SPRAYABLE COSMETIC COMPOSITION AND MATRIX WHICH MAY BE USED IN THIS COMPOSITION FOR DERMAL ADMINISTRATION

The present invention relates to a novel composition for dermal administration of an active substance or active principle. This composition may be a cosmetic composition, for example a slimming composition.

The terms "active principle" and "active substance(s)" mean one or more medicinal or non-medicinal active principles. It may thus be, for example, a peptide or non-peptide compound, a cell or tissue extract of animal or plant origin or a product obtained by fermenting a microorganism, for example a bacterium or a fungus. Thus, in the present description, the terms "active principles" and "active substance(s)" will be used without discrimination, according to the definitions given above.

More specifically, the invention relates to a composition for dermal administration which is capable of forming a supple film after drying on the skin, and also to a matrix which may be used in such a composition.

The dermal administration of active substances is an advantageous technique, endowed with certain advantages such as the absence of side effects.

However, in order to be effective, this technique must allow penetration into the skin over a prolonged period and in a manner which is sufficient to reach the intended cells and obtain the desired effect.

To date, various systems or devices for this type of administration have been proposed. They make it possible to introduce controlled doses of active substances.

For example, the transdermal administration device known commonly as a "patch" is known, this device consisting of a reservoir formed from synthetic plastics containing the active principle. This reservoir may be covered, on its face in contact with the skin, with a microporous membrane whose permeability to the active substance regulates its diffusion and consequently its dosage.

Despite the genuine possibilities offered by this device, in particular for an application, other systems may be preferred to it. The reason for this is that it is known that the patch may become detached from the skin and that it may moreover often have an unsightly appearance.

Gels containing active substances have also been proposed. However, this mode of use may have certain drawbacks in practice, generally a sticky feel which is unpleasant for the person using it, and also difficulty in controlling the dose administered.

Other systems which help in transdermally administering active substances have also been reported.

In this respect, mention may be made of sprayable compositions especially comprising polymers capable of forming a film on contact with the skin and of releasing the active principle, for transcutaneous administration. Compositions of this type, disclosed, for example, in patent EP 319 555, comprise an active principle, a polymer matrix forming a supple film after drying, a solvent for controlling the release of the active substance, namely a sorbitan macrogollaurate, a parrafin, a medium-chain fatty acid diglyceride or triglyceride or propylene carbonate, and also a solvent, for the matrix, which is capable of evaporating on the skin, and finally a propellant for spraying this composition contained in a suitable device.

Furthermore, due to the presence of polymethacrylic derivatives, the compositions of patent EP 319 555 give a characteristic odor which is relatively unpleasant for the user and those in his or her vicinity.

Other pharmaceutical compositions for topical administration containing an active principle, a solvent and various other ingredients are also known.

By way of example, mention may be made of patent EP 55396 which discloses antimycotic compositions formed:

- from a cellulose ether
- from 2% to 10% of a spreading agent such as isopropyl myristate or isopropyl palmitate
- from 1% to 8% of a solubilizing agent
- from 0.05% to 1% of active principle, and
- from a solvent such as isopropanol.

However, although these compositions may be used for dermatological topical applications, they are found to be entirely unsuitable for application by spraying, even after adding from 10% to 40% of a propellent gas as recommended, since they appear to be too viscous and liable to have various drawbacks such as blockage of the spraying device.

Mention may also be made of patent EP 319 964 which discloses antifungal compositions capable of forming a film, comprising:

- from 0.1% to 1.5% of tolnaphthalate
- from 10% to 20% of a dimethylaminoethyl methacrylate/methacrylate copolymer
- from 0.5% to 10% of a fatty acid ester
- a solvent of alcohol type and optionally from 0.1% to 5% of a cellulose derivative.

This composition does not appear to be suitable for spraying either. In addition, as already

mentioned previously, the presence of methacrylic derivatives gives it an acceptable odor.

Mention may also be made of patent EP 289 900 which relates to antibacterial compositions for topical use, comprising:

- from 0.5% to 10% of an antibacterial active principle
- from 1% to 30% of a water-insoluble polymer, in particular ethylcellulose or a polyvinylpyrrolidone copolymer
- from 0.5% to 40% of a plasticizer, generally an essential oil, which also acts as a transcutaneous absorption promoter
- from 50% to 95% of a solvent such as ethanol.

Finally, mention may be made of patent application WO 96/30000, the main subject of which is a pharmaceutical composition for transdermal administration, comprising:

1) a polymeric release matrix capable of forming a supple film after drying
2) an active principle
3) a promoter of transcutaneous absorption of the active principle
4) a physiologically acceptable non-aqueous solvent capable of dissolving the release matrix, the active principle and the transcutaneous absorption promoter, and also of being rapidly removed by

evaporation on contact with the skin, which is intended, after administration of the medicinal substance, to bring about a preventive or therapeutic response.

The medicinal product particularly used in said patent application is estradiol.

The search for a composition allowing the diffusion of active substances through the dermis, from an area of low coverage and at rates that are compatible with a treatment while at the same time being free of the drawbacks reported previously, thus remains of major interest.

Now, it has been discovered, surprisingly, according to the invention, that it is possible to provide compositions, more particularly cosmetic compositions for dermal administration, using a film formed on the skin, these compositions lacking the drawbacks mentioned above but being capable, using a small and controllable area of coverage, of delivering the active substance uniformly, continuously and at rates largely reaching the possibility of achieving the desired effect.

Thus, one subject of the invention is a cosmetic composition for dermal administration, comprising:

1) a polymeric release matrix capable of forming a supple film after drying,

2) one or more active substances,

3) a promoter of cutaneous absorption of the active principle,

4) a non-aqueous solvent capable of dissolving the release matrix, the active principle and the cutaneous absorption promoter and also of being rapidly removed by evaporation on contact with the skin,

5) at least one propellent gas.

In the present context, both in the description and in the claims, the term "[lacuna]" means either a substance which is intended, after administration, to bring about a preventive or curative response, or a combination of two or more substances of this type.

The polymeric matrix is generally chosen from polymeric or copolymeric substances capable both of forming a supple film after evaporation of the solvent and of releasing the active substance.

This matrix is formed in the stratum corneum after evaporation of the solvent capable of releasing the active substances.

This matrix is generally present in a proportion of from 0% to 7% relative to the weight of the composition according to the invention, for instance from 4% to 7%, for example 3%. From 1% to 5%

by weight of matrix and in particular 3% is preferably used.

The choice of this matrix will relate mainly to polymeric or copolymeric substances that are soluble in the physiologically acceptable solvent so as to form a homogeneous solution.

Among the polymers or copolymers capable of satisfying the above criteria, those more particularly selected are cellulose polymers or copolymers, especially because they have a suitable abrasion strength and mechanical stability after drying. For this reason, cellulose matrices of this type may be placed in contact with water without any fear of deterioration.

As examples of cellulose polymers or copolymers which may be used in the compositions of the invention, mention may be made of ethylcellulose, cellulose acetate butyrate, cellulose acetate propionate or a hydroxypropylmethylcellulose which may or may not be grafted, such as hydroxypropylmethylcellulose acetate succinate.

However, ethylcellulose represents the preferred cellulose polymer and, consequently, the polymeric release matrix of choice for the formation of a film which is supple on contact with the skin.

In addition, the polymeric matrix may consist of a vinylpyrrolidone/vinyl acetate copolymer such as

polyvinylpyrrolidone/vinyl acetate, referred to hereinbelow as PVP/VA.

Consequently, according to another of its aspects, a subject of the invention is a cosmetic composition for dermal administration, comprising:

1) a polymeric release matrix capable of forming a supple film after drying, chosen from cellulose polymers or copolymers and vinylpyrrolidone/vinyl acetate copolymers,
2) active substances,
3) a promoter of cutaneous absorption of the active principle,
4) a non-aqueous solvent(s) capable of dissolving the release matrix, the active principle and the cutaneous absorption promoter and also of being rapidly removed by evaporation on contact with the skin,
5) at least one propellent gas.

As regards the active substance, it will be chosen from substances that are soluble in the solvent and capable of continuously crossing the epidermis and/or the dermis with a flow which is sufficient to give an effective concentration using a small but sufficient area of skin.

These active substances will be incorporated into the compositions of the invention in a proportion, in particular, of from 0.1% to 20% relative to the

weight of these compositions, it being understood that each active substance will be introduced at individualized concentrations known in the art for dermal administration or at concentrations adapted to this route of administration.

In order to achieve an effective concentration of active principle without, however, using too large an area of skin, a cutaneous absorption promoter is combined with the polymeric matrix and the active principle. This promoter is advantageously incorporated in the compositions of the invention in a proportion of from 15% to 30% relative to the weight of this composition, preferably from 15% to 25%, for example 20%.

This absorption promoter is chosen such that it can bring large dermal flows in order to obtain the desired effects by means of an acceptable skin coverage, i.e. a coverage of less than 150 cm^2 but preferably between 10 and 40 cm^2, for example 30 cm^2.

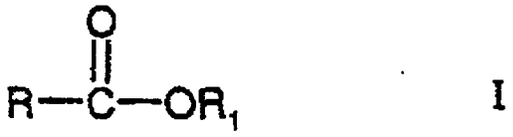
In order to be effective, the skin absorption promoter under consideration must be capable of transiently disorganizing the skin barrier so as to increase the permeability of the skin without irritating it, while at the same time promoting the diffusion of the active principle chosen according to kinetics and a concentration which are sufficient and which may be maintained for a certain amount of time.

This skin absorption promoter will be selected from substances that are compatible with the non-aqueous solvent capable of rapidly evaporating on contact with the skin. It will preferably be selected from the following compounds which have the required degree of solubility in the physiological solvent under consideration and which combine the best qualities reported above, that is to say:

- esters of aliphatic fatty acids, essentially esters containing in total from 10 to 30 carbon atoms optionally substituted with one or two hydroxyl, carboxylic or C_1-C_4 acyloxy groups such as acetoxy, or optionally interrupted with one or two ethylenic bonds or with one or two ether oxygens,
- aliphatic fatty alcohols, essentially C_{10}-C_{30} alcohols optionally substituted with one or two hydroxyl, carboxylic or C_1-C_4 acyloxy groups such as acetoxy, or optionally interrupted with one or two ethylenic bonds or with one or two ether oxygens.

Absorption promoters that are particularly preferred, which may be selected from the esters of aliphatic fatty acids and aliphatic fatty alcohols mentioned above, are given below, namely:

a) aliphatic fatty acid esters of general formula:



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in which R represents a linear or branched C_2-C_7 alkyl or alkenyl group optionally substituted with a hydroxyl, carboxylic or C_1-C_4 acyloxy group and R_1 represents a linear or branched C_3-C_8 alkyl group optionally substituted with one or two hydroxyl groups such as, for example, an isopropyl or 2-ethyldihydroxyethyl group or R_1 represents a $-CH_2-CH_2-O-(CH_2)_2-O-CH_2-CH_3$ group, the aliphatic fatty acid ester comprising a minimum of 10 carbon atoms and a maximum of 2 hydroxyl groups;

b) aliphatic fatty acid alcohols of general formula:

R_2-OH II

in which R_2 represents a C_{10}-C_{20} alkyl group.

As examples of specific compounds which have shown the best potential for promoting the cutaneous absorption of active substances, mention may be made of:

2-ethylhexyl 2-ethylhexanoate

isopropyl myristate

diethylene glycol monoethyl ether myristate

isopropyl palmitate

2-octyldecanol

2-ethylhexyl undecylenate

2-ethylhexyl succinate

2-ethylhexyl 12-hydroxystearate

2-ethylhexyl 12-acetoxystearate

glyceryl isostearate

hexyl laurate

isononyl isononanoate

2-ethylhexyl palmitate

2-ethylhexyl stearate

diethylene glycol monoethyl ether

2-ethylhexyl 2-ethylhexanoate represents the preferred absorption promoter, in particular for cosmetic compositions according to the invention. This compound is sold under the name Dragoxat® and is also known as octyl octanoate.

As regards the non-aqueous solvent capable of dissolving the release matrix, the active principle and the cutaneous absorption promoter, it will be selected from compounds with a relatively low boiling point, that is to say a boiling point of less than 100°C at atmospheric pressure, such that it can be rapidly removed by evaporation on contact with the skin and similarly help to form a film by drying without, however, causing any local irritation.

Such solvents are generally used in a proportion of from 44% to 84.9% relative to the weight of the final composition and may be selected from volatile compounds such as dichloromethane, ethanol, isopropanol and ethyl acetate.

Ethanol and isopropanol are solvents of choice. However, ethanol is a preferred solvent according to the invention since it efficiently contributes toward the formation of films on the skin while at the same time rapidly evaporating on contact with the skin.

The propellent gases which may be used according to the invention are chosen from:

butane
propane
isobutane
carbon dioxide
dimethyl ether
hydrochlorofluorocarbon
hydrofluorocarbon
nitrogen
isopentane
nitrogen oxide
pentane

Butane or propane is preferred.

Consequently, according to one of its particular aspects, the invention relates to a cosmetic composition comprising:

1) from 0% to 7% of a polymeric release matrix capable of forming a supple film after drying, chosen in particular from cellulose polymers or copolymers such as ethylcellulose

2) from 0.1% to 20% of an active substance

3) from 15% to 30% of a promoter of cutaneous absorption of the active principle, in particular from 15% to 25% of a fatty acid ester or of a fatty alcohol chosen from:

2-ethylhexyl 2-ethylhexanoate

isopropyl myristate

diethylene glycol monoethyl ether myristate

isopropyl palmitate

2-octyldecanol

2-ethylhexyl undecylenate

2-ethylhexyl succinate

2-ethylhexyl 12-hydroxystearate

2-ethylhexyl 12-acetoxystearate

glyceryl isostearate

hexyl laurate

4) from 44% to 84.9% of a non-aqueous solvent capable of dissolving the release matrix, the active principle and the cutaneous absorption promoter, and also of being rapidly removed by evaporation on contact with the skin, in particular ethanol or isopropanol

5) at least one propellent gas.

In the context of the present invention, a sprayable composition to be applied from a dosing vaporizer bottle onto the skin, which is cosmetically satisfactory and whose application area and dose

characteristics are controlled and reproducible, has been investigated more particularly.

There is thus formation of a "film" on the skin. Active substances may thus be applied according to the invention to the skin in the form of a film.

Several biocompatible formulations which promote cutaneous penetration were prepared.

The active substances used may be intended for the manufacture of a film, for example a film intended for slimming purposes.

In particular, the film according to the present invention relates to a cosmetic composition containing slimming substances. This slimming substance may be a neuropeptide Y receptor antagonist. Neuropeptide Y, referred to hereinbelow as "NPY" for short, is a neuromediator which participates in a certain number of physiological processes and for which an involvement in regulating lipolysis has been demonstrated (P. Valet. J. Clin. Invest. 1990, *85*, 291-295).

It has been disclosed in EP 838 217 that NPY antagonists may be used to prepare cosmetic compositions.

These cosmetic compositions containing an NPY-antagonist component may be used as lipolysis/lipogenesis regulators on the skin without, however, interfering with the skin's natural functions.

It has also been disclosed that cosmetic slimming compositions containing an NPY-antagonist component and an α2-antagonist component are particularly advantageous.

Thus, according to one of its aspects, the present invention relates to a film containing a cosmetic slimming composition containing at least one NPY-antagonist component with another active substance such as an α2-antagonist. The NPY antagonist contained in the cosmetic composition may be a non-peptide compound, a peptide, a cell or tissue extract of animal or plant origin or a product obtained by fermenting a microorganism, for example a bacterium or a fungus.

These components are themselves non-peptide synthetic compounds, peptides or products obtained by fermenting a microorganism, for example a bacterium or a fungus, or by extracting cells or tissues of animal or plant origin.

Of course, the applied film needs to be well tolerated, but also needs to have an appealing cosmetic appearance with rapid evaporation of the vehicles, leaving little in the way of residues on the surface of the skin.

The cosmetic evaluation of a series of formulations applied as a film to the skin was carried out.

More particularly, the objective was to characterize all of the cosmetic properties of the spray solutions by means of a sensory analysis study.

This is a sensory study according to six criteria identified as being favorable (the implementation of the protocols and the type of calculation adopted correspond to the AFNOR standards published for the agrifood sector).

These criteria are as follows:

- ease of penetration: absorption and evaporation
- the residue: greasy/dry (the feel is evaluated by sliding the index finger over the film deposited)
  gloss (visual presence of the residue)
  stickiness (the feel is observed by tapping the film with the index finger)
  odor
- overall assessment of the product: taking into account only the above criteria.

The application method is as follows:

After priming the pump by pressing several times, the formulation is sprayed onto the skin at a measured distance of 10 cm. The observations begin 10 minutes after the application, and this duration is standardized for the sensory analysis protocols.

One spray corresponds to 130 µl of formulation onto an area of about 35 to 40 cm^2.

The excipients used are as follows:

- film-forming agent: ethylcellulose 99 N7NF (7 mPa.s: Aqualon)
- solvent: isopropanol (SDS), ethanol (Labover),
- promoter and texture agent: Dragoxat ® E.H. (penetrating cosmetic oil: Dragoco), Dow Corning 556 silicone, light liquid paraffin (Sanofi Winthrop Gentilly).

The spray system used is as follows:

- VP7/130 pump: Valois
- push-button dispenser IN3 GP4/5: Valois
- 20 ml ONC varnished aluminium can.

The formulations contain:

- 66% to 67% solvent: ethanol, isopropanol or a combination of the two.
- 20% to 30% promoter: Dragoxat® E.H.
- 3% to 5% ethylcellulose

The formulation disclosed in WO 98/30000, which was the subject of studies with estradiol as medicinal agent, serves as reference and will be referred to hereinbelow as (R).

The details of the compositions are given in Table A.

All the criteria measured and the overall assessment for each formulation are evaluated on a scale ranging from +3 to -4 and reported in the form of histograms.

The average values obtained for the ten experimenters are accompanied by the high and low values.

The evaluation of the formulations is detailed herein relative to the reference formulation (R) by demonstrating the changes in composition which affect or improve its cosmetic appearance.

Table B summarizes the main interpretations regarding the effect of the various excipients relative to the reference formulation.

The perception of the reference formulation (R) is improved by limiting the amount of ethylcellulose to 3% (A) (less greasy, less sticky and less residue). An improved sprayability by means of better dispersion of the formulation by the pump of the device is thus obtained. With these 3%, it is even possible to increase the Dragoxat® incorporated to 30% while at the same time maintaining very good perception of the sprayed formulation (C).

The formulation which is classified immediately after (E) has a slightly larger amount of residue. It still contains 3% ethylcellulose, but the solvent comprises a fraction of isopropanol which is more difficult to spray. The application area must be smaller for the same volume of solution and thus the residue must be thicker on the skin. The formulations which found least favor (B, R, F and G) because they

were too greasy or sticky all contain 4 to 5% ethylcellulose. The result is the same with ethanol or isopropanol. No improvement is observed by adding 1% of compound described as optimizing the spraying (silicone or liquid paraffin) (F and G). Formulation (D) gave very dispersed results. It comprises 4% ethylcellulose and 30% Dragoxat®. The solution is not easy to spray.

The use of ethanol or isopropanol is equivalent in overall terms.

The reference formulation is slightly greasy and sticky. By limiting only the amount of ethylcellulose to 0.5 to 3%, the results are much improved and satisfactory.

There is little to very little residue, which is rather glossy but is not greasy and is hardly sticky at all.

The penetration is quite rapid to very rapid.

More particularly, according to the invention, a film formulation containing slimming active agents was developed.

These slimming active agents are preferably neuropeptide Y (NPY) receptor antagonists or $\alpha 2$ receptor antagonists. A large number of them are disclosed in patent application EP 838 217.

In cosmetology and also in the slimming sector, the cutaneous absorption of an active principle is similar to a passive diffusion, the limiting step

being the moment of crossing the horny layer, which is 1000 times more impermeable than the epidermis or the dermis.

One of the main advantages expected of the films according to the invention is that of removing this cutaneous resistance to diffusion. This increase in cutaneous absorption is the result of an increase in the moisturization and the temperature of the horny layer, following the semi-occlusion of the site of application, brought about by the film.

The expected benefits of slimming films relate mainly to the areas of the body characterized by the presence of stubborn cellulite.

For these sites in which cellulite is firmly established, it is necessary to be able to renew and maintain the action of the active substances before they are naturally metabolized by the adipocytes.

The technology of films makes it possible, using active substances, to create on the horny layer a reservoir effect, from which a uniform and continuous diffusion of the active agents into the lower layers of the skin is exerted. On account of this continuous diffusion, permanent presence of active agents in the region of the adipocytes is ensured.

This results in a constant saturation of the storage receptors, which will make it possible to act

on reducing the orange peel effect present in the areas of stubborn cellulite.

The advantageous aspect of the films results firstly from the structure of the matrix containing the active substances and secondly from its application system.

Since it can be sprayed directly onto the skin, the film forms a thin, supple and invisible film, from which the active substances are diffused.

The low thickness of the film formed makes it possible not to disrupt the gaseous and aqueous exchanges existing between the skin and the external environment, thereby further improving the tolerability of the product. The suppleness of the film moreover offers a greater sensation of comfort.

As regards the active substances, the film contains NPY antagonist and $\alpha 2$ antagonist active agents, in a concentration 10 times greater than that used in the conventional fluid as disclosed in EP 838 217.

Thus, by virtue of its bioavailability which is subject to two-fold control over time, by means of continuous diffusion of the active substances and locally by means of an activity strictly limited to the sites of spraying, the film makes it possible to provide effective and long-lasting saturation of the adipocyte storage receptors by the NPY receptor

antagonist and the α2 receptor antagonist, resulting in a reduction of the areas that are traditionally resistant to slimming treatments.

The compositions according to the invention for dermal administration may be prepared in a conventional manner, by a person skilled in the art, by mixing together the various constituents in the chosen proportions.

For example, the cutaneous absorption promoter may be dissolved, with stirring, in the solvent, followed by addition of the active principle and finally the release matrix.

All of the substances forming part of the compositions of the invention are known products or may be prepared by known methods, some of these products being commercially available.

The dermal compositions of the invention thus obtained may be applied by any means to an area of skin, for example to an area of between 10 and 40 cm^2, for example 30 cm^2, in particular and preferably by direct spraying using a dosing pump of a type which is known and sold, with the aid of a propellant such as a compressed or liquefied gas.

Although the prior art asserts the contrary, it has been found, surprisingly, that a release matrix formed from ethylcellulose does not, with the composition used, cause any obstruction by blocking the

outlet of the spraying head nozzle, such that the compositions of the invention may be sprayed in the presence of a propellent gas without any fear of deterioration of the spray container.

The compositions of the invention may thus be administered by spraying using a container fitted with metering valve, also containing a propellent gas such as nitrogen or nitrous oxide, or a liquefied gas such as butane or propane.

According to another subject, the invention relates to a matrix intended for cosmetic compositions for dermal administration, comprising:

a) a polymeric matrix, for releasing an active principle, which is capable of forming a supple film after drying

b) a promoter of cutaneous absorption of an active principle

c) a non-aqueous solvent capable of dissolving the release matrix and the cutaneous absorption promoter and also of being rapidly removed by evaporation on contact with the skin

d) a propellent gas

The polymeric matrix will be selected from polymeric and copolymeric substances, in particular from cellulose polymers or copolymers as specified previously, while the cutaneous absorption promoter will be selected from aliphatic fatty acid esters or

from aliphatic fatty alcohols as described above, in particular esters of formula I or alcohols of formula II.

As regards the non-aqueous solvent, it is a compound with a boiling point of less than 100°C at atmospheric pressure, as mentioned previously.

These various components of the matrix for the dermal cosmetic composition will be distributed such that, in the cosmetic composition under consideration containing the active principle, the release matrix represents from 0% to 7%, the cutaneous absorption promoter represents from 15% to 30% and the non-aqueous solvent represents from 44% to 84.9%, these percentages being expressed relative to the weight of the final cosmetic composition.

These matrices for dermal compositions according to the invention may be conventionally prepared by mixing together the various ingredients of which they are made in the selected proportions.

The propellent gases are advantageously chosen from propanol and butanol.

The film-forming compositions of the invention and the matrices for dermal compositions according to the invention have unquestionable advantages since they are capable of bringing about the cutaneous diffusion of an active substance, so as to produce constant and controlled effective levels over a

prolonged period of at least 12 hours from an area of skin coverage of about from 10 to 40 cm^2.

In addition, the compositions and matrices for dermal compositions according to the invention, while lacking any unpleasant odor, spread out to form a uniform film over the entire area of skin selected.

These films are sufficiently supple and abrasion resistant to avoid any deterioration on the skin of the user and exhibit better tolerability than the known dermal devices since, on account of their thinness and the absence of any coverage, gaseous and aqueous exchanges with the external environment are not disrupted.

Finally, the compositions of the invention, in the form of a supple film, afford the user a greater sensation of comfort and, by virtue of their transparency, are entirely invisible.

Various tests were performed both *in vitro* and *in vivo* so as to demonstrate the characteristics and particular features of the compositions of the invention.

The cosmetic compositions according to the invention preferably contain slimming active substances.

The slimming active substances are preferably chosen from NPY or α2 receptor antagonists.

In this case, the active substances used are, for example, the extracts of the *Streptomyces sp* strain SEBR 2794, filed at the C.N.C.M. of the Institut Pasteur under No. I-1332 and the extracts of the *Bacillus licheniformis* strain SEBR 2464 filed at the C.N.C.M. of the Institut Pasteur under No. I-1778. They will be referred to hereinbelow as slimming active substance.

A clinical efficacy study was carried out with a slimming composition containing NYP and α2 receptor antagonists. The object of this study was to evaluate the efficacy of the film used in combination with Lipofactor® fluid (Lipofactor: registered trademark of Sanofi).

a) Protocol

The test is carried out over a period of 28 days and is performed on 31 women. The individuals were included after a clinical examination and verification of the presence of areas of established cellulite. The individuals applied the fluid and the film to the same leg, defined randomly, the other leg being used as the untreated control.

The fluid is applied in the desired amount to the entire thigh, from the knee to the buttock fold. The application is carried out in the evening, with no massaging beyond that required for penetration of the product.

The film is applied in the morning in a highly localized manner to the following 4 sites:

- outer superior lateral face of the thigh,
- inner superior face of the thigh,
- posterior face (buttock fold),
- inner face of the knee.

The amount of film used per day corresponds to two adjacent sprayings so as to cover the area concerned.

The evaluation of the efficacy is performed at T_0 (before treatment) and at $T_{28\ days}$ and uses three different methods:

- echography to measure the thickness of the adipose tissue taken at three locations on the thigh plus one on the knee;
- clinical evaluation of the macrorelief (orange peel effect) of the outer face of the thighs;
- analysis of images of the relief of the orange peel effect.

b) Results

↳ Echography

Table 1 shows the main characteristics of the individuals.

The weight of the individuals was measured at the end of the 28 days of the test. No significant changes were observed, which will thereby make it

possible to confirm the attribution of the results observed to the activity of the test products.

Table 1: Characteristics of the individuals

Criteria	Average	Maximum values	Minimum values
Age	37 years old	53 years old	19 years old
BMI (a)	21.8	26.9	18.5

(a) Body Mass Index

Table 2 and Figure 1 show the average reduction in thickness of the adipose tissue after one month of testing.

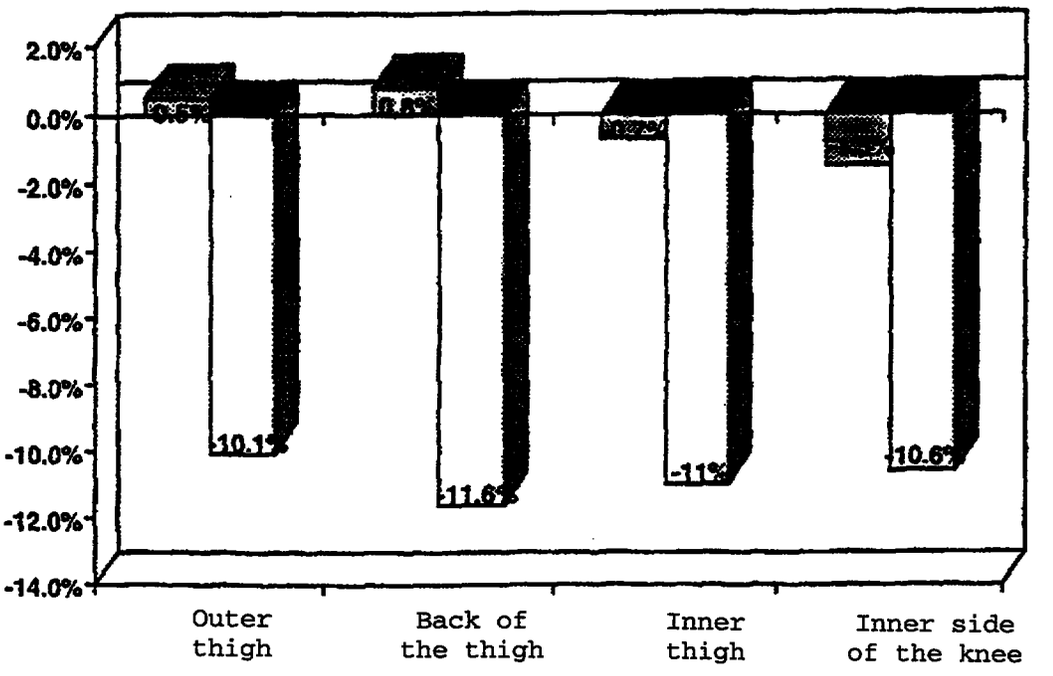
Depending on the area, a marked reduction in the thickness of the adipose tissue, of the order of -10% compared with the values measured at T_0, is observed.

Table 2: Average reductions of the adipose tissue as a function of the sites treated (expressed as a % change relative to T_0)

Location	Treated	Control	Tr-control	Standard deviation
Outer thigh	-10.1%	0.5%	-19,5%*	±2.8%
Back of the thigh	-11.6%	0.8%	-12.4%*	±2.4%
Inner thigh	-11.0%	-0.7%	-10.3%*	±2%
Inner side of the knee	-10.6%	-1.5%	-9.1%	±1.9%

*S($p<<0.05$)

Figure 1: Percentage change between T_0 and T_{28} days for each location



These results appear to be very significant and concern only the treated side. At the same time, good stability of the controlateral control locations, which show non-significant variations ranging from -0.3 to ±0.1 mm, is observed.

↳ Clinical evaluation and image analysis

The clinical evaluation of the macrorelief is carried out using photographic negatives by five evaluators. After random distribution, all the negatives are graded by the evaluators by comparison with a calibration range (reference photographs), structured around 7 degrees of intensity.

For five individuals, a preliminary profilometric analysis was carried out so as to calculate the average relief of a defined area on each

image and corresponding to an area of skin equivalent to 3 × 130 mm.

The negatives of the outer sides of the treated and control thighs of the 31 volunteers made it possible to confirm clinically, after analysis by the 5 evaluators, an improvement in the skin relief.

This improvement is significant ($p<<0.05$) for the thighs treated between T_0 and T_{28} d, whereas, in the same period, no significant result is obtained on the untreated sides.

Table 3: Results compared on 5 individuals between the clinical change and the image analysis

Individual	Clinical change (improvement)	Image analysis (attenuation of the skin relief)
1	30%	-35%
2	43%	-24%
3	18%	-14%
4	18%	-22%
5	52%	-11%

The concept of the film was evaluated in the course of the study carried out on 113 women recruited for having cellulite.

The film is applied for 4 weeks at a rate of two adjacent sprayings so as to cover the area concerned. The efficacy of the film is evaluated at the end of the study.

It emerges from this study, as regards the efficacy, that the film generally allows a significant improvement in the orange peel effect located on the lower limbs.

EXAMPLE 1

Dermal composition containing [lacuna]

100 g of a dermal composition having the formulation below is prepared:

	% by weight
Ethylcellulose 6 mPa.s	5%
Slimming active substance	2%
2-Ethylhexyl 2-ethylhexanoate	20%
Ethanol	73%
Propylene glycol	0.5%
Propellent gas	

by mixing together, for 30 seconds and with magnetic stirring, 73 g of ethanol and 20 g of 2-ethylhexyl 2-ethylhexanoate. 2 g of slimming active substance(s) are then added portionwise to the mixture obtained and, after complete dissolution (5 minutes), 5 g of ethylcellulose 6 mPa.s are added with vigorous stirring, so as to avoid the formation of lumps. The final solution obtained is homogeneous and slightly opalescent. For the purpose of administration by spraying, aluminum cans are filled with 5 ml of the solution obtained above and are fitted with a crimping vasopump comprising a push-button dispenser. The pump

is actuated twice to prime it before its first use.

EXAMPLE 2

Matrix for a dermal composition

98 g of a dermal matrix are prepared by mixing together 73 g of ethanol and 20 g of 2-ethylhexyl 2-ethylhexanoate for 30 seconds. 5 g of ethylcellulose 6 mPa.s are then added with vigorous stirring, so as to avoid the formation of lumps. The matrix thus obtained is ready to receive an active agent, by incorporation, so as to form a cosmetic composition containing 2% by weight of this active agent, which may be applied by spraying.

EXAMPLE 3

Matrix for a dermal composition

The process is performed according to Example 2, by mixing together:

Ingredients	% by weight
Ethanol	75
Isononyl isononanoate	20
Ethylcellulose	5

EXAMPLE 4

Matrix for a dermal composition

The process is performed as in Example 2, by mixing together:

Ingredients	% by weight
Ethanol	80
Isononyl isononanoate	15
Ethylcellulose	5

EXAMPLE 5

Matrix for a dermal composition

The process is performed as in Example 2, by mixing together:

Ingredients	% by weight
Ethanol	75
Isononyl isononanoate	15
Ethylcellulose	5
Diethylene glycol monoethyl ether	5

EXAMPLE 6

Matrix for a dermal composition

The process is performed as in Example 2, by mixing together:

Ingredients	% by weight
Ethanol	70
Isononyl isononanoate	15
Ethylcellulose	5
Diethylene glycol monoethyl ether	10

EXAMPLE 7

The following composition is prepared:

Ingredients	% by weight
Alcohol	44.016
Butane	23.20
Octyl octanoate	12.00
Propane	11.20
Isobutane	5.60
Ethylcellulose	3.00
Panthenol	0.30
Propylene glycol	0.30
Diethyl phthalate	0.258
Slimming active substance(s)	0.126

Table A: Composition of the formulations

Reference formulation:	A	B	R	C	D	E	F	G
Percentage								
Ethanol 95	77	76	75	67	66	18		
Isopropanol						54	74	74
Dragoxat® EH	20	20	20	30	30	25	20	20
Ethylcellulose 7 mPa.s	3	4	5	3	4	3	5	5
Silicone DC 556							1	
Light liquid paraffin								1

Reminder of the reference formulation: 95° ethanol: 75%; Dragoxat®: 20%; ethylcellulose: 5%.

Table B: Classification of the evaluation of the excipients relative to the reference formulation

Criteria	Overall assess-ment	Sticky skin	Penetra-tion	Gloss	Greasi-ness	Resi-due	Odor
	EFFECT RELATIVE TO THE REFERENCE						
	(+ Better, - Worse, = equivalent)						
EXCIPIENTS							
Isopropanol	=	=	=	=	=	-	-
3% ethyl-cellulose	+	+	+	+	+	+	+
4% ethyl-cellulose	=	=	=	=	=	=	=
25% Dragoxat®	-	-	-	-	=	-	=
30% Dragoxat®	-	-	-	-	=	-	=

CLAIMS

1. Cosmetic composition for dermal administration, characterized in that it comprises:

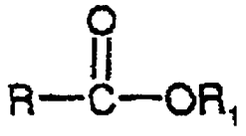
a) optionally, a polymeric release matrix capable of forming a supple film after drying, chosen from cellulose polymers or copolymers;

b) an active principle;

c) 5% to 30%, relative to the weight of the composition, of a promoter of transcutaneous absorption of the active principle,

d) a non-aqueous solvent capable of dissolving the release matrix, the active principle and the cutaneous absorption promoter and also of being rapidly removed by evaporation on contact with the skin, the cutaneous absorption promoter being chosen from:

- an aliphatic fatty acid ester which is soluble in the physiologically acceptable non-aqueous solvent and of general formula:



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in which R represents a linear or branched C_2-C_{17} alkyl or alkenyl group optionally substituted with a hydroxyl, carboxylic or C_1-C_4 acyloxy group and R_1 represents a linear or branched C_3-C_8 alkyl group optionally substituted with one or two hydroxyl groups or R_1 represents a $-CH_2-CH_2-O-(CH_2)_2-O-CH_2-CH_3$

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group, the aliphatic fatty acid ester comprising a minimum of 10 carbon atoms and a maximum of 2 hydroxyl groups

- an aliphatic fatty alcohol which is soluble in the physiologically acceptable non-aqueous solvent, of general formula

$$R_2\text{-OH} \qquad \text{II}$$

in which R_2 represents a C_{10}-C_{20} alkyl group

e) at least one propellent gas.

2. Composition according to claim 1, characterized in that the polymeric release matrix is present in a proportion of from 0% to 7% relative to the weight of the composition.

3. Composition according to claim 2, characterized in that the polymeric release matrix is present in a proportion of from 1% to 5% relative to the weight of the composition.

4. Composition according to one of claims 1 to 3, characterized in that the active principle is present in a proportion of from 0.1% to 20% relative to the weight of the composition.

5. Composition according to one of claims 1 to 4, characterized in that the cutaneous absorption promoter is present in a proportion of from 15% to 25% relative to the weight of the composition.

6. Composition according to one of claims 1 to 5, characterized in that the non-aqueous solvent is

present in a proportion of from 44% to 84.9% relative to the weight of the composition.

7. Composition according to one of claims 1 to 6, characterized in that the polymeric release matrix is a cellulose polymer or copolymer which is soluble in the non-aqueous solvent.

8. Composition according to claim 7, characterized in that the cellulose polymer or copolymer is ethylcellulose, cellulose acetate butyrate, cellulose acetate propionate or a hydroxypropylmethylcellulose which may or may not be grafted.

9. Composition according to claim 7, characterized in that the cellulose polymer or copolymer is ethylcellulose.

10. Composition according to one of claims 1 to 9, characterized in that the active principle is a slimming active substance which is an NPY receptor antagonist and/or an $\alpha 2$ receptor antagonist.

11. Composition according to one of claims 1 to 10, characterized in that the active principle is chosen from extracts obtained by fermenting a microorganism.

12. Composition according to claim 11, characterized in that the active substances are present in a proportion of from 0.5% to 6% relative to the weight of the composition.

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13. Composition according to claim 12, characterized in that the active substances are present in a proportion of from 1% to 2% relative to the weight of the composition.

14. Composition according to one of claims 1 to 10, containing a combination of active substances consisting of an NPY antagonist and of an α2 antagonist, characterized in that the active substances used are the extracts of the *Streptomyces sp* strain SEBR 2794 filed at the C.N.C.M. of the Institut Pasteur under No. I-1332, and the extracts of the *Bacillus licheniformis* strain SEBR 2464 filed at the C.N.C.M. of the Institut Pasteur under No. I-1778.

15. Composition according to one of claims 1 to 14, characterized in that R_1 represents an isopropyl, 2-ethylhexyl or 1,2-dihydroxyethyl group.

16. Composition according to claim 1, characterized in that the cutaneous absorption promoter is chosen from:

- 2-ethylhexyl 2-ethylhexanoate
- isopropyl myristate
- diethylene glycol monoethyl ether myristate
- isopropyl palmitate
- 2-octyldecanol
- 2-ethylhexyl undecylenate
- 2-ethylhexyl succinate
- 2-ethylhexyl 12-hydroxystearate

* C L M S *

- 2-ethylhexyl 12-acetoxystearate
- glyceryl isostearate
- hexyl laurate

17. Composition according to claim 1 or 15, characterized in that the cutaneous absorption promoter is 2-ethylhexyl 2-ethylhexanoate.

18. Composition according to one of claims 1 to 17, characterized in that the non-aqueous solvent is a compound with a boiling point of less than 100°C at atmospheric pressure.

19. Composition according to claim 18, characterized in that the compound with a boiling point of less than 100°C is dichloromethane, ethanol, isopropanol or ethyl acetate.

20. Pharmaceutical composition according to claim 18, characterized in that the non-aqueous solvent is ethanol.

21. Composition according to claim 1, characterized in that:

- the cellulose polymer or copolymer is ethylcellulose
- the active substance is a slimming active substance
- the cutaneous absorption promoter is 2-ethylhexyl 2-ethylhexanoate
- the solvent is ethanol
- the propellent gas is butane.

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22. Composition according to claim 21, characterized in that it comprises:

- 3% ethylcellulose;
- 2% slimming active substance(s);
- 20% 2-ethylhexyl 2-ethylhexanoate; and
- 75% ethanol
- propellent gas.

23. Composition according to claim 1 or 21, characterized in that it comprises:

- 5% ethylcellulose;
- 2% slimming active substance(s);
- 20% 2-ethylhexyl 2-ethylhexanoate; and
- 73% ethanol
- propellent gas.

24. Composition according to claim 1, characterized in that it comprises:

- 5% ethylcellulose;
- 2% slimming active substance(s);
- 20% 2-ethylhexyl 2-ethylhexanoate; and
- 74% ethanol
- propellent gas.

25. Composition according to claim 1, characterized in that it comprises:

- 2% ethylcellulose;
- 1% slimming active substance(s);
- 20% 2-ethylhexyl 2-ethylhexanoate; and
- 77% ethanol

- propellent gas.

26. Composition according to one of claims 1 to 25, characterized in that it is intended to be applied by spraying using compressed or liquefied propellent gas.

27. Composition according to one of claims 1 to 26, characterized in that it is applied to an area of skin of from 10 to 40 cm^2.

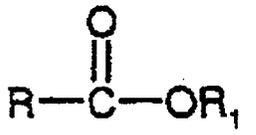
28. Matrix for a cosmetic composition intended for dermal administration, characterized in that it comprises:

a) a polymeric matrix for the release of an active principle, capable of forming a supple film after drying, chosen from cellulose polymers or copolymers;

b) 15% to 30%, relative to the weight of the composition, of a promoter of transcutaneous absorption of the active principle;

c) a non-aqueous solvent capable of dissolving the release matrix and the cutaneous absorption promoter, and also of being rapidly removed by evaporation on contact with the skin, the cutaneous absorption promoter being chosen from:

- an aliphatic fatty acid ester which is soluble in the physiologically acceptable non-aqueous solvent and of general formula:



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in which R represents a linear or branched C_2-C_{17} alkyl or alkenyl group optionally substituted with a hydroxyl, carboxylic or C_1-C_4 acyloxy group and R_1 represents a linear or branched C_3-C_8 alkyl group optionally substituted with one or two hydroxyl groups or R_1 represents a $-CH_2-CH_2-O-(CH_2)_2-O-CH_2-CH_3$ group, the aliphatic fatty acid ester comprising a minimum of 10 carbon atoms and a maximum of 2 hydroxyl groups

- an aliphatic fatty alcohol which is soluble in the non-aqueous solvent, of general formula

R_2-OH II

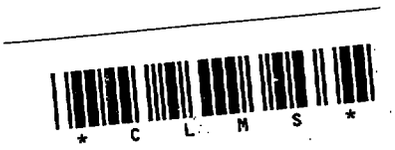
in which R_2 represents a C_{10}-C_{20} alkyl group

d) a propellent gas.

29. Matrix for a composition according to claim 28, characterized in that the cellulose polymer or copolymer is ethylcellulose, cellulose acetate butyrate, cellulose acetate propionate or a hydroxypropylmethylcellulose which may or may not be grafted.

30. Matrix for a composition according to claim 29, characterized in that the cellulose polymer or copolymer is ethylcellulose.

31. Matrix for a composition according to



one of claims 28 to 30, characterized in that the cutaneous absorption promoter is chosen from:

- 2-ethylhexyl 2-ethylhexanoate
- isopropyl myristate
- diethylene glycol monoethyl ether myristate
- isopropyl palmitate
- 2-octyldodecanol
- 2-ethylhexyl undecylenate
- 2-ethylhexyl succinate
- 2-ethylhexyl 12-hydroxystearate
- 2-ethylhexyl 12-acetoxystearate
- glyceryl isostearate
- hexyl laurate.

32. Matrix for a composition according to claim 31, characterized in that the cutaneous absorption promoter is 2-ethylhexyl 2-ethylhexanoate.

33. Matrix for a composition according to one of claims 28 to 32, characterized in that the non-aqueous solvent is a compound with a boiling point of less than 100°C at atmospheric pressure.

34. Matrix for a composition according to claim 33, characterized in that the compound with a boiling point of less than 100°C is dichloromethane, ethanol, isopropanol or ethyl acetate.

35. Matrix for a dermal composition according to claim 33, characterized in that the

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compound with a boiling point of less than 100°C is ethanol.

36. Matrix for a composition according to one of claims 28 to 35, characterized in that, in said composition containing the active substances, the release matrix represents from 0 to 7%, the cutaneous absorption promoter represents from 15% to 30% and the non-aqueous solvent represents from 44% to 84.9%, these percentages being expressed relative to the weight of the final composition.

37. Pump-spray device containing a composition according to any one of claims 1 to 27.

38. Cosmetic composition according to claim 1, characterized in that it contains at least one slimming active substance.

39. Cosmetic slimming composition according to claim 38, characterized in that it contains an NPY receptor antagonist and an α2 receptor antagonist.

40. Cosmetic slimming composition according to claim 39, characterized in that it contains the extracts of the *Streptomyces sp* strain SEBR 2794 filed at the C.N.C.M. of the Institut Pasteur under No. I-1332, and the extracts of the *Bacillus licheniformis* strain SEBR 2464 filed at the C.N.C.M. of the Institut Pasteur under No. I-1778.