole, clotrimazole, miconazole, voriconazole and mixtures thereof, preferably the antifungal compound is efinaconazole.

36. A pharmaceutical batch comprising at least 2000 units of the device according to claim 32, preferably the batch comprises at least 5000 units.

37. A cardboard box with a patient information leaflet comprising at least one unit of the device according to any of claims 13 to 32 containing a liquid composition comprising an antifungal compound, preferably an azole antifungal, more preferably efinaconazole, itraconazole, posaconazole, fluconazole, ketoconazole, clotrimazole, miconazole, voriconazole and mixtures thereof, most preferably the antifungal compound is efinaconazole.

38. A method for preparing a pharmaceutical dossier to obtain the marketing authorization of the device according to claim 32 comprising the following steps:

i) manufacturing at least one pharmaceutical batch according to claim 36;

ii) performing stability tests of the batches of step (i);

iii) compiling the results obtained in steps (i) to (iii); and

iv) providing the compiled results of step (iii) in a data carrier.

39.- A data carrier comprising the compiled results of a pharmaceutical dossier obtained by the method of the preceding claim, preferably said data carrier is selected from the group consisting of a digital data carrier such as CD, DVD, USB, hard drive; and paper.

40. A pharmaceutical composition comprising efinaconazole, a solvent selected form the group consisting of C1-C5 linear or branched alcohols and/or water or mixtures thereof, pH regulator and at least one preservative.

41. The pharmaceutical composition according to claim 40 comprising from 8 to 15 % of efinaconazole.

42. The pharmaceutical composition according to claim 40 to 41 wherein the preservative is selected from Vitamin E (alfa-tocoferol), BTA, EDTA or Disodium edetate or mixture thereof. Preferably, preservative is selected from Vitamin E (alfa-tocoferol), BTA, or mixture thereof.

43. The pharmaceutical composition according to claim 40 to 42 wherein the

composition comprises the preservative is selected from Vitamin E (alfa-tocoferol), BTA, or mixture thereof in combination with citric acid as a pH regulator.

44. The pharmaceutical composition according to claim 40 to 43 further comprising polyethylene glycol.

45. The pharmaceutical composition according to claim 40 to 44 further comprising a wetting agent. Preferably, the wetting agent is selected from diisopropyl adipate and C12-C15 alkyl lactate.

46. A pharmaceutical composition according to claim 40 to 45 for use in the device according to claims 13 or claims 15 to 32.

47. The device according to any of claims 15 to 32, comprising the pharmaceutical compositions according to claims 40 to 46.

DRAWINGS

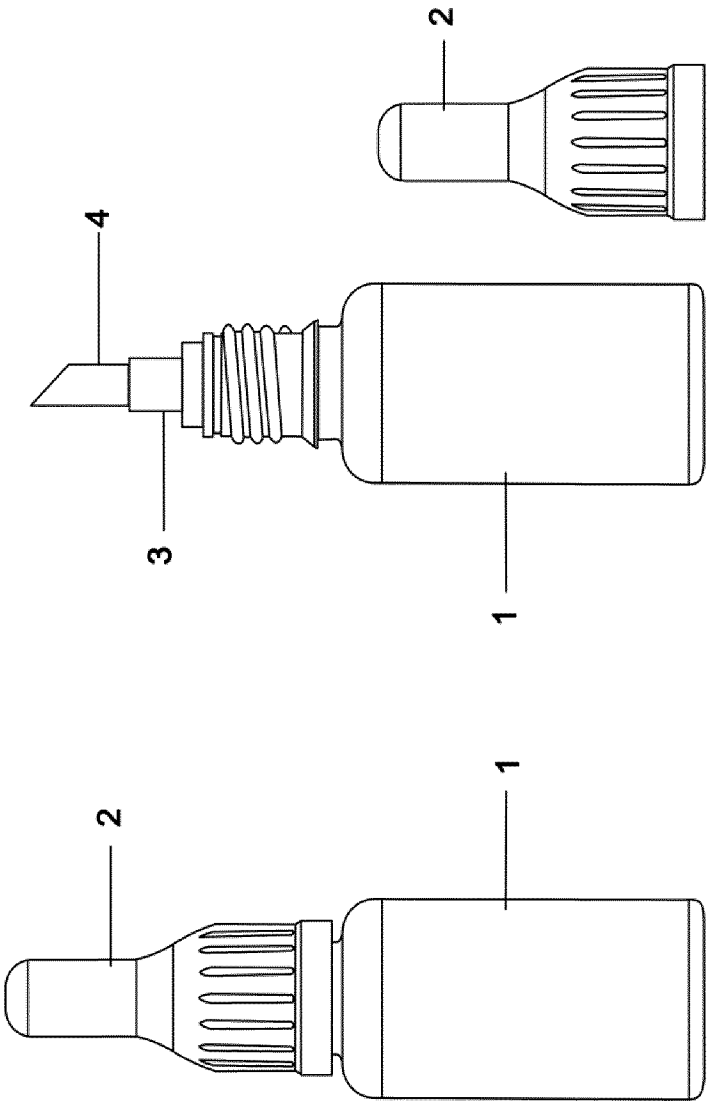

FIG. 1

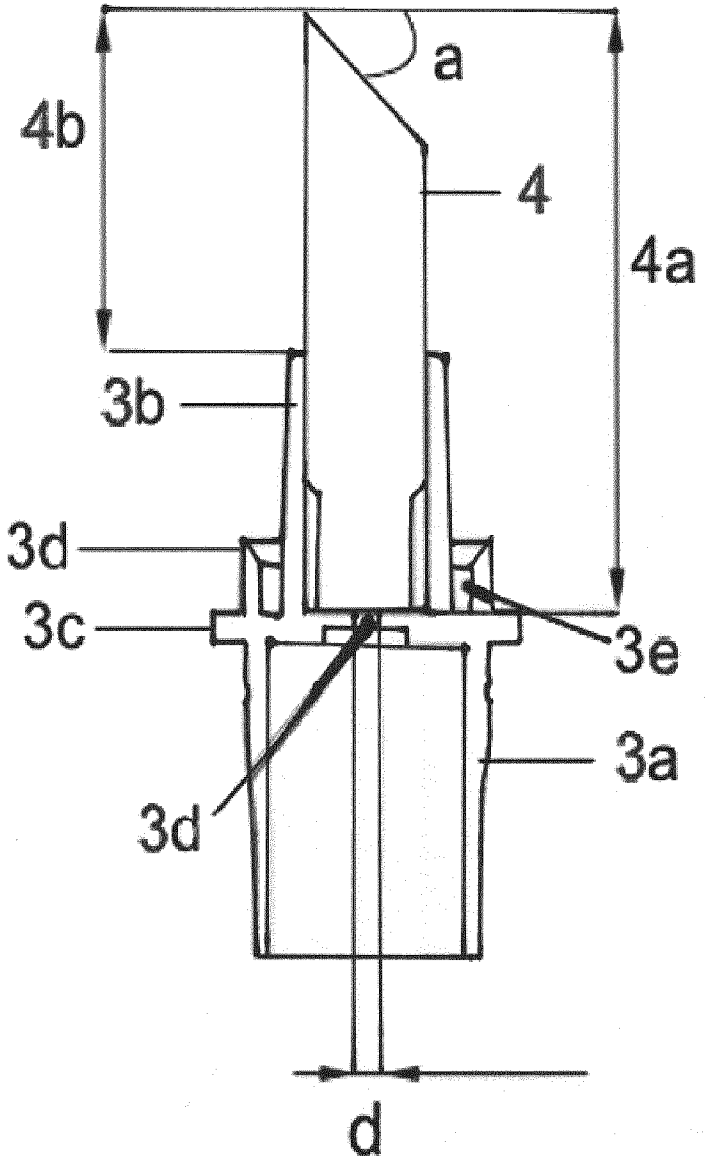

FIG. 2

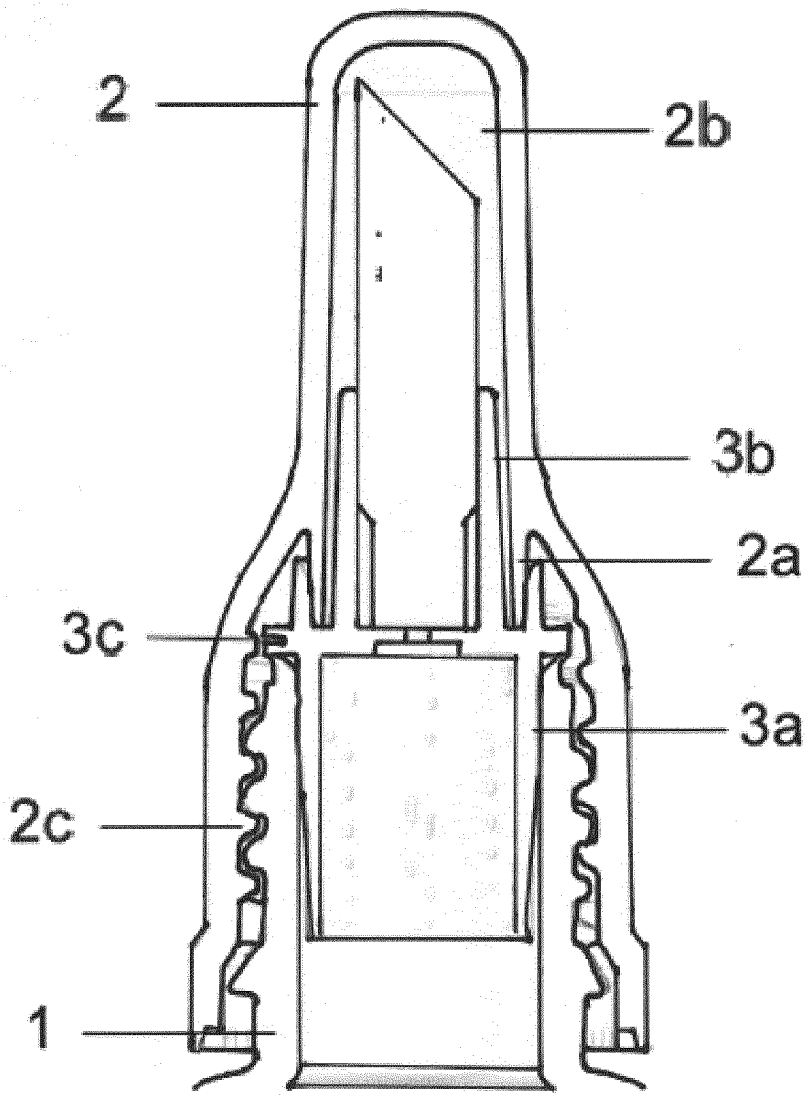

FIG. 3