The present invention relates to pharmaceutical, in particular dermatological or cosmetic compositions, comprising hydrous lipidic lamellar phases or liposomes containing a retinoid or a structural analogue thereof such as a carotenoid.

It is well known that certain retinoids such as the tretinoin are used in therapeutics, in particular in the treatment against acne.

The tretinoin or its homologues such as the 13-cis-retinoic acid constitute medicines most used at the present time in the treatment of acne. One also knows the anti-acneic action of the carotenoids. Various galenic forms have been proposed among which the most active one is based upon an alcoholic solution of the tretinoin intended for local administering. One may cite in this respect a medicine having the commercial denomination ABEREL®. There exists various formulations of ABEREL with 0.025%, 0.05% and 0.1% of tretinoin. The excipient is based on ethyl alcohol at 95°. The effects of the tretinoin are summarized in the dictionary VIDAL, "Specialités Pharmaceutiques Françaises" in particular in the 1985 edition and more complete comments may be obtained from the article of Lorraine Kligman et al. published in "The Journal of Investigative Dermatology", Volume 73, N°5, part I, pages 354-358, published in 1979, with an experimentation on the skin of hairless Rhino mice which is the most suitable model for the experimentation relating to the inhibition of comedos. In this article Kligman emphasizes that the tretinoin in addition has a positive effect to make vanish the folds and wrinkles of the skin of the hairless Rhino mouse.

There also exists medicines intended for the oral administration containing retinoids such as the 13-cis-retinoic acid or the etretinate for the treatment of serious acnes, of the psoriasis and of other serious troubles of the keratinization.

The major inconvenience of the tretinoin is through the general tract its systemic toxicity (teratogenicity an undesirable effects due to A-hypervitaminosis) and through the local pathway its irritant action which may necessitate in some cases the stopping of the treatment. One is emphasizing in the dictionary VIDAL that this action characterized by a dry, slightly smarting erythema having its seat especially about the peribuccal region and the neck is directly linked to the activity of the product but it however disappears when one makes the application less frequent.

According to some authors the systemic toxicity of the tretinoin even through the local tract is a limiting factor for its use (see last but one paragraph, page 357 of the above-mentioned article).

It thus appears that the irritant effect of the tretinoin is directly connected to the activity of the latter.

One may moreover observe that one is stating that the ABEREL® forms in conventional excipients, in a solution at 0.2% and 0.3% which have a great dose of tretinoin are contra-indicated in the acne and reserved for the treatment of the disturbances of the keratinization.

At last the alcoholic solution used in the ABEREL® form with a dose of 0.025% also proves to exhibit an irritant effect.

In another therapeutic application one may cite the US patent N°3,856,934 to Albert Kligman relating to a composition for the depigmentation of the skin, containing tretinoin (also called acid Ⓐ-vitamin or also trans-retinoic acid).

Lorraine Kligman et al. are further describing in the review "Connective Tissue Research" 1984, volume 12, pages 139-150 that the tretinoin with a dose of 0.05%, applied for 5 and 10 weeks stimulates the fibroblasts and promotes the repair of the damages caused by an ultra-violet irradiation. Thus Kligman discloses in this article that the tretinoin has an activity promoting the formation of a zone of subepidermic reconstruction which is considered as being favourable for "rejuvenating" the epidermis.

Furthermore Yamamoto and others in Chemical Abstracts, volume 88, N° 19, May 8, 1978, page 171 and in Biochim. Biophys. Acta 1978, 507(1), 119-27 as well as S.S. Brody and others in Chemical Abstracts, volume 101, N°13, September 24, 1984, page 246 and in Photobiochemistry, Photobiophysics 1984, 7(4), 205-19 are describing liposomes which may contain in particular various carotenoids but these liposomes are not described as being capable of constituting pharmaceutical, in particular dermatological or cosmetic compositions.

Finally in the book of F. Puisieux and S. Delattre with the title "Les liposomes - Applications Thérapeutiques", Technique et Documentation Lavoisier, 1985, pages 297-312, there is described that one may encapsule in niosomes liposoluble compounds which are inserting themselves into the lipidic layers. But as to the therapeutical applications of the niosomes there is only described that the niosomes allow to prevent the phenomenon of dry skin induced by various aggressions.

Thus the present invention has as its object to solve the new technical problem consisting in the provision of a new therapeutic formulation of active agents comprising retinoids, carotenoids or compounds with an analogous chemical structure allowing to potentiate their effectiveness while decreasing their toxic effects in particular the irritant effect on the skin upon the local application of some of them.

The present invention allows for the first time to solve this new technical problem within the scope of a certain number of particular therapeutic applications.

Thus the present invention has as its subject the utilization of a composition based upon hydrous lamellar lipidic phases or liposomes which contain as an active agent a retinoid or a carotenoid for the obtaining of a pharmaceutical in particular dermatological or cosmetic composition intended for the treatment through topical application of the various forms of acne, of the hyperkeratosis, of the psoriasis, for the fight against the actinic or chronological cutaneous aging, for the suppression or the attenuation of the cutaneous pigmental spots, for promoting the cicatrization, for the reconstitution of the blood micro-vessels, in particular in the derm and for the stimulation of the hair growth or intended for the oral administration in particular for the treatment of the various forms of acne, of the hyperkeratosis and of the psoriasis.

According to a particular embodiment the retinoid is advantageously selected among the tretinoin or its derivatives, in particular salts or esters; the 13-cis-retinoic acid or its derivatives, in particular salts or esters; the A-vitamin or its esters such as acetate, propionate, palmitate or stearate; the etretinate. On the other hand the aforesaid carotenoid is preferably selected among the group consisting of the α- or ß-carotene, the γ-carotene or the δ-carotene.

According to a preferred embodiment the weight content of the tretinoin with respect to the total composition is from 10^{-6} to 10^{-3}, and preferably from 5.10^{-6} to 10^{-4}.

Naturally the hydrous lamellar lipidic phases or the aforesaid liposomes may also contain other hydrophobic substances such as sterols (sistosterol, cholesterol, stigmasterol, etc.) as this is usual and has been described in FR-A-2,521,565.

One may combine the aforesaid active agent with other therapeutically, dermatologically or cosmetically active agents. Thus it is possible to combine this active agent with a complementary or secondary active agent incorporated either into the said lipidic layer of liposome, and in this case its quantity should not exceed 40% by weight of the totality of the lipidic phase, or into the aqueous phase in accordance with their solubility. This complementary active agent may in particular be selected among the erythromycin, the clindamycin, the metronidazole or another antibiotic or antiseptic agent or the derivatives of the aforesaid compounds, notably the esters. In this case the complementary active agent content may reach 4% for the erythromycin, 2% for the clindamycin or 2% for the metronidazole by weight with respect to the total composition. Thus the usual concentrations of these complementary active agents may be used in combination with the aforesaid main active agent. A particularly effective combination consists of a tretinoin concentration of 5.10^{-5} with 1% of erythromycin.

It is also advantageous and in some cases very important to add to the lipidic phase an antioxidant such as the α-tocopherol up to at most 1% by weight, the B.H.T. or the TBHQ. It moreover is further advantageous to add to the aqueous phase hydrosoluble antioxidants such as the ascorbic acid, the sodium sulphite, the sodium disulphite, the EDTA and stabilizers such as citric acid, histidine in the usual proportions of their use.

One may also provide the presence of a compound constituting an ultra-violet filter.

Preferably the proportion of the retinoid or of its structural analogue as the keratinoid in the lipidic phase constituting the double layer of the lamellar phases or liposomes is not critical and may reach 40% by weight. Preferably this proportion is comprised between 10^{-4}% and 10%, and still preferably between 0.01% and 5%.

The hydrous lamellar lipidic phases or liposomes according to the invention containing one or several of the various constituents cited above may be advatageously subjected to a lyophilization according to the usual techiques so as to yield a lipidic powder. The said powder which may be kept for a long time in this state without any alteration is dispersed in a suitable aqueous medium with a view to its utilization in order to prepare a pharmaceutical in particular dermatological or cosmetic composition according to the invention.

This pharmaceutical, dermatological or cosmetological composition according to the invention may be formulated to treat the various forms of acne, of the hyperkeratosis, of the psoriasis and other disturbances of the keratinization, for fighting against actinic skin aging due for example to repeated exposures to the sun, against the chronological skin aging, for attenuating or removing the pigmental skin spots, for promoting a cicatrization for the reconstitution of the blood micro-vessels in particular in the derm and for promoting the stimulation of the hair growth. This composition may be also prepared in a form suitable for the oral administration, in particular for the treatment of the various forms of acne, of the hyperkeratosis, of the psoriasis.

Further purposes, characteristics and advantages of the invention will appear in the light of the explanatory description which will follow, giving several examples given merely by way of illustration and which therefore should not limit in any way the scope of the invention and reporting the results of the evaluations of activity, of hyperacanthosis and of irritation. The annexed figure shows the comedolytic activity as a function of the concentration in acid A vitamin either contained in the liposomes (curve L-o-o-o) or in the alcohol (curve A-▲-▲-▲). The percentages are given in weight unless otherwise stated.

Example 1.

Preparation of suspensions of liposomes containing the tretinoin.

One dissolves in 30 ml of dichloromethane, 2 g of soya lecithin, 0.1 g of tretinoin in the presence of a lipophilic antioxidant, e.g. 0.006g of α-tocopherol.

The obtained solution may be processed to obtain a suspension of liposomes through the well known method of evaporation in a rotary container and which consists in depositing a lipidic layer in the flask of the rotary evaporator through evaporation of the solvent and then adding water or a suitable aqueous solution.

One may also use the so-called reverse phase technique described in the document FR-A-2,399,242.

One however prefers atomizing the obtained solution at 65°C as described in the document FR-A-2,521,565 in a manner to produce a fine powder which one disperses in 200 ml of an aqueous solution buffered at a pH of

about 7.5. Generally one uses a solution containing 0.8% of NaCl and 1.5% of NaH_2PO_4, called "phosphate buffer", to which is added an antioxidant stabilizer such as the ascorbic acid with the concentration of 0.05%.

One thus obtains after homogenization either with ultra-sounds or in a homogenizer under pressure, for example according to the method described in the document FR-A-2,534,487 the said suspension of liposomes in which the tretinoin concentration is of about 5.10^{-4} and the lecithin concentration is 1%.

One should observe that one may thus perform various dilutions by modifying the amount of tretinoin added from the start or by increasing the volume of the dispersion solution, which constitutes an easy process for the preparation of various tretinoin concentrations.

Example 2.

Utilization of compositions according to the example 1 to constitute a pharmaceutical or cosmetic composition.

One checks the utilization of the composition of the example 1 as a pharmaceutical or cosmetic composition by effecting the following experimentation in vivo on the hairless Rhino mouse.

A - Comedolytic activity

To study the comedolytic activity on the hairless Rhino mouse one uses suspensions of liposomes with 3% of lecithin and with different doses of 10^{-6}; 5.10^{-6}; 10^{-5}; 5.10^{-5}; 10^{-4}; 10^{-3}; 3.10^{-3}, respectively, of tretinoin.

One prepares solutions with the same tretinoin concentration in alcohol at 95° containing 5% of polyethylene glycol 400.

One also prepares reference solutions, a first reference solution only containing liposomes with 3% of lechitin without tretinoin, a second composition only containing alcohol at 95° with 5% of polyethylene glycol 400.

Each one of these compositions is applied daily for 3 weeks upon the scapular area of the hairless Rhino mice at a dose of 0.1 ml.

At the end of this period the animals are sacrificed and biopsies are carried out on the zone of application. An optical microscopy examination coupled with an image analyser permits to quantify the cuts by the measurement of the diameter (D) of the comedo and of its aperture (d). This method of mesurement of the comedolytic activity is in accordance with that described by Claude BONNE et al. in International Journal of Cosmetic Science 3, 23-28 (1981).

Thus for each animal the mean of the ratio r=d/D allows to characterize the comedolytic activity of the composition. One proceeds in the usual manner by using a composition according to the invention containing tretinoin in the liposomes (composition L) in comparison with a comparison composition according to which the tretinoin is contained in an alcoholic solution (composition A). As a reference solution one uses a reference solution containing liposomes with 3% of lecithin. The results obtained form the subject of the curves A (composition A) and L (composition L) of the attached figure as well as of the table I herebelow.

To obtain the aforesaid ratio r=d/D the procedure has been changed with respect to that described by Claude Bonne by counting all the existing or potential comedos for a given length of the epidermis. Thus one makes the average of all the d/D of each comedo by including the value d/D=1 for the open comedos which tend to disappear when observed.

With the reference solution one does not observe any significant comedolytic activity.

TABLE I

COMEDOLYTIC ACTIVITY

Concentration of acid A-vitamin (tretinoin)	in Liposome r=d/D	in alcohol at 95° + 55% of PEG 400 r=d/D
Reference	0.58	0.64
10^{-6}	0.64	
5.10^{-6}	0.88	
10^{-5}	0.95	0.67
5.10^{-5}		0.85
10^{-4}	0.98	0.93

PEG = Polyethylene glycol

From the curves of Figure 1 one may observe that the dose of 10^{-5} of the tretinoin contained in liposomes brings about a maximum comedolytic activity which is only reached with the dose of 10^{-4} of tretinoin in an alcoholic solution. The formulation of the tretinoin in the liposomes or hydrous lamellar lipidic phases therefore is ten times more active.

It is to be remarked that the animal model (hairless Rhino mouse) is substantially more sensitive than the man, i.e. the maximum activity is reached at a lower concentration.

On the other hand the threshold of effectiveness in the hairless Rhino mouse is at $5x10^{-6}$ of tretinoin contained in the liposomes according to the invention whereas it only is $5x10^{-5}$ in an alcoholic solvent.

Thus the invention permits to potentiate the activity of the tretinoin by incorporating it into liposomes or more or less hydrous lamellar lipidic phases.

We shall now look at the results obtained as regards hyperacanthosis.

B. Hyperacanthosis

One knows that tretonoin increases the mitosis of the cells of the basement membrane of the epidermis; these cells then rise towards the horny layer and produce the hyperacanthosis.

The hyperacanthosis (H) is determined on the sections having served to the evaluation of the comedolytic activity. One measures by means of the image analyser the increase H in the thickness e of the epidermis of the treated animals with respect to the reference animals, the reference solution being the solution based on liposomes with 3% of lecithin.

The evaluation of the hyperacanthosis is obtained from the following formula:

$$H = \frac{e^t - e^o}{e^o}$$

wherein e_t is the thickness of the epidermis of the treated animals and e_0 is that of the reference animals.

One obtains the results listed in the table II herebelow.

TABLE II

HYPERACANTHOSIS

Tretinoin Concentration	LIPSOMES			ALCOHOL		
Thickening	0	10^{-4}	5.10^{-4}	0	10^{-3}	3.10^{-3}
H_1 (8 days)	50.7	88.5	85.3	14.3	59.45	58.1
H_2 (16 days)	45	37.7	41.8	19.8	78.8	80.5
$H = \frac{H_1 + H_2}{2}$	47.85	63.1	63.55	17.05	69.125	69.3

P.S.: one has listed the values obtained after 8 days and after 15 days of treatment by then giving the mean value.

One observes that the tretinoin contained in the liposomes leads much more quickly in eight days only to a thicknening of the epidermis, which is beneficial for the treatment of the comedos whereas the tretinoin in an alcoholic solution brings about this effect after some fifteen days only.

On the other hand one also observes that in the case of the liposomes after 16 days the thicknening of the epidermis is decreasing which is favourable too.

C. The Irritation

The irritation is studied in the rabbit which constitutes a better adapted model than the Rhino mouse for this phenomenon.

A daily application of the products to be tested is effected with the dose of 0.03 ml/cm^2 in open patch on the right flank of each rabbit of a group of six, the left flank serving as a reference. The duration of the treatment is 2 weeks at the rate of 5 days a week (i.e. 10 days of treatment).

One effects a microscopic reading everyday according to the protocol on the irritation tests published in the Journal Officiel on February 1982. One marks the erythema and the oedema from 0 to 4.

The irritation index I is the mean of the sums of the erythema + oedema marks per day of application and per animal according to the following formula:

$$I = \frac{\Sigma \text{ erythema} + \Sigma \text{ oedema}}{60}$$

When the irritation index obtained is ≤ 0.5 one considers that the treatment composition or product is non-irritant;

When I is comprised between 0.5 and 2 one considers that the product or the composition is slightly irritant;

When I is higher than 2 and ≤ 5 one considers that the product or the composition is irritant;

When I is higher than 5 one considers that the product or the composition is very irritant.

The results obtained are listed in Table III, page 25.

One observes that the irritation phenomenon only appears when using higher concentrations than in the study of the comedolytic activity. The tested concentrations have been chosen as a function of the results of the comedolytic activity hence by proceeding with a factor of concentration difference of 10 to effect a comparison of the irritation at an equal comedolytic activity, which is determining for the practitioner.

One observes that under these conditions both values of the irritation obtained for the liposomes are markedly lower than those obtained for the alcoholic solution.

Of course unlike the study on the comedolytic activity where the action-dose quantizing is clear and precise, the evaluation of the irritation is more fluctuating and one only obtains a global trend.

One may therefore say that the incorporation of the tretinoin into the liposomes permits to obtain the same result on the treatment of the comedos with 10 times less product without therefor increasing the irritant effects, indeed even it tends to decrease them.

Moreover the fact of being able to treat the cutaneous diseases such as the acne with ten times lower tretinoin doses accordingly decreases the risk of toxicity of the tretinoin often linked to the dose. In effect numerous publications describe the toxicity of the tretinoin and of its structural homologues (C.E. Orfanos et al. Hautarzt, June 1981, 32 (6), pages 275-280; J.M. Wishart et al. New Zealand Medical Journal Oct. 28, 1981, 94 (694), pages 307-308). In addition to the already mentioned irritation these are: the hypervitaminosis A resulting in particular in a generalized pruritis, loss of hair (C.E. Orfanos already cited), bone tumours (exostoses) (P.E. Pochi, New England J. Med., April 28, 1983, 308 (17), pages 1024-1025), the dryness of the mucuous membranes in particular of the lips (C.E. Orfanos already cited), allergic dermatoses (C. Romaguera et al., Contact Dermatitis, October 1980, 6 (6), page 442), a teratogenicity evidenced in the animal (L. Newell-Morris et al., Teratology, August 1980, 22 (1), pages 87-101; A.G. Hendrickx et al., Teratology, August 1980, 22 (1), pages 13-22; I.M. Taylor et al., Teratology, April 1980, 21 (2), pages 193-7).

Thus the results of the in vivo experimentations reported hereabove allow to conclude that the compositions according to the invention in which the tretinoin is incorporated into liposomes or into hydrous lamellar lipidic phases are usable to prepare pharmaceutical or cosmetic compositions in particular in the local treatment of the acne with doses located below the threshold of activity in an alcoholic medium while practically inducing no irritation phenomenon.

Otherwise said, the incorporation of the tretinoin into liposomes or hydrous lamellar lipidic phases has led to a particularly unexpected potentiation at very small doses of from 5.10^{-6} to 10^{-4}, without inasmuch potentiating the irritation phenomenon, contrary to what

could be expected by a man skilled in art since the irritation was considered as directly linked to the activity. It is thus possible to decrease the dose for an equivalent comedolytic activity by lowering in a radical manner the risk of the irritation phenomenon.

Example 3. Dermatological Composition

One prepares according to the preferred mode of the example 1 a suspension of liposomes containing:

Tretinoin	0.005 g
Hydrogenated soya bean lecithin	5 g
Sitosterol	0.5 g
α-tocopherol	0.005 g

Buffered aqueous solution containing antioxidants and preservatives, sufficient quantity for 50 g.

The said suspension is then mixed with 50 g of a gel of Carbopol 940® at 1.25%.

This final composition in the form of a gel is recommended in the treatment of the acne in daily application on the skin area to be treated.

Example 4. Dermo-cosmetic Composition

One operates as in the example 3 with the following composition:

Tretinoin	0.001 g
Hydrogenated soya bean lecithin	1.0 g
Cholesterol	0.1 g
α-tocopherol	0.003 g

The obtained gel is used for the treatment of acneic skins.

Example 5. Dermatological Composition

With the suspension of liposomes of the example 3 one mixes an equal amount of gel of Carbopol 940® at 1.25% containing preservatives, antioxidants and an A+B ultra-violet filter, at the usual concentrations.

This gel may be used for the treatment of the solar elastosis.

Example 6. Dermo-cosmetic Composition

One provides a suspension of liposomes according to the example 1 containing:

Tretinoin	0.002 g
Hydrogenated soya bean lecithin	10.00 g
Sitosterol	1.4 g
α-tocopherol	0.06 g
"Phosphate buffer" containing antioxidants and preservatives in a quantity sufficient for	100 g

This suspension is mixed with 125 g of gel of Carbopol 940® at 1.25%.

The gel obtained is emulsified with 50 g of an oily phase based upon perhydrosqualene containing an A+B ultra-violet filter and a perfume.

The gelled emulsion obtained is used for the regeneration of the skin of the face and of the body and as a dermic or cicatrizing restructuration agent.

Example 7. Lyophilized Dermatological Composition

One provides a suspension of liposomes according to the example 1 with the following composition:

Tretinoin	0.005 g
Hydrogenated soya bean lecithin	5 g
Sitosterol	0.5 g
B. H. T.	0.005 g
"Phosphate buffer", quantity sufficient for	100 g

to which one adds 5 g of glucose in the aqueous phase as a lyophilization adjuvant.

This suspension is lyophilized.

At the time of use one mixes 1 g of the lyophilisate with 20 g of sterile distilled water in the presence of usual hydrosoluble preservatives.

The extemporaneous suspension may be used in the treatment of the acne, of the hyperkeratoses or of the solar elastosis.

Example 8. Lyophilized Dermo-cosmetic Composition

One prepares a lyophilisate according to example 7 by using 0.001 g of tretinoin only.

The suspension prepared at the time of use may be utilised for the treatment of the acneic skins, of the harsh skins and of the wrinkled skins.

Example 9. Dermatological Composition

One prepares according to the example 3 a gel with the following composition:

Tretinoin	0.005 g
Soya bean lecithin	5 g
Sitosterol	0.5 g
Erythromycin	1.0 g
α-tocopherol	0.003 g
Excipients for the gel, sufficient quantity for	100 g

One should note that in the present case the erythromycin is introduced into the organic solution of dichloromethane prior to the atomization.

The obtained gel is used in the treatment of the acne.

Example 10. Dermatological Composition

One prepares according to the example 1 an atomized lipidic powder containing:

Tretinoin	0.005 g
Lecithin	1.0 g
Sitosterol	0.1 g
α-tocopherol	0.003 g

The latter is dispersed in a "phosphate buffer" containing 1% of clindamycin chlorhydrate as well as antioxidants, quantity sufficient for 100 g.

One obtains a suspension of liposomes which contains clindamycin chlorhydrate in the encapsuled aqueous phase.

This suspension may be lyophilized, in this case one previously adds 100 ml of an aqueous solution of glucose at 10%.

At the time of use one mixes 1 g of the lyphilisate with 20 ml of sterile distilled water in the presence of usual hydrosoluble preservatives.

The extemporaneous suspension is used advantageously in the treatment of the acne.

Example 11. Dermatological Composition

One prepares a gel according to the example 3, the buffered aqueous solution however contains hydroquinone.

The composition of the suspension of liposomes before the mixture with the gel of Carbopol 940® is the following:

Tretinoin	0.005 g
Hydrogenated soya bean lecithin	5.0 g
Sitosterol	0.5 g
Liposoluble antioxidant	0.2 g
Hydroquinone	3.0 g
Sodium sulphite	0.4 g
Ascorbic acid	0.5 g
"Phosphate buffer", sufficient quantity for	50 g

The gel will be used in a topical application for the treatment of pigmental spots.

Example 12. Dermo-cosmetic Composition

One operates according to the example 11 but by decreasing the proportions of tretinoin and of hydroquinone.

The final composition of the gel is the following:

Tretinoin	0.001 g
Hydrogenated soya bean lecithin	5.0 g
Sitosterol	0.5 g
Liposoluble antioxidant	0.2 g
Hydroquinone	2.0 g
Sodium sulphite	0.4 g
Ascorbic acid	0.5 g
Carbopol 940® gel at 1.25%, sufficient quantity for	100 g

This gel is utilized in applications upon pigmental spots of the skin such as so-called old-age spots in order to make them vanish or at least to attenuate them.

Example 13. Dermo-cosmetic Composition

One prepares a suspension of liposomes according to the example 1 with the following composition:

Tretinoin	0.0005 g
soya bean lecithin	0.5 g
Cholesterol	0.05 g
α-tocopherol	0.0003 g

Aqueous excipients consisting of a "phosphate buffer" of preservatives, of antioxidants and of perfumed aqueous extracts, sufficient quantity for	100 ml

The suspension obtained is a lotion used to promote the hair growth.

TABLE III

IRRITATION OF THE RABBIT SKIN

AFTER 15 DAYS OF TREATMENT

		Mean Irritation Value						
	Tretinoin concentration	Reference (0)	5.10^{-6}	5.10^{-5}	10^{-4}	5.10^{-4}	10^{-3}	3.10^{-3}
Composition	In liposomes (invention)	2.34	NS	NS	2.67	3.24		
	In the alcohol + PEG (comparative) 400 5%	1.08	NS	NS			3.13	3.95

N.S. = Not Significant

Example 14. Dermatological Composition

One prepares through atomization according to the preferred mode of the example 1 a powder A with the following composition:

Tretinoin	0.05 g
Hydrogenated soya bean lecithin	20.0 g
Erythromycin stearate	10.0 g
α-tocopherol	0.05 g

One on the other hand prepares an aqueous solution B with the following composition:

Ascorbyl acetate	0.01 g
E.D.T.A.	0.01 g
Saccharose	5.0 g
Glycine	2.5 g
Water, sufficient quantity for	100.0 g

1 g of the powder A is then dispersed in 100 g of the solution B under magnetic stirring for 2 hours at room temperature.

There is formed a suspension of liposomes which is then homogenized with ultra-sounds at 4°C for 10 minutes with the power of 200 W. The mean size of the liposomes after this homogenization is 200 nanometers.

The suspension of liposomes obtained is then lyophilized at -40°C to produce a powder which may be preserved in a closed container for several years. With a view to its utilization in dermatology this lyophilized powder is stirred in the presence of a suitable aqueous medium such as a gel of Carbopol 940® having a good viscosity (about 100 to 1,000 centipoises). The proportion of lyophilized powder in the gel is for example 1%.

The gel obtained in an extemporaneous manner may be used in daily application on the skin for the treatment of the acne.

Example 15. Dermo-cosmetic Composition

One prepares a gel according to the example 3 with the following composition:

A-vitamin acetate	0.2 g
Hydrogenated soya bean lecithin	1.8 g
B.H.T.	0.02 g
Excipient for the gel, sufficient quantity for	100.0 g

In the present example the A-vitamin acetate and the B.H.T. are introduced into the dichloromethane solution before the atomization.

The obtained gel in application on the skin promotes the renewal of the epidermis.

Example 16. Dermo-cosmetic Composition

One prepares a gel according to the example 15 but by replacing the 0.2 g of A-vitamin acetate by 0.4 g of A-vitamin palmitate. The amount of lecithin is 1.6 g only.

This gel also promotes the renewal of the epidermis.

Example 17. Dermo-cosmetic Composition

One prepares a gel according to the example 3 with the following composition:

Beta-carotene	0.2 g
Soya bean lecithin	1.8 g
Alpha-tocopherol	0.002 g
Excipient for the gel, sufficient quantity for	100.0 g

The obtained gel is emulsified with 100 g of an oily phase based upon perhydrosqualene containing a perfume.

The gelled emulsion obtained is used to prepare the skin before the exposure to the sun.

Claims

1. Utilization as a cosmetic product of a composition based upon hydrous lipidic lamellar phases or liposomes containing as an active agent a retinoid or a carotenoid intended for the treatment of skin diseases, carotenization troubles, solar elastosis, comedos, acneic skins, harsh skins, wrinkled skins, for the fight against actinic or chronological skin ageing, for the attenuation or the removal of pigmental skin spots, in particular of the so-called senile spots, for promoting the cicatrization, for the regeneration of blood microvessels in particular in the derm; for stimulating hair growth, for regenerating the skin of the face or of the body, for the dermic restructuring, for promoting the renewal or the thickening of the epiderm, or for preparing the skin prior to the exposure to the sun.

2. Utilization according to claim 1, characterized in that the aforesaid retinoid is selected among tretinoin or its derivatives, in particular salts or esters; the 13-cis-retinoic acid or its derivatives, in particular salts or esters, the A vitamin or its esters, the etratinate.

3. Utilization according to claim 1, characterized in that the aforesaid carotenoid is selected among the α-or β-carotene; or the γ-carotene or the δ-carotene.

4. Utilization according to claim 1 or 2, characterized in that the aforesaid retinoid is the tretinoin.

5. Utilization according to claim 4, characterized in that the tretinoin concentration with respect to the total composition is from 10^{-6} to 10^{-3}.

6. Utilization according to claim 4, characterized in

that the tretinoin concentration with respect to the total composition is from 5.10^{-6} to 10^{-4}.

7. Utilization according to one of claims 1 to 6, characterized in that the proportion of retinoid or carotenoid in the lipidic phase constituting the bilayer of the aforesaid lipidic lamellar phase or of the liposome may reach 40% by weight, preferably is comprised between 10^{-4} % and 10% or still preferably is from 0.01% to 5%.

8. Utilization according to one of the foregoing claims, characterized in that the hydrous lipidic lamellar phases or the liposomes further contain hydrophobic substances such as sterols, like the sistosterol, the cholesterol, the stigmasterol.

9. Utilization according to any one of claims 1 to 8, characterized in that the lipidic phase of the aforesaid hydrous lipidic lamellar phase or of the aforesaid liposome contains an anti-oxidant such as the α-tocopherol up to at most 1% by weight, B.H.T. or T.E.H.Q.; and/or the aqueous phase contains a water-soluble anti-oxidant such as the ascorbic acid, the sodium sulfite, the sodium bisulfite, the EDTA, also advantageously stabilizers such as the citric acid and the histidine.

10. Utilization according to any one of claims 1 to 9, characterized in that the aforesaid composition preferably contains a compound constituting an ultraviolet filter.

11. Utilization according to any one of claims 1 to 10, characterized in that the aforesaid composition is prepared from a lyophilised lipidic powder.

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12. Utilization of a composition based upon hydrous lipidic lamellar phases or on liposomes containing as an active agent a retinoid or a caretonoid for the manufacture of a medicine intended for the treatment, by a topical application, of skin diseases such as various forms of acne, hyperkeratosis, psoriasis or other troubles of the keratinization, solar elastosis, comedos, acneic skins, harsh skins, wrinkled skins, for the fight against actinic or chronological skin ageing, for the attenuation or the removal of pigmental skin spots, in particular of the so-called senile spots, for promoting the cicatrization, for the reconstitution of blood microvessels, in particular in the derm, for stimulating hair growth, for regenerating the skin of the face or of the body, for the dermic restructuring, for promoting the renewal or the thickening of the epiderm and for preparing the skin before exposure to the sun, or intended for oral administration, in particular for the treatment of various forms of acne, of the hyperkeratosis and of the psoriasis.

13. Utilization according to claim 12, characterized in that the aforesaid retinoid is selected among tretinoin or its derivatives, in particular salts or esters; the 13-cis-retinoic acid or its derivatives, in particular salts or esters, the A vitamin or its esters, the etretinate.

14. Utilization according to claim 12, characterized in that the aforesaid carotenoid is selected among the α- or β-carotene; or the γ-carotene or the δ-carotene.

15. Utilization according to claim 12 or 13, characterized in that the aforesaid retinoid is the tretinoin.

16. Utilization according to claim 15, characterized in

that the tretinoin concentration with respect to the total composition is from 10^{-6} to 10^{-3}.

17. Utilization according to claim 15, characterized in that the tretinoin concentration with respect to the total composition is from 5.10^{-6} to 10^{-4}.

18. Utilization according to one of claims 12 to 17, characterized in that the proportion of the retinoid or of the carotenoid in the lipidic phase constituting the bilayer of the aforesaid lipidic lamellar phase or of the liposome may reach 40% by weight, preferably is comprised between 10^{-4}% and 10% and still preferably is from 0.01% to 5%.

19. Utilization according to one of claims 12 to 18, characterized in that the aforesaid hydrous lipidic lamellar phases or the aforesaid liposomes further contain an antibiotic or antiseptic agent such as the erythromycin, the clindamycin, the metronidazole or their derivatives, in particular the esters.

20. Utilization according to claim 19, characterized in that the aforesaid hydrous lipidic lamellar phases or the aforesaid liposomes contain the tretinoin or one of its derivatives, in particular salts or esters, in combination with the erythromycin or one of its derivatives the proportion of which may reach 4% by weight with respect to the total composition and is lying preferably at 1%.

21. Utilization according to claim 19, characterized in that the aforesaid hydrous lipidic lamellar phases or the aforesaid liposomes contain the tretinoin or one of its derivatives, in particular salts or esters, in combination with the clindamycin or one of its derivatives the proportion of which may reach 2% by weight with respect to the total composition.

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22. Utilization according to one of claims 12 to 21, characterized in that the hydrous lipidic lamellar phases or the liposomes further contain hydrophobic substances such as sterols, like the sistosterol, the cholesterol, the stigmasterol.

23. Utilization according to any one of claims 12 to 22, characterized in that the lipidic phase of the aforesaid hydrous lipidic lamellar phase or of the aforesaid liposome contains an anti-oxidant such as the α-tocopherol up to at most 1% by weight, B.H.T. or T.E.H.Q.; and/or the aqueous phase contains a water-soluble anti-oxidant such as the ascorbic acid, the sodium sulfite, the sodium bisulfite, the EDTA, also advantageously stabilizers such as the citric acid and the histidine.

24. Utilization according to any one of claims 12 to 23, characterized in that the aforesaid composition preferably contains a compound constituting an ultraviolet filter.

25. Utilization according to any one of claims 12 to 24, characterized in that the aforesaid composition is prepared from a lyophilised lipidic powder.